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Phosphine–phosphite, a new class of auxiliaries in highly active and enantioselective hydrogenation

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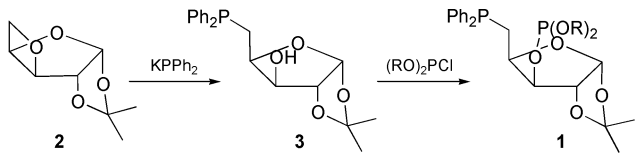
Excellent enantioselectivities (ee > 99%) and good activities (TOF > 1200 h^{-1}) are achieved under mild reaction conditions in the Rh-catalyzed hydrogenation of α,β-unsaturated carboxylic acid derivatives with the first family of phosphine–phosphite ligands containing a sugar backbone; these ligands are better than their diphosphine, diphosphite and phosphinite analogues.

The scope of asymmetric hydrogenation of alkenes has been gradually extended both in reactant structure and catalyst efficiency over many years.[1] Chiral bidentate phosphorus ligands have played a dominant role in the success of asymmetric hydrogenation.[1,2] The early excellent enantioselectivities obtained with Binap[3] and Dipamp[4] promoted the synthesis and application of a wide variety of new diphosphanes.[2] Recent reports on the use of chiral diphosphite[5] and diphosphinite[6] ligands in asymmetric hydrogenation have demonstrated their potential utility. Nevertheless, the search for new highly efficient ligand systems derived from readily available simple starting materials is still of great importance. Chiral auxiliaries from the chiral pool have attracted much attention, making tedious optical resolution procedures unnecessary. Carbohydrates are particularly advantageous because they are inexpensive compounds. Nevertheless, despite the accessibility and the excellent enantioselectivities obtained with sugar-derived ligands,[5–7] their full potential in providing chiral ligands has scarcely been exploited.[2a] In a previous paper, different types of phosphorus ligands with a xylofuranoside backbone have been applied to asymmetric hydrogenation with varying degrees of success. Moderate enantioselectivities (up to 35%) with phosphine–phosphinite and diphosphinite ligands have been reported by Brunner and Pieronczyk.[8] More recently, we reported moderate (up to 35%) and good (up to 91%) enantiomeric excesses at room temperature with diphosphites[9] and diphosphines,[10] but in both cases the activities were low.

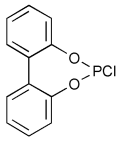
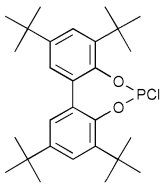
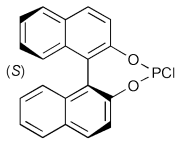
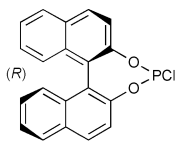
Continuing our interest in carbohydrates as an available chiral source for preparing ligands and encouraged by the success of diphosphine[2] and diphosphite[5] ligands, we have designed a new family of chiral bidentate phosphine–phosphite ligands **1** with a xylofuranoside backbone which combines the advantages of both ligand types (Scheme 1). A feature of these ligands is that they have two different phosphorus donor sites than can *a priori* match the intermediates better, thus influencing their reactivity and achieving good enantioselectivity.[11] We also report their highly active and enantioselective rhodium catalyzed asymmetric hydrogenation of α,β-unsaturated carboxylic acid derivatives. To the best of our knowledge this is the first example of phosphine–phosphite ligands applied to hydrogenation.[12]



Scheme 1

The new ligands **1a–d** were synthesized very efficiently in two steps from oxetane **2**, as shown in Scheme 1. Compound **2** is easily prepared on a large scale from D-(+)-xylose.[13] The key step is the oxetane ring opening using a slight excess of potassium diphenylphosphide in DMF to afford phosphine **3** in 80% yield after column chromatography.[14] This step is a novel strategy for easily synthesizing related ligands. Reacting **3** with 1 equivalent of the corresponding phosphorochloridite formed *in situ*[15] in the presence of base provided easy access to the desired ligands **1a–d**. These were isolated in good yields as air-stable solids that are fairly robust towards hydrolysis. Selected spectroscopic data are shown in Table 1.

Table 1 ^{31}P NMR spectroscopic data for ligands **1a–d**[a]

Ligand	$(RO)_2PCl$	$\delta(P_1)$[b]	$\delta(P_2)$[c]	$J(P_1–P_2)$/Hz
1a		−18.3	148.2	17.0
1b		−21.5	144.7	11.9
1c		−22.5	150.0	33.1
1d		−22.5	148.4	15.5

[a] In $CDCl_3$. [b] P_1 = phosphine. [c] P_2 = phosphite.

In a first set of experiments, we used the rhodium-catalyzed hydrogenation of methyl *N*-acetamidoacrylate **4** to investigate the potential of ligands **1a–d** for asymmetric catalysis (Table 2).[16] The reaction proceeded smoothly at 1 bar of H_2 at room temperature in CH_2Cl_2. Ligand **1a**, with the achiral biphenyl moiety at the phosphite, not only showed high asymmetric induction (88.2%) but also very high catalytic activity (Table 2, entry 1). The presence of bulky *tert*-butyl groups in the *ortho*-positions of the biphenyl moiety (ligand **1b**) have an extremely positive effect on enantioselectivity (ee > 99%, Table 2, entry 2).[17] Interestingly, the sense of the enantioselectivity is reversed; the (*S*) enantiomer was obtained with ligand **1a** and the (*R*)-enantiomer was obtained with ligand **1b**. Ligands **1c** and

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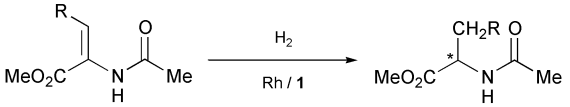
Table 2 Asymmetric hydrogenation of methyl *N*-acetamidoacrylate **4** and methyl (*Z*)-*N*-acetamidocinnamate **5** with $[Rh(cod)_2]BF_4$/**1**[a]



4 R = H
5 R = Ph

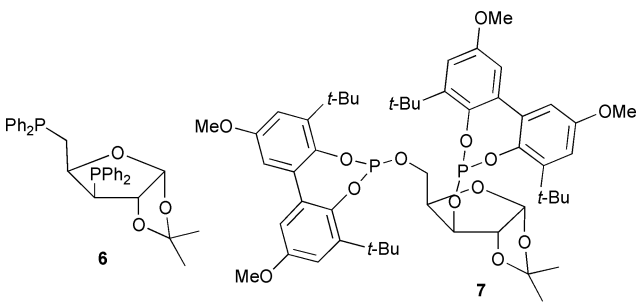
Entry	Ligand	Substrate	TOF[b]	% Conv[c] (*t*/min)	% ee[d]
1	**1a**	**4**	>1200	100 (<5)	88.2 (*S*)
2	**1b**	**4**	40	100 (150)	>99 (*R*)
3	**1c**	**4**	330	100 (20)	98.3 (*S*)
4	**1d**	**4**	318	100 (20)	97.6 (*R*)
5	**1a**	**5**	653	100 (10)	84.1 (*S*)
6	**1b**	**5**	31	100 (180)	98.8 (*R*)
7	**1c**	**5**	245	100 (30)	98.0 (*S*)
8	**1d**	**5**	212	100 (30)	94.3 (*R*)
9[e]	**6**	**4**	50	100 (120)	91 (*S*)
10[f]	**7**	**4**	4.2	99 (1440)	35 (*S*)

[a] $[Rh(cod)_2]BF_4$ = 0.01 mmol. **1**/Rh = 1.1. Substrate/Rh = 100. *P* = 1 atm. CH_2Cl_2 = 6 mL. [b] TOF in mol product × mol Rh^{-1} × h^{-1} measured by GC after 5 min. [c] % Conversion measured by GC. [d] % Enantiomeric excess measured by GC using an L-Chirasil-Val column. [e] Data from ref. 10. [f] Data from ref. 9.

1d containing a stereogenic binaphthyl moiety result in a high reaction rate and a high enantioselectivity (Table 2, entries 3 and 4). Ligand **1c**, which has an (*S*)-binaphthyl moiety, produces an ee of 98.3% (*S*), while diastereomer **1d**, which has an (*R*)-binaphthyl moiety, produces an ee of 97.6% (*R*). Therefore, if we compare the results with ligands **1a**–**d**, we can assume that the fast interchanging atropoisomers of ligand **1a** predominantly adopt the same configuration as that of **1c**, while the biphenyl moiety in ligand **1b** predominantly adopts an (*R*) configuration, probably due to the presence of the *tert*-butyl group in the *ortho*-position. We can conclude that the sense of the enantiodiscrimination is predominantly controlled by the configuration of the biphenyl or the binaphthyl at the phosphite moiety.

In general, the hydrogenation of **5** (Table 2, entries 5–8) follows the same trend as for **4**. However, the enantiomeric excesses are somewhat lower and the reaction rate was slightly slower. The configuration of the hydrogenated product is not affected by the presence of the phenyl group in **5**. The catalyst precursor containing ligand **1b** produced the highest enantiomeric excess (98.8%; Table 2, entry 6).

It is remarkable that these phosphine–phosphite ligands showed higher degrees of enantioselectivity and higher reaction rates than their corresponding diphosphine **6**[10] (Table 2, entry 9) and diphosphite **7**[9] (Table 2, entry 10) analogues under the same reaction conditions.



In summary, we have described the first application of phosphine–phosphite ligands in asymmetric hydrogenation. The combination of high enantioselectivities and high performances in simple unoptimized reactions and the low cost of the ligands makes these catalyst systems very attractive for further investigation. Moreover, these ligands were better than their diphosphine and diphosphite counterparts. These results open up a new class of ligands for asymmetric hydrogenation. Research into other substrates and the use of these ligands in other metal-catalyzed reactions is the subject of further investigations.

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17 Detailed kinetic studies are under way.