Journal of Molecular Catalysis B: Enzymatic 55 (2008) 146–151

Contents lists available at ScienceDirect

Journal of Molecular Catalysis B: Enzymatic

journal homepage: www.elsevier.com/locate/molcatb

Evaluation of enantioselectivity in lipase-catalyzed acylation of hydroxyalkylphosphine oxides

Kosei Shioji*, Takafumi Ueyama, Nobuaki Ueda, Emiko Mutoh, Tsutomu Kurisaki, Hisanobu Wakita, Kentaro Okuma

Department of Chemistry, Faculty of Science, Fukuoka University, Jonan-ku, Fukuoka 814-0180, Japan

ARTICLE INFO

Article history:
Received 19 November 2007
Received in revised form 12 March 2008
Accepted 12 March 2008
Available online 21 March 2008

Keywords:
Lipase
Optical resolution
Hydroxyalkylphosphine oxides

ABSTRACT

The lipase-catalyzed optical resolution of 2-, 3-, and 5-hydroxyalkyl phosphorus compounds **1** provided the corresponding optically pure diastereomers in good yields. (S_P, R)- and (R_P, S)-**1** were acylated faster than (S_P, S)- and (R_P, R)-**1**. The stereoselectivity at the phosphorus atom changed with the flexibility of the active sites in the lipases. The stereoselectivity at the phosphorus atom was higher in the reaction of **1a** than in the reaction of **1b**,**c**. The reaction rate of ε-hydroxyalkylphosphine oxide **1c** was faster than that of **1a**, although less enantioselectivity was observed at the phosphorus atom.

1. Introduction

Biotransformations of organic substrates containing chiral heteroatoms are one of the most powerful methods for the synthesis of optically active chemicals. Kielbasinski et al., who are pioneers in this area, previously demonstrated the lipase-catalyzed optical resolution of *P*-chiral phosphorus and *S*-chiral sulfur compounds [1–4]. Chiral phosphorus compounds possessing a chiral center at the phosphorus atom are particularly useful for asymmetric syntheses [5–9]. In a previous paper, we reported the lipase-catalyzed optical resolution of α-hydroxymethylphosphine oxides and the corresponding phosphine-borane analogs (Scheme 1a and b) [10,11]. We have also reported the lipase-catalyzed optical resolution of the versatile ethyl(1-hydroxyalkyl)phenylphosphinates, possessing two chiral centers at the phosphorus atom and carbon atom adjacent to the hydroxyl group, yielding optically pure diastereomers (Scheme 1c) [12,13].

In order to explain the enantiopreference of lipases toward secondary alcohols, Kazlauskas et al. proposed an empirical rule, which was based on fitting the substrate to the active site of the lipase [14]. However, the stereoselectivity at the stereocenter situated at a remote distance from the lipase active site was not assumed by the empirical rules. Here, we describe the stereoselectivity in the resolution of *tert*-butyl(2-hydroxypropyl)phenylphosphine oxide (**1a**), *tert*-butyl(3-hydroxybutyl)phenylphosphine oxide (**1b**), and *tert*-butyl(5-hydroxyhexyl)phenylphosphine oxide (**1c**), which have 2, 3, and 5 methylene carbons situated between the phosphorus atom and the hydroxyl group, respectively.

2. Experiment

2.1. General

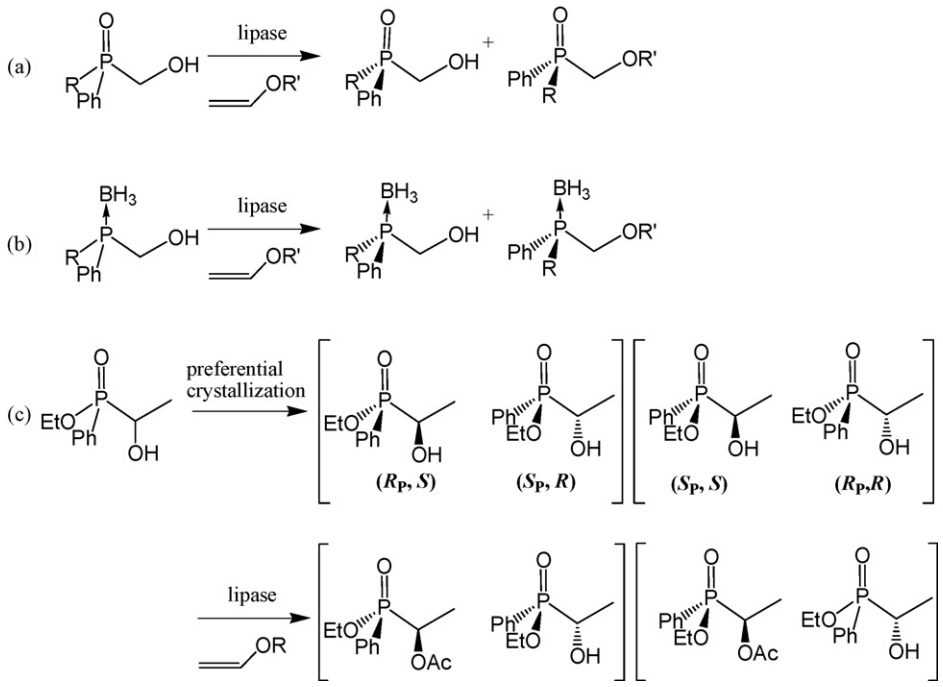
All the solvents were distilled prior to use. The lipase from *Pseudomonas fluorescence* (Amano AK) was purchased from Amano Pharmaceutical Co. Ltd. The lipase from *Candida antarctica* (Chirazyme® L-2, c.-f., C2, lyo.) was purchased from Roche Molecular Biochemicals. The HPLC analyses were performed with a Waters 600 dual pump equipped with a tunable absorbance detector (Waters 484) on a Chiralpak AD (0.46 cm × 25 cm), with hexane/2-propanol (97/3) containing 0.1% trifluoroacetic acid as the eluent.

2.2. Preparation of tert-butyl(2-hydroxypropyl)phenylphosphine oxide (*1a*)

A solution of ethyl phenylphosphinate (8.0 ml, 53.1 mmol) in 200 ml of THF was cooled to −78 °C, and *tert*-butyllithium (117 mmol, 78.9 ml of 1.41 M solution in *n*-pentane) was added dropwise. After stirring for 1 h, propylene oxide (5.57 ml, 79.7 mmol) was added dropwise, and the mixture was stirred for 12 h. During this period, the reaction flask reached room

* Corresponding author. Tel.: +81 928716631; fax: +81 928656030.
E-mail address: shioji@fukuoka-u.ac.jp (K. Shioji).

1381-1177/$ – see front matter © 2008 Elsevier B.V. All rights reserved.
doi:10.1016/j.molcatb.2008.03.004



Scheme 1.

temperature. The reaction mixture was quenched with sat. NH_4Cl. The solution was filtered, and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and evaporated. The residue was purified by column chromatography on silica gel (EtOAc) to afford **1a** ((*S*P, *R*) and (*R*P, *S*):(*R*P, *R*) and (*S*P, *S*) = 1.2:1) in 63% yield. These diastereomer pairs were purified by preferential crystallization from ethyl acetate.

(*S*P, *R*) and (*R*P, *S*)-**1a**: mp 143–144 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.13 (d, J = 14.8 Hz, 9 H), 1.28 (d, J = 6.4 Hz, 3 H), 2.12–2.21 (m, 1H), 2.38–2.44 (m, 1H), 4.37–4.47 (m, 1H), 7.46–7.72 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 24.0, 24.8, 32.3 (J_{PC} = 62.4 Hz), 33.1 (J_{PC} = 68.2 Hz), 64.5 (J_{PC} = 5.0 Hz), 128.1, 128.2, 131.0, 131.2, 131.3, 131.5, 131.6; ^{31}P NMR (162 MHz, $CDCl_3$) δ = 50.6; Anal. Calcd. for $C_{13}H_{21}O_2P$: C, 64.98; H, 8.81%. Found: C, 64.83; H 8.88%.

(*R*P, *R*) and (*S*P, *S*)-**1a**: mp 108–109 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.15 (d, J = 14.8 Hz, 9H), 1.25 (d, J = 6.4 Hz, 3H), 2.07–2.24 (m, 2 H), 3.95–4.05 (m, 1H), 7.49–7.73 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 23.9, 24.9, 31.1 (J_{PC} = 62.4 Hz), 32.6 (J_{PC} = 62.4 Hz), 63.2 (J_{PC} = 62.4 Hz), 128.2, 128.3, 128.7, 129.5, 131.6, 131.7, 131.7; ^{31}P NMR (162 MHz, $CDCl_3$) δ = 53.6; Anal. Calcd. for $C_{13}H_{21}O_2P$: C, 64.98; H, 8.81%. Found: C, 65.28; H, 8.85%.

2.3. Synthesis of tert-butylmethylphenylphosphine oxide (*2*)

To a solution of dichlorophenylphosphine (1.8 g, 10 mmol) in 20 ml of dry THF was added a 2.0 M diethyl ether solution of *tert*-butylmagnesium bromide (6.0 ml, 12 mmol) at −15 °C. After stirring for 2 h at room temperature, the reaction mixture was added to a 3.0 M methylmagnesium bromide-THF solution (4.0 ml, 12 mmol) at −15 °C. The reaction mixture was stirred at this temperature for 2 h and quenched with sat. NH_4Cl. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2. The organic components were combined and dried over $MgSO_4$. The solution was concentrated and dissolved in 20 ml of water, and 30% H_2O_2 (3.0 ml) was added to it. The reaction mixture was stirred for 1 h and extracted with CH_2Cl_2. The extract was dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography (ethyl acetate) to afford phosphine oxide **2** in 85% yield (colorless crystals). The structure of **2** was identified by comparing its ^{1}H NMR with literature values. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.13 (d, J = 14.8 Hz, 9H), 1.73 (d, J = 12.4 Hz, 3H), 7.47–7.75 (m, 5H).

2.4. Synthesis of tert-butyl(3-hydroxybutyl)phenylphosphine oxide (*1b*)

A solution of **2** (4.0 g, 20.4 mmol) in 60 ml of THF was cooled to −10 °C, and butyllithium (24.3 mmol, 9.37 ml of 2.59 M solution in *n*-pentane) was added dropwise. After stirring for 1 h, propylene oxide (1.85 ml, 26.5 mmol) was added dropwise, and then stirred for 12 h. During this period, the reaction flask reached room temperature. The reaction mixture was quenched with sat. NH_4Cl. The solution was filtered, and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and evaporated. The residue was purified by column chromatography on silica gel (EtOAc:MeOH = 9:1) to afford **1b** ((*S*P, *R*) and (*R*P, *S*):(*R*P, *R*) and (*S*P, *S*) = 10:9) in 92% yield.

(*S*P, *R*) and (*R*P, *S*)-**1b**: Colorless crystals. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.14 (d, 9H), 1.15 (dd, 3H), 1.77–1.85 (m, 1H), 1.52–1.59 (m, 1H), 2.04–2.26 (m, 2H), 3.81–3.85 (m, 1H), 7.46–7.70 (m, 3H), 7.71–7.73(m, 2H); ^{31}P NMR (162 MHz, $CDCl_3$) δ = 52.7; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 18.60, 19.25, 23.38, 24.67, 31.16, 32.53, 33.21, 67.08, 67, 18, 76.96, 77.28, 77.60, 128.28, 128.58, 129.223, 130.08, 131.73, 132.08, 132.16, (some are coupled by phosphorus).

(*R*P, *R*) and (*S*P, *S*)-**1b**: Colorless crystals. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.14 (d, 9H), 1.15 (dd, 3H), 1.77–1.85 (m, 1H), 1.52–1.59 (m, 1H), 2.04–2.26 (m, 2H), 3.81–3.85 (m, 1H), 7.46–7.70 (m, 3H), 7.71–7.73 (m, 2H); ^{31}P NMR (162 MHz, $CDCl_3$) δ = 54.1; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 18.60, 19.25, 23.38, 24.67, 31.16, 32.53, 33.21, 67.08, 67, 18, 76.96, 77.28, 77.60, 128.28, 128.58, 129.223, 130.08, 131.73, 132.08, 132.16, (some are coupled by phosphorus).

2.5. Synthesis of tert-butyl(5-hydroxyhexyl)phenylphosphine oxide (**1c**)

To a THF (8 ml) solution of **2** (0.16 g, 0.82 mmol) was added 1 ml of 2.4 M *tert*-BuLi ether solution at −15 °C. After stirring for 2 h, tert-butyldimethylsilyl (TBS) ether **3** (0.6 ml, 5.1 mmol) was added dropwise to the reaction mixture, and the resulting mixture was further stirred for 12 h. The reaction was quenched by the addition of sat. NH_4Cl. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$. The mixture was concentrated and purified by column chromatography on silica gel (EtOAc) to afford TBS ether in 53% yield (colorless oil). TBS ether was hydrolyzed with Bu_4NF in THF to afford the four diastereomers (1:1:1:1) of **1c** in 80% yield. These diastereomers were separated by GPC (JAIGEL-H, $CHCl_3$) to afford (S_P, R)- and (R_P, S)-**1c** and (R_P, R)- and (S_P, S)-**1c** as colorless oils. (S_P, R)- and (R_P, S)-**1c**: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.11 (d, J = 14.4 Hz, 9H), 1.14 (d, J = 4.4 Hz, 3H), 1.29–1.55 (m, 5H), 1.65–1.80 (m, 1H) 2.00–2.07 (m, 2H) 3.69–3.79 (m, 1H) 7.44–7.71 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 21.8 (J_{PC} = 4.5 Hz), 22.7, 23.3, 23.9, 25.0, 27.5 (J_{PC} = 13.0 Hz), 32.7, 33.4, 38.9, 67.5, 128.3, 128.5, 131.6, 131.9, 132.0, 132.1; ^{31}P NMR (162 MHz, $CDCl_3$) δ = 51.7. (R_P, R)- and (S_P, S)-**1c**: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.11 (d, J = 14.4 Hz, 9H), 1.14 (d, J = 4.4 Hz, 3H), 1.29–1.55 (m, 5H), 1.65–1.80 (m, 1H) 2.00–2.07 (m, 2H) 3.69–3.79 (m, 1H) 7.44–7.71 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 21.9 (J_{PC} = 3.8 Hz), 22.6, 23.3, 23.8, 25.0, 27.6 (J_{PC} = 9.9 Hz), 32.7, 33.4, 39.0, 67.6, 128.3, 128.5, 131.6, 131.9, 132.0, 132.1; ^{31}P NMR (162 MHz, $CDCl_3$) δ = 51.4.

2.6. General procedure for lipase-catalyzed optical resolution of phosphorus compounds

A mixture of racemic phosphorus compounds **1** (5 mg), enzyme (20 mg), molecular sieves 3A (20 mg), and vinyl acetate (7 eq.) was stirred in diisopropyl ether (2 ml) at 36 °C. The reaction was monitored by HPLC. The optical resolutions on a preparative scale were carried out with 40 times the quantity of the materials used for the analytical scale. The reactions were monitored by HPLC and were stopped at the appropriate conversion stage. The reaction mixture was separated by column chromatography.

2.7. Crystal structure of optically active phosphine oxide (**1a**)

The crystal structure of the optically active phosphine oxide **1a** was determined using a Rigaku AFC5R diffractometer with graphite-monochromated Mo Kα radiation and a rotating anode generator. The unit-cell parameters were determined by the least-square refinement of 25 reflections. The intensity data were collected at room temperature by the ω-2θ technique up to a maximum 2θ value of 60.0°. The structure was solved according to the heavy-atom Patterson method, and expanded using Fourier techniques. The non-hydrogen atoms were refined anisotropically, while the hydrogen atoms were refined isotropically. The final cycle of the full-matrix least-squares refinement was based on 2893 observed reflections (I > 2.00 σ (I)) and 231 variable parameters, and converged with the unweighted and weighted agreement factors of R (R_W) = 0.038 (0.049). All the calculations were performed using the teXsan crystallographic package. The crystallographic data for the structures reported in this paper have been deposited at the Cambridge Crystallographic Data Centre: Deposit No. CCDC 680486. Copies of this information may be obtained free of charge from the Director, CCDC, 12 Union Road, Cambridge 1EZ, UK [fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk]

2.8. Synthesis of optically active phosphine oxide (R_P, S)-**1b**

The optically active phosphine oxides (R_P)-, and (S_P)-**2** were prepared according to literature methods [10]. To a solution of both the phosphine oxides **2** (300 mg, 1.41 mmol) in toluene (3 ml) were added triethylamine (0.39 ml, 2.82 mmol) and trimethylamine hydrochloride (67.9 mg, 0.71 mmol), and the resulting solution cooled to 0 °C. To the mixture was added *p*-toluenesulfonyl chloride (404 mg, 212 mmol). After stirring for 9 h, the reaction was quenched with water, and extracted with ethyl acetate (20 ml × 3 ml), and dried over $MgSO_4$. The solvent was removed under reduced pressure. The residue was purified by column chromatography (AcOEt) to afford tosylate in 95% yield. To a solution of the obtained tosylate (468 mg, 1.28 mmol) in ethylene glycol dimethyl ether (3 ml) was added NaI (441 mg, 2.94 mmol), and the reaction mixture was stirred for 0.5 h. After stirring, tributyl tin hydride (669 mg, 2.3 mmol) was added dropwise, and the mixture refluxed for 24 h. The reaction mixture was filtered, and the solvent removed under reduced pressure. By column chromatography (AcOEt), the crude residue was confirmed to be phosphine oxide (R_P)- and (S_P)-**2**, produced as colorless crystals in 92% and 93% yield, respectively. (R_P)-**2**: $[\alpha]_D^{24}$ + 21.7 (>98% ee), c = 1.83, C_6H_6, (S_P)-**2**: $[\alpha]_D^{24}$ − 19.3 (92% ee), c = 2.36, C_6H_6.

The reaction of phosphine oxide (R_P)-, or (S_P)-**2**, with the optically active alcohol (*S*)-propylene oxide was carried out by a method similar to that described above. (S_P, S)-**1c**; $[\alpha]_D^{24}$ + 36.4 (>90% ee), c = 1.75, $CHCl_3$.

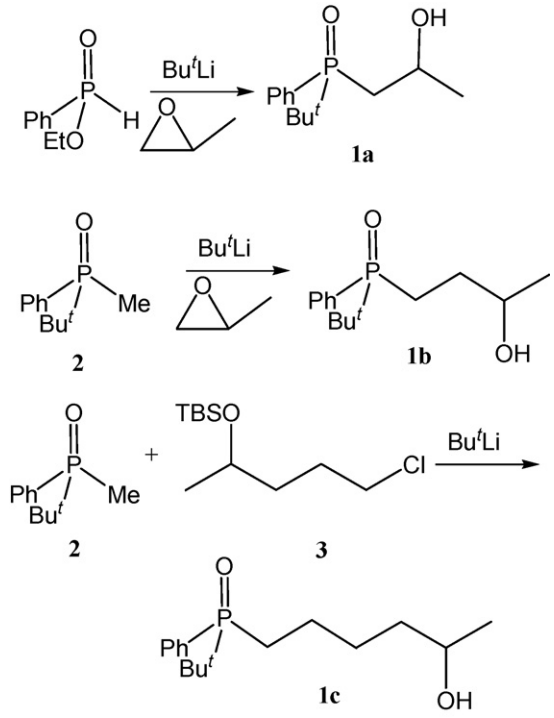
2.9. Synthesis of optically active phosphine oxide (S_P, S)-, and (R_P, S)-**1c**

To a solution of 5-chloro-2-pentanol (200 mg, 1.63 mmol) in diisopropylether (80 ml) were added vinyl acetate (1.06 ml, 11.4 mmol), molecular sieves 3A (800 mg), and CAL (800 mg), and the reaction mixture was stirred at 36 °C for 10 min. The reaction mixture was filtrated, and the solvent was removed. The residue was separated by column chromatography (EtOAc) to afford (*S*)-5-chloro-2-pentanol ($[\alpha]_D^{24}$ + 16.58, >98% ee, c = 1.19). The reaction of phosphine oxide (R_P)- or (S_P)-**2**, with the optically active TBS ether (*S*)-**3** prepared from (*S*)-5-chloro-2-pentanol was carried out by a method similar to that described above. (R_P, S)-**1c**; $[\alpha]_D^{24}$ + 15.4 (>98% ee), c = 1.08, $CHCl_3$, (S_P, S)-**1c**; $[\alpha]_D^{24}$ − 0.32 (>98% ee), c = 1.07, $CHCl_3$.

3. Results and discussion

3.1. Preparation of phosphine oxides **1**

Racemic hydroxyalkyl phosphorus compounds were prepared by the reaction of lithiated phosphorus compounds, which were generated by the abstraction of hydrogen from ethyl phenylphosphinate with electrophiles such as aldehydes or oxiranes [15]. The synthesis of 2-hydroxypropylphenylphosphine oxide **1a** was carried out by a one-pot reaction between *tert*-butyllithium, ethyl phenylphosphinate, and propene oxide, affording a 1.2:1 mixture of (S_P, R)-, (R_P, S)-**1a** and (S_P, S)-, (R_P, R)-**1a** (Scheme 2). The mixture of (S_P, R)-, (R_P, S)-**1a** and (S_P, S)-, (R_P, R)-**1a** was also separated by preferential crystallization from ethyl acetate. 3-Hydroxybutylphosphine oxide **1b** was synthesized from *tert*-butylmethylphenylphosphine oxide (**2**) and propylene oxide. The product ratio of (S_P, R)-, (R_P, S)-**1b** and (S_P, S)-, (R_P, R)-**1b** was 10:9. This mixture was also separated by preferential crystallization. 5-Hydroxyhexylphosphine oxide **1c** was synthesized from **2** and chloropentanol. No diastereoselectivity of (S_P, R)-, (R_P, S)-**1c**



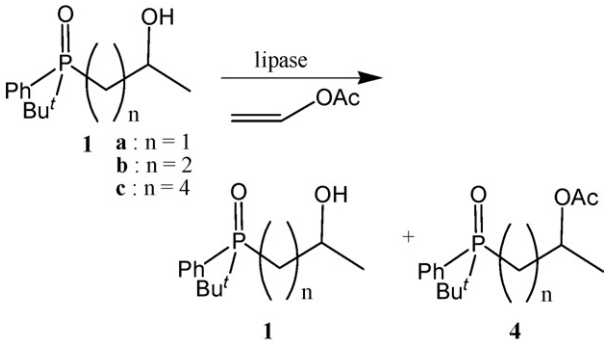
Scheme 2.

and (S_P, S)-, (R_P, R)-**1c** was observed. Since **1c** was a liquid, these diastereomers were separated by GPC.

3.2. Lipase-catalyzed optical resolution of β-hydroxyphosphine oxide *1*

The acylation of phosphine oxides (S_P, R)- and (R_P, S)-**1** by using CAL afforded the optically pure ester **4** (Scheme 3). The enantiomeric excesses of the recovered alcohol **1** and esters **4** were determined by chiral HPLC (see Section 2). These results are summarized in Table 1.

The absolute configuration of recovered **1a** in the acylation of (S_P, R)- and (R_P, S)-**1a** was determined by single-crystal X-ray analysis. The ORTEP drawing of **1a** (Fig. 1) clearly indicates that the phosphorus atom has an (*R*)-configuration, while the carbon atom attached to the hydroxyl group has an (*S*)-configuration.



Scheme 3.

The absolute configurations of the preferential substrates of **1b** and **1c** were determined as follows. Previously, we investigated the absolute configurations of the hydroxymethylphosphine oxides (R_P)- and (S_P)-**5** prepared by the lipase-catalyzed resolution [11]. The optically active phosphine oxides (R_P)-**2** and (S_P)-**2** were pre-

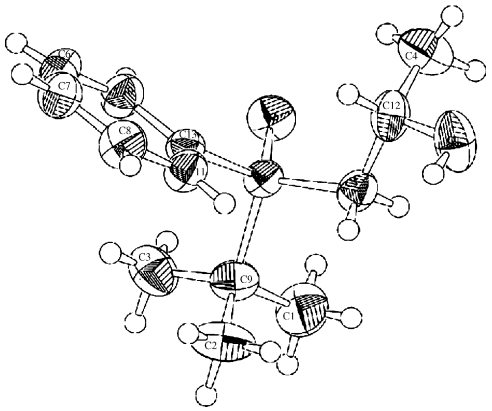
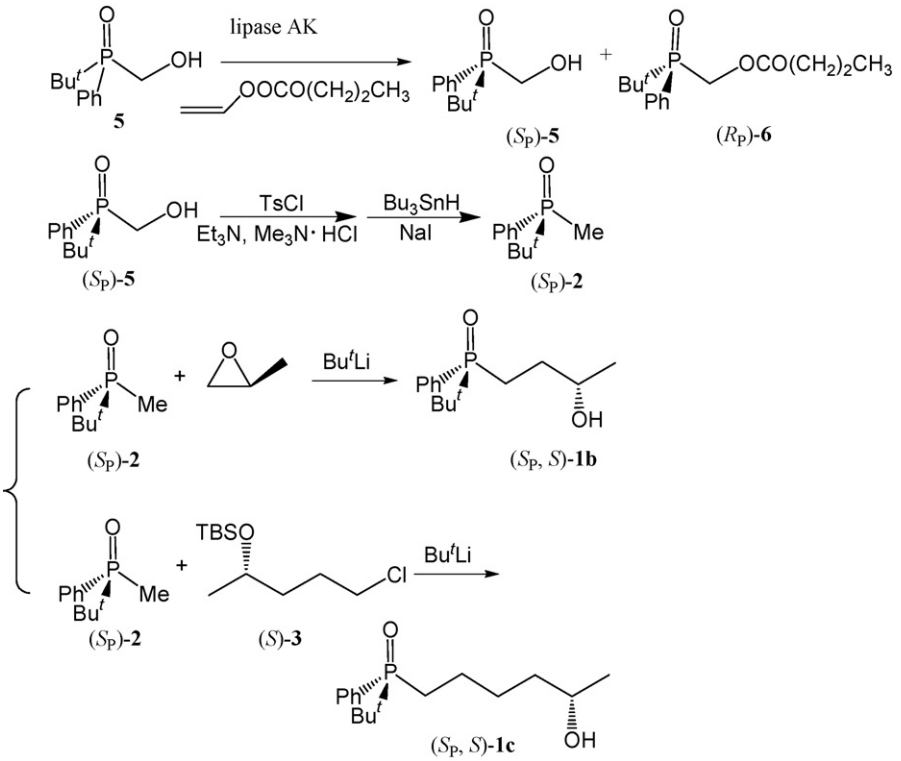


Fig. 1. ORTEP drawing of optically active phosphine oxide **1a**.

Table 1
Enantioselectivity in the lipase-catalyzed acylation of hydroxyalkylphosphine oxide **1**

Entry	Substrate	Lipase	Time (h)	ee_s (%)	ee_p (%)	Conv.	*E*
1	(S_P, R)- and (R_P, S)-**1a**	AK	65	93	>98	49	100
2		CAL	24	>98[a]	>98	50	>400
3		PCL	29	>98	>98	50	>400
4		CRL	96	21.0	45.5	31.6	3.25
5	(R_P, R)- and (S_P, S)-**1a**	AK	98	43	>98	31	100
6		CAL	38	70	86	45	26.8
7		PCL	127	12.7	>98	11.4	174
8		CRL	96	3.52	26.2	11.8	1.73
9	(S_P, R)- and (R_P, S)-**1b**	AK	36	>98[b]	>98	50	>400
10		CAL	0.2	94.2	96	50	119
11		PCL	96	89.7	98	47.8	298
12		CRL	60	18.2	22.6	4.6	1.87
13	(R_P, R)- and (S_P, S)-**1b**	AK	40	81.1	>98	45.3	241
14		CAL	0.25	64.4	>98	40.0	113
15		PCL	56	85.1	98	46.5	259
16		CRL					
17	(S_P, R)- and (R_P, S)-**1c**	AK	1.0	30.0	74.8	28.6	9.5
18		CAL	0.17	64.3	78.8	44.9	16.3
19	(R_P, R)- and (S_P, S)-**1c**	AK	1.0	34.4	74.6	34.4	9.5
20		CAL	0.17	66.0	79.1	45.5	16.8

[a] $[\alpha]_D^{24}$ + 7.61 (*c* = 1.2, $CHCl_3$).
[b] $[\alpha]_D^{24}$ + 36.39 (*c* = 1.0, $CHCl_3$).



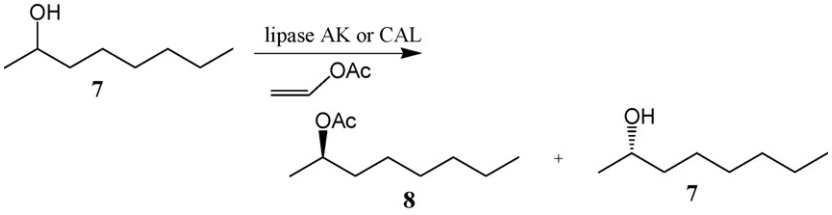
Scheme 4.

pared from (R_P)-**5** and (S_P)-**5**, respectively. (*S*)-Propylene oxide was reacted with (S_P)-**2** to afford (S_P, *S*)-**1b**. TBS ether (*S*)-**3** was prepared from (*S*)-5-chloro-2-pentanol, which was obtained by acetylation with CAL. TBS ether (*S*)-**3** was coupled with (S_P)-**2** or (R_P)-**2** using BuLi to afford (S_P, *S*)- or (R_P, *S*)-**1c**, respectively (Scheme 4). These compounds were then compared with respect to their HPLC retention times, and it was determined that (R_P, *R*)- and (S_P, *R*)-**1b**, and (R_P, *R*)- and (S_P, *R*)-**1c** showed greater preference as substrates for the lipase. In the acylation of each phosphine oxide **1**, the stereoselectivity at the carbon atom follows similar enantiopreferences, which were assumed from the empirical rules of lipase-catalyzed transformations [14].

The lipase-catalyzed acylation of both the diastereomer pairs **1** is shown in Table 1. The acylation using lipases AK, CAL, and PCL also afforded ester **4** with high enantioselectivity. However, poor enantioselectivity was observed in the reaction using CRL. A comparison of the acylations of (S_P, *R*)- and (R_P, *S*)-**1** with those of (R_P, *R*)- and (S_P, *S*)-**1** showed that the reaction rate of the latter was reduced due to the difference in the configuration at the phosphorus atom. Moreover, the stereoselectivity in the acylation of (R_P, *R*)- and (S_P, *S*)-**1** was lower than that in the acylation of (S_P, *R*)- and (R_P, *S*)-**1**. The stereoselectivity in the acylation of secondary alcohols toward the β-stereocenter corresponds to the stereoselectivity of the large hydrophobic pocket of the lipase [16]. Thus, the difference in the reactivity and stereoselectivity may be caused by interactions between the enzyme peptide wall and the phosphinoyl moiety.

The stereoselectivity at the phosphorus atom can be assumed by comparing the conversions and *E* values of the acylation between the diastereomer pairs of **1**. In the acylation using PCL, the reaction rate of (S_P, *R*)- and (R_P, *S*)-**1a** was faster than that of another pair, suggesting that PCL has a high molecular-recognition ability for the β-stereocenter (entries 3 and 7). On the other hand, the CAL-catalyzed acylation has low stereoselectivity at the phosphorus atom (entries 2 and 6). For each lipase, the stereoselectivity at the phosphorus atom was reduced with an increase in the length of the alkyl chain between the hydroxyl group and the phosphorus atom. These observations indicated that increasing the length between the active center of the lipase and the recognized moiety of the substrate decreased the interactions between the enzyme peptide wall and the phosphinoyl moiety.

The reactions of **1c** using both lipase AK and CAL were extremely fast as compared to those of **1a** and **1b**. However, the enantioselectivities in the reaction of **1c** on the carbon at the reaction center were lower than those in the reactions of **1a** and **1b**, and no stereoselectivity at the phosphorus atom was observed (entries 17–20). The stereo-recognizing ability of the ε-position of **1c** was found to be lower than that of the β- or γ-position of **1a** and **1b**. Although the enantioselectivity and reaction rate in the AK-catalyzed opti-



Scheme 5.

Table 2
Enantioselectivity in the lipase-catalyzed acylation of **7**

Substrate	Lipase	Time (h)	ee_s (%)	ee_p (%)	Conv.	*E*
2-Octanol	AK	1.0	14.1	52.5	21.2	3.7
2-Octanol	CAL	0.17	86.4	98.3	46.8	313

cal resolution of 2-octanol (**7**) were similar to those in the reaction of **1c** (Scheme 5), the enantioselectivity in the reaction of **7** using CAL differed from that of **1c**, suggesting that the difference in the stereoselectivity between lipases AK and CAL toward **1c** and **7** was caused by the flexibility of the pockets at the active sites (Table 2).

4. Conclusion

The work presented in this paper demonstrated the preparation of optically active hydroxyalkyl phosphorus compounds by preferential recrystallization, and the subsequent lipase-catalyzed optical resolution. Each lipase has an (*S*)-preference on the carbon atom adjacent to the hydroxyl group. The stereoselectivity at the phosphorus atom might be caused by the remoteness of the pocket walls from the reactive center of the lipase. The preference decreased with an increase in the length of the alkyl chain.

References

[1] P. Kielbasinski, M. Mikolajczyk, in: T. Matsuda (Ed.), Future Directions in Biocatalysis, Elsevier, 2007, pp. 159–203.
[2] P. Kielbasinski, M. Albrycht, J. Luczak, M. Mikolajczyk, Tetrahedron: Asymmetry 13 (2002) 735–738.
[3] R. Zurawinski, K. Nakamura, J. Drabowicz, P. Kielbasinski, M. Mikolajczyk, Tetrahedron: Asymmetry 12 (2001) 3139–3145.
[4] P. Kielbasinski, J. Omelanczuk, M. Mikolajczyk, Tetrahedron: Asymmetry 9 (1998) 3283–3287.
[5] K.M. Pietrusiewicz, M. Zablocka, Chem. Rev. 94 (1994) 1375–1411, and references therein.
[6] K.M. Pietrusiewicz, M. Zablocka, J. Monkiewicz, J. Org. Chem. 49 (1984) 1522–1526.
[7] A. Brandi, P. Cannavo, K.M. Pietrusiewicz, M. Zablocka, M. Wieczorek, J. Org. Chem. 54 (1989) 3073–3077.
[8] K.M. Pietrusiewicz, M. Zablocka, Tetrahedron Lett. 30 (1989) 477.
[9] R. Bodalski, E. Rutkowska-olma, K.M. Pietrusiewicz, Tetrahedron 36 (1980) 2353–2355.
[10] K. Shioji, Y. Kurauchi, K. Okuma, Bull. Chem. Soc. Jpn. 76 (2003) 833–834.
[11] K. Shioji, Y. Ueno, Y. Kurauchi, K. Okuma, Tetrahedron Lett. 42 (2001) 6569–6571.
[12] K. Shioji, A. Tashiro, S. Shibata, K. Okuma, Tetrahedron Lett. 44 (2003) 1103–1105.
[13] The absolute configurations of phosphinate in Ref. [4] are represented in an opposite manner because of the use of an erroneous sequence rule.
[14] R.J. Kazlauskas, A.N.E. Wiessfloch, A.T. Rappaport, L.A. Cuccia, J. Org. Chem. 56 (1991) 2656–2665.
[15] R.K. Haynes, W.W.-L. Lam, L.-L. Yeung, Tetrahedron Lett. 37 (1996) 4729–4732.
[16] A.N.E. Wiessfloch, R.J. Kazlauskas, J. Org. Chem. 60 (1995) 6959–6969.