ORGANIC LETTERS

2001
Vol. 3, No. 23
3687−3690

Phosphonites Based on the Paracyclophane Backbone: New Ligands for Highly Selective Rhodium-Catalyzed Asymmetric Hydrogenation

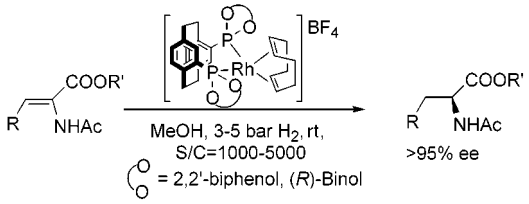
Antonio Zanotti-Gerosa,* Christophe Malan, and Daniela Herzberg

Chirotech Technology Limited, Cambridge Science Park, Milton Road, Cambridge CB4 0WG, U.K.

antoniozanotti-gerosa@chirotech.com

Received August 21, 2001

ABSTRACT



The synthesis of new phosphonites with a chiral paracyclophane backbone is described. The rhodium complexes derived from the phosphonites bearing biphenoxy and binaphthoxy substituents are highly active and highly selective catalysts for the asymmetric hydrogenation of dehydroamino acids and esters.

Hydrogenation, among all catalytic asymmetric reactions, has a particular industrial relevance because of its high efficiency and reduced environmental impact.[1] Rhodium and ruthenium catalysts bearing chiral chelating diphosphine ligands have proved, over the past 30 years, to be the most effective catalysts for asymmetric hydrogenation. However, it has recently been shown that some of the results obtained with chelating phosphines can be matched by the use of bidentate phosphinites,[2] phosphonites,[3] phosphites,[4] or phosphoroamidites.[5] In addition, chiral monodentate phosphonites,[6] phosphites,[7] and phosphoroamidites[5] have in some cases proved to be as effective as the analogous bidentate ligands. The driving force is the search for new ligands that are easier and cheaper to prepare than phosphines.

The chiral bidentate phosphonites so far reported in the literature are composed of three building blocks: an achiral backbone (e.g., 1,1′-disubstituted ferrocene) and two P/O heterocycles derived from a chiral diol (e.g., Binol).[3] We considered that the use of a chiral backbone would have advantages over the systems mentioned above, by opening the possibility of using a large number of commercially available achiral diols or monodentate alcohols. In addition, the use of chiral diols may enhance the chiral discrimination

(1) (a) *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfalz, A., Yamamoto, H., Eds.; Springer: New York, 1999. (b) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; John Wiley & Sons: New York, 1993.

(2) (a) RajanBabu T. V.; Ayers, T. A.; Halliday, G. A.; You, K. K.; Calabrese, J. C. *J. Org. Chem.* **1997**, *62*, 6012. (b) Selke, R.; Ohff, M.; Riepe, A. *Tetrahedron* **1996**, *52*, 15079.

(3) (a) Reetz, M.; Gosberg, A.; Goddard, R.; Kyung, S. *Chem. Commun.* **1998**, 2077. (b) Reetz, M.; Gosberg, A. PCT Appl. WO 00/14096, 2000. (c) Pastor, S. D.; Shum, S. P. Ciba Speciality Chemical Corporation U.S. Patent 5,817,850, 1998.

(4) Reetz, M.; Neugebauer, T. *Angew. Chem., Int. Ed.* **1999**, *38*, 179.

(5) Van den Berg, M.; Minnaard, A. J.; Schudde, E. P.; van Esch, J.; de Vries, A. H. M.; de Vries, J. G.; Feringa, B. L. *J. Am. Chem. Soc.* **2000**, *122*, 11539.

(6) (a) Reetz, M.; Sell, T. *Tetrahedron Lett.* **2000**, *41*, 6333. (b) Claver, C.; Fernandez, E.; Gillon, A.; Heslop, K.; Hyett, D. J.; Martorell, A.; Orpen, G. A.; Pringle, P. G. *Chem. Commun.* **2000**, 961.

(7) Reetz, M.; Mehler, G. *Angew. Chem., Int. Ed.* **2000**, *39*, 3889.

10.1021/ol0166193 CCC: $20.00
Published on Web 10/23/2001

produced by the catalyst when a matching between the chirality of the backbone and the chirality of the P/O heterocycle exists.[8]

pseudo-ortho-Disubstituted paracyclophane has planar chirality. The chiral phosphine PhanePhos (4,12-bis(diphenylphosphino)-[2.2]-paracyclophane) (Figure 1) based on

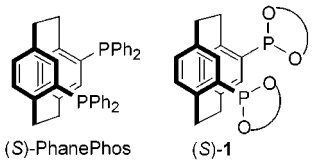
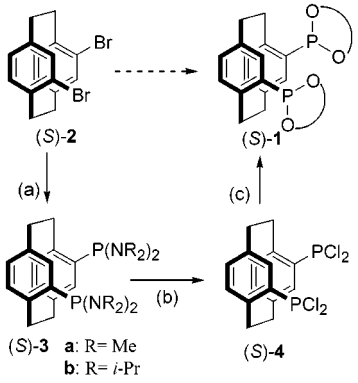


Figure 1.

this backbone has been very successfully used in rhodium-catalyzed hydrogenations of dehydroamino acids[9] and in ruthenium-catalyzed hydrogenation of ketones.[10] No attempt has so far been reported to expand the range of ligands based on this backbone by replacing two P−C bonds with two P−O bonds. The preparation of such ligands of general structure **1** (Figure 1), their metal complexes, and their application to asymmetric catalysis was a previously unexplored area.

Enantiomerically pure *pseudo-ortho*-dibromo-paracyclophane (**2**, 4,12-dibromo-paracyclophane)[11] was the starting material for the chemistry described herein. Although various procedures have been reported for the synthesis of phosphonites, we found that a stepwise procedure via intermediates **3** and **4** was easy to implement and flexible and eventually yielded clean products (Scheme 1).

Scheme 1. Synthesis of Phosphonites **1**



(a) (i) *t*-BuLi, Et_2O, −78°C; (ii) $ClP(NR_2)_2$, rt, 74−84% yield; (b) HCl in Et_2O, rt, 62−73% yield; (c) Li salts of the diol, THF, rt, 48−72% yield.

Metalation of the dibromo precursor **2** with *t*-BuLi, followed by reaction with an appropriate chloro diaminophosphine gave products **3a**−**b**.[12] These compounds were transformed into **4** by treatment with a solution of hydrogen chloride in diethyl ether. *pseudo-ortho*-Bis(dichlorophosphino)paracyclophane (**4**)[12] was found to be a convenient general intermediate. The reaction of **4** with the conjugate bases of a number of diols and phenols proceeded smoothly and provided the corresponding phosphonites in good yields. A range of phenols, as well as aromatic and aliphatic diols, was tested.[13] Biaryl diols emerged as the best complement to the chirality of the paracyclophane backbone.

Phosphonites **1a**−**c** derived from 2,2′-biphenol (**1a**), 2,2′-binaphthol (Binol) (**1b**), and 3,3′-di-*tert*-butyl-5,5′,6,6′-tetramethyl-biphenol (**1c**) were isolated and characterized by NMR spectroscopy (Figure 2).[12] All phosphonites **1a**−**c** were

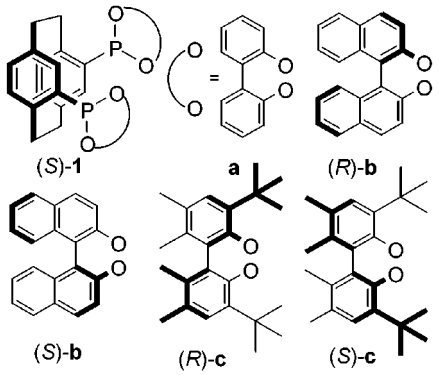


Figure 2.

relatively insoluble in MeOH and were isolated from the crude reaction by simply removing the reaction solvent and washing the product with MeOH (the salts generated in the reaction being soluble in MeOH). Configurationally flexible 2,2′-biphenol could give rise, in principle, to different diastereoisomers with the two P/O heterocycles having (*R*/*R*), (*S*/*S*), or (*R*/*S*) configuration. The ^{31}P NMR spectrum, however, indicated that in effect compound **1a** was isolated as a single diasteroisomer.

The rhodium complexes of general formula [(**1a**−**c**)-Rh-COD]BF_4 were prepared by reacting ligands **1a**−**c** with [$Rh(COD)_2$]BF_4 in dichloromethane at room temperature. When phosphonites **1c** bearing bulky P/O units were used, only the "matched" ligand (*S*)-**1**-(*R*)-**c** gave the desired rhodium complex. The "mismatched" ligand (*S*)-**1**-(*S*)-**c** did not react with [$Rh(COD)_2$]BF_4.

The catalysts derived from rhodium complexes [(**1a**−**c**)-Rh-COD]BF_4 were tested in the catalytic hydrogenation of

(8) A similar concept has recently been applied to the synthesis of phosphite ligands; see ref 4.

(9) Pye, P. J.; Rossen, K.; Reamer, R. A.; Tsou, N. N.; Volante, R. P.; Reider, P. J. *J. Am. Chem. Soc.* **1997**, *119*, 6207.

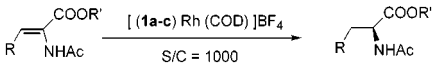
(10) Burk, M. J.; Hems, W.; Herzberg, D.; Malan, C.; Zanotti-Gerosa, A. *Org. Lett.* **2000**, *2*, 4173.

(11) Pye, P. J.; Rossen, K.; Volante, R. P. Merck & Co., PCT Appl. WO 97/47632, 1997. Pye, P. J.; Rossen, K.; Volante, R. P., Maliakal, A. *J. Org. Chem.* **1997**, *62*, 6462.

(12) See Supplementary Information

(13) The ligands derived from 2,6-dimethylphenol, 2-naphthol, both enantiomers of TADDOL and 1,2-diphenyl-ethane-diol, were prepared and tested in rhodium-catalysed hydrogenation of dehydroamino acids. The results were inferior to the ones obtained with ligands **1a,b**.

Table 1. Asymmetric Hydrogenation of *N*-Acetyl Dehydroamino Acids and Esters



entry[a]	[(**1a**−**c**)Rh(COD)]BF_4	R	R′	solvent	time (h)[b]	conv (%)[c]	ee (%)[c]
1	(*S*)-**1a**	H	Me	MeOH	0.5	>99	96 (*S*)
2	(*S*)-**1a**	H	Me	MeOH/H_2O 9/1	3	>99	96 (*S*)
3	(*S*)-**1a**	H	Me	CH_2Cl_2	1	>99	98 (*S*)
4	(*S*)-**1a**	H	Me	toluene	0.5	>99	99 (*S*)
5	(*S*)-**1**-(*R*)-**b**	H	Me	MeOH	0.5	>99	99 (*S*)
6	(*S*)-**1**-(*S*)-**b**	H	Me	MeOH	1	5	–
7	(*S*)-**1**-(*S*)-**b**	H	Me	MeOH	16	98	74 (*S*)
8	(*S*)-**1**-(*R*)-**c**	H	Me	MeOH	21	25	46 (*S*)
9	(*S*)-**1**-(*R*)-**b**	H	H	MeOH	0.5	>99	97 (*S*)
10	(*S*)-**1a**	Ph	Me	MeOH	0.5	>99	95 (*S*)
11	(*S*)-**1**-(*R*)-**b**	Ph	Me	MeOH	0.5	98	97 (*S*)
12	(*S*)-**1**-(*R*)-**b**	Ph	Me	toluene	2	>99	99 (*S*)
13	(*S*)-**1a**	Ph	H	MeOH	0.5	>99	93 (*S*)
14	(*S*)-**1**-(*R*)-**b**	Ph	H	MeOH	0.5	>99	99 (*S*)

[a] Reactions were carried out at room temperature under an initial hydrogen pressure of 3.5 bar; see Supplementary Information. [b] Time after which no further hydrogen consumption was detected. [c] Conversion and enantiomeric excess were obtained by GC analysis, as detailed in the Supplementary Information.

a range of *N*-acetyl deyhdroamino acids and esters (Table 1). Under mild conditions (room temperature, 3.5 bar H_2) and at a molar substrate to catalyst ratio (S/C) of 1000, some catalysts displayed high activity and selectivity.

First, the catalyst bearing ligand (*S*)-**1a** was tested in the hydrogenation of methyl 2-acetamidoacrylate in different solvents. Contrary to what was expected on the basis of literature data[14] the hydrogenation worked well in protic solvents such as MeOH and MeOH/H_2O (entries 1 and 2), although the use of aprotic solvents produced a small increase in selectivity (entries 3 and 4).

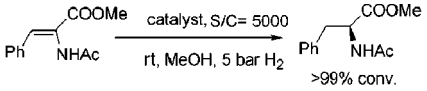
Ligands **1b** derived from enantiomerically pure Binol displayed a very strong matching/mismatching effect in the rhodium-catalyzed hydrogenations studied. It was found that the binaphthoxy substituents with *R* stereochemistry matched positively with the paracyclophane backbone having *S* stereochemistry (ligand (*S*)-**1**-(*R*)-**b**) (entry 5). The "mismatched" ligand (*S*)-**1**-(*S*)-**b** gave a catalyst considerably less active and selective (entries 6 and 7). Interestingly, both catalysts produced the *S* enantiomer of *N*-acetyl alanine methyl ester, indicating that the stereochemistry of the product is mainly dictated by the chirality of the paracyclophane backbone.[15]

Moving to ligand (*S*)-**1**-(*R*)-**c**, it was found that increasing the steric bulk of the biaryloxy moiety had a detrimental effect on both activity and selectivity (entry 8).

It is worth noting that the catalyst with ligand (*S*)-**1a**, derived from the configurationally flexible 2,2′-biphenol, gave only slightly lower selectivity than the ligand (*S*)-**1**-(*R*)-**b,** derived from the "matched" (*R*)-Binol (entries 1 and 5, 10 and 11, 13 and 14). The chiral paracyclophane backbone therefore seems to be capable of effectively controlling the configuration of the flexible P/O units. We can speculate that a "matched" *R* configuration is induced in the P/O heterocycle by the *S* paracyclophane backbone. This would be consistent with the fact that when the two enantiomers of Binol were used, only the combination of (*R*)-Binol and (*S*)-*pseudo-ortho*-paracyclophane led to a highly active and selective rhodium catalyst. Attempts to grow crystals suitable for X-ray analysis are currently on going.

Achieving high productivity should be considered as being as important as achieving high selectivity in the development of new hydrogenation catalysts. A promising level of activity was displayed by the rhodium catalyst bearing ligands (*S*)-**1a** and (*S*)-**1**-(*R*)-**b** in the hydrogenation of methyl 2-acetamido cinnamate (Table 2): at S/C = 5000 the starting material was fully converted to the product with practically the same selectivity achieved at lower substrate to catalyst ratio.

Table 2. Asymmetric Hydrogenation of Acetamidocinnamate



catalyst	time (h)	ee (%)
[{(*S*)-**1a**} Rh (COD)] BF_4	2	95 (*S*)
[{(*S*)-**1**-(*R*)-**b**} Rh (COD)] BF_4	6	98.5 (*S*)

In conclusion, the synthesis of the common reactive intermediate *pseudo-ortho*-bis(dichlorophosphino)paracy-

(14) Reetz, M. T.; Gosberg, A. *Tetrahedron: Asymmetry* **1999**, 2129.
(15) See ref 4 for bidentate phosphites having a chiral backbone and their use in rhodium-catalyzed hydrogenation of dimethyl itaconate. The stereochemistry of the product is determined by the stereochemistry of the P/O unit.

clophane (**4**) and the ready availability of the bisaryloxy building blocks has allowed the generation of a new class of phosphonites based on the paracyclophane backbone. Two ligands bearing the biphenoxy unit and the chiral binaphthoxy unit were identified as useful ligands for asymmetric hydrogenation. Their potential is demonstrated by the high level of activity and stereoselectivity obtained in the rhodium-catalyzed hydrogenation of dehydroamino acids and esters. These results match and complement the results so far reported for the known rhodium-phosphonite systems.

The scope of the asymmetric hydrogenation with catalysts based on ligands **1a**,**b** on a wider range of substrates is currently under study. The results will be reported in due course.

Acknowledgment. The authors thank Ms. Natasha Cheesman and Ms. Catherine Rippe of the *Chiro*Tech analytical team for their skilled support and Dr. Julian Henschke, Dr. Chris Cobley, Dr. Ian Lennon, Dr. Guy Casy, and Dr. Ray McCague for useful discussions.

Supporting Information Available: NMR spectral data, experimental procedures for the synthesis of ligands **1a**−**c** and their rhodium complexes, hydrogenation experiments, and GC analytical data. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0166193