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Rhodium-catalyzed enantioselective hydrogenation using chiral monophosphonite ligands

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Abstract

Surprisingly high enantioselectivities in the Rh-catalyzed hydrogenation of itaconic acid dimethyl ester and methyl-2-acetamido acrylate are observed upon using chiral monophosphonite ligands derived from binaphthol (ee up to 94%). Although appropriate chelating diphosphonites are more effective, the easy modular synthesis of the chiral monophosphonites may allow for the optimization of a given asymmetric hydrogenation reaction.

Keywords: enantioselection; reduction; rhodium and compounds; phosphorus compounds; amino acids and derivatives.

We have recently shown that chiral diphosphonites with achiral backbones such as ethano- or ferroceno-bridged derivatives derived from binaphthol (BINOL), e.g. **1** and **2**, are excellent ligands for Rh-catalyzed hydrogenation.[1–3] Of all variants tested so far, the ferroceno-bridged ligand **2** was found to be the most effective. For example, the hydrogenation of itaconic acid dimethyl ester (**4**) and methyl-2-acetamido acrylate (**6**) proceeded with ee values of $>99.5\%$. A recent publication by Pringle et al.[4] in which they show that related monophosphonites **3a**,**c**,**d** lead to enantioselectivities of up to 92% ee in the hydrogenation of **6**, prompts us to report our own results in this area.

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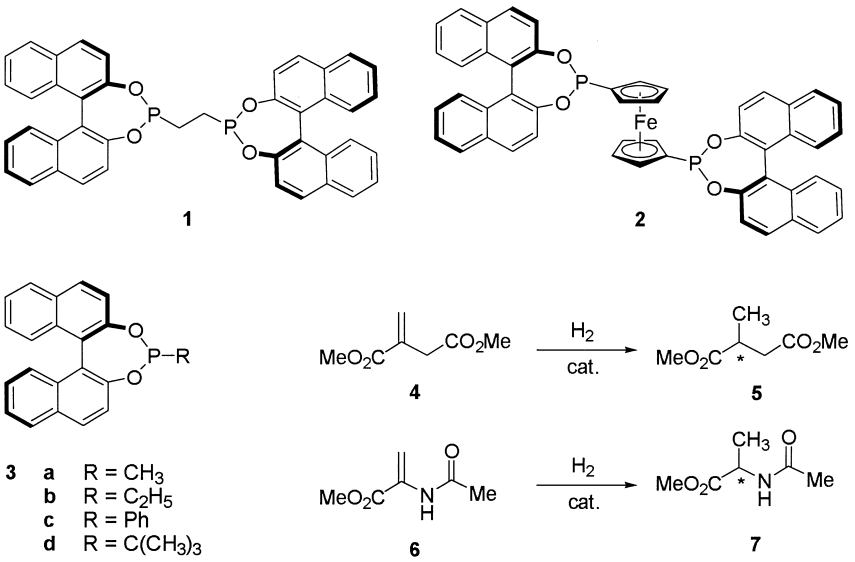

The monophosphonites **3a–d** were readily prepared using known procedures[5] based on the reaction of $RPCl_2$ with (*R*)-binaphthol (BINOL) in the presence of NEt_3 (yields: 59% **3a**; 71% **3b**; 73% **3c**; 66% **3d**). Standard reaction of $Rh(COD)_2BF_4$[6–10] with two parts of ligands **3a–d** afforded complexes $Rh[(\mathbf{3})_2(COD)]BF_4$ which were used as the precatalysts in hydrogenation experiments. The results as summarized in Table 1 show that the degree of enantioselectivity depends very much on the nature of the R-group in the ligand. In the hydrogenation of itaconic acid dimethyl ester, the methyl derivative **3a** results in the highest ee (90%). This value is quite respectable for a monodentate ligand, but it is considerably lower than the enantioselectivities achieved by **1** and **2** (> 99.5% ee)[1,2] in the same reaction. Increasing the steric bulk of the R-group lowers enantioselectivity down to 60% ee in the case of the *t*-butyl-derived ligand **3d**. In the

Table 1
Asymmetric Rh-catalyzed hydrogenation of **4** and **6** using (*R*)-BINOL-derived phosphonites[a]

Entry	Substrate	Ligand	Conversion (%)	% *ee* (abs. config.)
1	**4**	**3a**	100	90 (*R*)
2	**4**	**3b**	100	71 (*R*)
3	**4**	**3c**	100	29 (*R*)
4	**4**	**3d**	100	57 (*R*)
5	**6**	**3a**	100	92 (*S*)
6	**6**	**3b**	100	94 (*S*)
7	**6**	**3c**	100	73 (*S*)
8	**6**	**3d**	100	93 (*S*)

[a] **3** : Rh = 2 : 1; Rh : substrate = 1 : 1000; solvent CH_2Cl_2.

reaction of methyl-2-acetamido acrylate **6**, which was studied by Pringle,[4] the situation is somewhat different. In this series the ethyl derivative **3b** delivers the highest enantioselectivity (94% ee), but a clear trend with respect to the variation of the R-group is not discernable. The *t*-butyl derivative **3d** leads to an ee value of 93%, in agreement with Pringle's data (92%).[4†] This value is slightly higher than that obtained by the use of **1** (90% ee) but considerably lower than the enantioselectivity resulting from the use of the ferroceno-based ligand **2** (> 99.5% ee).[1–3] Both **1** and **2** are chelating bidentate ligands in contrast to the monodendate phosphonites **3a**–**d**.

The results presented here and those discussed recently[4] are relevant with respect to the long-term discussion concerning the origin of enantioselectivity in Rh-catalyzed hydrogenation.[6–10] The first examples of asymmetric transition metal-catalyzed hydrogenation of prochiral olefins were reported in 1968 independently by Horner[11] and Knowles.[12] They used chiral monophosphines such as methyl-*n*-propylphenylphosphine which resulted in low enantioselectivities (ee = 3–15%). Other monodendate ligands also turned out to be rather ineffective.[6–10] In 1971 Kagan introduced the concept of chiral chelating diphosphines (DIOP) having stereogenic centers in the backbone, which marked a breakthrough because high enantioselectivities were possible for the first time (70–80% ee).[13] Shortly thereafter Knowles described the chelating diphosphine DIPAMP, the P-atoms being the stereogenic centers.[14] The highly efficient BINAP, first described by Takaya and Noyori, is also a bidentate ligand.[15] The success of these and other chelating ligands was explained by hindered rotational freedom around the metal–donor atom bond in the intermediate metal chelates.[6–10,13–16] On the basis of limited data Pringle has concluded that the above dogma does not necessarily pertain.[4] We agree to a certain extent. However, upon scrutinizing all of the present data concerning the monophosphonites **3a**–**d**, it becomes clear that the effects are not as pronounced as perhaps suggested.[4] Firstly, in no case concerning the use of **3** has an ee value been observed which exceeds 94%. Secondly, Pringle cites only the enantioselectivities resulting from ligand **1** as reported by us, yet the ee values obtained from the use of **2** are consistently much higher (> 99% ee).[1–3] Thus, the positive chelation effect on enantioselectivity is in fact operating, provided the appropriate backbone is chosen.[‡]

In summary, surprisingly high enantioselectivities are observed upon using BINOL-derived monophosphonites in the Rh-catalyzed hydrogenation of two different types of prochiral olefins (up to 94% ee).[§] However, data more extensive than that considered by Pringle[4] show that enantioselectivities are considerably higher when using the proper chelating diphosphonites.[1–3] The potential advantage of chiral monophosphonites **3** in asymmetric hydrogenation has to do with their ready synthesis and the possibility to vary the R-group. Thus, the modular synthesis of chiral monophosphonites constructed from BINOL (or other optically active diols) and from a wide variety of phosphorus compounds $RPCl_2$ may well allow the optimization of a given asymmetric hydrogenation reaction.

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† The ee value obtained from the use of the methyl derivative **3a** (92%; Table 1, Entry 5) differs somewhat from the one reported by Pringle[4] (78% ee). The source of this discrepancy is unclear; all other relevant ee values are identical within experimental error. Our ee values are the average of two runs; in no case did the respective two values differ considerably.

‡ The butano-bridged analog of **1** shows considerably lower ee values in Rh-catalyzed hydrogenation.[1–3]

§ Typical procedure for hydrogenation: All hydrogenations were carried out under the conditions previously reported using chiral diphosphonites:[1,2] 1.3 bar H_2; solvent CH_2Cl_2; rt; 20 h (most reactions are complete within 3–4 h). The catalyst was separated from the reaction mixture by filtering through a short SiO_2 column. Conversion and ee value were determined by gas chromatography using a chiral stationary phase.

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