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Synthesis of bifunctional P-chiral hydroxy phosphinates; lipase-catalyzed stereoselective acylation of ethyl (1-hydroxyalkyl)phenylphosphinates

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Abstract—Lipase-catalyzed acylation of ethyl (1-hydroxyalkyl)phenylphosphinates afforded a single diastereomer in high enantiomeric excess. The substituent effect of the alkyl group toward the acylation using *Candida antractica* (CAL) was larger than that of an immobilized lipase from *Pseudomonas fluorescens* lipase (lipase AK). © 2003 Elsevier Science Ltd. All rights reserved.

The synthesis, stereochemistry, and utility of P-chiral phosphorus compounds possessing a stereocenter at the phosphorus are of current interest.[1] Phosphorus compounds having other optically active functionalities such as hydroxyl and amino groups are useful for homogeneous asymmetric metal catalysis in the reaction[2] and as chiral auxiliaries in the synthesis of allylic alcohols[3] and oxazolidinones.[4] Warren et al. synthesized P-chiral 1,2-hydroxyphosphine oxides as precursors of optically active alcohol.[5] Recently, Granell et al. reported the synthesis and resolution of a P-chiral benzyl(α-hydroxybenzyl)phenylphosphine by palladium metallacycles.[6] Lipase-catalyzed optical resolution is a most powerful method for the synthesis of optically pure alcohols and esters. Kielbasinski et al. have reported that P-chiral methyl α-hydroxymethylphosphinate was a good substrate of lipase-catalyzed kinetic resolution ($E = \sim 51$).[7] We have also reported lipase-catalyzed optical resolution of primary alcohol-type phosphine oxides ($E = \sim 95$).[8] However, there is no report on the optical resolution of phosphinates with two stereogenic centers. We describe here the synthesis and kinetic resolution of phosphinates containing two stereogenic centers, the phosphorus and α-carbon atom, via lipase-catalyzed acylation.

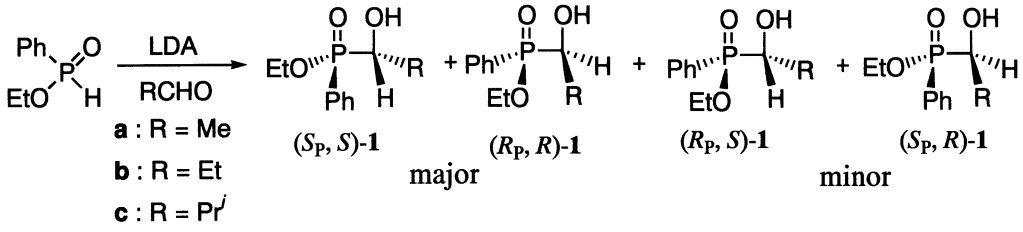
The preparation of racemic phosphinates **1** was carried out by a slightly modified Haynes's method.[9,10] The nucleophilic addition of lithiated ethyl phenylphosphinate to appropriate aldehydes gave the major and minor products (Scheme 1).

The products ratios depended on reaction temperature. The ratio of major **1a** to minor product was 2:1 at

Table 1. The reaction of lithiated ethyl phenylphosphinate with aldehydes at −78°C

Substrate	R	Yield (%)	Major:minor[a]
1a	Me	52	4:1
1b	Et	58	5:1
1c	Pr^i	69	6:1

[a] Determined by ^{1}H NMR.



Scheme 1.

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−15°C, whereas it was 1:1 at 0°C. The yields and products ratios of the reactions at −78°C are summarized in Table 1.

The kinetic separation of the major phosphinates (S_P,S) and (R_P,R)-**1** was carried out by CAL and lipase AK-catalyzed acylation using vinyl acetate as an acyl donor. The acylation of a mixture of (S_P,S) and (R_P,R)-**1** afforded the corresponding enantiomerically pure esters **2** (Scheme 2). These results are shown in Table 2. Using CAL, hydroxy phosphinates **1a** and **b** were esterified to give acetyl phosphinates **2** with high optical purity (>98%). Using lipase AK, each methyl and ethyl derivative **1a**,**b** also reacted to reach 50% conversion with high enantioselectivity. After being stirred for 48 h, the yield of recovered phosphinates **1a** was 50% with >98% enantiomeric excess. Thus, perfect resolution was achieved in the present acylation. Methyl derivative **1a** was acylated rapidly by using CAL compared with lipase AK. Lipase AK acylated isopropyl derivative **1c**, which was not acylated by using CAL. Thus, the difference of acylation rates of **1** using CAL was larger than those using lipase AK. The difference in the sensitivity toward substituent R indicates that the hydrophobic pocket of lipase AK was much flexible than that of CAL.

The reacting optically pure diastereomer **2a** was hydrolyzed in the presence of a small amount of H_2SO_4 in methanol to give optically pure diastereomer **1a** in 85% yield. The obtained optically pure diastereomer **1a** was converted into Mosher's MTPA ester **3a*** using (*R*)-MTPA chloride in 90% yield.[11] The absolute configuration of reacting **1a** was assumed by comparing the ^{1}H NMR spectrum of (*R*)-MTPA esters **3a*** with that of MTPA esters of (R_P,R) and (S_P,S)-**1a**. ^{1}H NMR chemical shifts of the methyl group of **3a** were observed at 1.54 and 1.44 ppm. The methyl group of ester **3a*** was observed at 1.44 ppm. The methyl signal of the (*S*) conformer was upfield shifted by the anisotropic effect of the phenyl group relative to the (*R*) conformer. Thus, acylating hydroxy phosphinate **1a** has (S_P,S) configuration (Fig. 1). The Cotton effect of other optically active hydroxy phosphinates, which were resolved by lipase-catalyzed acylation, was similar to that of (R_P,R)-**1a**. In view of these results, lipase AK and CAL favored (S_P,S)-**1** rather than the (R_P,R)-diastereomer. There is an empirical rule for the enantiopreference of lipase-catalyzed optical resolution toward secondary alcohols.[12]

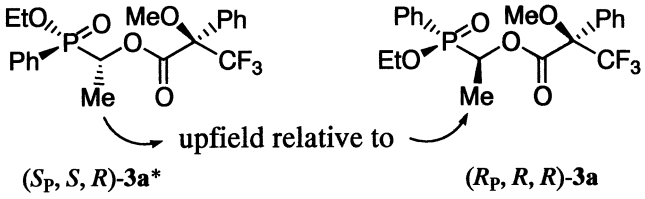
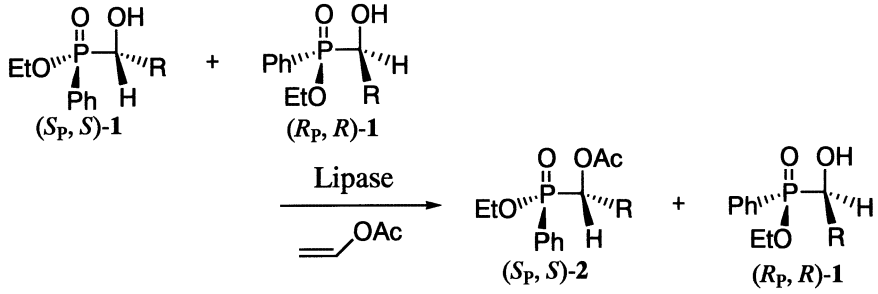


Figure 1. Configurational correlation model for (*R*)-MTPA esters **3a**.

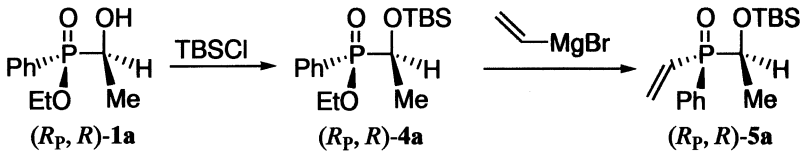


Scheme 2.

Table 2. Lipase-catalyzed kinetic resolution of **1**[a]

Substrate	Lipase[b]	Time (h)	Conv. (%)	Ee (%) of recovered **1**[c]	Ee (%) of esters **2**[c]
1a	CAL	1	50	>98	>98
1b	CAL	32	17	28	>98
1c	CAL			No reaction	
1a	AK	8	50	>98[d]	>98[e]
1a	AK	48	50	>98	>98
1b	AK	29	50	>98[f]	>98[g]
1c	AK	75	9	2	>98

[a] Lipase (20 mg) was added to a mixture of (S_P,S) and (R_P,R)-**1** (0.023 mmol), vinyl acetate (0.165 mmol) and 3 Å molecular sieves (20 mg) in diisopropyl ether (2.0 ml) at 36°C.
[b] AK; *Pseudomonas fluorescens* lipase (Amano AK), CAL; immobilized lipase from *Candida antractica* (Chirazyme® L-2, cf. C2, lyo.).
[c] Enantiomeric excess (ee%) was determined by HPLC (CHIRALPAK AD, Daicel).
[d] $[\alpha]_D$ +15.4 (c=2.7, $CHCl_3$).
[e] $[\alpha]_D$ −8.82 (c=1.0, $CHCl_3$).
[f] $[\alpha]_D$ +11.5 (c=0.21, $CHCl_3$).
[g] $[\alpha]_D$ −4.65 (c=0.16, $CHCl_3$).



Scheme 3.

The obtained phosphinates **1** and **2** are converted into P-chiral phosphine oxides by several organomagnesium reagents without racemization.[13] We then tried substitution of the ethoxy ligand of P-chiral phosphinate (R_P,R)-**1a** to a vinyl group.

Reaction of TBS ether (R_P,R)-**4a**, which was prepared from (R_P,R)-**1a** with *tert*-butyldimethylsilyl chloride (TBSCl), with vinylmagnesium bromide afforded the corresponding vinylphosphine oxide (R_P,R)-**5a** in 48% yield (Scheme 3). ^{1}H NMR and HPLC analysis of **5a** indicated that racemization did not occur in the course of substitution. Thus, the optically active vinyl phosphine oxide, which is used as precursor of other functional phosphine oxides, was obtained.[1]

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10. The major products (S_P,S) and (R_P,R)-**1** were purified by preferential crystallization from ethyl acetate–hexane. Satisfactory elemental analyses were obtained for all new compounds. Ethyl (1-hydroxyethyl)phenylphosphinate (**1a**); major products; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.33 (dd, J = 6.8, 16.8 Hz, 3H), 1.36 (t, J = 6.8 Hz, 3H), 3.97–4.22 (m, 3H) 7.45–7.85 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 16.4 (J_{PC} = 5.0 Hz), 16.97 (J_{PC} = 3.2 Hz), 61.5 (J_{PC} = 7.5 Hz), 65.9 (J_{PC} = 116.0 Hz), 128.4, 128.6, 128.8, 132.4, 132.5, 132.6, 132.7; ^{31}P NMR (162 MHz, $CDCl_3$) δ = 42.4. Ethyl (1-hydroxypropyl)-phenylphosphinate (**1b**); major products; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.03 (t, J = 7.4 Hz, 3H), 1.35 (t, J = 6.8 Hz, 3H), 1.50–1.77 (m, 2H), 3.86–4.00 (m, 1H), 4.01–4.21 (m, 2H), 7.49–7.86 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 10.50 (J_{PC} = 12.5 Hz), 16.5 (J_{PC} = 4.9 Hz), 24.2, 61.4 (J_{PC} = 5.8 Hz), 71.7 (J_{PC} = 87.1 Hz), 127.8, 128.4, 128.5, 132.4, 132.5, 132.6, 132.7; ^{31}P NMR (162 MHz, $CDCl_3$) δ = 41.4. Ethyl (1-hydroxy-2-methyl-propyl)phenylphosphinate (**1c**); major products; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.02 (d, J = 2.0 Hz, 6H), 1.34 (t, J = 7.0 Hz, 3H) 1.92–2.04 (m, 1H), 3.73–3.78 (m, 1H), 3.94–4.22 (m, 2H) 7.47–7.87 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 16.5 (J_{PC} = 5.8 Hz), 17.3 (J_{PC} = 5.8 Hz), 20.2 (J_{PC} = 10.0 Hz), 29.4, 75.2 (J_{PC} = 109.0 Hz), 128.6, 128.7, 129.9, 132.1, 132.3, 132.4, 132.5; ^{31}P NMR (162 MHz, $CDCl_3$) δ = 40.7.
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