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Highly Enantioselective Hydrogenation of Enol Ester Phosphonates: A Versatile Procedure for the Preparation of Chiral β-Hydroxyphosphonates

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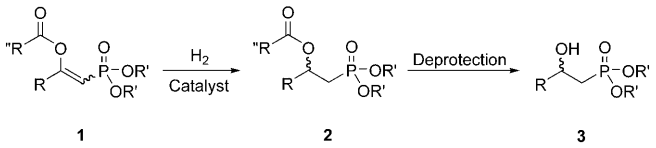
Chiral β-hydroxyphosphonates constitute an interesting class of compounds, owing to their wide variety of biological applications, such as antibacterial agents,[1] enzyme inhibitors[2] or intermediates in biosynthetic processes.[3] Furthermore, owing to the widespread interest in phosphonates as bioisosteric derivatives of carboxylic acid derivatives,[4] several β-hydroxyphosphonates, such as phosphogabob and phosphocarnitine among others, have been subject to considerable attention.[5] These alcohols are also synthetically valuable compounds, as they can be readily converted into biologically active β-aminophosphonates.[6]

The need for the development of versatile and efficient methods for the preparation of enantiopure β-hydroxyphosphonates is therefore apparent,[7] although studies to this end have not been widely reported. For instance, investigation of particularly advantageous asymmetric catalytic procedures[8,9] is mainly restricted to ketone hydrogenation reactions using ruthenium catalysts. Noyori and co-workers have reported the use of 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (binap) derivatives in the reduction of several β-alkyl- and β-phenylketophosphonates, including the application of this catalytic system to a convenient synthesis of fosfomycin.[10] Genêt and co-workers have applied 2,2′-bis(diphenylphosphino)-6,6′-bis-methoxy-1,1′-biphenyl (MeO-biphep) catalysts to several substrates including a β-(3-thienyl) derivative.[11] Further study of synthetic methods for the preparation of highly enantioenriched β-hydroxyphosphonates is thus of interest, either to widen the range of available examples or to provide an alternative to ketone hydrogenation.

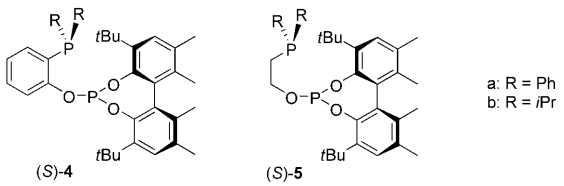
A convenient procedure to generate alcohols using a hydrogenation reaction is based on the reduction of an enol ester, followed by deprotection of the resulting product.[12] This strategy relies on the efficiency of the asymmetric hydrogenation of chelating olefins.[13] Regarding α,β-unsaturated phosphonates, several groups have reported the highly enantioselective hydrogenation of α-acyloxy derivatives.[14] However, to our knowledge, the hydrogenation of enol



Scheme 1. Synthesis of β-hydroxyphosphonates **3**.

esters **1** has not been investigated as a useful approach for the synthesis of β-hydroxyphosphonates **3** (Scheme 1). Herein, we investigate this reaction sequence and demonstrate the validity of this approach. We report an unprecedented olefin hydrogenation reaction, which gives access to a wide variety of chiral β-acyloxyphosphonates **2** with excellent levels of asymmetric induction which, in addition, can easily be converted into the corresponding alcohols.

In recent years, progress in the field of enantioselective olefin hydrogenation has identified an important number of interesting applications for catalysts bearing bifunctional chiral ligands.[15] In this context, we have studied the application of phosphane–phosphite ligands (P–OP, Scheme 2) **4**



Scheme 2. Structure of P–OP ligands **4** and **5**.

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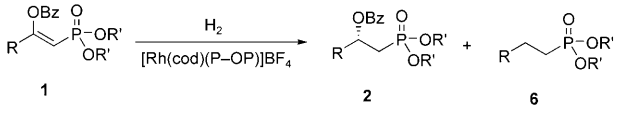
and **5** in diverse hydrogenation reactions.[16] In an effort to broaden the scope of these catalysts, unsaturated phosphonates **1** were chosen as substrates. Studies were initiated by the development of a convenient procedure for the synthesis of a set of olefins **1**. These derivatives can be easily prepared from readily available β-ketophosphonates by simple treatment with sodium hydride and an acylating agent (either BzCl or Bz_2O see the Supporting Information). Notably, this reaction yields olefins **1** as the *Z* isomers exclusively. This feature is of practical interest, as separation of geometric isomers is avoided, and confers a challenging aspect to the hydrogenation of these olefins, since structurally related *Z*-β-*N*-acylaminoacrylates usually give slower and less enantioselective reactions than their *E* counterparts.[17] In addition, steric effects, resulting from the size of the phosphonate group, can further reduce the reactivity of these alkenes.[18]

A set of rhodium precatalysts of formulation [Rh(cod)(P–OP)]BF_4 (cod = cycloocta-1,5-diene, P–OP = **4**, **5**; Scheme 2)



a: R = Me, R' = Me
b: R = *i*Pr, R' = Me
c: R = *n*Bu, R' = Me
d: R = Ph, R' = Et
e: R = 4-MeC_6H_4, R' = Me
f: R = 4-MeOC_6H_4, R' = Me
g: R = 4-BrC_6H_4, R' = Me
h: R = 2-naphthyl, R' = Me

Scheme 3. Hydrogenation of **1**. cod = cycloocta-1,5-diene, P–OP = phosphane–phosphite ligand **4** or **5**.

Table 1. Hydrogenation of **1a** with [Rh(cod)(P–OP)]BF_4.[a]

Entry	P–OP	Conv[b]	Product distribution [%]		*ee* **2a** [%][c]	Configuration
			2a[d]	**6a**[d]		
1	(*S*)-**4a**	46	36	10	33	*R*
2	(*S*)-**4b**	100	98	2	99	*R*
3	(*S*)-**5a**	41	33	8	31	*R*
4	(*R*)-**5b**	100	32	68	59	*S*

[a] Conditions: 4 atm H_2, 25 °C, CH_2Cl_2, S/C (substrate/catalyst ratio) = 100, 24 h. [b] Conversion was determined by ^{1}H NMR spectroscopy. [c] Enantiomeric excess determined by chiral HPLC. Absolute configuration assigned by comparison of optical rotation of alcohol **3a** (resulting from debenzylation of **2a**), with literature value.[8c] [d] Based on starting material **1a**.

has been examined in the hydrogenation of the representative substrate **1a** (Scheme 3, Table 1). Notably, this kind of hydrogenation produces, in addition to the desired saturated phosphonate **2a**, a second product **6a**, generated by elimination of the OBz group. Interestingly, both the amount of this by-product and the enantioselectivity of the reaction can be optimized by an appropriate choice of P–OP ligand. Thus, among the catalysts investigated, that derived from phosphane–phosphite **4b** produced excellent results, giving full conversion and affording **2a** with excellent chemo- and enantioselectivity (Table 1, entry 2). Interestingly, catalysts based on ligands **4a** and **4b** had low activity in the hydrogenation of related α-acyloxyphosphonates.[16b]

Following the pleasing result obtained in the reduction of **1a**, the scope of catalyst precursor [Rh(cod)(**4b**)]BF_4 was examined. A variety of β-acyloxyphosphonates were hydrogenated with very high enantioselectivities using this catalyst. Thus, β-alkyl product **2b** was obtained with high chemoselectivity and 99% *ee* (Table 2, entry 2). Conversely,

Table 2. Hydrogenation of **1** with [Rh(cod)(**4b**)]BF_4.[a]

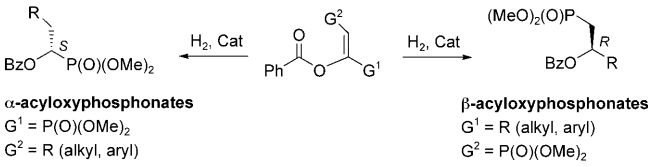
Entry	Substrate	Product distribution [%]		Yield **2** [%][b]	*ee* **2** [%][c]	Configuration
		2	**6**			
1	**1a**	98	2	90	99	*R*
2	**1b**	98	2	82	99	*R*
3	**1c**	68	32	55	99	*R*
4	**1d**	98	2	93	99	*R*
5	**1e**	90	10	85	99	*R*
6	**1f**	73	27	73	95	*R*
7	**1g**	96	4	87	99	*R*
8	**1h**	97	3	86	99	*R*

[a] Conditions: 4 atm H_2, 25 °C, CH_2Cl_2, S/C = 100, 24 h. Full conversion, determined by ^{1}H NMR spectroscopy, was detected in all reactions. [b] Yield of isolated product. [c] Enantiomeric excess determined by chiral HPLC. Absolute configuration was determined in **2g** by X-ray crystallography. This configuration has tentatively been assigned to the rest of compounds of the series, assuming the same stereochemical course of the reaction in all substrates.

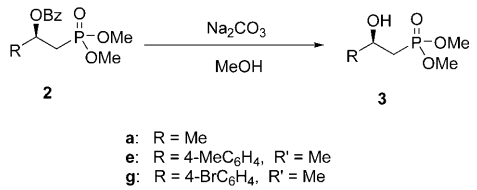
*n*Bu-substituted **1c** offered a lower selectivity for the desired **2c**, although this compound was also obtained with very high enantioselectivity. A range of β-aryl derivatives were also examined and, with exception of the *p*-anisyl derivative **2f** , which showed a moderate chemoselectivity (73%, Table 2, entry 6), gave high selectivities for the chiral derivatives **2d**–**h**. Moreover, for all aromatic substrates investigated, the reaction proceeds with very high enantioselectivity, from 95% *ee* for **2f** to greater than 99% *ee* for the other substrates.

We next examined the configuration of compounds **2a**–**h**. Firstly, X-ray crystallography, performed on derivative **2g**, established an absolute *R* configuration for this compound.[19] Moreover, the same configuration has been assigned to β-alkyl **2a** by comparison of the specific rotation of the corresponding alcohol **3a** (see below) with the value reported in the literature.[8c] It is interesting to compare the configuration of products resulting from hydrogenation of α- and β-acyloxyvinylphosphonates.[20] According to a previous study, catalysts based on P–OP ligands with an *S* phosphite fragment produce *S* products from α-acyloxy derivatives.[16b] Therefore, product configuration indicates that hydrogen addition occurs on opposed faces of the unsaturated phosphonates (Scheme 4).

We then explored if compounds **2** can be deprotected to the corresponding alcohols **3**. A set of representative compounds were converted into the desired alcohols without loss of enantiomeric purity by a simple treatment with Na_2CO_3 in methanol (Scheme 5).

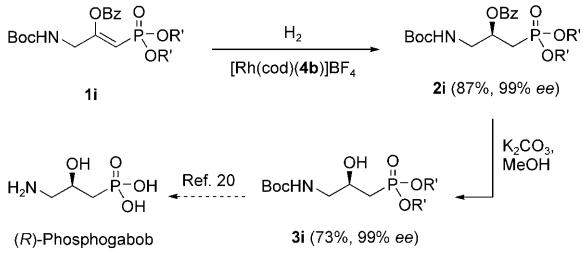


Scheme 4. Sense of asymmetric induction in hydrogenation of unsaturated phosphonates, with catalysts based on *S* configured phosphite groups.



Scheme 5. Ester deprotection.

γ-Amino-β-hydroxyphosphonates are of interest, owing to their biological activity.[1,5–7] We thus investigated the efficiency of our catalyst in the generation of species of this type. For this purpose, the hydrogenation of substrate **1i** was investigated (Scheme 6). Notably, our catalyst also hydrogenated this substrate with a 99% *ee*. The structure of hydrogenated **2i** closely resembles those of phosphogabob and phosphocarnitine.[5] For instance, **2i** has been converted into the corresponding highly enantioenriched alcohol **3i** which can be readily converted into phosphogabob.[21]



Scheme 6. Preparation of a phosphogabob precursor (R′ = Me).

In summary, a versatile and highly enantioselective procedure, based on asymmetric olefin hydrogenation reactions, has been described for the synthesis of β-hydroxyphosphonates. The catalyst reported herein is active for the, usually rather sluggish, reduction of *Z*-olefins, which are the sole isomers obtained in the synthesis of substrates **1**. The utility of this hydrogenation reaction is enhanced by an easy conversion of the products into valuable β-hydroxyphosphonates without racemization. Further examination of mechanistic and synthetic aspects of this reaction is currently in progress.

Experimental Section

General procedure for asymmetric hydrogenation of olefins **1** (as exemplified by **1a**): In a nitrogen filled glove-box, a Fischer–Porter reactor (80 mL) was charged with **1a** (0.060 g, 0.22 mmol) and catalyst precursor [Rh(cod)(**4b**)]BF_4 (0.002 g, 0.002 mmol) in CH_2Cl_2 (4 mL). The vessel was brought outside the glove box, submitted to five evacuation–hydrogen cycles and, finally, pressurized to 4 atm. The reaction mixture was stirred for 24 h, before the reactor was depressurized and the mixture evaporated to dryness. Conversion and product distribution were determined by ^{1}H NMR analysis of the resulting residue. Purification of the residue by column chromatography on silica with ethyl acetate yielded **2a** as a colorless oil (0.054 g, 0.2 mmol, 90%). Chiral HPLC analysis (Chiralcel OJ, 30 °C, 1.0 mL min^{-1}, *n*-hexane/isopropanol: 90/10; (*S*) t_1 = 10.3 min, (*R*) t_2 = 12.3 min) indicated a 99% *ee*.

General procedure for deprotection of benzyloxy esters **2** (as exemplified by **2g**): Na_2CO_3 (0.147 g, 1.4 mmol) was added to a solution of **2g** (0.141 g, 0.34 mmol) in MeOH (5 mL). The reaction mixture was stirred for 16 h and the solvent removed under reduced pressure. The resulting mixture was dissolved in ethyl acetate (10 mL), and washed with saturated aqueous solutions of $NaHCO_3$ (10 mL) and NaCl (10 mL). The organic phase was dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure. The residue was purified by column chromatography on silica (eluent EtOAc/MeOH 9:1), affording **3g** as a colorless oil (0.055 g, 67%). HPLC analysis (Chiralcel OB, 30 °C, 1.0 mL min^{-1}, *n*-hexane/isopropanol: 97/3; *(S)* t_1 = 28.4 min, *(R)* t_2 = 36.4 min) indicated a 99% *ee*.

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Keywords: asymmetric catalysis · hydrogenation · P ligands · rhodium

[1] A. E. Wróblewski, A. Halajewska-Wosik, *Tetrahedron: Asymmetry* **2004**, *15*, 3201.
[2] a) J. F. Dellaria, R. G. Maki, H. H. Stein, J. Cohen, D. Whittern, K. Marsh, D. J. Hoffman, J. J. Plattner, T. J. Perun, *J. Med. Chem.* **1990**, *33*, 534; b) P. Cui, J. L. Tomsig, W. F. McCalmont, S. Lee, C. J. Becker, K. R. Lynch, T. L. Macdonald, *Bioorg. Med. Chem. Lett.* **2007**, *17*, 1634.
[3] a) P. Liu, K. Murakami, T. Seki, X. He, S. M. Yeung, T. Kuzuyama, H. Seto, H. W. Liu, *J. Am. Chem. Soc.* **2001**, *123*, 4619; b) R. D. Woodyer, G. Li, H. Zhao, W. A. van der Donk, *Chem. Commun.* **2007**, 359.
[4] A. Macchiarulo, R. Pellicciari, *J. Mol. Graphics Modell.* **2007**, *26*, 728.
[5] a) M. Ordóñez, A. González-Morales, H. Salazar-Fernández, *Tetrahedron: Asymmetry* **2004**, *15*, 2719; b) M. Mikolajczyk, J. Luczak, P. Kielbasinski, *J. Org. Chem.* **2002**, *67*, 7872; c) M. Ordóñez, R. de La Cruz-Cordero, C. Quiñones, A. González-Morales, *Chem. Commun.* **2004**, 672.
[6] F. Palacios, C. Alonso, J. M. de Los Santos, *Chem. Rev.* **2005**, *105*, 899.
[7] For a review on the asymmetric synthesis of hydroxyphosphonates see: O. I. Kolodiazhnyi, *Tetrahedron: Asymmetry* **2005**, *16*, 3295.
[8] For the synthesis of β-hydroxyphosphonates using enzymatic kinetic resolution, see: a) O. Pàmies, J. E. Bäckwall, *J. Org. Chem.* **2003**, *68*, 4815; b) A. Woschek, W. Lindner, F. Hammerschmidt, *Adv. Synth.*

Catal. **2003**, *345*, 1287; c) Y. Zhang, C. Yuan, Z. Li, *Tetrahedron* **2002**, *58*, 2973.

[9] For the asymmetric reduction of β-ketophosphonates using boron reagents, see: a) V. V. Nesterov, O. I. Kolodiazhnyi, *Tetrahedron* **2007**, *63*, 6720; b) Meier, W. H. G. Laux, *Tetrahedron* **1996**, *52*, 589.

[10] a) M. Kitamura, M. Tokunaga, R. Noyori, *J. Am. Chem. Soc.* **1995**, *117*, 2931; b) M. Kitamura, M. Tokunaga, T. Pham, W. D. Lubell, R. Noyori, *Tetrahedron Lett.* **1995**, *36*, 5769.

[11] a) I. Gautier, V. Ratovelomanana-Vidal, P. Savignac, J. P. Genêt *Tetrahedron Lett.* **1996**, 37, 7721; b) J. Madec, X. Pfister, P. Phansavath, V. Ratovelomanana-Vidal, J. P. Genêt, *Tetrahedron* **2001**, *57*, 2563.

[12] a) M. J. Burk, C. S. Kalberg, A. Pizzano, *J. Am. Chem. Soc.* **1998**, *120*, 4345; b) P. Chereku, S. Gohil, P. G. Andersson, *Org. Lett.* **2007**, *9*, 1659; c) M. T. Reetz, L. J. Goossen, A. Meiswinkel, J. Paetzold, J. F. Jensen, *Org. Lett.* **2003**, *5*, 3099; d) Q. Jiang, D. Xiao, Z. Zhang, P. Cao, X. Zhang, *Angew. Chem.* **1999**, *111*, 578; *Angew. Chem. Int. Ed.* **1999**, *38*, 516.

[13] a) M. J. Burk, *Acc. Chem. Res.* **2000**, *33*, 363; b) W. Tang, X. Zhang, *Chem. Rev.* **2003**, *103*, 3029.

[14] a) D. Y. Wang, X. P. Hu, J. D. Huang, J. Deng, S. B. Yu, Z. C. Duan, X. F. Xu, Z. Zheng, *Angew. Chem.* **2007**, *119*, 7956; *Angew. Chem. Int. Ed.* **2007**, *46*, 7810; b) I. D. Gridnev, M. Yasutake, T. Imamoto, I. P. Beletskaya, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5385; c) M. J. Burk, T. A. Stammers, J. A. Straub, *Org. Lett.* **1999**, *1*, 387; d) Ref 16b.

[15] a) M. Engman, J. S. Diesen, A. Paptchikhine, P. G. Andersson, *J. Am. Chem. Soc.* **2007**, *129*, 4536; b) S. Bell, B. Wüstenberg, S. Kaiser, F. Menges, T. Netscher, A. Pfaltz, *Science* **2006**, *311*, 642; c) J. Zhou, J. W. Ogle, Y. Fan, V. Banphavichit, Y. Zhu, K. Burgess, *Chem. Eur. J.* **2007**, *13*, 7162.

[16] a) A. Suárez, M. A. Méndez-Rojas, A. Pizzano, *Organometallics* **2002**, *21*, 4611; b) M. Rubio, S. Vargas, A. Suárez, E. Álvarez, A. Pizzano, *Chem. Eur. J.* **2007**, *13*, 1821; c) A. Suárez, A. Pizzano, *Tetrahedron: Asymmetry* **2001**, *12*, 2501.

[17] a) X. P. Hu, Z. Zheng, *Org. Lett.* **2005**, *7*, 419; b) W. Tang, W. Wang, Y. Chi, X. Zhang, *Angew. Chem. Int. Ed.* **2003**, *42*, 2509; c) J. You, H. J. Drexler. S. Zhang, C. Fischer, D. Heller, *Angew. Chem.* **2003**, *115*, 942; *Angew. Chem. Int. Ed.* **2003**, *42*, 913; d) G. Zhu, Z. Chen, X. Zhang, *J. Org. Chem.* **1999**, *64*, 6907.

[18] M. Rubio, A. Suárez, E. Álvarez, A. Pizzano, *Chem. Commun.* **2005**, 628.

[19] CCDC-695565 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data centre via www.ccdc.cam.ac.uk/data request/cif.

[20] For studies comparing asymmetric hydrogenation of structurally related α- and β-dehydroaminoacids, see: a) H. J. Drexler, W. Baumann, T. Schmidt, S. Zhang, A. Sun, A. Spannenberg, C. Fischer, H. Buschmann, D. Heller, *Angew. Chem.* **2005**, *117*, 1208; *Angew. Chem. Int. Ed.* **2005**, *44*, 1184; b) M. Yasutake, I. D. Gridnev, N. Higashi, T. Imamoto, *Org. Lett.* **2001**, *3*, 1701.

[21] A. E. Wróblewski, A. Halajewska-Wosik, *Tetrahedron: Asymmetry* **2003**, *14*, 3359.

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