ORGANIC LETTERS

2005
Vol. 7, No. 22
4991−4994

# A Biocatalytic Route to P-Chirogenic Compounds by Lipase-Catalyzed Desymmetrization of a Prochiral Phosphine–Borane

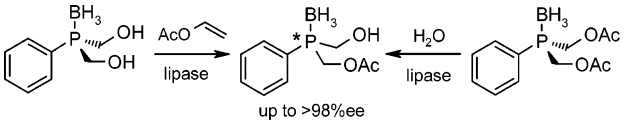
**Daniel Wiktelius,*,† Magnus J. Johansson,*,‡ Kristina Luthman,† and Nina Kann‡**

*Medicinal Chemistry, Department of Chemistry, Göteborg University, SE-41296 Göteborg, Sweden, and Organic Chemistry, Department of Chemical and Biological Engineering, Chalmers University of Technology, SE-41296 Göteborg, Sweden*

*daniel.wiktelius@chem.gu.se; magjo@chembio.chalmers.se*

**Received August 17, 2005**

## ABSTRACT




**Available methods for synthesis of P-chirogenic compounds are limited. We set out to find biocatalytical means to introduce asymmetry in a phosphine–borane. After screening different lipases, *Candida antarctica* lipase B was found to give excellent results in the desymmetrization of prochiral phosphine–boranes. Both enantiomers can be obtained in up to >98% optical purity via acetylation or hydrolysis in processes that allow recycling of the substrates.**

Asymmetric catalysis is a rapidly growing area of research, much due to the demands from the pharmaceutical industry to be able to prepare chiral material in high optical purity using atom efficient methods. Thus, ligand design and the development of new asymmetric reactions are becoming increasingly important. The challenging task of preparing P-chirogenic phosphines is a bottleneck in the search for new ligands in transition metal catalysis, since the number of methods whereby one can synthesize such compounds is still limited. The preparation and use of P-chirogenic phosphines has been reviewed.[1]

In recent years, focus has been directed toward ligand design utilizing already established methods to prepare P-chirogenic compounds.[2] Two procedures have gained the most interest; Evans' method for the desymmetrization of prochiral phosphine-boranes using (−)-sparteine/*s*-BuLi[3] and the (−)-ephedrine chiral auxiliary approach by Jugé et al.[4] However, they are both stoichiometric in either chiral base or auxiliary and have limitations in substrate scope and in giving high enough optical purity of the desired P-chirogenic phosphine (the optical purity can, however, often be improved by recrystallization). The preparation of both enantiomers of a P-chirogenic phosphine is rarely reported.[2d,5]

Herein, we wish to report a biocatalytic approach as a highly interesting alternative for the preparation of P-

† Göteborg University.
‡ Chalmers University of Technology.

(1) (a) Pietrusiewicz, K. M.; Zabłocka, M. *Chem. Rev.* **1994**, *94*, 1375. (b) Brunel, J. M.; Faure, B.; Maffei, M. *Coord. Chem. Rev.* **1998**, *180*, 665. (c) Quin, L. D. *A Guide to Organophosphorous Chemistry*; John Wiley & Sons: New York, 2000. (d) Crépy, K. V. L.; Imamoto, T. *Top. Curr. Chem.* **2003**, *229*, 1. (e) Valentine, D. H.; Hillhouse, J. H. *Synthesis* **2003**, 2437. (f) Tang, W.; Zhang, X. *Chem. Rev.* **2003**, *103*, 3029. (g) Johansson, M. J.; Kann, N. C. *Mini-Rev. Org. Chem.* **2004**, *1*, 233.

(2) (a) Imamoto, T.; Watanabe, J.; Wada, Y.; Masuda, H.; Yamada, H.; Tsuruta, H.; Matsukawa, S.; Yamaguchi, K. *J. Am. Chem. Soc.* **1998**, *120*, 1635. (b) Yamanoi, Y.; Imamoto, T. *J. Org. Chem.* **1999**, *64*, 2988. (c) Tang, W.; Zhang, X. *Angew. Chem., Int. Ed.* **2002**, *41*, 1612. (d) Hoge, G. *J. Am. Chem. Soc.* **2003**, *125*, 10219.

(3) Muci, A. R.; Campos, K. R.; Evans, D. A. *J. Am. Chem. Soc.* **1995**, *117*, 9075.

(4) Jugé, S.; Stephan, M.; Laffitte, J. A.; Genêt, J. P. *Tetrahedron Lett.* **1990**, *31*, 6357.

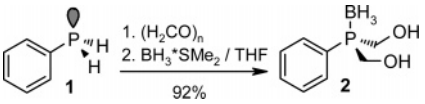
(5) (a) Johansson, M. J.; Schwartz, L. O.; Amedjkouh, M.; Kann, N. C. *Eur. J. Org. Chem.* **2004**, 1894. (b) Johansson, M. J.; Schwartz, L. O.; Amedjkouh, M.; Kann, N. *Tetrahedron: Asymmetry* **2004**, *15*, 3531. (c) Liu, D.; Zhang, X. *Eur. J. Org. Chem.* **2005**, 646.

10.1021/ol0519893 CCC: $30.25 
**Published on Web 10/07/2005**

chirogenic compounds. This route comprises the first reported desymmetrization of a prochiral phosphine−borane using lipases, yielding both enantiomers of the corresponding P-chirogenic phosphine−borane independently. Earlier work with lipases to obtain enantioenriched P-chirogenic products include kinetic resolution of hydroxymethyl(dialkyl)phosphine−boranes[6] and desymmetrization of prochiral phosphine oxides.[7]

The prochiral starting material bis(hydroxymethyl)phenylphosphine−borane (**2**, Scheme 1) was synthesized using

**Scheme 1.** Synthesis of Bis(hydroxymethyl)phenylphosphine−Borane (**2**)



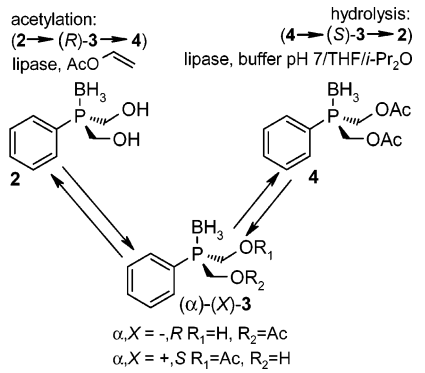

a one-pot solvent-free condensation between paraformaldehyde and phenylphosphine (**1**) followed by dilution with THF and protection of the phosphorus atom by $BH_3{\cdot}SMe_2$. Compound **2** was obtained in 92% yield after recrystallization in toluene.

The prochiral diol **2** is similar in structure to its "all carbon" analogues, the 1,3-propanediols, which are known substrates for lipase catalyzed desymmetrization.[8] Although recent spectroscopic and computational studies have contributed significantly to the understanding of lipase enantioselectivity,[9] empirical rules are still widely used to predict the enantiotope that reacts fastest. Application of the spacial size preferences of BCL[10] for primary alcohols suggested by Weissfloch and Kazlauskas[11] on the desymmetrization of **2** into acetyloxymethyl(hydroxymethyl)phenylphosphine−borane (**3**, Figure 1, Scheme 2) suggested the resulting


**Figure 1.** Preferred orientation of a primary alcohol in the active site of BCL,[10] with the relative directions of the large (L), medium (M), and small (S) substituents.[11] An alignment of prochiral diol **2** according to this model indicates that the *pro*-(*R*) group is the favored site of reaction.

stereochemistry to be *R*. The rule has good, but not perfect accuracy,[11] and although the interactions of diol **2** with the enzyme may differ significantly from that of carbon analogues, data on kinetic resolution of hydroxymethyl(dialkyl)-

**Scheme 2.** Stereoselective Desymmetrization of **2** or **4** by Lipase[a]-Catalyzed Acetylation or Hydrolysis[b]




[a] Lipases used along with ee's are given in Table 1 and text. [b] See ref 12 for reaction conditions.

phosphine−boranes[6] indicated that it may have relevance also for this type of compounds.

Five lipases[10] were screened for their ability to desymmetrize diol **2** by acetylation using vinyl acetate as acyl donor and solvent (Scheme 2, Table 1), and the conversion was monitored by HPLC.

**Table 1.** Lipase Screening for Enantioselective Desymmetrization of **2** by Acetylation[a]

| lipase[b] | reaction time | prod distrib (%)[c] **2**:**3**:**4** | ee of (*R*)-**3**[d] (%) |
|---|---|---|---|
| ANL | 7 d | 63:36:1 | 70 |
| BCL | 96 h | 75:23:2 | 21 |
| PPL | 19 d | 65:34:1 | 21 |
| PFL | 28 h | 41:53:6 | 62 |
| CALB | 140 min | 50:49:1 | 60 |
| CALB | 6 h | 0:48:52 | 92 |

[a] See ref 12 for reaction conditions. [b] For explanation of lipase abbreviations, see ref 10. [c] Determined by HPLC of the filtered reaction mixture. [d] Determined by chiral HPLC of the isolated product.

The screening procedure began with ANL, BCL, PFL, and PPL,[10,12a] but disappointingly the conversion was slow, and the formation of bis(acetyloxymethyl)phenylphosphine−borane (**4**) limited the yield of monoacetate **3**. The optical purity of the isolated product **3** was assessed by chiral HPLC (Table 1). The stereoselectivity of BCL and PPL was low

(6) Shioji, K.; Kurauchi, Y.; Okuma, K. *Bull. Chem. Soc. Jpn.* **2003**, *76*, 833.
(7) Kiełbasiński, P.; Żurawiński, R.; Albrycht, M.; Mikołajczyk, M. *Tetrahedron: Asymmetry* **2003**, *14*, 3379.
(8) For a recent review, see: García-Urdiales, E.; Alfonso, I.; Gotor, V. *Chem. Rev.* **2005**, *105*, 313.
(9) For a recent review, see: Ema, T. *Curr. Org. Chem.* **2004**, *8*, 1009.
(10) Lipases are abbreviated according to species of origin: ANL = *Aspergillus niger* lipase (Amano lipase A); BCL = *Burkholderia cepacia* lipase (formerly known as *Pseudomonas cepacia*, Amano lipase PS); CALB = *Candida antarctica* lipase B (Novozym 435); PFL = *Pseudomonas fluorescens* lipase (Amano lipase AK); PPL = Pig pancreatic lipase (Fluka).
(11) Weissfloch, A. N. E.; Kazlauskas, R. J. *J. Org. Chem.* **1995**, *60*, 6959.
(12) (a) Typical procedure for the lipase catalysed desymmetrization by acetylation: **2** (100 mg, 0.54 mmol) and lipase (100 mg) were stirred at rt in vinyl acetate (2.5 mL). (b) Typical procedure for the lipase catalyzed desymmetrization by hydrolysis: **4** (75 mg, 0.28 mmol) and CALB (75 mg) were shaken vigourusly in a mixture of 0.1 M phosphate buffer pH 7 (2 mL), diisopropyl ether (1 mL) and THF (0.5 mL).

(21% ee), whereas PFL and ANL gave **3** in moderate ee, 62 and 70%, respectively. With these discouraging results at hand we tried CALB,[10] and to our delight the rate of conversion was excellent in this case. The reaction was stopped at 50% conversion and the appearance of **4**, but the ee of the product was a rather disappointing 60%. Considering the good catalytic efficiency of CALB, the possibility of kinetic amplification of the optical purity of (*R*)-**3** by tandem resolution if the second acetylation reaction proceeded with stereoselectivity was raised. Rewardingly, resymmetrization to **4** was fastest for the minor (*S*)-enantiomer of **3** formed in the desymmetrization step. The self-correcting process afforded (*R*)-**3** in 92% ee at a product distribution of 0:48:52 of **2**:**3**:**4**.

This result prompted us to investigate the dependence of the optical purity of **3** on the extent of conversion into **4**. An experiment was set up in which the conversion and ee were monitored at intervals during the reaction. The results are summarized in Figure 2.

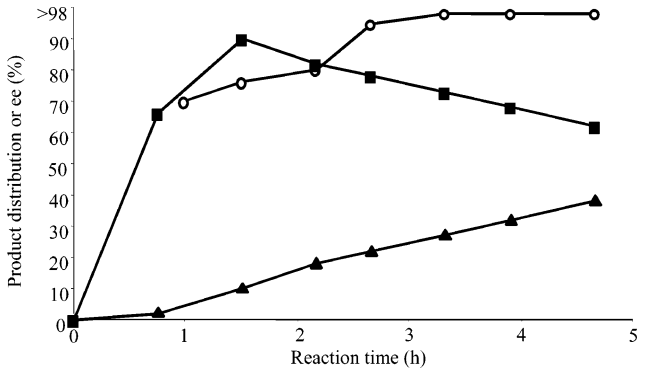



**Figure 2.** Optical purity of (*R*)-**3** (○) and product distribution (monoacetate **3** (■), diacetate **4** (▲)) monitored by HPLC during desymmetrization of diol **2** by CALB-catalyzed acetylation. See ref 12 for reaction conditions.

These data indicate that the second acetylation proceeded with high enantiopreference, and that at most 27% resymmetrization into diacetate **4** is required to improve the ee of monoacetate (*R*)-**3** from 60 to >98%. However, after running the reaction at even higher conversion (Table 1), the ee of the isolated product was 92%, thus we suspect some racemization during purification, probably via acyl migration. With this in mind, we desymmetrized **2** into (*R*)-**3** in 92% ee and 59% isolated yield along with 32% of **4** to be used for subsequent hydrolysis experiments.

An advantage of lipase catalyzed desymmetrization of prochiral diols is that it can give access to both enantiomers via stereoselective hydrolysis of the corresponding diacetate.[8] The diacetate **4** was conveniently obtained as a byproduct of the desymmetrization of diol **2** and could be used to synthesize monoacetate (*S*)-**3** by the reverse reaction catalyzed by CALB (Scheme 2). As in the acetylation experiment, the conversion and optical purity of **3** was monitored during the reaction (Table 2).

**Table 2.** Optical Purity of (*S*)-**3** during Desymmetrization of Diacetate **4** by Hydrolysis Catalyzed by CALB[a]

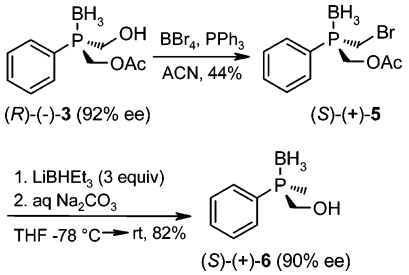
| reaction time (h) | prod distrib[b] (%) **2**:**3**:**4** | ee of (*S*)-**3**[c] (%) |
|---|---|---|
| 8 | 4:22:74 | 19 |
| 31 | 26:50:24 | 28 |
| 70 | 37:54:9 | 69 |
| 97 | 48:49:3 | 90 |

[a] For reaction conditions, see ref 12. [b] Determined by HPLC of the filtered reaction mixture. [c] Determined by chiral HPLC of the reaction mixture after filtration and extraction.

The hydrolysis of **4** was slower and proceeded with lower stereoselectivity in the first step than the acetylation reaction, which may reflect the smaller size difference between the acetyloxymethyl and the phenyl substituent compared to the hydroxymethyl. The resymmetrization into diol **2** improved the low stereoselectivity in the first step; however, an ee of 90% was only obtainable at high conversion when approximately half of the monoacetate **3** was converted into **2**. At this stage, the reaction was impractically slow for further improvement of the optical purity, and (*S*)-**3** was isolated in 89% ee and 31% yield along with 36% of **2**.

To verify the stereochemistry of monoacetate **3** and explore some possible transformations of this compound, we wanted to transform enantiomerically enriched **3** into the known P-chirogenic compound hydroxymethyl(methyl)-phenylphosphine−borane (**6**, Scheme 3), of which the

**Scheme 3.** Confirmation of Stereochemistry of (−)-**3** by Chemical Correlation: Synthesis of (*S*)-**6**




levorotary (*R*)-enantiomer is avaliable via desymmetrization of dimethylphenylphosphine−borane by enantioselective deprotonation with (−)-sparteine/*s*-BuLi and quenching with triethyl phosphite and oxygen.[13] The effort began with the presumed (*R*)-enantiomer of **3** (92% ee) obtained by stereoselective acetylation by CALB of diol **2** (Scheme 2). Transformation into (*S*)-**6** requires deoxygenation and cleavage of the acetate of (*R*)-**3**. We realized that if the hydroxy function of **3** is exchanged for a halide, simultaneous reduction of the ester and halide can be accomplished by treatment with lithium triethylborohydride. To this end, (*R*)-**3** was reacted with tetrabromomethane and triphenylphosphine

(13) Nagata, K.; Matsukawa, S.; Imamoto, T. *J. Org. Chem.* **2000**, *65*, 4185.

which furnished (*S*)-acetyloxymethyl(bromomethyl)phenylphosphine−borane (**5**) in 44% yield. The reduction of (*S*)-**5** to the target compound **6** with $LiBHEt_3$ proceeded smoothly and afforded (*S*)-**6** in 82% yield with minimal racemization detected (90% ee, $[\alpha]_D$ +8.2) (Scheme 3).

The chemical correlation (Scheme 3) confirmed that the absolute configuration of monoacetate (−)-**3** (Scheme 2) is *R* as anticipated. (*R*)-**6** was synthesized according to the previously reported method[13] in 80% ee and was found to be identical to (*S*)-**6** by NMR, but with the opposite sign of optical rotation ($[\alpha]_D$ −7.1) and we could further confirm the stereochemical correlation by chiral HPLC. Thus, the current enzymatic method gives access to the opposite enantiomer of **6** from that obtained by enantioselective deprotonation with (−)-sparteine/*s*-BuLi. Some interesting transformations of **6** have been studied by Imamato et al., such as synthesis of the BisP*-type ligands[14] by dimerization, oxidation, and decarboxylation or direct decarbonylation into phosphine-borane precursors of secondary P-chirogenic phosphines.[13] In a related study on enzymatic desymmetrization of the phosphine oxide analogues of **2** and **4**, Kiełbasiński and co-workers obtained monoacetate products in fair yields and up to 79% optical purity and a chemical correlation with **6** in nine steps was reported which proceeded with substantial racemization.[7] Reported attempts on kinetic resolution of hydroxymethyl(dialkyl)phosphine−boranes[6] gave analogues of **6** in varying yields and optical purities; however, the enantioselectivity of the resolutions were unpractically low.

We believe that the current results may provide an entry to new methodology in the field of asymmetric synthesis of P-chirogenic phosphine-boranes. High optical purity is attained at the expense of yield with the current method, but since **2**, **3**, and **4** can be interconverted (Scheme 2), this confers minimal loss of material. We chose to focus thoroughly on the phenyl derivative of bis(hydroxymethyl)-phoshine−borane in this study; however, other compounds of this type are of course candidates for enzymatic desymmetrization, which will be the aim of further research.

The new compounds **3**, **5**, and (*S*)-**6** (Scheme 3) are highly interesting for further exploration of their potential as precursors in syntheses of other optically active derivatives. The main use of P-chirogenic phosphine-boranes is as ligands within the field of transition metal catalyzed asymmetric reactions.[1] We find it intriguing that compounds presented in this study (or derivatives thereof) may give the opportunity to utilize the inherent chirality of a lipase in such reactions by relaying the asymmetry of the enzyme onto the reactants via the phosphine-borane.

In summary, we have shown that enantiomerically enriched phosphine-boranes are accessible by lipase catalyzed desymmetrization of prochiral diol or diacetate precursors. The developed methods allow the preparation of both enantiomers of monoacetate analogues in excellent ee with defined absolute configurations. The obtained products are highly interesting for further elaboration into useful compounds in ligand development. The method is atom efficient since the enzymatic reactions allow recycling of material.

**Acknowledgment.** Financial support was obtained from the Knut and Alice Wallenberg Foundation, the Swedish Research Council, and the Swedish Foundation for Strategic Research.

**Supporting Information Available:** Experimental procedures and spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0519893

(14) Crépy, K. V. L.; Imamoto, T. *Tetrahedron Lett.* **2002**, *43*, 7735.