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

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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 phosphine–boranes 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 lipase-catalyzed 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(1-hydroxymethyl)phenylphosphine–boranes (**1**) via the lipase-catalyzed optical resolution.

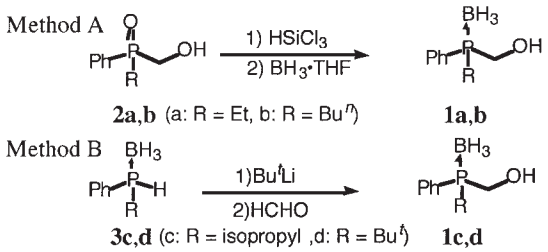
Results and Discussion

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).

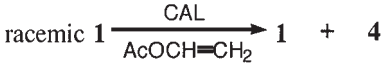
The acylation of phosphine–boranes **1** in diisopropyl ether (IPE) or cyclohexane (c-C_6H_{12}) was carried out using CAL from *Candida antarctica* or Lipase AK from *Pseudomonas fluorecence*. In preliminary work, other lipases, such as lipase PS from *Pseudomonas cepacia* and CRL from *Candida rugosa*, 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–boranes **1a**,**b** took place with poor stereoselectivity. On the other hand, in c-C_6H_{12}, 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 mode[6] 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 BH_3 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 BH_3 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



Scheme 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
c	c-C_6H_{12}	3	47	29	33	3
d	c-C_6H_{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.

Table 2. Lipase AK-Catalyzed Optical Resolution of Phosphine–Boranes **1** Using Vinyl Butyrate in c-C_6H_{12}

Entry	**1**	Time/h	Conv./%	Ee% of **1**	Ee% of **4**	*E*
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	**c**	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-C_6H_{12} ($\log P = 3.2$), 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 $HSiCl_3$ (2.2 mmol) at room temperature. After stirring for 3 h, to the reaction mixture was added THF·BH_3 (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 × 3). The extract was dried over $MgSO_4$ and evaporated. The residue was purified by column chromatography on silica gel (CH_2Cl_2) to give **1a**,**b**. Ethyl(1-hydroxymethyl)phenylphosphine–borane (**1a**). colorless oil, 70% yield, ^{1}H NMR (400 MHz, $CDCl_3$) 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). ^{13}C NMR (100 MHz, $CDCl_3$) δ 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 C_9H_{16}BOP: C, 59.39; H, 8.86%. Found: C, 59.79; H, 8.77%. Butyl(1-hydroxymethyl)phenylphosphine–borane (**1b**). Colorless oil, 48% yield, ^{1}H NMR (400 MHz, $CDCl_3$) 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, $CDCl_3$) 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 $C_{11}H_{20}$BOP: 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 CH_2Cl_2 (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, ^{1}H NMR (400 MHz, $CDCl_3$) 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). ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{10}H_{18}$BOP: 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, ^{1}H NMR (400 MHz, $CDCl_3$) 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). ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{11}H_{20}$BOP: C, 62.90; H, 9.60%. Found: C, 62.64; H, 9.44%.

Lipase-Catalyzed Optical Resolution of Phosphine–Boranes 1. A mixture of a racemic phosphine–borane **1** (5 mg), the enzyme (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), $[\alpha]_D^{25} - 23.3$ ($c = 1.7$, $CHCl_3$). **4a**: 58% yield, 34% ee ((*S*)-form rich). **1b**: 23% yield, 91% ee ((*R*)-form rich), $[\alpha]_D^{25} - 15.3$ (*c* 1.2, $CHCl_3$). **4b**: 62% yield, 55% ee ((*S*)-form rich). **1c**: 32% yield, 79% ee ((*R*)-form rich), $[\alpha]_D^{25} - 10.1$ (*c* 1.1, $CHCl_3$). **4c**: 61% yield, 67% ee ((*S*)-form rich). **1d**: 44% yield, 53% ee ((*R*)-form rich), $[\alpha]_D^{25} + 2.9$ (*c* 1.0, $CHCl_3$). **4d**: 42% yield. Enantiomeric excesses were determined by HPLC (Daicel Chiralpak AD-H). **1a**: $t_R = 40.8$ (*R*) and 76.0 (*S*) min, **4a**: $t_R = 14.7$ (*R*) and 19.8 (*S*) min (hexane/2-propanol (97/3) including 0.1% TFA). **1b**: $t_R = 37.4$ (*R*) and 46.3 (*S*) min, **4b**: $t_R = 8.4$ (*R*) and 11.3 (*S*) min (hexane/2-propanol (99/1) including 0.1% TFA). **1c**: $t_R = 34.4$ (*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**: $t_R = 32.4$ (*R*) and 44.6 (*S*) min (hexane/2-propanol (99/1) including 0.1% TFA).

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