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Synthesis of the first water-soluble chiral tetrahydroxy diphosphine Rh(I) catalyst for enantioselective hydrogenation

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Abstract

The synthesis of the first chiral polyhydroxy diphosphine-Rh(I) catalyst for asymmetric hydrogenation is described. Based on a simple synthetic pathway starting from D-mannitol the new metal complex is constructed. A special feature of the approach is the protection of the air-sensitive phosphine groups by the catalytically active metal in the final synthetic steps. Therefore, tedious *P*-protection–deprotection procedures could be advantageously avoided. The new water-soluble catalyst hydrogenates functionalized olefins by up to 99.6% ee in water as solvent.

Keywords: asymmetric synthesis; hydrogenation; phosphines; rhodium; rhodium compounds.

Chiral phosphines play a pivotal role as ligands of late transition metals in homogeneous asymmetric catalysis e.g. hydrogenation, alkylation or hydroformylation.[1] Especially interesting are phosphines bearing additional functional groups able to act as so-called hemilabile ligands.[2] From this point of view hydroxy groups attract particular attention.[3] Besides their property to interact temporarily with the metal center (hemilabile behavior) they can establish secondary interactions with suitable groups of the substrate by formation of hydrogen bonds.[4] Such cooperative effects can dramatically change the catalytic performance of the metal complex.[5] Another important aspect concerns the hydrophilicity of the phosphine metal catalysts, the more hydroxy groups incorporated the better their solubility is in water.[6] Moreover, hydroxy groups in the phosphine ligand can be utilized for the smooth incorporation of sulfonate groups similarly helpful for catalytic reactions in this ubiquitous and non-toxic solvent.[7]

Several strategies have been investigated for the construction of chiral hydroxy phosphines.[3] Due to the close retrosynthetic relationship between phosphine and hydroxy functionality they are frequently synthesized starting from chiral polyalcohols by selective conversion of hydroxy into phosphine groups.[8] This approach necessitates an appropriate protective group strategy and requires often the intermediate protection of hydroxy groups as well as the protection of phosphine groups. For the latter the protection

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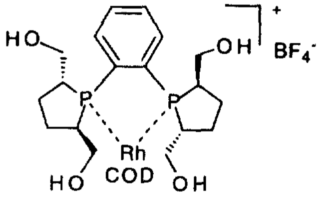
as phosphine–BH_3 adduct, phosphine oxide or phosphine sulfide has been shown to be highly versatile.[9] However, the final liberation of the phosphine as an additional step has to be taken always into consideration.

Herein, we demonstrate that the protection of phosphine groups by a catalytically active metal represents an efficient alternative. In contrast to other *P*-protection procedures two steps are saved. We will exemplify our new strategy by means of the synthesis of 1,2-bis(2′,5′-dihydroxymethylphospholanyl)benzene–Rh(I) cyclooctadiene tetrafluoroborate **1**. To the best of our knowledge this complex is the first chiral diphosphine metal complex which bears more than two hydroxy groups.[10]



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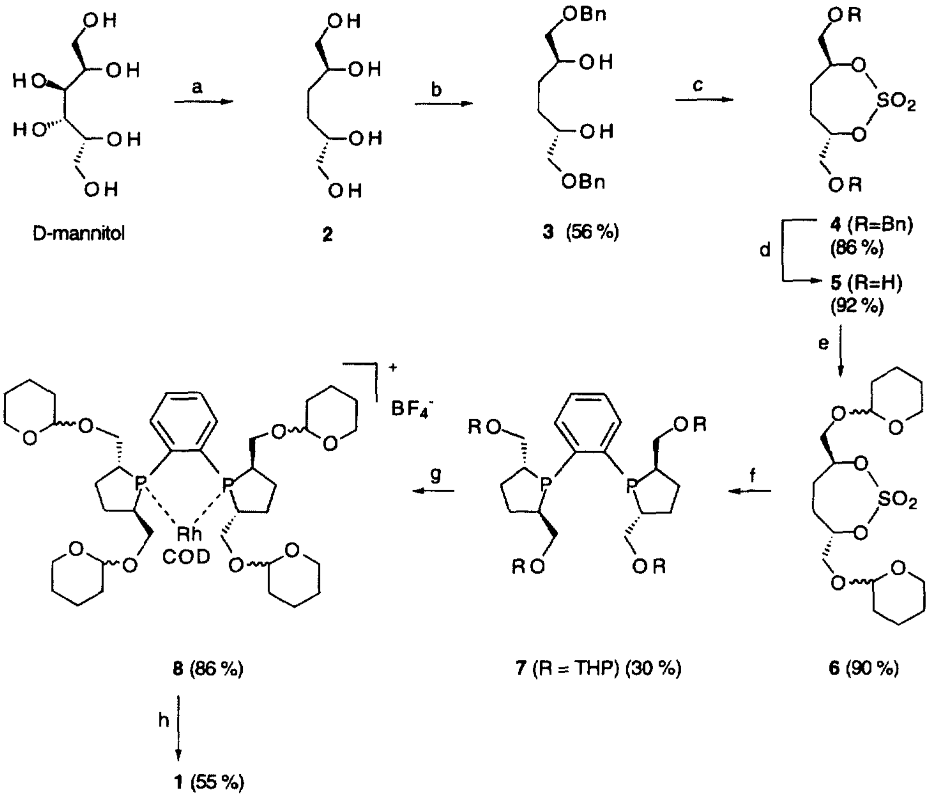
The new phosphine ligand named BASPHOS[11] represents a water-soluble analogue of DuPHOS [chiral 1,2-bis(2′,5′-dimethylphospholanyl)-benzene].[12] Catalysts based on this and related bis-phospholanes are known to exhibit excellent enantioselectivity in the asymmetric hydrogenation of olefins, ketones and imines in organic solvents over a broad front.[12,13]

In contrast to the synthesis of chiral non-functionalized phospholanes usually starting from achiral material we commence our synthetic pathway from the chiral pool which provides a large number of suitable chiral polyhydroxy compounds.

By application of simple protective group chemistry the new precatalyst **1** can be prepared. The starting point of our synthesis is commercially available and cheap D-mannitol, which has been converted into 3,4-dideoxy-D-threo-hexitol **2** by known and efficient procedures (Scheme 1).[14]

Selective benzylation of the primary hydroxy groups in compound **2** afforded 1,6-di-*O*-benzyl ether **3**.[15] Esterification of the hydroxy groups with thionyl chloride and in situ oxidation of the intermediate sulfite with catalytic amounts of RuO_4 gave the cyclic sulfate **4**. Removal of the benzyl groups by hydrogenolysis employing palladium on charcoal afforded alcohol **5**. The subsequent protection of the hydroxy groups with an acid labile protective group was performed with 3,4-dihydro-2*H*-pyran in the presence of *p*-toluene sulfonic acid (PPTS). Due to the non-stereoselective formation of two chiral acetal centers a mixture of four diastereomeric THP-acetals **6** were yielded in different ratios. Without separation, this material was reacted with 1,2-diphosphinobenzene in the presence of *n*-BuLi to give the diastereomic bis-phospholanes **7**. Cleavage of the acetal groups at this stage may afford the tetrahydroxy-bisphospholane. However, due to the high polarity of this phosphine isolation was difficult and afforded only poor yield. Therefore, a complexation reaction of the mixture of ligands to rhodium(I) was revealed to be more advantageous. After treatment with $[Rh(COD)_2]BF_4$ the corresponding diastereomeric complexes **8** were obtained. Without separation this mixture was treated with aqueous HBF_4 in methanol at room temperature overnight to give the desired Rh(I) tetrahydroxy–diphosphine complex **1**. Under these smooth conditions complete cleavage of all acetal groups occurred. The $^{31}P\{^1H\}$ NMR spectrum of the product is characterized by a single doublet at δ 62.0. The $^1J_{Rh-P}$ coupling constant of 148.8 Hz gives evidence for the formation of the expected five-membered *cis*-chelate in the complex.

The Rh(I) complex **1** was tested in the hydrogenation of the water-soluble 2-acetamido acrylic acid and its methylester, respectively, in water as solvent. It is remarkable that in contrast to the large majority of known chiral phosphine metal complexes featuring diminished reactivity and poor



Scheme 1. Key: (a) lit.[14]; (b) BnBr, NaH, THF, lit.[15]; (c) 1. $SOCl_2$, 2. $RuCl_3$, $NaIO_4$, CH_3CN, H_2O, CCl_4; (d) H_2, Pd/C, MeOH, rt; (e) 3,4-dihydro-2*H*-pyran, PPTS, CH_2Cl_2 rt; (f) BuLi, 1,2-diphosphinobenzene, THF; (g) $[Rh(COD)_2]BF_4$, THF, rt; (h) aq. HBF_4, MeOH, rt

enantioselectivity in the asymmetric hydrogenation in this unique solvent the catalytic performance of the cationic Rh(BASPHOS) catalyst is excellent.[16] Thus, both substrates were rapidly reduced to give the corresponding alanine derivatives. In the hydrogenation of the acid 99.6% ee of the (*S*)-product was obtained. The reaction of the methyl ester afforded (*S*)-methyl *N*-acetylalaninate in 93.6% ee. Our preliminary results clearly show that the 2,5-disubstituted bisphospholane motif is also highly efficient for asymmetric reactions in water under conditions that sufficient hydrophilicity of the catalyst is provided by incorporation of hydrophilic functional groups. Work is progress to also investigate other applications of this polar metal catalyst.

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References

1. (a) Koenig, K. E. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: Orlando, 1985; Vol. 5, Chapter 3, p. 71. (b) Takaya, H.; Ohta, T.; Noyori, R. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH: Weinheim, 1993; Chapter 1,

p. 1. (c) Seyden-Penne, J. *Chiral Auxiliaries and Ligands in Asymmetric Synthesis*; John Wiley & Sons: New York, 1995; Chapter 7, p. 367.

2. (a) Jeffrey, J. C.; Rauchfuss, T. B. *Inorg. Chem.* **1979**, *18*, 2658. (b) Bader, A.; Lindner, E. *Coord. Chem. Rev.* **1991**, *108*, 27. (c) Lindner, E.; Pautz, S.; Haustein, M. *Coord. Chem. Rev.* **1996**, *155*, 145.
3. For a review see: Holz, J.; Quirmbach, M.; Börner, A. *Synthesis* **1997**, 983.
4. Sawamura, M.; Ito, Y. *Chem. Rev.* **1992**, *92*, 857.
5. (a) Börner, A.; Kless, A.; Kempe, R.; Heller, D.; Holz, J.; Baumann, W. *Chem. Ber.* **1995**, *128*, 767. (b) Borns, S.; Kadyrov, R.; Heller, D.; Baumann, W.; Spannenberg, A.; Kempe, R.; Holz, J.; Börner, A. *Eur. J. Inorg. Chem.* **1998**, 1291. (c) Carmichael, D.; Doucet, H.; Brown, J. M. *Chem. Commun.* **1999**, 261. (d) Borns, S.; Kadyrov, R.; Heller, D.; Baumann, W.; Holz, J.; Börner, A. *Tetrahedron: Asymmetry* **1999**, *10*, 1425.
6. (a) Herrmann, W. A.; Kohlpaintner, C. W. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1524. (b) Beller, M.; Krauter, J. G. E.; Zapf, A. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 772. (c) Fukuoka, A.; Kosugi, W.; Morishita, F.; Hirano, M.; McCaffrey, L.; Henderson, W.; Komiya, S. *Chem. Commun.* **1999**, 489.
7. (a) Trinkhaus, S.; Holz, J.; Selke, R.; Börner, A. *Tetrahedron Lett.* **1997**, *38*, 807. (b) Trinkhaus, S.; Kadyrov, R.; Holz, J.; Selke, R.; Götze, L.; Börner, A. *J. Mol. Catal. A.: Chemical* **1999**, *144*, 15.
8. See for example: (a) Börner, A.; Holz, J.; Ward, J.; Kagan, H. B. *J. Org. Chem.* **1993**, *58*, 6814. (b) Börner, A.; Ward, J.; Ruth, W.; Holz, J.; Kless, A.; Heller, D.; Kagan, H. B. *Tetrahedron* **1994**, *50*, 10419.
9. For reviews see: (a) Ohff, M.; Holz, J.; Quirmbach, M.; Börner, A. *Synthesis* **1998**, 1391. (b) Brunel, J. M.; Faure, B.; Maffei, M. *Coord. Chem. Rev.* **1998**, *178–180*, 665.
10. Achiral polyhydroxy phosphines have been synthesized preferentially by a P-C-coupling reaction. Their metal complexes were investigated for biomedical application: (a) Katti, K. V.; Gali, H.; Smith, C. J.; Berning, D. E. *Acc. Chem. Res.* **1999**, *32*, 9. (b) Smith, C. J.; Reddy, V. S.; Katti, K. V. *Chem. Commun.* **1996**, 2557.
11. The name is derived from BASF AG.
12. (a) Burk, M. J.; Gross, M. F.; Harper, T. G. P.; Kalberg, C. S.; Lee, J. R.; Martinez, J. P. *Pure & Appl. Chem.* **1996**, *68*, 37 and references cited therein. (b) Burk, M. J.; Bienewald, F.; Challenger, S.; Derrick, A.; Ramsden, J. A. *J. Org. Chem.* **1999**, *64*, 3290.
13. RoPHOS ligands: Holz, J.; Quirmbach, M.; Schmidt, U.; Heller, D.; Stürmer, R.; Börner, A. *J. Org. Chem.* **1998**, *63*, 8031. PennPHOS ligands: Jiang, Q.; Xiao, D.; Zhang, Z.; Cao, P.; Zhang, X. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 516 and references cited therein. CnrPHOS ligand: Marinetti, A.; Genêt, J.-P.; Jus, S.; Blanc, D.; Ratovelomanana-Vidal, V. *Chem. Eur. J.* **1999**, *5*, 1160.
14. (a) Corey, E. J.; Hopkins, P. B. *Tetrahedron Lett.* **1982**, *23*, 1979. (b) Marzi, M.; Misiti, D. *Tetrahedron Lett.* **1989**, *30*, 6075. (c) Haines, A. *Carbohydrate Res.* **1965**, *1*, 214. (d) Machinaga, N.; Kibayashi, C. *J. Org. Chem.* **1992**, *57*, 5178.
15. Marzi, M.; Minetti, P.; Misiti, D. *Tetrahedron* **1992**, *48*, 10127.
16. In some cases improvement of the efficiency of non-polar phosphine catalysts in water has been achieved by the reaction in micelles (Selke, R.; Holz, J.; Riepe, A.; Börner, A. *Chem. Eur. J.* **1998**, *5*, 769 and references cited therein). However, this approach necessitates the removal of the additives after the reaction.