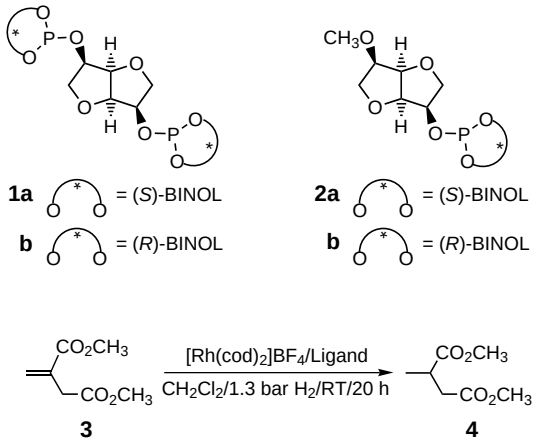
Highly Enantioselective Rh-Catalyzed Hydrogenation Reactions Based on Chiral Monophosphite Ligands

Manfred T. Reetz* and Gerlinde Mehler

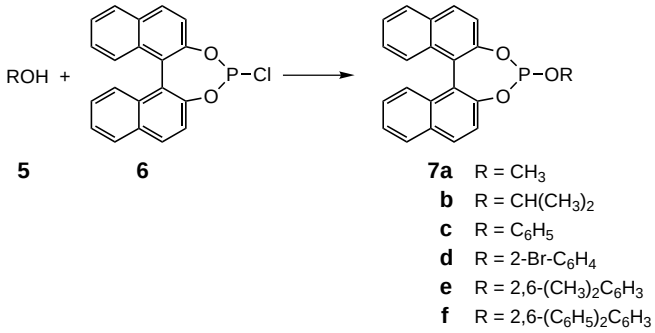
The first examples of asymmetric transition metal catalyzed hydrogenation reactions of prochiral olefins were described in 1968 independently by Horner et al.[1] and Knowles and Sabacky.[2] The ligands were chiral monophosphanes (e.g., methyl-*n*-propylphenylphosphane). However, the Rh-complexes derived thereof gave low enantioselectivities (*ee* = 3–15%). Other ligands possessing only one donor function were also rather ineffective in hydrogenation reactions.[3] It was Kagan's group who in 1971 showed for the first time that a Rh-complex of a chelating diphosphane (diop) with chiral information in the backbone gives enantioselectivities of 70–80% *ee*.[4] Shortly thereafter Knowles et al. demonstrated that in hydrogenation reactions the Rh-complex of a chelating diphosphane having stereogenic centers at phosphorus (dipamp) is also consistently superior than the corresponding monophosphane (*ee* > 90%).[5] Likewise, Takaya and Noyori described highly efficient catalysts based on the chelating ligand 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (BINAP).[6] To explain the high degrees of enantioselectivity resulting from these and other chiral diphosphanes, conformational control as a result of decreased rotational freedom around the donor-atom–metal bond in the metallacycle was postulated.[3] Herein we now show that this long-standing rule is not as general as usually assumed.[7]

Recently we described the first highly enantioselective Rh-catalyzed hydrogenation reactions using chiral chelating diphosphites **1a**, **b**.[8] In the hydrogenation of itaconic acid dimethyl ester **3** *ee* values of 88% and 95% were observed in favor of (*S*)-**4** and (*R*)-**4**, respectively, an indication that the chiral information in the P heterocycle is decisive and that the combination of (*R*)-BINOL and dianhydro-D-mannite in the form of **1a** represents the matched case.



[*] Prof. Dr. M. T. Reetz, G. Mehler
Max-Planck-Institut für Kohlenforschung
Kaiser-Wilhelm-Platz 1, 45470 Mülheim/Ruhr (Germany)
Fax: (+49) 208-306-2985
E-mail: reetz@mpi-muelheim.mpg.de

Surprisingly, the monophosphite units **2a** and **2b** give similar stereoselectivities. The precatalysts were prepared as usual[3, 8] by the reaction of the ligands with $[Rh(cod)_2]BF_4$. By using a Rh:ligand ratio of 1:1, a Rh:substrate ratio of 1:1000, and otherwise identical conditions the hydrogenation of substrate **3** led to enantioselectivities of 97.8% (100% conversion) and 95.2% (73% conversion) in favor of the products(*S*)-**4** and (*R*)-**4**, respectively. Although the matched case (**2a**) results in a much more active Rh-catalyst than the mismatched combination (**2b**), the additional increase in enantioselectivity is not pronounced. This could be because one of the three ether moieties behaves as a hemilabile ligand, and thus reduces the conformational freedom. To test this hypothesis the very simple monophosphites **7a**–**7f**, some of



which have been described already,[9, 10] were prepared and tested as ligands in the Rh-catalyzed hydrogenation of **3**. All the hydrogenation reactions were carried out at room temperature, under a slight positive pressure of H_2, and with a Rh:ligand ratio of 1:1. Although a standard reaction time of 20 h was chosen,[8] most of the reactions were complete within 3 h.

The results of the Rh-catalyzed hydrogenation reactions are summarized in Table 1 and show that simple BINOL-based monophosphites are excellent ligands provided that in the ligand synthesis the appropriate achiral alcohol **5** is chosen, for example, isopropanol (**5b**) in the case of **7b** (97.6% *ee* in the hydrogenation product **4**). Upon incorporating a sterically smaller alcohol such as methanol (**7a**), the *ee* value drops to 89.2%. Although the phenol-based ligand leads to a high *ee* value (96.6%) and is therefore comparable to the isopropanol derivative **7b**, the introduction of ortho-substituents reduces enantioselectivity (Table 1, entries 4–6). Dichloro-

Table 1. Enantioselective Rh-catalyzed hydrogenation of itaconic acid dimethyl ester (**3**) using ligands **7a**–**7f**.[a]

Entry	Ligand	Conversion [%]	*ee* [%][b]
1	(*S*)-**7a**	100	89.2
2	(*S*)-**7b**	100	97.6
3	(*S*)-**7c**	100	96.6
4	(*S*)-**7d**	100	89.8
5	(*S*)-**7e**	78	39.2
6	(*S*)-**7f**	8	28.6

[a] In all cases the Rh:ligand ratio is 1:1 and the Rh:substrate ratio is 1:1000. Solvent: CH_2Cl_2; $p(H_2) = 1.3$ bar; $T = 20\,^{\circ}C$; reaction time: 20 h. [b] *S* configuration of **4** in each case.

  1433-7851/00/3921-3889 $ 17.50+.50/0

methane was usually chosen as the solvent. In pure isopropanol inferior results were obtained.

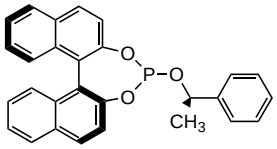
To see if BINOL in combination with simple *chiral* alcohols lacking additional functional groups also leads to efficient ligands, the two phosphites **8a**,**b**,[11] prepared from (*S*)-**6** and (*R*)- and (*S*)-1-phenylethanol (76% and 80% yield, respectively), were tested in the Rh-catalyzed hydrogenation of **3**. Under otherwise identical conditions *ee* values of 99.2% and 98.2% were observed in favor of (*S*)-**4** (100% conversion) (Table 2). Thus, it is clear that 1-phenylethanol is a better component than isopropanol, however, the additional stereogenic center appears to play a minor role. Indeed, upon

Table 2. Enantioselective Rh-catalyzed hydrogenation of itaconic acid dimethyl ester (**3**) using ligands **8a**,**b**.[a]

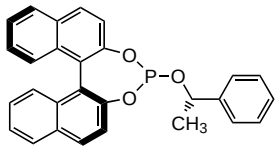
Entry	Ligand	Rh:ligand	Rh:substrate	Conversion [%]	*ee* [%][b]
1	**8a**	1:1	1:1000	100	99.2
2	**8b**	1:1	1:1000	100	98.2
3	**8a**	1:1	1:2500	100	99.4
4	**8a**	1:1	1:5000	100	99.4
5	**8a**	1:1	1:10000	49	96.2
6	**8a**	1:2	1:1000	100	99.6
7	**8a**	1:4	1:1000	100	99.5

[a] Solvent: CH_2Cl_2; $p(H_2) = 1.3$ bar; $T = 20\,^{\circ}C$; reaction time: 20 h. [b] *S*-Configuration of **4** in each case.

employing an approximately 1:1 mixture of diastereomeric ligands **8a** and **8b** in the hydrogenation of **3** (Rh:ligand = 1:1; Rh:substrate = 1:1000), the *ee* value of the product (*S*)-**4** was found to be 98.8% (100% conversion). A practical consequence of this result is that the synthesis of the ligand **8** does



8a



8b

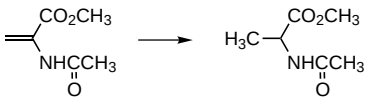
not require enantiomerically pure 1-phenylethanol. However, the possible role of nonlinear effects[12] upon using diastereomeric mixtures[8b] cannot be assessed at this time. In the case of pure **8a** the catalyst/substrate ratio was reduced to 1/5000 without any loss in yield or enantioselectivity (Table 2, entry 4). That the Rh:ligand ratio has no influence on enantioselectivity is synthetically significant and constitutes an important starting point for future mechanistic studies (Table 3, entries 1, 6 and 7). A 1:2 ratio appears to be optimal.

Table 3. Enantioselective Rh-catalyzed hydrogenation of 2-acetamido acrylic acid methyl ester (**9**).[a]

Entry	Ligand	Conversion [%]	*ee* [%]
1	(*S*)-**7a**	100	72.8
2	(*S*)-**7b**	100	94.8
3	(*S*)-**7c**	100	80.6
4	(*S*)-**7d**	67	70.0
5	**8a**	100	95.5
6	**8b**	100	93.3

[a] Reaction conditions as in Table 1. [b] *R* configuration of **10** in each case.

Finally, the Rh-catalyzed hydrogenation of 2-acetamido acrylic acid ester (**9**) to the alanine derivative **10** was investigated. Here again a strong dependence of enantioselectivity upon the nature of the alcohol **5** used in the preparation of the ligands was observed (Table 3). The methanol- and phenol-derived ligands **7a** and **7c** give *ee* values of only 72.8% and 80.6%, respectively, whereas the isopropanol-based ligand **7b** gives an enantioselectivity of 94.8%. Ligand **8a** is even more selective (*ee* = 95.5%). In all cases the monophosphite ligands contain (*S*)-BINOL, which results in preferential formation of the *R*-configured product **10**.



9 **10**

This study disproves the long-standing notion that chelating ligands are necessary for high enantioselectivities to be observed in hydrogenation reactions. This is not only of theoretical, but also of practical interest. For example, phosphites are less sensitive to oxidation than phosphanes. Moreover, because of the modular construction of the monophosphites, structural diversity is easily possible so that enantioselectivity can be maximized for each new substrate as necessary. Studies of this kind as well as mechanistic investigations are underway in our laboratories.

Received: May 31, 2000 [Z15200]

[1] L. Horner, H. Siegel, H. Büthe, *Angew. Chem.* **1968**, *80*, 1034–1035; *Angew. Chem. Int. Ed. Engl.* **1968**, *7*, 942–943.

[2] W. S. Knowles, M. J. Sabacky, *Chem. Commun.* **1968**, 1445–1446.

[3] K. E. Koenig in *Chiral Catalysis (Asymmetric Synthesis, Vol. 5* (Ed.: J. D. Morrison)), Academic Press, Orlando, **1985**, pp. 71–101; b) J. Halpern in *Chiral Catalysis (Asymmetric Synthesis, Vol. 5* (Ed.: J. D. Morrison)), Academic Press, Orlando, **1985**, pp. 41–69; c) H. Brunner, W. Zettlmeier, *Handbook of Enantioselective Catalysis with Transition Metal Compounds, Vol. I–II*, VCH, Weinheim, **1993**; d) R. Noyori, *Asymmetric Catalysis in Organic Synthesis*, Wiley, New York, **1994**; e) *Comprehensive Asymmetric Catalysis, Vol. I–III* (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer, Berlin, **1999**.

[4] T. P. Dang, H. B. Kagan, *J. Chem. Soc. D* **1971**, 481.

[5] W. S. Knowles, M. J. Sabacky, B. D. Vineyard, D. J. Weinkauff, *J. Am. Chem. Soc.* **1975**, *97*, 2567–2568.

[6] A. Miyashita, A. Yasuda, H. Takaya, K. Toriumi, T. Ito, T. Souchi, R. Noyori, *J. Am. Chem. Soc.* **1980**, *102*, 7932–7934.

[7] Isolated cases of *ee* values up to 90% have been reported; see review by F. Lagasse, H. B. Kagan, *Chem. Pharm. Bull.* **2000**, *48*, 315–324.

[8] a) M. T. Reetz, T. Neugebauer, *Angew. Chem.* **1999**, *111*, 134–137; *Angew. Chem. Int. Ed.* **1999**, *38*, 179–181; b) D. G. Blackmond, T. Rosner, T. Neugebauer, M. T. Reetz, *Angew. Chem.* **1999**, *111*, 2333–2335; *Angew. Chem. Int. Ed.* **1999**, *38*, 2196–2199.

[9] Synthesis of **7c**: P. H. Dussault, K. R. Woller, *J. Org. Chem.* **1997**, *62*, 1556–1559.

[10] We thank M. Pastó (MPI für Kohlenforschung) for the synthesis of the phosphite **7d**.

[11] The synthesis of **8** as a diastereomeric mixture starting from racemic 1-phenylethanol is known: A. A. Bredikhin, Z. A. Bredikhina, F. F. Nigmatzyanov, *Russ. Chem. Bull.* **1998**, *47*, 411–416.

[12] a) C. Girard, H. B. Kagan, *Angew. Chem.* **1998**, *110*, 3088–3127; *Angew. Chem. Int. Ed.* **1998**, *37*, 2922–2959; b) monophosphoramidite ligands in conjugate additions: B. L. Feringa, *Acc. Chem. Res.* **2000**, *33*, 346–353.

[13] Whereas nonlinear effects in enantiomeric catalysts are well known,[12] related phenomena in the case of diastereomeric catalysts have only recently been described: a) S. Y. Zhang, C. Girard, H. B. Kagan, *Tetrahedron: Asymmetry* **1995**, *6*, 2637–2640; b) C. Bolm, K. Muñiz, J. P. Hildebrand, *Org. Lett.* **1999**, *1*, 491–493; c) see reference [8b].

  1433-7851/00/3921-3890 $ 17.50+.50/0