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Synthesis of an Optically Active Hydroxy Diphosphine, A New Ligand for Asymmetric Catalysis

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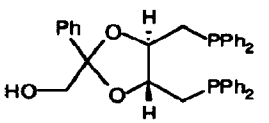
Abstract. The synthesis of (4R,5R)-4,5-bis(diphenylphosphinomethyl)-2-hydroxymethyl-2-phenyl-1,3-dioxolane **1** which is related to DIOP is described. The application of this new ligand in asymmetric catalysis is illustrated in the stereodifferentiating hydrogenation.

Optically active diphosphines such as DIOP[1] or norphos[2] are useful ligands for asymmetric catalysis.[3] We previously showed that a ligand derived from norphos bearing a hydroxyl group was superior compared to the original diphosphine in the rhodium catalyzed hydrogenation of dehydroamino acids.[4] This result prompted us to synthesize other chiral hydroxy phosphines in order to elucidate the influence of the hydroxyl group in the course of the catalytic reduction.[5] Moreover it seems to us that this class of compounds is particularly attractive for the construction of bifunctional catalysts.[6,7] Other groups showed that chiral hydroxy phosphines and the related hydroxy phosphine oxides serve as precursors for the synthesis of ligands which can be successfully applied in asymmetric catalyzed hydroformylation[8], hydrogenation[9] and allylic alkylation[10].

We report here our preliminary results in the synthesis and catalytic application of the hydroxy diphosphine **1**. For the purpose of comparison we synthesized the hitherto unknown analogue of DIOP **2** by a similar procedure.



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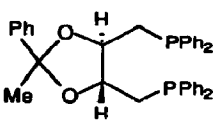

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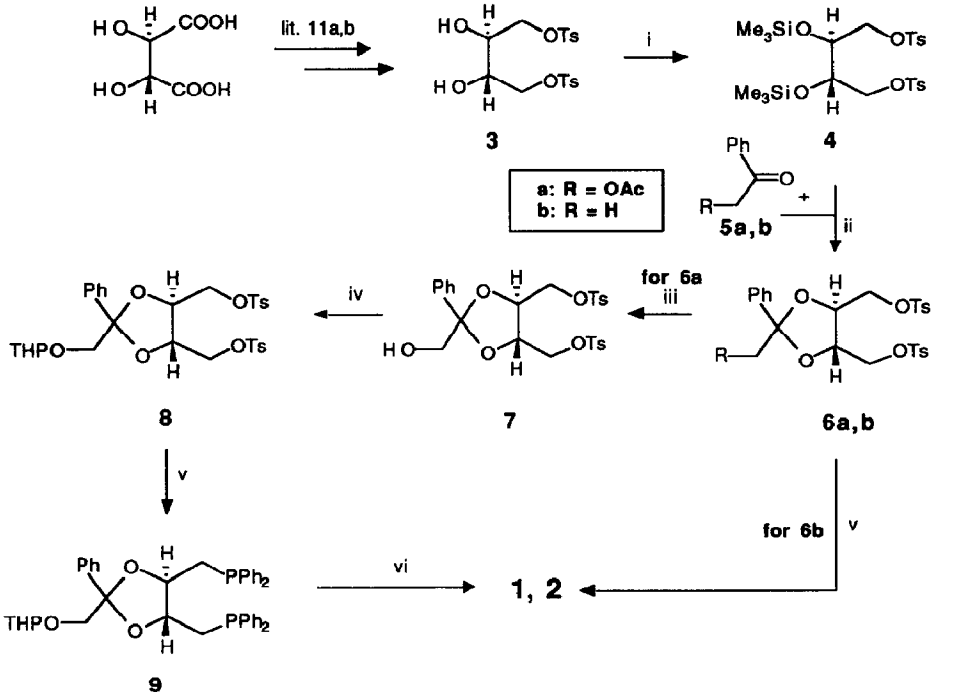
In the first step of our synthesis (R,R)-tartaric acid was converted into the ditosylate **3** by established methods.[11] Silylation of the free hydroxyl groups with hexamethyldisilazane (HMDS) in the presence of catalytic amounts of trimethylsilyl chloride (TMSCl) gave rise to the alkoxysilane **4**. Acetalization of this compound with acetic acid-2-oxo-2-phenyl-ethylester **5a** or acetophenone **5b**, respectively, using trimethylsilyl trifluoromethanesulfonate (TMSOTf) as catalyst following the procedure of Noyori[12] furnished the dioxolane derivatives **6a,b** in 70 % yield. Now, **6b** could be directly converted into the diphosphine **2** by treatment with lithium diphenylphosphide in THF.



Reagents and conditions: i, HMDS, TMSCl, CH_2Cl_2, 12 h, r.t., 65%; ii, cat.TMSOTf, $HClO_4$, $CHCl_3$, 8 h, r.t. 70%; iii, NaOMe, MeOH, 12 h, r.t., 80 %; iv, 3,4-Dihydro-2H-pyran, PPTS, CH_2Cl_2, 4 h, r.t., 98%; v, $LiPPh_2$, THF, 4 h, 0 °C, for 9: 70%, for 2: 73%; vi, CF_3COOH, MeOH, H_2O, 3 h, reflux, 80%.

For the preparation of the hydroxy phosphine **1** starting from **6a** it was necessary to change the O-protective group. Thus cleavage of the ester group in compound **6a** with sodium methanolate afforded the alcohol **7**. Under the mild conditions applied, no cyclization product, which may arise from the alkylation of the alcohol by one of the tosyl groups, could be detected. Protection of the

alcohol as tetrahydropyranyl ether in order to avoid the cyclization during the subsequent substitution step with basic phosphide gave the O-THP-protected alcohol **8** in almost quantitative yield. Displacement of the tosyl groups with lithium diphenylphosphide in THF furnished the diphosphine **9**. Deprotection of the hydroxyl group with catalytic trifluoroacetic acid, as proposed recently by us,[5] gave the desired hydroxy phosphine **1**[13] in 80 % yield.

To check the catalytic properties of the new ligands their cationic rhodium complexes were prepared by reaction of the corresponding phosphine with [Rh(COD)acac] in THF and subsequent addition of HBF_4. The isolated analytically pure complexes were proved in the standard hydrogenation of N-acetyl dehydrophenylalanine (AH) and its methyl ester (AMe), respectively. It was satisfying to see that the complex derived from the hydroxy phosphine **1** gave higher enantiomeric excess in the reduction of AMe to (R)-N-acetyl phenylalanine than the corresponding complex which derived from **2** or DIOP, respectively (**1**: 73.6 ee%, **2**: 68.7 ee%, **DIOP**: 67.0 ee%). Moreover, it seemed to us that the **1**-catalyst which bears a hydroxyl group is more active than the complex which derived from **2** as well as that derived from DIOP. However, under the conditions applied (catalyst/substrate = 1/100, 1 atm total pressure above the reaction mixture) all catalysts tried were too fast to allow a reliable assessment of their activity.[14] Surprisingly, a significant decrease of the enantiomeric excess in comparison to DIOP was found when **1** and **2** were applied to the hydrogenation of AH (**1**: 59.3 ee%, **2**: 61.2 ee%, **DIOP**: 80.0 ee%). This result is in sharp contrast to the high enantiomeric excess that we obtained with hydroxy norphos in the reduction of AH. Therefore further work is required to clarify the role of a hydroxyl group in the ligand throughout the course of the asymmetric reduction.

Besides these investigations we are now in progress to modify the backbone of the presented hydroxy phosphine for applications to various types of asymmetric reactions.

Acknowledgments

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13 Analytical data of **1**: mp. 38-42°C, $[\alpha]_D^{23}$ = -30 (c 1, $CHCl_3$); ^{13}P-NMR ($CDCl_3$) δ -22.7 (s); ^{1}H-NMR ($CDCl_3$) δ 7.50-7.15 (25H, aromat), 4.12 (1H, m); 3.86 (1H, m), 3.46 (2H, s); 2.49 (1H, dd, J=14.0Hz, 5.2Hz); 2.39 (1H, dd, J=14.0Hz, 6.7Hz); 2.24 (1H, dd, J=13.7Hz, 7.3Hz), 2.08 (1H, dd, J=13.7, 5.9Hz); 1.90 (1H, b, exchangeable with D_2O); ^{13}C-NMR ($CDCl_3$) δ 140.8 - 125.9 (aromat), 109.5 (C), 80.7 (CH, dd, J=17.2Hz, 8.6Hz), 80.3 (CH, dd, J=14.0Hz, 6.7Hz), 67.8 (CH_2), 32.6 (CH_2, d, J=16.1Hz), 31.8 (CH_2, d, J=15.3Hz); IR (KBr, cm^{-1}) 3433 (s).

14 Therefore reductions under reduced H_2 pressure are envisaged to get a better insight into the role of the hydroxyl group during the catalysis.

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