8.03 (d, $J = 2.0$ Hz, 4H, Ar-2,6-H), 8.17 (t, $J = 1.8$ Hz, 2H, Ar-4-H), 8.37 (d, $J = 1.5$ Hz, 2H, Ar-4-H), 8.62 (d, $J = 4.5$ Hz, 1H, β-H), 8.81 (d, $J = 5.0$ Hz, 2H, β-H), 8.82 (d, $J = 4.5$ Hz, 1H, β-H), 8.96 (d, $J = 5.0$ Hz, 2H, β-H), 9.08 (d, $J = 5.0$ Hz, 3H, β-H), 9.25 (d, $J = 5.0$ Hz, 1H, β-H), 9.33 (d, $J = 4.5$ Hz, 2H, β-H), 9.34 (d, $J = 4.5$ Hz, 1H, β-H), 9.40 (d, $J = 5.0$ Hz, 1H, β-H), 9.78 (s, 1H, *meso*-H), 9.88 (s, 1H, *meso*-H), 10.31 (s, 1H, *meso*-H), 10.35 (s, 1H, *meso*-H); FAB MS: *m/z*: 1581.1 (calcd for $C_{96}H_{102}N_8Pd_2$: 1580.6); UV/Vis ($CHCl_3$): $\lambda_{max} = 414.0$, 522.2, 549.2, 681.2 nm.

11: ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = -2.69$ (s, 1H, N-H), -2.53 (s, 1H, N-H), -2.50 (s, 2H, N-H), 1.49 (s, 18H, *t*Bu-H), 1.50 (s, 18H, *t*Bu-H), 1.506 (s, 18H, *t*Bu-H), 1.512 (s, 18H, *t*Bu-H), 7.76 (m, 4H, Ar-2,6-H), 8.07 (d, $J =$ 2.0 Hz, 2H, Ar-2,6-H), 8.09 (t, $J = 1.5$ Hz, 2H, Ar-2,6-H), 8.19 (t, $J = 1.5$ Hz, 2H, Ar-4-H), 8.44 (d, $J = 2.0$ Hz, 2H, Ar-4-H), 8.66 (d, $J = 4.5$ Hz, 1H, β-H), 8.84 (d, $J = 4.5$ Hz, 2H, β-H), 8.88 (d, $J = 4.5$ Hz, 1H, β-H), 8.98 (d, $J =$ 5.0 Hz, 2H, β-H), 9.11 (d, $J = 4.5$ Hz, 1H, β-H), 9.13 (d, $J = 4.5$ Hz, 2H, β-H), 9.36 (d, $J = 4.5$ Hz, 1H, β-H), 9.41 (d, $J = 4.5$ Hz, 1H, β-H), 9.42 (d, $J =$ 4.5 Hz, 2H, β-H), 9.55 (d, $J = 4.5$ Hz, 1H, β-H), 9.81 (s, 1H, *meso*-H), 9.96 (s, 1H, *meso*-H), 10.33 (s, 1H, *meso*-H), 10.40 (s, 1H, *meso*-H); HR FAB MS: m/*z*: 1371.8608 (calcd for $C_{96}H_{107}N_8$: 1371.8619); UV/Vis ($CHCl_3$): $\lambda_{max} = 414.8$, 431.6, 514.4, 545.6, 583.6 nm.

13: ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = -2.31$ (s, 4H, N-H), 1.46 (s, 72H, *t*Bu-H), 7.72 (t, $J = 1.8$ Hz, 4H, Ar-4-H), 8.08 (d, $J = 5.0$ Hz, 4H, β-H), 8.10 (d, $J = 1.8$ Hz, 8H, Ar-2,6-H), 8.66 (d, $J = 5.0$ Hz, 4H, β-H), 9.10 (d, $J = 5.0$ Hz, 4H, β-H), 9.42 (d, $J = 5.0$ Hz, 4H, β-H), 10.34 (s, 2H, *meso*-H); HR FAB MS: *m/z*: 1370.8542 (calcd for $C_{96}H_{106}N_8$: 1370.8540); UV/Vis ($CHCl_3$): $\lambda_{max} = 412.6$, 446.6, 520.0, 589.8, 647.0 nm.

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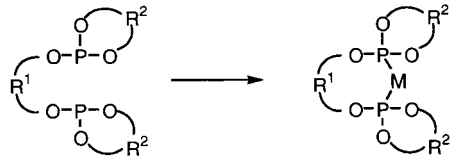
New Diphosphite Ligands for Catalytic Asymmetric Hydrogenation: The Crucial Role of Conformationally Enantiomeric Diols

Manfred T. Reetz* and Torsten Neugebauer

Dedicated to Reinhard W. Hoffman on the occasion of his 65th birthday

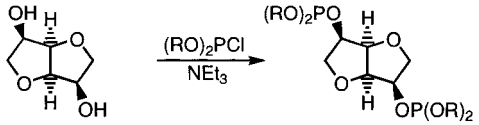
Many chiral diphosphanes[1] and diphosphinites[2] have been synthesized as ligands for enantioselective transition metal catalyzed hydrogenations. On the other hand, little is known about chelating, chiral diphosphites as ligands in asymmetric hydrogenations,[3] although such ligands are increasingly being used in other transition metal catalyzed reactions such as hydrocyanations, hydroformylations, and hydrosilylations.[4] The availability of many enantiomerically pure diols allows the production of electron-deficient, bidentate phosphite ligands. Topologically different possibilities arise, for example the use of chiral or achiral diols HO–R^1–OH and HO–R^2–OH as the backbone or as a component of two P/O heterocycles, as is schematically represented in **1** and **2**. If the backbone is chiral, defined



1 **2**

local chirality in the P/O heterocycle of the transition metal catalyst **2** may be possible even when seemingly achiral diols such as *meso*-1,2-cyclohexanediol[5] or diphenol serve as the second component. In such cases the catalyst exists in the form of three rapidly interconverting conformational diastereomers, one of which could kinetically control the reaction. It is therefore possible that the conformationally enantiomeric diols in the P/O heterocycle play a crucial role in determining the direction as well as the extent of enantioselectivity in hydrogenation reactions.[6] Herein we describe the first examples of such a phenomenon.

As the chiral diol for the backbone we chose the easily accessible and commercially available C_2-symmetric 1,4:3,6-dianhydro-D-mannite (**3**),[7] which exhibits a vaultlike geom-



3 **4**

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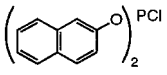
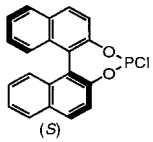
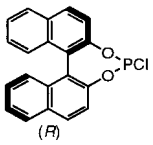
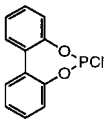
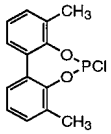
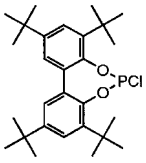
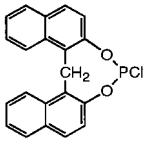
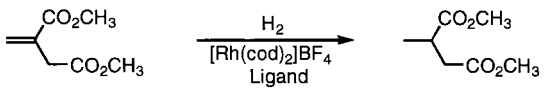
Table 1. Synthesis of the chelating ligands **4**.

$(RO)_2PCl$	Chelating ligand	Yield [%]
	**4a**	62
	**4b**	87
	**4c**	96
	**4d**	99
	**4e**	89
	**4f**	99
	**4g**	86

etry with two hydroxyl groups on the concave side. Reactions with chlorophosphoric acid diaryl ester (2 equiv each) provide access to many different ligands of type **4** (Table 1).

The Rh-catalyzed hydrogenation of dimethyl itaconate (**5**) was examined as the model reaction (Table 2). When the ligand **4a** with two achiral β-naphthoxy residues at each phosphorus center is used, the reactions at room temperature provide (*S*)-**6** with an *ee* value of only 21%. Clearly, the transfer of the chiral information present in the backbone of the catalyst onto the product is inefficient. The catalysts derived from ligands **4b** and **4c** which contain (*S*)- and (*R*)-binaphthol, respectively, in the P/O heterocycle behave differently. The *ee* values of 88% and 95% attained for (*S*)- and (*R*)-**6**, respectively, prove that the chirality in the P/O heterocycles is decisive and that the *R*-selective combination **3**/(*R*)-binaphthol is the matched case.[8] This is no contradiction to the fact that the rhodium catalyst from **4a** is weakly



5 **6**

Table 2. Enantioselective hydrogenation of **5** and **8**.

Ligand[a]	Substrate	*T* [°C]	Conversion [%]	*ee* [%]	Config.
4a[b]	**5**	20	65	21.0	(*S*)-**6**
4b[c]	**5**	20	> 99	87.8	(*S*)-**6**
4c[c]	**5**	20	> 99	94.5	(*R*)-**6**
4c	**5**	− 10	> 99	96.2	(*R*)-**6**
4d[c]	**5**	20	74	38.9	(*S*)-**6**
4e	**5**	20	> 99	96.8	(*R*)-**6**
4e	**5**	− 10	> 99	98.2	(*R*)-**6**
4f[d]	**5**	20	24	5.2	(*R*)-**6**
4g	**5**	20	> 99	49.3	(*R*)-**6**
4a	**8**	20	66	43.8	(*S*)-**9**
4b	**8**	20	77	23.2	(*S*)-**9**
4c	**8**	20	> 99	88.8	(*R*)-**9**
4e	**8**	20	> 99	80.7	(*R*)-**9**

[a] General conditions: substrate:catalyst (s:c) = 1000:1; t = 20 h; ligand:rhodium = 1:1. [b] s:c = 500:1. [c] The catalysis was carried out with preformed catalyst. [d] s:c = 250:1.

S-selective (21% *ee*), since the spatial position of the naphthyl groups in **4a** with respect to the catalytically active center is probably not fixed.

In the case of ligands with atropoisomeric biphenol units in the P/O heterocycle, three defined diastereomeric metal complexes are possible (*R*/*R*, *S*/*S*, and *R*/*S* combinations in the biphenol moieties) which can rapidly interconvert due to the energetically low barrier[9] for rotation about the biaryl axis. In the case of the unsubstituted biphenol derivative **4d** an *ee* value of only 39% is reached in the production of (*S*)-**6**. In contrast, ligand **4e** with *ortho* methyl groups shows an entirely different behavior, leading almost exclusively to the *R* enantiomer (*ee* = 96 – 98%)! Evidently, one diastereomer of the three possible complexes determines the reaction. Under the assumption that the configurations of the binaphthol and the 2,2′-dihydroxy-3,3′-dimethyl-1,1′-biphenyl units in the respective catalysts induce the same direction of enantioselectivity, it can be concluded that the most active and therefore reaction-determining catalyst contains P/O heterocycles having the *R*/*R* configuration. Moreover, it was observed that hydrogenations with **4c** are significantly faster than those with **4b**, and that the most active catalyst is formed with **4e**.[10] Therefore, pronounced in situ selection between conformationally diastereomeric catalysts take place in reactions based on **4e**.[11] Interestingly, **4f** with sterically demanding *tert*-butyl groups leads to low activity as well as poor enantioselectivity.

Finally, **4g** was tested in the Rh-catalyzed hydrogenation. In this reaction (*R*)-**6** was obtained with an *ee* value of 50%. Thus, when going from **4d** to **4g**, reversal of the direction of enantioselectivity is effected while retaining the backbone diol **3**. In the case of **4g** several chiral conformers of the P/O heterocycle are possible which are in fast equilibrium. Force-field calculations of the P/O heterocycles with hydrogen bonded to the phosphorus centers as model compounds identified the enantiomeric structures **7a** and **7b** (Figure 1) to be equivalent energetic minima.[12] In the metal complex, they therefore lead to local chirality close to the catalytically active center, as in the case of the catalyst based on **4e**. Similar effects were also observed in the hydrogenation of methyl *N*-

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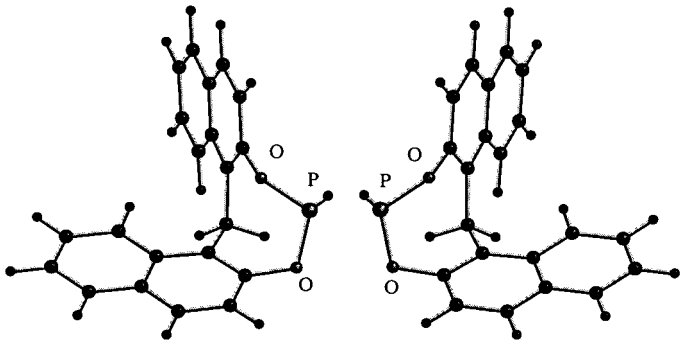
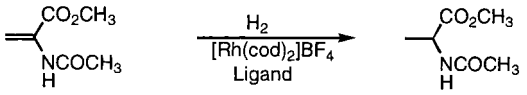


Figure 1. The enantiomers **7a** (left) and **7b** (right) generated from force-field calculations of the P/O-heterocycles with hydrogen at the phosphorus centers as model compounds.

acetamidoacrylate (**8**) with formation of the alanine derivative **9** (Table 1, cod = 1,5-cyclooctadiene).



8 **9**

In summary, we have described the first diphosphite ligands capable of inducing highly enantioselective hydrogenations. Significantly, the ligand **4e** with conformational flexibility in readily epimerizing diastereomeric P/O heterocycles proved superior to those with fixed chirality (binaphthol derivatives). This principle presents the opportunity to synthesize efficient ligands for asymmetric catalysis from chiral auxiliaries and suitable conformationally enantiomeric compounds. The advantage is that the chiral selectivity-determinging ligand need not (and cannot) be separated into antipodes. Research concerning other substrates and the use of the ligands in other metal-catalyzed reactions is the subject of further investigations.

Experimental Section

4e: Under an inert atmosphere, the chlorophosphoric acid diaryl ester (0.408 g, 1.46 mmol) from 2,2′-dihydroxy-3,3′-dimethyl-1,1′-biphenyl was dissolved in THF (120 mL) and treated with triethylamine (0.40 mL, 2.9 mmol). To this slightly cloudy solution, **3** (0.107 g, 0.732 mmol) in THF (15 mL) was slowly added with stirring. After 3 h of stirring at room temperature, half of the solvent was removed under reduced pressure, the precipitate was removed by filtration, and all solvent was removed from the clear filtrate in vacuo. The yellow solid was dried under high vacuum. Yield: 0.41 g (89 %). $\{^1H\}^{31}P$ NMR (81 MHz, $CDCl_3$): $\delta = 134.4$ (s).

Hydrogenations: In a Schlenk vessel, an aliquot (0.5 mL) of a 2×10^{-3} M solution of the ligand in CH_2Cl_2 is added to a 2×10^{-3} M solution of $[Rh(cod)_2]BF_4$ in CH_2Cl_2 (0.5 mL) under inert conditions. The mixture is stirred for 5 min at room temperature. Subsequently, dimethyl itaconate (1.0 mmol) in CH_2Cl_2 (9.0 mL) is added, and the vessel is briefly evacuated and vented with H_2 three times in order to remove dissolved argon. The mixture is then hydrogenated (0.3 bar H_2) for 20 h at 20 °C. To remove the catalyst, the solution is placed on a short silica gel column and eluted with CH_2Cl_2. Conversion and enantiomeric excess is determined by means of gas chromatography. The absolute configuration of the products was determined by comparison with a commercially available sample of dimethyl (*R*)-methylsuccinate.

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[6] A few examples of ligands with a chiral backbone and additional biphenol units which are not stereochemically fixed have recently been described for hydroformylations. However, the direction of asymmetric induction is determined exclusively by the chiral backbone.[4e,f] See also K. Nozaki, N. Sakai, T. Nanno, T. Higashijima, S. Mano, T. Horiuchi, H. Takaya, *J. Am. Chem. Soc.* **1997**, *119*, 4413 – 4423.

[7] a) P. Stoss, R. Hemmer, *Adv. Carbohydr. Chem. Biochem.* **1992**, *49*, 93 – 173; b) Bakos et al. synthesized the corresponding 2,5-bis(diphenylphosphino)idite from ditosylated 1,4:3,6-dianhydro-D-mannite by means of double nucleophilic substitution under inversion of configuration with lithium diphenylphosphide and used this nonchelating diphosphane in the asymmetric Rh-catalyzed hydrogenation (*ee* = 21 – 58 %): J. Bakos, B. Heil, L. Marko, *J. Organomet. Chem.* **1983**, *253*, 249 – 252.

[8] These results were obtained with preformed catalysts. If the hydrogenation is carried out with catalysts formed in situ, no differences in selectivity are observed. Both ligands lead to similarly high conversions and selectivities, the results for the *S*-selective ligand **4b** being subject to variation: **4b** (conversion 73 – 98 %; *ee* = 89 – 95 % (*S*)); **4c** (conversion > 99 %; *ee* = 93.5 % (*R*)). In contrast, the hydrogenation with **4e** leads to identical results with catalyst formed in situ and with preformed catalyst.

[9] S. D. Pastor, S. P. Shum, R. K. Rodebaugh, A. D. Debellis, F. H. Clarke, *Helv. Chim. Acta* **1993**, *76*, 900 – 914.

[10] Detailed kinetic studies are under way in cooperation with T. Rosner and D. Blackmond (Max-Planck-Institut für Kohlenforschung).

[11] Low-temperature ^{31}P NMR studies of **4e** showed that three diastereomers occur. At room temperature the spectrum contains one single ^{31}P NMR signal.

[12] The force-field calculations were carried out with the SYBYL program (Tripos Ass. Inc.). Other than the lowest energy pair of enantiomers **7a**/**7b**, no minimum was found for an achiral conformer. We thank Dr. K. Angermund for performing the calculations.

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