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[15] If the reduction of the aryl halides **1a** – **c** leading to the formation of **3** occurs via a radical pathway, the higher energy of the σ* orbital of the C–Cl bond as compared to that of a C–I or C–Br bond might explain the observed selectivities.

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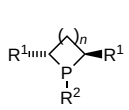
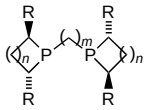
Mono- and Bidentate Phosphinanes—New Chiral Ligands and Their Application in Catalytic Asymmetric Hydrogenations**

Markus Ostermeier, Jan Prieß, and Günter Helmchen*

Dedicated to Professor Dieter Hoppe on the occasion of his 60th birthday

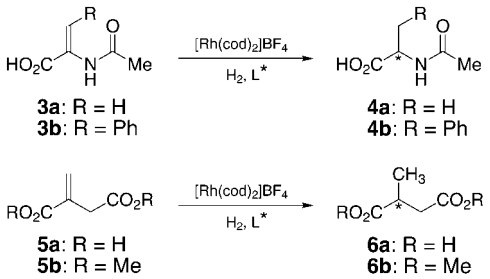
Chiral phosphanes possessing a modular make-up are important as ligands for asymmetric catalysis with transition metal complexes. The ethylene-bridged BPE ligands **2** and the 1,2-phenylene-bridged DuPHOS ligands,[1] introduced by Burk et al., and analogues[2] belong to the most effective ligands and were found to be particularly successful in enantioselective hydrogenations. Even with the monodentate phosphanes **1a** and **1b** enantiomeric excesses of up to 84 and 82 % *ee,* respectively, were achieved in the hydrogenation of





1a: n = 1; R^1 = CH_3, R^2 = Ph **2a**: m = n = 2; R = Me
1b: n = 2; R^1 = Ph, R^2 = Ph **2b**: m = n = 2; R = Et

acetamidocinnamic acid (**3a**) (Scheme 1); however, only 12 % *ee* were obtained with **1a** in the case of substrate **5b**.[3, 4] With the chelate ligands **2a** and **2b** hydrogenations of methyl 2-acetamidoacrylate furnished 91 and 98 % *ee*, respectively.[1b]



Scheme 1. Asymmetric catalytic hydrogenations. cod = cycloocta-1,5-diene, L* = chiral ligand.

Upon inspection of the literature it was observed that phosphetanes[5] (**1**, $n = 1$) and phospholanes[1–4] (**1**, $n = 2$) had been studied intensively and phosphiranes[6] marginally, surprisingly however, analogous phosphinanes (**1**, $n = 3$) were found to be unknown. Since there is a marked influence of ring size on the properties of ligands, we decided to fill this void in the arsenal of ligands. We now report the first ligands

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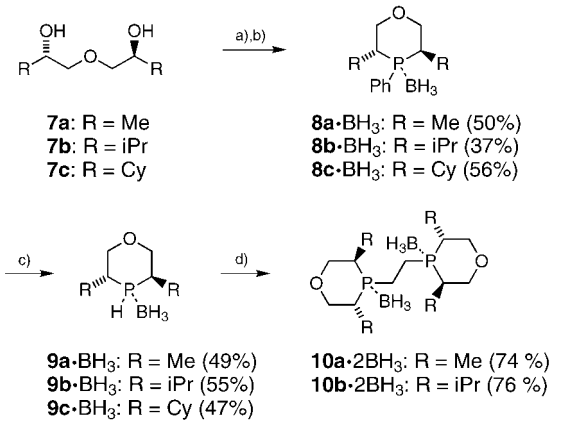
of this type and their use in asymmetric hydrogenation. In the course of these studies another void in the arsenal of ligands was discovered, namely the fact that so far only tertiary phosphanes were employed as P ligands in asymmetric hydrogenation. We were able to fill this void too and now report the first, to the best of our knowledge, asymmetric hydrogenations with secondary phosphanes.

To provide a system with a modular make-up, an additional heteroatom was incorporated into the phosphinane ring (Scheme 2). The syntheses started with the diol ethers **7**; these were obtained by known procedures involving deamination of amino acids to give hydroxy acids, reduction of these to diols, and subsequent Williamson synthesis.[7] Reaction of the mesylates of the diol ethers **7** with dilithiophenylphosphane[1a] furnished the oxaphosphinanes **8**; because of their sensitivity against oxygen, these were transformed with $BH_3\cdot$ THF to the storable protected phosphanes $\mathbf{8}\cdot BH_3$.[8]



Scheme 2. Synthesis of the ligands **8**–**10**. a) MsCl (2.5 equiv), NEt_3 (3.5 equiv), DMAP (0.25 equiv), CH_2Cl_2, 0 °C, 2 h; b) 1. H_2PPh (1 equiv), *n*BuLi (2.1 equiv), THF, −78 °C, 30 min, then mesylate, THF, −78 °C→RT, 16 h, 2. $BH_3\cdot$THF, −78 °C→20 °C, 12 h; c) 1. Li (4 equiv), THF, 20 °C, 6 h, 2. MeOH, 20 °C, 10 min; d) *n*BuLi (1.05 equiv), THF, −78 °C, 30 min, then $TsOCH_2CH_2OTs$ (0.475 equiv), −78 °C→20 °C, 48 h.

Rhodium-catalyzed asymmetric hydrogenations were initially carried out with acetamidocinnamic acid (**3b**) and itaconic acid (**5a**) as typical substrates (Scheme 1). The precatalysts were prepared by reaction of the oxaphosphinanes, obtained after removal of the protective BH_3 group, with $[Rh(cod)_2]BF_4$ in THF (molar ratio ligand:Rh = 2.2:1). Conditions used for the hydrogenations are given in Table 1.

In view of recent successes with monodentate ligands,[9] the oxaphosphinane **8b** was initially tested. This gave rise to slow reactions and enantiomeric excesses (Table 1, entries 1 and 2) were lower than those obtained with analogous monodentate phospholanes[4] and phosphetanes.[3] Seemingly, the steric bulk of the ligands prevented an arrangement in the catalyst complex favorable for hydrogenation. Therefore, the phenyl group at the phosphorus center was replaced by hydrogen. This was achieved by reaction of the borane adducts $\mathbf{8}\cdot BH_3$ with lithium (4 equiv) in THF to give borane adducts $\mathbf{9}\cdot BH_3$ (Scheme 2).[10] For the formation of the precatalyst, the borane adduct was heated with 1.2 equivalents of 1,4-diazabicyclo[2.2.2]octane (DABCO) in THF for 2 h at reflux and the resultant solution was added to a cooled (−78 °C) solution of $[Rh(cod)_2]BF_4$ in CH_2Cl_2. NMR spectroscopic analysis showed that, independent of the amount of ligand, only precatalyst complexes with two coordinated ligands were formed.[11]

Table 1. Enantioselective Rh-catalyzed hydrogenations.[a]

Entry	Ligand	Substrate	Solvent	Rh: Substrate	*ee* [%] (Config.)
1[c]	**8b**	**3b**	MeOH	1:100	46.5 (*S*)
2	**8b**	**5a**	MeOH	1:100	72.9 (*R*)
3	**9b**	**3b**	MeOH	1:100	86.0 (*S*)
4[b]	**9b**	**3a**	*i*PrOH	1:100	80.0 (*S*)
5	**9b**	**5a**	*i*PrOH	1:100	92.1 (*R*)
6	**9b**	**5a**	*i*PrOH	1:500	92.6 (*R*)
7	*ent*-**9c**	**3a**	*i*PrOH	1:100	92.2 (*R*)
8	*ent*-**9c**	**3b**	CH_2Cl_2	1:100	90.0 (*R*)
9	*ent*-**9c**	**5a**	*i*PrOH	1:100	96.0 (*S*)
10	*ent*-**9c**	**5a**	*i*PrOH	1:500	95.5 (*S*)
11	**10a**	**3a**	MeOH	1:100	97.5 (*R*)
12	**10a**	**3a**	MeOH	1:1000	97.4 (*R*)
13	**10a**	**3b**	MeOH	1:100	94.6 (*R*)
14	**10a**	**3b**	MeOH	1:1000	94.2 (*R*)
15	**10a**	**5a**	*i*PrOH	1:100	94.2 (*S*)

[a] Reaction conditions: 1.1 bar of H_2; 20 °C; 24 h; *c*(substrate) = 0.1 mol L^{-1}; molar ratio ligand:Rh = 2.2:1, catalyst preparation see text. For ligand **10a** the molar ratio **10a**:Rh = 1.1:1 was used. In every case complete conversion was achieved. For determinations of enantiomeric purities the crude reaction products were transformed into the methyl esters and these were analyzed by GC; column Chrompack-CP-Chiralsil-L-Val (25 m × 0.25 mm), flow: 100 mL h^{-1}, 105 °C: t_R[(*R*)-**4a**-Me] = 4.3 min, t_R[(*S*)-**4a**-Me] = 5.0 min; 150 °C: t_R[(*R*)-**4b**-Me] = 11.3 min, t_R[(*S*)-**4b**-Me] = 12.3 min; column: Chrompack-CP-γ-Cyclodextrin-TA (30 m × 0.25 mm), flow: 60 mL h^{-1}, 70 °C: t_R[(*S*)-**6b**] = 22.8 min, t_R[(*R*)-**6b**] = 25.6 min. Absolute configurations were determined by comparison with known signs of optical rotations: a) R. D. Larsen, R. A. Reamer, E. G. Corley, P. Davis, E. J. J. Grabowski, P. J. Reider, I. Shinkai, *J. Org. Chem.* **1991**, *56*, 6034–6038; b) R. Eck, H. Simon, *Tetrahedron* **1994**, *50*, 13631–13640; c) H. Takahashi, K. Achiwa, *Chem. Lett.* **1989**, 305–308. [b] Reaction temperature: 5 °C. [c] Conversion: 15 %.

In all cases, enantioselectivities of the hydrogenations were higher and the reactions faster[12] with the ligands **9** (Table 1, entries 3–10) than with the P-phenyl ligands **8**. Using ligand **9b**, we obtained 92.6 % *ee* for the hydrogenation of itaconic acid (**5a**) after optimization of the solvent (Table 1, entry 6). The catalyst system is very robust against acidic (AcOH) or basic (NEt_3) additives, which did not significantly influence the level of enantioselectivity. With substrate/catalyst ratios of 100:1 and 500:1 turnover frequencies of 91 and 313 h^{-1}, respectively, were obtained. In the case of itaconic acid the enantiomeric excess was increased to 96.0 % *ee* with the more bulky ligand *ent*-**9c** (Table 1, entries 7–10).

So far we could not obtain crystals of a Rh^I complex suitable for X-ray crystallography; however, we were successful with an analogous platinum complex $[PtCl_2(\mathbf{9b})_2]$ (Figure 1).[13] Oxaphosphinane rings display the chair conformation and are arranged in such a way that the axial P–H bonds are in juxtaposition. Because of the relative rotational state of the rings, a simple sector model for an analogous Rh complex with classification of substituents according to their steric effects cannot be established at present.

For the preparation of the bidentate chelate ligands the oxaphosphinanes $\mathbf{9}\cdot BH_3$ were deprotonated with *n*BuLi and the resultant phosphides were allowed to react with 1,2-

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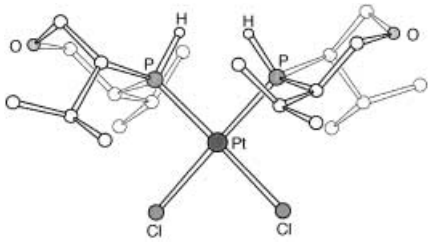
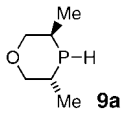
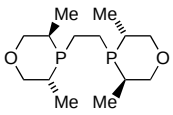
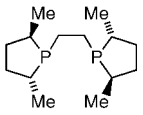


Figure 1. Structure of the complex $[PtCl_2(\mathbf{9b})_2]$ in the crystal.

ditosyloxyethane to give the crystalline ligands $\mathbf{10}\cdot 2BH_3$. Attempted decomplexation with DABCO was not successful, good results were obtained with a method developed by Livinghouse et al. (1. $HBF_4\cdot Et_2O$, 2. K_2CO_3).[14] The hydrogenations were carried out using a molar ratio ligand:Rh = 1.1:1 (Table 1, entries 11–15). Enantioselectivities were distinctly higher with ligand **10a** than with ligand **2a**.[15] However, the more bulky ligand **10b** induced lower levels of enantiomeric excess and conversion. Generally, bulky substituents R (Scheme 2) were found to be favorable for monodentate oxaphosphinanes **9** but unsuited for chelate ligands **10**.

The configurational relationships for hydrogenations with the various ligands are summarized in Table 2. As found for most monodentate ligands,[9] a simple rationale is so far not apparent. The inverse configurations of product **6b** induced by ligands **10a** and **2a** in the case of substrate **5b** demonstrate that analogous five- and six-membered-ring systems differ considerably.

Table 2. Configurational relationships between hydrogenation products and the ligands **9a**, **10a**, and **2a**.

Products	Configuration of the hydrogenation products with ligand		
	 **9a**	 **10a**	 **2a**
4a	*S*	*R*	*R*[a]
4b	*S*	*R*	*R*[a]
6a	*R*	*S*	–
6b	*S*	*S*	*R*

[a] In the case of ligand **2a** Burk et al. have used the corresponding methyl esters as substrates.

In conclusion, the results described above demonstrate that six-membered-ring phosphanes are promising new ligands. Oxaphosphinanes, whose modular make-up allows numerous variations, give rise to high degrees of enantioselectivity in asymmetric hydrogenations as secondary monodentate P ligands and also when they are combined into chelate ligands. It is expected that the new ligands will be applied in other catalyzed reactions.

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[12] Here too, a reaction time of 24 h was chosen, although hydrogenations were completed sooner.

[13] CCDC-173871 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).

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[15] For the methyl esters of **3a** and **3b** 91.4 and 85% *ee*, respectively, for **5b** 90% *ee*.[1a,1b]

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