Chiral diphosphites and diphosphoramidites as cheap and efficient ligands in Rh-catalyzed asymmetric olefin hydrogenation

Manfred T. Reetz,* Gerlinde Mehler and Oleg Bondarev

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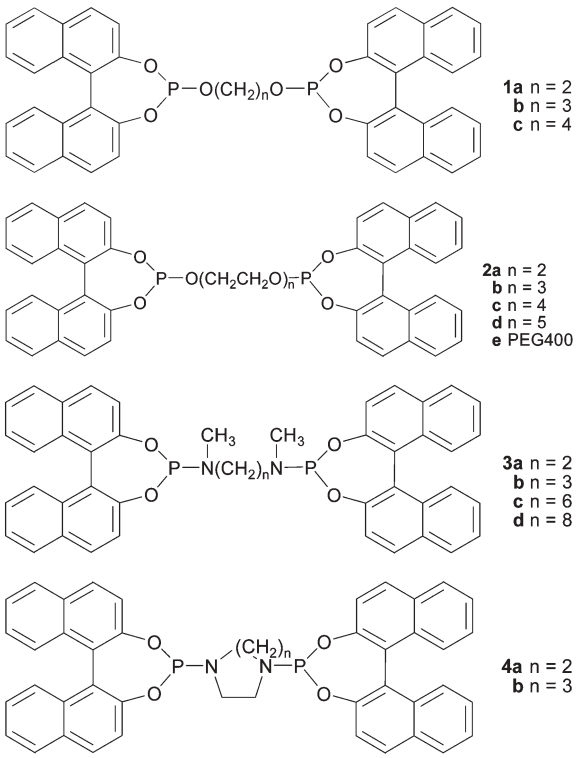
Chiral diphosphites and diphosphoramidites derived from BINOL or diphenylprolinol are efficient ligands in asymmetric Rh-catalyzed olefin hydrogenation, provided the proper achiral backbone is chosen.

Several years ago it was reported that BINOL-derived monodentate phosphites,[1] phosphonites[2] and phosphoramidites[3] are efficient ligands in Rh-catalyzed olefin hydrogenation (90–99% ee). These observations were surprising, because it had been accepted that chelating bidentate P-ligands are generally necessary for high levels of enantioselectivity, probably due to restricted rotations in the respective Rh-complexes.[4] Recently, we published a mechanistic study which showed that two monodentate phosphites are attached to rhodium with formation of defined conformers, and that the lock-and-key mechanism holds in which the major Rh/olefin diastereomer leads to the product (anti-Halpern).[5] Oddly enough, the analogous diphosphites and diphosphoramidites having achiral backbones appear not to be well suited. In fact, up to 1999 the highest ee-value in any olefin hydrogenation using chiral diphosphites had been reported not to exceed 34%.[6] At that time we described a BINOL-derived diphosphite with a chiral backbone (dianhydro-D-mannitol) as the first case of high efficiency (ee up to 96%).[7] However, although BINOL constitutes one of the cheapest chiral auxiliaries, the chiral diol used as the backbone is not readily available. Therefore, such diphosphites are not practical. In the case of diphosphoramidites, ethane- and propane-diamine as backbones lead to only 70–72% ee.[3] All of these observations suggest that chiral diphosphites and diphosphoramidites having achiral backbones are not suited for efficient olefin hydrogenation. Here we report that this is not the case.

Based on our mechanistic study regarding the efficiency of BINOL-derived monophosphites,[5] we thought that it might be possible to design analogous diphosphites which might in fact be well suited for Rh-catalyzed olefin hydrogenation. We suspected that the nature of the achiral backbone may be crucial, and therefore prepared bidentate ligands having different spacers between the two phosphorus centers. Diphosphites **1** and **2** and diphosphoramidites **3** and **4** were easily prepared by phosphorylating the corresponding diols or diamines using standard procedures[1,3] (yields: 75–95%).

We also considered combining the functional moieties of BINOL-derived phosphites and phosphoramidites in a new class of bidentate ligands, as in **5** prepared by phosphorylating commercially available 4-hydroxypiperidine (non-optimized yield: 55%).

Max-Planck-Institut für Kohlenforschung, D-45470, Mülheim/Ruhr, Germany. E-mail: reetz@mpi-muelheim.mpg.de; Fax: +49 208 306 2985



As a model reaction for testing the performance of ligands **1–5** in Rh-catalyzed olefin hydrogenation, we chose the transformation of itaconate **6** to methyl succinate **7**. The standard procedure, used previously in related cases,[1,3,7] was applied in which $[Rh(cod)_2]BF_4$ is treated with one equivalent of a bidentate ligand leading to the respective precatalyst in which one 1,5-cyclooctadiene (cod) has been replaced.

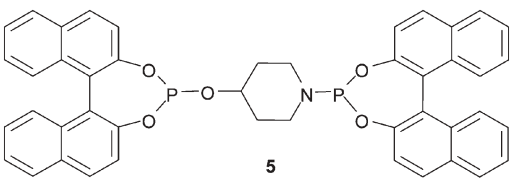


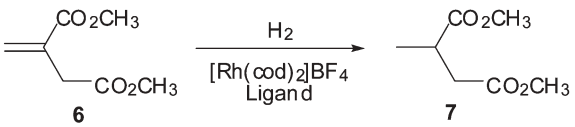
Table 1 shows some remarkable trends. Conversion and ee depend much on the nature of the achiral backbone. If the backbone is short as in the ligands derived from ethylene glycol (**1a**), 1,3-propane diol (**1b**), ethylene diamine (**3a**) or 1,3-propane diamine (**3b**), enantioselectivity is poor to mediocre and conversion varies greatly (Table 1, entries 1, 2, 9, 10). In contrast, longer backbones such as those in **1c**, **2a**, **2c** and **3c** lead to 93–97% *ee*

Table 1 Rh-catalyzed asymmetric hydrogenation of itaconate **6**[a]

Entry	Ligand	Conversion (%)	*ee* (%)
1	**1a**	99	73
2	**1b**	44	38
3	**1c**	96	93
4	**2a**	97	97
5	**2b**	10–40	50–90
6	**2c**	97	96
7	**2d**	23	66–77
8	**2e**	50	88
9	**3a**	100	89
10	**3b**	100	33
11	**3c**	100	93
12	**3d**	100	90
13	**4a**	100	96
14	**4b**	100	99
15	**5**	100	96

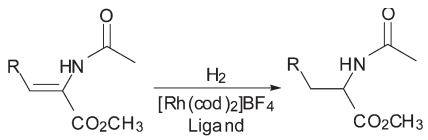
[a] Rh:substrate = 1 : 1000; 1.3 bar H_2; CH_2Cl_2; 22 °C; 20 h. (*S*)-BINOL-derived ligands provide (*S*)-**6**.

(Table 1, entries 3, 4, 6, 11). The ligands derived from tri- and pentaethylene glycol provide results which appear not to be reproducible, which may be due to the presence of small amounts of water. Remarkably, the diphosphoramidites derived from piperazine (**4a**) and homopiperazine (**4b**) result in 96–99% ee (entries 13, 14), which stands in contrast to the mediocre results obtained from the structurally related ethano-bridged ligand **3a**[3] (entry 9). The phosphite/phosphoramidite **5** is also a high performance ligand (ee = 96%; entry 15).



6 **7**

The ligands were then tested in the Rh-catalyzed hydrogenation of *N*-acyl amino acrylate **8a**. Table 2 shows that many of them are again well suited, the diphosphoramidites **4a,b** once more being particularly noteworthy (entries 7, 8).



8 a R = H, b R = Ph **9** a R = H, b R = Ph

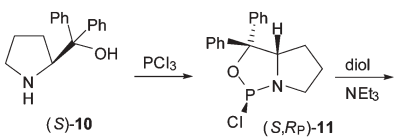
In order to determine whether BINOL can be replaced by other chiral auxiliaries, several ''standard'' diols such as (*R*,*R*)-hydrobenzoin were employed. Such bidentate ligands resulted in poor enantioselectivity. In sharp contrast, bidentate P-ligands derived from commercially available (*S*)-α,α-diphenylprolinol **10** turned out to be surprisingly efficient, provided the correct achiral backbone is chosen. The synthesis of this new type of ligand involves diastereoselective phosphorylation of **10** by PCl_3 with exclusive formation of (S,R_P)-**11** followed by standard phosphorylation of achiral diols such as ethylene glycol, 1,4-butane diol or diethylene glycol. The conclusion regarding the relative configuration of **12** is based on the X-ray structure of an analogous compound produced by phosphorylation of a phenol by (S,R_P)-**11**).[8] Structurally related P-heterocycles derived from amino

Table 2 Rh-catalyzed asymmetric hydrogenation of *N*-acyl amino acrylate **8a**[a]

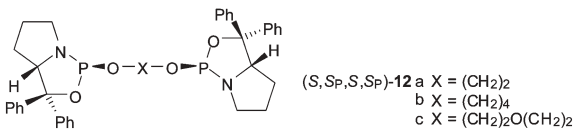
Entry	Substrate	Ligand	ee (%)
1	**8a**	**1c**	70
2	**8a**	**2a**	79
3	**8a**	**3a**	80
4	**8a**	**3b**	50
5	**8a**	**3c**	96
6	**8a**	**3d**	98
7	**8a**	**4a**	99
8	**8a**	**4b**	99
9	**8a**	**5**	95

[a] Same conditions as in Table 1; 100% conversion in all cases; (*S*)-BINOL-derived ligands afford (*R*)-**9a**.

alcohols have been described previously.[9]



(*S*)-**10** (S,R_P)-**11**



(S,S_P,S,S_P)-**12** a X = $(CH_2)_2$, b X = $(CH_2)_4$, c X = $(CH_2)_2O(CH_2)_2$

The ligands were then tested in the hydrogenation of **6** and **8a,b**. Table 3 shows that **12a** results in low enantioselectivity in all cases (entries 1, 4, 7), whereas **12b** and **12c** with longer backbones lead to high levels of asymmetric induction. Thus, an effect analogous to the previous observation regarding ligands **1–5** is operating.

The results provoke the question whether well defined Rh-chelates are formed or whether dinuclear species or oligomers are involved. An unambiguous answer is difficult because we were able to obtain data only of the pre-catalysts in which one of the cyclooctadiene (cod) ligands has been replaced by a bidentate P-ligand. It is well known that as hydrogenation is initiated, the second cod ligand is hydrogenated with formation of the reactive catalyst.[4] All attempts to obtain spectroscopic data of the latter failed. An ESI-MS study of the Rh-precatalysts derived from **3**, **4** and **12** clearly shows the existence of the respective Rh-chelates, in which one cyclooctadiene (cod) is bonded to the metal. Although we searched intensely in the higher mass region, no evidence for possible dinuclear or oligomeric complexes was found. The NMR spectra of the complexes at 100-fold higher concentrations relative to hydrogenation conditions (and about 10 times higher than

Table 3 Rh-catalyzed asymmetric hydrogenation of **6** and **8a,b**

Entry	Substrate	Ligand	ee (%)
1	**6**	**12a**	2 (*R*)
2	**6**	**12b**	92 (*R*)
3	**6**	**12c**	90 (*R*)
4	**8a**	**12a**	32 (*S*)
5	**8a**	**12b**	91 (*S*)
6	**8a**	**12c**	89 (*S*)
7	**8b**	**12a**	10 (*S*)
8	**8b**	**12b**	94 (*S*)
9	**8b**	**12c**	86 (*S*)

[a] Same conditions as in Table 1; 100% conversion in all cases.

under MS-conditions) also show the presence of the expected complexes. However, under these conditions (concentrations higher than when hydrogenating) about 10–20% of species appear which may be dinuclear or oligomeric. The influence of concentration, *e.g.*, in the range 0.05–0.2 M, on ee was tested in several cases, *e.g.*, **4a** and **12a**. No appreciable effect was observed. Thus, bidentate-Rh species are probably involved, although other intermediates under the actual reaction conditions cannot be excluded with certainty at this time. Finally, the effect of varying the Rh : ligand ratio was studied using two different diphosphoramidites. In the case of **3a**, doubling the Rh : **3a** ratio from 1 : 1 to 1 : 2 shuts down the reaction, as does a 1 : 3 ratio. In the case of **3d**, the rate also decreases when using more ligands, but not as drastically. At Rh:**3d** ratios of 1 : 2 and 1 : 3, only 44 and 12% conversion at low enantioselectivity, 58 and 25% ee, respectively, are observed. These results show that binding more than one bidentate ligand to rhodium is detrimental.

In summary, we have shown, inter alia, that BINOL-derived diphosphites and diphosphoramidites, which had previously been thought to be ligands leading to low or mediocre levels of enantioselectivity in Rh-catalyzed olefin hydrogenation, may in fact be very efficient. A prerequisite is the proper choice of the achiral backbone. In general, it needs to be fairly long, allowing for an optimal degree of flexibility. The piperazine- and homopiperazine-derived ligands (**4a,b**) appear to constitute exceptions to this guideline. The present findings open the door for industrial applications[10] because BINOL is one of the cheapest chiral auxiliaries currently available. Moreover, our concept of using mixtures of two different monodentate P-ligands[11] can now be used as a basis to design corresponding bidentate ligands, most likely with sufficiently long achiral backbones.

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