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First enzymatic resolution of a phosphane–borane complex

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Abstract

The borane adduct of (2-hydroxypropyl)diphenylphosphane **1** was resolved by enantioselective esterification with CAL-B. (*S*)-**1** was thus obtained with 91% enantiomeric excess. Its absolute configuration was determined by chemical correlation from (*S*)-propylene oxide.

Keywords: Enzymatic resolution; Phosphane–borane complexes; Chiral organophosphorus compounds; CAL-B; (*S*)-propylene oxide

1. Introduction

Due to their peculiar properties, phosphane–borane complexes are useful compounds (see for reviews on phosphine borane adducts [1]), namely for the synthesis of air sensitive phosphines. Indeed, the boranato group can be easily removed, and thus constitutes a temporary protecting group for the trivalent phosphorus moiety. This feature has been used frequently for the preparation of optically active organophosphorus compounds [1b,2], which have found a widespread use in catalytic asymmetric synthesis. Therefore, the synthesis of chiral phosphine–borane complexes is of interest. In this area, the synthesis of several analogues through dynamic resolution [3] or enantioselective additions of diorganozincs [4] to selected intermediates was reported. Since enzymatic resolution is a powerful tool for the preparation of optically active compounds, we thought it would offer a valuable alternative for the synthesis of chiral phosphane–borane adducts. Thus, we selected the borane adduct of (2-hydroxypropyl)diphenylphosphane **1** [5] as a model substrate (Scheme 1).

The related (2-hydroxypropyl)diphenylphosphane has been already resolved with rabbit gastric lipase (enantiomeric factor $E = 16$) [6], whereas its oxide exhibited a low reactivity under the same conditions. The latter was recently used in its optically active form as a bidentate ligand for titanium [7]. Furthermore, **1** was used for the synthesis of a [1,3] oxaphosphole–borane complex [8].

2. Experimental

2.1. Materials

The following commercial enzyme preparations were tested: lipase from *Penicillium roqueforti* (Amano R10), lipase from *Pseudomonas fluorescens*

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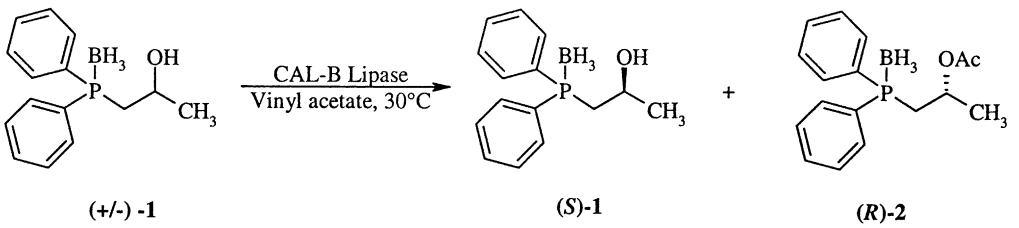


(+/-) -1 (S)-1 (R)-2

Scheme 1.

(Biocatalysts), lipase from *Mucor miehei* (Biocatalysts), lipase from *Candida sp*. (lipase B Biocatalysts), lipase from *Aspergillus niger* (Biocatalysts), lipase from *Candida lipolytica* (Biocatalysts), lipase from porcine pancreas (PPL, Sigma), Acylase I (Sigma), Trypsin from Hog pancreas (Fluka), Proteinase 6 (Fluka), lipase from *Pseudomonas sp*. (Amano AK), lipase from *Candida rugosa* (Amano AY) and lipase from *Candida antartica* (CAL-B, Novo). THF was distilled over benzophenone ketyl. All reagents were used as received. Diphenyl phosphane–borane was prepared as already described [9].

2.2. Synthesis of (±)-(2-hydroxypropyl)-diphenylphosphane borane complex *1*

To a cooled (−78 °C) solution of diphenyl phosphane–borane complex (2.0 g; 10 mmol) in THF (20 ml) under argon, was added a 1.6 M solution of butyl lithium in hexanes (6.6 ml; 10.6 mmol). The orange-yellow solution was stirred at −78 °C for 15 min., and a solution of propylene oxide (0.6 g; 10.3 mmol) in THF (5 ml) was added. The resulting yellow suspension was allowed to reach room temperature, and was stirred overnight. It was then quenched at 0 °C by addition of 7 ml of 5% HCl, and most of the THF was removed in vacuo. The product was taken in ether, washed with water (20 ml), dried over $MgSO_4$, the solvent evaporated and the residue was purified by flash chromatography (silica, diethyl ether/pentane, 60/40) to yield 1.3 g (50%) of **1** as a very viscous colourless oil. ^{1}H NMR: 0.42–1.34 (3H, br.m.,BH_3); 1.07 (3H, dd, $^4J_{PH}$ = 1.5 Hz, $^3J_{HH}$ = 6 Hz); 2.39 (1H, br.s., OH); 2.45 (2H, dd, $^2J_{PH}$ = 11 Hz; $^3J_{HH}$ = 5.8 Hz); 4.17 (1H, m); 7.4–7.8 (10H, m.). ^{13}C NMR: 24.9 (CH_3, d, $^3J_{PC}$ = 11.5 Hz); 36.0 (CH_2, d, $^1J_{PC}$ = 36.1 Hz); 63.6 (CH–OH, s); *the two aromatic rings are non-equivalent*: 128.8 (d, J_{PC} = 7.4 Hz); 128.9 (d, $^1J_{PC}$ = 44.8 Hz); 129.0 (d, J_{PC} = 6.9 Hz); 129.6 (d, $^1J_{PC}$ = 45.8 Hz); 131.2 (d, J_{PC} = 2.3 Hz); 131.4 (d, J_{PC} = 2.3 Hz); 131.9 (d, J_{PC} = 9.2 Hz); 132.3 (d, J_{PC} = 9.2 Hz). ^{31}P NMR: 11.4 ($^1J_{PB}$ = 63 Hz).

2.3. Enzymatic resolution of the borane adduct of (2-hydroxypropyl)diphenylphosphane (±)-*1*

2.3.1. Lipase screening

In a screw cap tube were placed 50 mg of (±)-**1**, 15 ml of vinyl acetate and 50 mg of enzyme. The tube was then placed at 30 °C on a linear shaker. The reactions were followed by TLC; eluent: diethyl ether/pentane (50/50), Rf: **1**: 0.26; **2**: 0.50. The formation of **2** was noticed only with the use of CAL-B.

2.3.2. Preparative scale resolution

In a screw cap tube were placed 250 mg of (±)-**1**, 15 ml of vinyl acetate and 250 mg of CAL-B (Novo). The tube was then placed at 30 °C on a linear shaker. The reaction was followed by TLC and 250 mg of CAL-B were added every 24 h. After 7 days, the enzyme was removed by filtration, the solvent was removed by evaporation and formed acetate **2** and remaining alcohol **1** purified by silica gel chromatography, eluent: diethyl ether/pentane (50/50). Spectral data for **2**: ^{1}H NMR: 0.6–1.5 (3H, br.m., BH_3); 1.30 (3H, dd, $^4J_{PH}$ = 1.2 Hz, $^3J_{HH}$ = 6.2 Hz); 1.65 (3H, s., CH_3); 2.34 (1H, ddd, $^2J_{HH}$ = 14.1 Hz, $^2J_{HP}$ = 9.9 Hz, $^3J_{HH}$ = 4.7 Hz); 2.78 (1H, ddd, $^2J_{HH}$ = 14.1 Hz, $^2J_{HP}$ = 12.1 Hz, $^3J_{HH}$ = 8.4 Hz); 5.23 (1H, m); 7.4–7.8 (10H, m.). ^{13}C NMR: 20.8 (CH_3C(O), s.); 22.1 (CH_3, d, $^3J_{PC}$ = 8.7 Hz); 32.7 (CH_2, d, $^1J_{PC}$ = 35.2 Hz); 67.0 (CH–O, s); *the two aromatic rings are non-equivalent*: 128.8 (d, J_{PC} = 9.2 Hz); 128.9 (d, $^1J_{PC}$ = 40.7 Hz); 129.0

(d, $J_{PC} = 9.5$ Hz); 130.0 (d, $^1J_{PC} = 41.5$ Hz); 131.3 (2C, not resolved); 132.0 (d, $J_{PC} = 9.4$ Hz); 132.5 (d, $J_{PC} = 10.0$ Hz); 169.9 (C=O, s.). ^{31}P NMR: 11.6 ($^1J_{PB} = 67$ Hz).

2.4. Chiral HPLC

Both e.e.'s of formed acetate and remaining alcohol were determined by chiral HPLC after column chromatography (Chiralcel OD-H, eluent 90/10 hexane/isopropanol delivered at 0.8 ml/min, UV detection at 254 nm). Retention times: (*R*)-**1** 21.0 min, (*S*)-**1** 35.2 min, (*S*)-**2** 15.1 min, (*R*)-**2** 16.7 min.

2.5. Synthesis of (S)-(+)-*1*

The same procedure as depicted in 2.2 was employed using (*S*)-propylene oxide. Additional data: $\alpha_D^{20} = +30.5$ (*c*: 1.31, CH_2Cl_2).

3. Results and discussion

In a first trial, we have tested 13 commercial enzyme preparations (see Section 2) on the analytical scale for the resolution of (±)-**1**, in the transesterification mode, using vinyl acetate as both solvent and irreversible acyl donnor. Among them only *Candida antartica* lipase B (CAL-B) from Novo was found to be effective whereas all other enzymes did not show any appreciable conversion after 7 days. Thus, we focused on CAL-B and performed a preparative scale resolution of (±)-**1**. After 7 days the reaction was stopped, the formed acetate and the remaining alcohol separated by flash chromatography over silica and the e.e.'s of both acetate and alcohol were determined by chiral HPLC. The results are summarized in Table 1.

It should be noted that the low yield of (+)-**2** was due to the presence of co-eluting by-products (probably arising from lipase preparation).

The enantiomeric factor ($E = 41$) has been calculated from e.e.'s of both substrate and product and proved satisfactory. It should be noted that CAL-B did not catalyse the hydrolysis nor *n*-butanolysis of (±)-**2**.

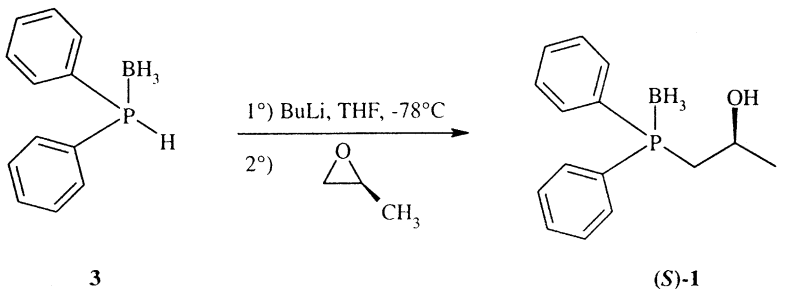
The absolute configuration of (*S*)-(+)-**1** was determined by an independent synthesis from (*S*)-propylene oxide and diphenyl phosphane–borane **3**, as depicted in Scheme 2, according to Pellon [5].

In conclusion, this work is the first example of an enzymatic resolution of a phosphane–borane complex, thus extending the applicability of lipases in organophosphorus chemistry. Over the 13 used enzyme preparations, only CAL-B was able to catalyse this reaction. Despite the low reactivity of **1**, the satisfactory enantiomeric factor value showed the usefulness of this kinetic resolution.

Table 1
Enzymatic resolution of **1** with CAL-B

Conversion[a]	Acetate (*R*)-**2**			Alcohol (*S*)-**1**			*E*
	Yield	α_D^{20} CH_2Cl_2	e.e.	Yield	α_D^{20} CH_2Cl_2	e.e.	
0.51	25.5%	+32.0 $c = 0.74$	86% (*R*)	44.4%	+26.4 $c = 1.11$	91% (*S*)	41

[a] Calculated using: conversion = e.e.(substrate)/[e.e.(substrate) + e.e.(product)] (see [10]). No competitive chemical acylation occurred.



3 (*S*)-**1**

Scheme 2.

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