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Lipase-catalyzed kinetic resolution of P-chiral phosphorus compounds: enantiopreference of *Pseudomonas* lipase and *Candida antarctica* lipase

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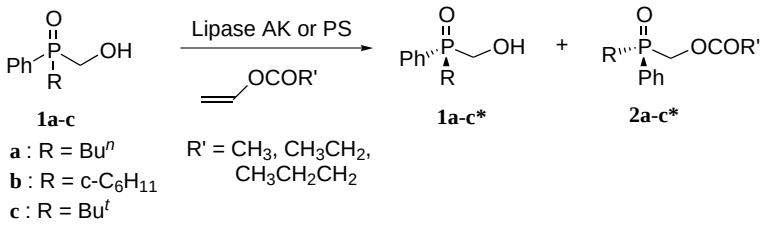
Abstract—Optically active 1-hydroxymethylalkylphenylphosphine oxides **1a–c** were prepared by *Pseudomonas fluorescens* lipase (lipase AK) and *Candida antarctica* lipase (CAL)-catalyzed optical resolution. Lipase AK-catalyzed resolution of *tert*-butyl derivative **1c** showed *R*-selectivity, whereas CAL preferred the *S*-enantiomer. © 2001 Elsevier Science Ltd. All rights reserved.

Optically active phosphines possessing a chiral center at the phosphorus are precursors of P-chiral bisphosphine ligands which are widely used as catalysts for asymmetric synthesis.[1] The synthesis of these enantiomerically pure phosphines requires chiral auxiliaries such as menthol, (−)-sparteine, (−)-ephedrine, a camphor derivative, or (*S*)-(−)-α-methylbenzylamine.[2] Since most of them were derived from natural products, it is difficult to obtain both enantiomers.

Recently, much attention is being paid to enzymatic optical resolution of hetero-organic compounds the stereogenic centers of which are located on the heteroatom such as sulfur, phosphorus, silicon, and germane.[3] Kielbasinski and co-workers have reported enzyme-promoted kinetic resolution of racemic, P-chiral phosphonyl and phosphorylacetates, P-chiral hydroxymethylphosphonate and phosphinates, and P-chiral phosphinyl acetate.[4] In this communication, we report lipase-catalyzed kinetic resolution of P-chiral phosphine oxide containing a 1-hydroxymethyl group. Racemic 1-hydroxymethylalkylphenylphosphine oxides **1a**,**c** were prepared by a one-pot alkylation of ethyl phenylphosphinate with alkyllithium and gaseous formaldehyde in 75 and 90% yields, respectively.[5] 1-Hydroxymethyl cyclohexylphenylphosphine oxide (**1b**) was prepared from dichlorophenylphosphine and cyclohexylmagnesium bromide in 34% overall yield.[6] Lipase-catalyzed acylation of **1** with an acyl donor in diisopropyl ether (IPE) afforded the corresponding acylated phosphine oxides **2** (Scheme 1). The chiral recognition of primary alcohols was generally difficult due to the lower bulkiness around the hydroxyl group compared to secondary alcohols. Only lipases from *pseudomonas* and porcine pancreas are known to resolve primary alcohols efficiently. Using lipase AK and PS, the acylation with vinyl acetate proceeded stereoselectively. These results are summarized in Table 1. Enol esters such as vinyl acetate are useful acyl donors.[7] The enantioselectivity in the lipase AK-catalyzed acylation increased with increasing bulkiness of the acyl moiety (entries 1–3, 7–9, and 13–15). When



Scheme 1.

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vinyl butyrate was used as an acyl donor, the ee of the recovered **1** was improved (entries 3, 9, 15).[8] On the other hand, there were no steric effects of the acyl moiety on the lipase PS-catalyzed acylations.

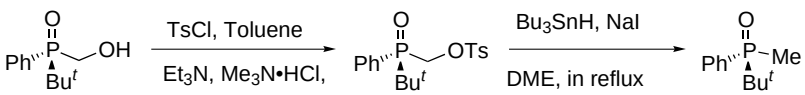
The absolute configuration of the remaining alcohol **1c** by using lipase AK-catalyzed resolution was determined as follows: Enantiomerically pure hydroxyalkyl phosphine oxide **1c** was converted into *O*-tosyl derivative **3c** in 90% yield, which was reduced to phosphine oxide **4c** by tributyltin hydride in DME in 94% yield $[\alpha]_D^{25}$ −21.0 (*c* 1.96, C_6H_6) (Scheme 2).[10,11] The sign of the optical rotation of **4c** was compared with the literature value.[12] The enantiomeric excess of (*S*)-**4c** was determined by HPLC (>98% ee). Since none of the conversion involved the chiral center at the phosphorus, the whole sequence did not cause any change in its absolute configuration. Hence, the remaining enantiomer of **1c** in AK-catalyzed resolution has (*S*)-configuration. Recently, Tuomi and Kazlauskas have shown that *Pseudomonas cepacia* lipase (PCL) binds to primary alcohols in a different mode from secondary ones.[13] The enantioselectivity of lipase AK for primary alcohols **1** suggested that the phenyl group of **1** binds to an alternative hydrophobic pocket in a narrow groove not used by secondary alcohols.

The CAL-catalyzed optical resolution of racemic **1a–c** using vinyl esters as an acyl donor proceeded with poor stereoselectivity (*E*<5). The *E* values were not influenced by the lengthening in the alkyl chain of vinyl esters. The higher enantioselectivity in the case of **1c** was observed by using isopropenyl acetate as an acyl donor (Scheme 3). Interestingly, reversed enantioselec-

Table 1. *Pseudomonas* lipase-catalyzed kinetic resolution of racemic 1-hydroxymethylalkylphenylphosphine oxides **1**[a]

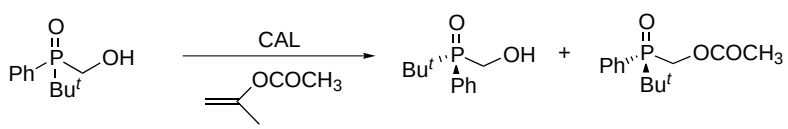
Entry	**1**	Lipase[b]	R′	Time (h)	Conv. (%)	Ee % of **1**[c]	Ee % of **2**[c]	*E*[d]	$[\alpha]_D^{25}$ of **1**[e]
1	**a**	AK	CH_3	0.75	50	83	84	28	
2	**a**	AK	CH_2CH_3	1	56	>98	77	34	
3	**a**	AK	$(CH_2)_2CH_3$	2	53	>98	86	65	−28.1
4	**a**	PS	CH_3	0.5	52	81	75	17	
5	**a**	PS	CH_2CH_3	0.7	58	84	60	10	
6	**a**	PS	$(CH_2)_2CH_3$	1	55	76	63	10	
7	**b**	AK	CH_3	0.75	52	94	86	50	
8	**b**	AK	CH_2CH_3	0.75	48	85	91	66	
9	**b**	AK	$(CH_2)_2CH_3$	1.5	49	90	94	95	−21.8
10	**b**	PS	CH_3	1	37	51	88	23	
11	**b**	PS	CH_2CH_3	1	45	67	83	20	
12	**b**	PS	$(CH_2)_2CH_3$	1	37	51	86	24	
13	**c**	AK	CH_3	3	42	32	45	4	
14	**c**	AK	CH_2CH_3	4	58	69	51	6	
15	**c**	AK	$(CH_2)_2CH_3$	7	59	>98	68	27	−44.0
16	**c**	PS	CH_3	3	50	23	23	2	
17	**c**	PS	CH_2CH_3	3	47	34	38	3	
18	**c**	PS	$(CH_2)_2CH_3$	6	70	78	34	4	

[a] Lipase (20 mg) was added to a mixture of (±)-**1** (0.023 mmol), acyl donor (0.165 mmol), and molecular sieves 3 Å (20 mg), in diisopropyl ether (2.0 ml) at 36°C.
[b] AK, *Pseudomonas fluorescens* lipase (Amano); PS; *Pseudomonas cepacia* lipase.
[c] Enantiomeric excess (ee %) was determined by HPLC (CHIRALPAK AD, Daicel).
[d] *E* values were calculated by the method according to Ref. 9.
[e] Compounds **1a** and **1c**; (*c* 2.00, C_6H_6), >98% ee. **1b**; (*c* 1.23, C_6H_6), >98% ee.



1c* **3c*** (*S*)-**4c**

Scheme 2.



1c (*R*)-**1c** (*S*)-**2c**

E = 21

+44.1 (*c* 0.78, C_6H_6)
40% yield, >98% ee

Scheme 3.

tivity in the resolution of **1c** between CAL and *pseudomonas* lipase (AK and P) was observed.

Although the binding mode of CAL for **1c** showing opposite enantioselectivity is unclear, these results are quite satisfactory for obtaining both enantiomers of **1c**. After the optical resolution of racemic **1c** using lipase AK, the partially resolved **2c** (68% ee) was hydrolyzed by H_2SO_4 in MeOH, followed by acylation by CAL to give enantiomerically pure (*S*)-**1c** and (*R*)-**1c** in 41 and 39% yields, respectively.

References

1. Pietrusiewicz, K. M.; Zablocka, M. *Chem. Rev*. **1994**, 1375 and references cited therein.
2. (a) Lewis, R. A.; Mislow, K. *J. Am. Chem. Soc*. **1969**, *91*, 7009; (b) Yamanoi, Y.; Imamoto, T. *J. Org. Chem*. **1999**, *64*, 2988; (c) Juge, S.; Stephan, M.; Laffitte, J. A.; Genet, J. P. *Tetrahedron Lett*. **1990**, *31*, 6357; (d) Corey, E. J.; Chen, Z.; Tanoury, G. J. *J. Am. Chem. Soc*. **1993**, *115*, 11000; (e) Haynes, R. A.; Freeman, R. N.; Mitchell, C. R.; Vonwiller, S. C. *J. Org. Chem*. **1994**, *59*, 2919.
3. (a) Fukai, T.; Kawamoto, T.; Tanaka, A. *Tetrahedron: Asymmetry* **1994**, *5*, 73; (b) Tacke, R.; Wagner, S. A.; Sperlich, J. *Chem. Ber*. **1994**, *127*, 639.
4. (a) Kielbasinski, P.; Zurawinski, R.; Pietrusiewicz, K. M.; Zablocka, M.; Mikolajczyk, M. *Polish J. Chem*. **1998**, *72*, 564; (b) Kielbasinski, P.; Goralczyk, P.; Mikolajczyk, M.; Wieczorek, M. W.; Majzner, W. R. *Tetrahedron: Asymmetry* **1998**, *9*, 2641; (c) Kielbasinski, P.; Omelanczuk, J.; Mikolajczyk, M. *Tetrahedron: Asymmetry* **1998**, *9*, 3283; (d) Kielbasinski, P.; Zurawinski, R.; Pietrusiewicz, K. M.; Zablocka, M.; Mikolajczyk, M. *Tetrahedron Lett*. **1994**, *35*, 7081; (e) Serreqi, A. N.; Kazulauskas, R. J. *J. Org. Chem*. **1994**, *59*, 7609.
5. To a solution of ethyl phenylphosphinate 3.0 g (17.6 mmol) in THF was added alkyllithium (38.8 mmol) at −78°C. After stirring for 1 h, to the reaction mixture was added gaseous formaldehyde. After stirring for 6 h at this temperature, the reaction mixture was warmed to room temperature. Standard work-up and recrystallization afforded the phosphine oxide **1**. Compound **1a**; colorless oil, ^{1}H NMR (400 MHz, $CDCl_3$): 0.83 (t, 3H, $J=7.2$ Hz), 1.31–1.62 (m, 4H), 1.85–1.96 (m, 1H), 2.12–2.25 (m, 1H), 4.05–4.14 (m, 2H), 7.27–7.74 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): 13.5, 32.6 (d, $J_{PC}=4.2$ Hz), 24.0 (d, $J_{PC}=14.1$ Hz), 26.0 (d, $J_{PC}=67.2$ Hz), 60.9 (d, $J_{PC}=79.6$ Hz), 128.1, 128.2, 129.4, 130.3, 130.4, 131.3, 131.52, 131.6. Compound **1c**: colorless crystals, ^{1}H NMR (400 MHz, $CDCl_3$): 1.14 (d, 9H, $J_{PH}=14.0$ Hz), 4.33 (dd, 2H, $J=68.0$, 14.0 Hz), 7.42–7.72 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): 24.7, 32.6 (d, $J_{PC}=64.9$ Hz), 57.3 (d, $J_{PC}=70.7$ Hz), 128.0, 128.1, 128.2, 128.8, 131.5, 131.55, 131.6, 131.62. Anal. calcd for $C_{11}H_{17}O_2P$: C, 62.25; H, 8.07. Found: C, 62.10; H, 8.05.
6. Compound **1b**: Colorless crystals, ^{1}H NMR (400 MHz, $CDCl_3$): 1.14–2.07 (m, 11H), 4.16 (dd, 2H, $J=68.0$, 14.0 Hz), 7.44–7.73 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): 24.7, 24.9, 25.7, 26.1, 26.2, 36.0 (d, $J_{PC}=66.6$ Hz), 59.0 (d, $J_{PC}=76.5$ Hz), 128.3, 128.4, 128.5, 129.1, 130.0, 130.9, 131.0, 131.7. Anal. calcd for $C_{11}H_{17}O_2P$: C, 65.53; H, 8.04. Found: C, 65.14; H, 7.91
7. Wang, Y. F.; Lalonde, J. J.; Momongan, M.; Bergbreiter, D. E.; Wong, C.-H. *J. Am. Chem. Soc*. **1988**, *110*, 7200.
8. Lipase AK (2.0 g), IPE (200 ml) containing racemic phosphine oxide **1** (0.5 g), vinyl lactate (3.0 ml), and molecular sieves 3 Å (2.0 g) were mixed in 500 ml flask and shaken at 36°C. The mixture was filtered off to stop the reaction at more than 50% conversion, and the filtrate was concentrated. The ester and alcohol were isolated by column chromatography on silica gel. Remaining alcohol **1**: 41% yield, >98% ee, $[\alpha]_D^{25}$ −44.0 (*c* 2.00, C_6H_6). Acetate **2**: 57% yield, 68% ee, $[\alpha]_D^{25}$ +9.0 (*c* 5.00, C_6H_6).
9. Chen, C. S.; Fujimoto, Y.; Girdauskas, G.; Sih, C. J. *J. Am. Chem. Soc*. **1982**, *104*, 7294.
10. Yoshida, Y.; Sakakura, Y.; Aso, N.; Okada, S.; Tanabe, Y. *Tetrahedron* **1999**, *55*, 2183.
11. Ueno, Y.; Tanaka, C.; Okawara, M. *Chem. Lett*. **1983**, 795.
12. Evan, P. K. *J. Am. Chem. Soc*. **1976**, *98*, 4805. *R*-form; $[\alpha]_D^{25}$ +21.7 (*c* 1.83, C_6H_6).
13. Tuomi, W. V.; Kazlauskas, R. J. *J. Org. Chem*. **1999**, *64*, 2638.