Novel Synthesis of P-Chiral Hydroxymethylphosphine–Boranes through Lipase-Catalyzed Optical Resolution

Kosei Shioji,* Yoshimitsu Kurauchi, and Kentaro Okuma

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

(Received October 16, 2002)

A novel approach toward the lipase-catalyzed acylation of alkyl(1-hydroxymethyl)phosphine–boranes was achieved. Up to 99% of enantiomerically enriched phosphine–boranes was obtained by using lipase AK and CAL.

Optically active phosphines possessing a chiral center at the phosphorus are precursors for a variety of C_2 -symmetrical bisphosphine ligands.¹ It has been reported that phosphineboranes are converted into phosphines under mild conditions without racemization.² In order to synthesize functional tertiary phosphine-boranes, secondary phosphine-boranes are key intermediates.³ Imamoto et al. reported that secondary phosphine-boranes were obtained through stereoselective decarboxylation, followed by the oxidation of dialkyl(1-hydroxymethyl)phosphine-boranes.⁴ Recently, we reported on the lipasecatalyzed optical resolution of 1-hydroxymethylphosphine oxides.⁵ These results prompted us to investigate the possibility of the lipase-catalyzed optical resolution of phosphine-boranes. We would like to propose a new synthesis of P-chiral alkyl(1hydroxymethyl)phenylphosphine-boranes (1) via the lipasecatalyzed optical resolution.

Results and Discussion

Substituted 1-hydroxymethylphosphine–boranes 1 were prepared by following two methods (Scheme 1). Racemic phosphine–boranes bearing a primary alkyl group, such as ethyl or butyl-derivatives **1a,b**, were synthesized in one-pot from phosphine oxides (**2a,b**) (Method A). Other racemic 1-hydroxymethylphosphine–boranes **1c–d** were prepared from secondary phosphine–boranes (**3c–d**) (Method B).

The acylation of phosphine–boranes 1 in diisopropyl ether (IPE) or cyclohexane (c- C_6H_{12}) was carried out using CAL from *Candida antarctica* or Lipase AK from *Pseudomonas fluorecence*. In preliminary work, other lipases, such as lipase PS from *Pseudomonas cepacia* and CRL from *Candida rugosa*, showed no reaction or poor stereoselectivity. Acylation using CAL with vinyl acetate as an acyl donor afforded the corresponding acetylated phosphine–boranes (4) (Scheme 2). The results are summarized in Table 1.

When IPE was used as a solvent, the acylation of phosphine-



racemic
$$1 \xrightarrow{ACOCH=CH_2} 1 + 1$$

Scheme 2.

Table 1. CAL-Catalyzed Optical Resolution of Phosphine-Boranes 1 in IPE or $c-C_6H_{12}$

1	Solv.	Time/h	Conv./%	Ee% of 1	Ee% of 4	E ^{a)}
a	IPE	0.2	56	46	37	3
b	IPE	0.2	45	56	68	9
c,d	IPE	48		no reaction		
a	$c-C_6H_{12}$	0.5	73	92	34	6
b	$c-C_6H_{12}$	0.8	63	91	55	10
с	$c-C_6H_{12}$	3	47	29	33	3
d	c-C ₆ H ₁₂	9	49 ^{b)}	53	n.d. ^{c)}	6

a) The E value was calculated according to Ref. 7. b) Isolated yield. c) n.d., not determined by HPLC.

boranes 1a,b took place with poor stereoselectivity. On the other hand, in c-C₆H₁₂, the stereoselectivity on the acylation increased moderately. When the reactions of 1a,b stopped at conversions of 73 and 63%, enantiomerically enriched compounds (R)-1a,b were obtained with 92 and 93% ee. The CD spectrum of (R)-Hydroxymethyl(methyl)phenylphosphine-borane indicates a negative Cotton effect.⁴ Similarly, phosphine-borane 1 showed a negative Cotton effect at the same wavelength, suggesting that the absolute configurations of recovered 1a-c were (R). The acylation of 1a-c favored the (S)-enantiomer. In contrast, (R)-1d was acylated faster than its counterpart. This kind of reversed enantioselectivity on the acylation of tert-butyl derivative 1d was observed in that of a phosphine oxide analogue. Thus, the binding mode⁶ between phosphine-borane 1 and CAL is similar to that of phosphine oxide.5 The lower steroselectivity in the acylation of phosphine-boranes than that of phosphine oxides was affected by the bulkiness of the BH₃ group compared to the oxygen atom. Actually, the acylation of phosphine-borane 1a proceeded with lower enantioselectivity than that of 1b because of a small difference in the bulkiness between BH3 and Et. Since the isopropyl group of 1c is too large to bind for the medium hydrophobic pocket of CAL, the acylation of 1c proceeded with low stereoselectivity compared to the acylation of **1a**,**b**. The E values of CAL-catalyzed acylation were not influenced by lengthening in the alkyl chain of vinyl esters.

We then tried the acylation of phosphine–borane **1** using lipase AK in the presence of vinyl butyrate. The lipase AK-catalyzed acylation of phosphine–borane **1** was more sensitive toward an organic solvent than CAL. It is well-known that the solvent variation of lipase-catalyzed optical resolutions can influence both the enantioselectivity and the reaction rate.⁸ In IPE

Table 2. Lipase AK-Catalyzed Optical Resolution of Phosphine–Boranes 1 Using Vinyl Butyrate in c-C₆H₁₂

Entry	1	Time/h	Conv./%	Ee% of 1	Ee% of 4	Ε
1	a	3	50	9	9	1
2 ^{a)}	b	48	32	20	42	3
3	b	48	53	56	49	5
4 ^{a)}	c	18	31	31	70	8
5	с	16	19	20	84	15
6	c	120	70	> 99	43	12
7	e	72		no reaction		

a) Using vinyl acetate as an acyl donor.

(log P = 1.9), a relatively non-polar solvent, as judged from log P^9 and other polar solvents, such as tetrahydrofuran (THF) and acetonitrile (log P = 0.49, -0.33), acylation did not take place after 5 days. In the case of c-C₆H₁₂ (log P = 3.2), which is less polar than IPE, acylation afforded the corresponding esters **4**. The enantioselectivity in the lipase AK-catalyzed acylation of **1b** using vinyl butyrate was moderately higher than that of using vinyl acetate (Table 2, Entry 2–5). The *E*-value for the acylation of isopropyl derivative **1c** was increased to 15.

Experimental

All solvents were distilled prior to use. Lipase PS (Amano PS) and lipase AK (Amano AK) were purchased from Amano Pharmaceutical Co., Ltd. CAL (Chirazyme[®] L-2,c.-f.,C2, lyo.) was purchased from Roche Molecular Biochemicals. CRL was purchased from Sigma. Secondary phosphine–boranes **3c–e** were prepared according to a procedure described in the literature.¹⁰

Preparation of Alkyl(1-hydroxymethyl)phosphine–Boranes (1). Method A: To a solution of 1-hydroxymethylalkylphosphine oxide $2a,b^5$ (0.5 mmol) in benzene (5.0 mL) was added HSiCl₃ (2.2 mmol) at room temperature. After stirring for 3 h, to the reaction mixture was added THF•BH₃ (2.5 mmol); the resulting solution was stirred for 2 h. To the reaction mixture was added 5 mL of benzene; the resulting solution was quenched by 6 M HCl and extracted with CH_2Cl_2 (5 mL \times 3). The extract was dried over MgSO₄ and evaporated. The residue was purified by column chromatography on silica gel (CH₂Cl₂) to give **1a**,**b**. Ethyl(1-hydroxymethyl)phenylphosphine-borane (1a). colorless oil, 70% yield, ¹H NMR (400 MHz, CDCl₃) δ 0.65 (bq, 3H, J = 91.6 Hz), 1.10–1.19 (m, 3H), 2.01–2.09 (m, 2H), 2.03 (bs, 1H), 4.13 (s, 2H), 7.46–7.78 (m, 5H). ¹³C NMR (100 MHz, CDCl₃) & 6.6, 14.3, 14.7, 58.9, 59.3, 125.5, 126.0, 128.6, 128.7, 131.5, 132.2, 132.3. Anal. Calcd for C₉H₁₆BOP: C, 59.39; H, 8.86%. Found: C, 59.79; H, 8.77%. Butyl(1-hydroxymethyl)phenylphosphine–borane (1b). Colorless oil, 48% yield, ¹H NMR (400 MHz, CDCl₃) δ 0.67 (bq, 3H, J = 94.8 Hz), 0.89 (t, 3H, J = 7.2 Hz), 1.37-1.46 (m, 3H), 1.54-1.58 (m, 1H), 1.86 (bs, 1H), 1.97-2.04 (m, 2H), 4.12 (s, 2H), 7.46–7.79 (m, 5H). 13 C NMR (100 MHz, CDCl₃) δ 13.4, 21.0, 21.4, 24.0, 24.1, 24.6, 59.5, 59.9, 125.9, 126.5, 128.7, 128.8, 131.6, 132.3. Anal. Calcd for C₁₁H₂₀BOP: C, 62.90; H, 9.90%. Found: C, 63.14; H, 9.60%.

Method B: To a solution of secondary phosphine–borane (**3c**–**d**) (3.3 g, 20 mmol) in THF (40 mL) was added Bu^{*t*}Li at -78 °C. After stirring for 2 h, gaseous formaldeyde was bubbled into the mixture. After stirring for 1 h, the solution was quenched by aq ammonium chloride and extracted with CH₂Cl₂ (40 mL × 3). The extract was dried over anhydrous magnesium sulfate and evaporated to give phosphine–borane (**1c**–**d**). 1-Hydroxymethyl(isopropyl)phenylphosphine–borane (**1c**). Colorless oil, 60% yield, ¹H NMR (400 MHz,

CDCl₃) δ 0.59 (bq, 3H, J = 85.2 Hz), 1.05 (q, 3H, J = 7.2 Hz), 1.28 (q, 3H, J = 7.2 Hz), 2.10 (bs, 1H), 2.43–2.50 (m, 1H), 4.22 (d, 2H, J = 2.4 Hz), 7.46–7.80 (m, 5H). ¹³C NMR (100 MHz, CDCl₃) δ 16.5, 16.7, 21.3, 21.7, 58.0, 58.4, 128.2, 128.4, 128.5, 131.8, 132.3. Anal. Calcd for C₁₀H₁₈BOP: C, 61.27; H, 9.25%. Found: C, 60.82; H, 9.12%. Cyclohexyl(1-hydroxymethyl)phenylphosphine–borane (1d). *t*-Butyl(1-hydroxymethyl)phenylphosphine–borane (1e). Colorless crystals, mp 58–59 °C, 68% yield, ¹H NMR (400 MHz, CDCl₃) δ 0.69 (bq, 3H, J = 97.2 Hz), 1.18 (d, 9H, J = 13.6 Hz), 2.10 (bs, 1H), 4.34–4.48 (m, 2H), 7.45–7.74 (m, 5H). ¹³C NMR (100 MHz, CDCl₃) δ 25.7, 28.9, 29.2, 55.7, 56.1, 124.6, 125.1, 128.3, 128.4, 131.4, 133.4. Anal. Calcd for C₁₁H₂₀BOP: C, 62.90; H, 9.60%. Found: C, 62.64; H, 9.44%.

Lipase-Catalyzed Optical Resolution of Phosphine-Boranes A mixture of a racemic phosphine–borane 1 (5 mg), the enzyme 1. (40 mg), molecular sieves 3A (20 mg), and vinyl acetate (7 equiv) was stirred in an organic solvent (2 mL) at 36 °C. The reaction was analyzed by HPLC (Daicel Chiralpak AD-H). Optical resolutions on a preparative scale were carried out with 40-times the quantity of the analysis scale. The reactions were monitored by HPLC (Daicel Chiralpak AD-H) and stopped at appropriate conversion. The reaction mixture was separated by column chromatography. 1a: 31% yield, 92% ee ((*R*)-form rich), $[\alpha]_{D}^{25} - 23.3$ (*c* = 1.7, CHCl₃). 4a: 58% yield, 34% ee ((S)-form rich). 1b: 23% yield, 91% ee ((R)-form rich), $[\alpha]_{D}^{25} - 15.3$ (c 1.2, CHCl₃). **4b**: 62% yield, 55% ee ((S)-form rich). 1c: 32% yield, 79% ee ((*R*)-form rich), $[\alpha]_{D}^{25} - 10.1$ (c 1.1, CHCl₃). 4c: 61% yield, 67% ee ((S)-form rich). 1d: 44% yield, 53% ee ((*R*)-form rich), $[\alpha]_{D}^{25} + 2.9$ (*c* 1.0, CHCl₃). **4d**: 42% yield. Enantiomeric excesses were determined by HPLC (Daicel Chiralpak AD-H). 1a: $t_{\rm R} = 40.8$ (R) and 76.0 (S) min, 4a: $t_{\rm R} = 14.7$ (R) and 19.8 (S) min (hexane/2-propanol (97/3) including 0.1% TFA). 1b: $t_{\rm R} = 37.4$ (R) and 46.3 (S) min, **4b**: $t_{\rm R} = 8.4$ (R) and 11.3 (S) min (hexane/2-propanol (99/1) including 0.1% TFA). 1c: $t_{\rm R} = 34.4$ (*R*) and 54.8 (S) min, 4c: $t_R = 6.8 (R)$ and 8.0 (S) min (hexane/2-propanol (98/2) including 0.1% TFA). **1d**: $t_{\rm R} = 32.4$ (*R*) and 44.6 (*S*) min (hexane/2-propanol (99/1) including 0.1% TFA).

References

1 a) T. Imamoto, *Pure Appl. Chem.*, **73**, 373 (2001). b) H. Tsuruta and T. Imamoto, *Tetrahedron: Asymmetry*, **10**, 877 (1999). c) K. M. Pietrusiewicz and M. Zablocka, *Chem. Rev.*, **94**, 1375 (1994), and references therein.

2 T. Imamoto, J. Watanabe, Y. Wada, H. Masuda, H. Yamada, H. Tsuruta, S. Matsukawa, and K. Yamaguchi, *J. Am. Chem. Soc.*, **120**, 1635 (1998).

3 M. Al-Masum, G, Kumaraswamy, and T. Livinghouse, *J. Org. Chem.*, **65**, 4776 (2000).

4 K. Nagata, S. Matsukawa, and T. Imamoto, J. Org. Chem., 65, 4185 (2000).

5 K. Shioji, Y. Ueno, Y. Kurauchi, and K. Okuma, *Tetrahedron Lett.*, **42**, 6569 (2001).

6 W. V. Tuomi and R. J. Kazlauskas, *J. Org. Chem.*, **64**, 2638 (1999).

7 C. S. Chen, Y. Fujimoto, G. Girdauskas, and C. J. Sih, *J. Am. Chem. Soc.*, **104**, 7294 (1982).

8 K. Faber, "Biotransformations in Organic Media," 3rd ed, Springer, Granz, Austria (1996).

9 C. Laane, S. Boeren, and C. Veeger, *Biotechnol. Bioeng.*, **30**, 81 (1987).

10 T. Imamoto, T, Oshiki, T. Onozawa, T. Kusumoto, and K. Sato, *J. Am. Chem. Soc.*, **112**, 5244 (1990).