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New monodentate chiral phosphite ligands for asymmetric hydrogenation

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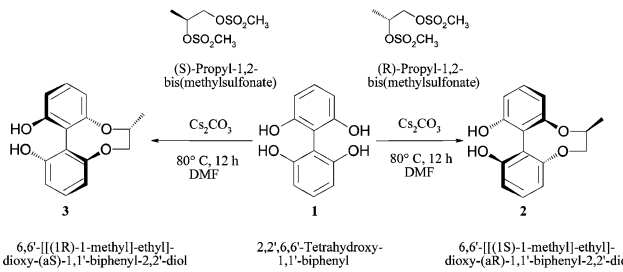
We report the synthesis of new chiral monodentate phosphite ligands with a biphenyl backbone, the axial chirality of which is introduced early in the synthesis and locked by a chiral alkylenedioxy bridge. We also describe results obtained with these ligands in rhodium-catalysed asymmetric hydrogenation of various substrates.

Among the most powerful ligands for asymmetric catalysis are bidentate phosphine ligands like BINAP[1] or DUPHOS.[2] Recently, Reetz *et al.* showed that excellent stereoselectivity in asymmetric hydrogenation can be achieved with monodentate phosphite ligands.[3] These are easily prepared from chiral diols (*e.g.* BINOL), PCl_3 and a further alcohol. This modular set-up allows for the facile synthesis of various substituted phosphite ligands necessary for screening assays.

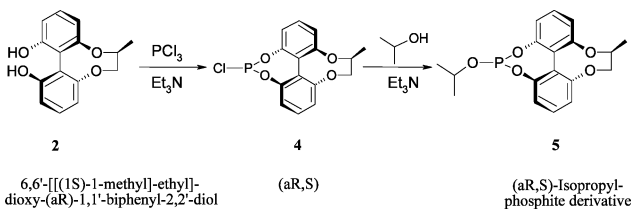
Our approach starts with achiral 2,2′,6,6′-tetrahydroxybiphenyl. Following a procedure published by Harada *et al.*, axial chirality is induced by anchoring two hydroxy groups of the biphenyl to a chiral auxiliary.[4] The configuration of the centrally chiral auxiliary induces the axial chirality of the biphenyl. Thus, only one diastereomer is formed. This strategy avoids locking the conformation of a biphenyl backbone by introducing bulky substituents in the *ortho* positions and subsequent laborious separation of the enantiomers.

We used enantiopure (*R*)- or (*S*)-1,2-propanediol as auxiliary and Cs_2CO_3 as base (Scheme 1). It is essential to convert the hydroxy groups of the auxiliary into good leaving groups, which is easily achieved by mesylation.



Scheme 1 Desymmetrisation of 2,2′,6,6′-tetrahydroxy-1,1′-biphenyl by anchoring it to enantiopure 1,2-isopropanol derivatives.

This desymmetrisation process is followed by condensation of the two remaining hydroxy functionalities of the backbone with PCl_3 and subsequent reaction of **4** with isopropanol in the presence of triethylamine as base (Scheme 2).

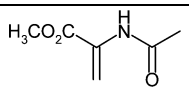
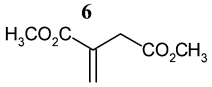
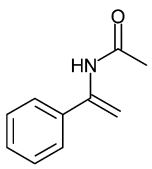
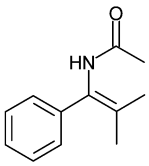
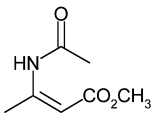
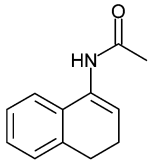


Scheme 2 Condensation of the two hydroxy groups of **2** and subsequent condensation of **4** with isopropanol to yield phosphite **5**.†

The condensation of the diols **2** and **3** with PCl_3 was performed at −78 °C in toluene to avoid side reactions of the reactive chlorophosphite intermediate **4**. The diol was added in small portions as a solid in order to avoid formation of the so-called 'Pringle-product'[5] which contains two equivalents of phosphorus, each of them bound to one aryloxy group.

It is noteworthy that the ^{31}P-NMR spectrum of **5**—and that of its enantiomer—shows two signals due to the two possible diastereomers caused by the phosphorus centre and the C_1 symmetrical propyldioxy backbone. Consequently, only one ^{31}P-signal was observed when enantiopure (*R*)- or (*S*)-butyl-

Table 1 Hydrogenation[a] of various substrates using **5** as ligand[b]

Entry	Substrate	Conversion (%)[c]	ee (%)[d]
1	 **6**	100	93 (*S*)
2	 **7**	100	96 (*R*)
3	 **8**	100	81
4	 **9**	64	8
5	 **10**	100	11
6	 **11**	100	66

[a] Reactions in CH_2Cl_2, room temperature, 3 bar H_2. [b] 2 mol% [Rh(cod)$_2$]OTf; ligand/Rh = 1.1. [c] Determined by GC. [d] Determined by chiral GC.

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2,3-bis(methylsulfonate) was used as the anchoring auxiliary in the desymmetrisation procedure, as this results in a C_2-symmetric ligand backbone.[6] For hydrogenation experiments, **5** was used as a mixture of the two diastereomers. The difference between them is the orientation of the methyl group introduced with the chiral auxiliary towards the phosphorus lone pair. For detailed studies on its influence on the ligand's catalytic behaviour separation of the diastereomers would be necessary.

Hydrogenation experiments were performed under a hydrogen pressure of 3 bar at room temperature over a period of 24 hours using a variety of substrates. In Table 1, entries 1, 2 and 3, quantitative conversion and very good enantiomeric excesses (ee) were achieved. The absolute stereochemistry for the products of entries 1 and 2 were determined as (*S*)-alanine-*N*-acetyl methyl ester and (*R*)-dimethyl-2-methylsuccinate respectively by comparison with authentic samples when using **5** as the ligand.

Entry 6 shows good conversion, however the selectivity reaches only 66% ee. Presumably due to the higher steric demand of substrates **9** and **10** we only observed low ee values with medium to high conversions (entries 3 and 5).

Substrate **11** was hydrogenated with complete conversion but only medium ee.

Beside ligand **5** we synthesised its enantiomer, which was also used in hydrogenation experiments showing identical results with opposite stereoinduction.

The synthesis of phosphites containing other alcohols like benzyl alcohol instead of isopropanol was also attempted. Due to the formation of considerable amounts of side products, isolation of the desired products is still challenging.

In conclusion, we have been able to synthesise new chiral, non-racemic phosphite ligands by inducing the stereochemistry right in the beginning of the synthetic pathway in order to avoid separation of racemates later in the synthesis. The resulting ligands exhibit good enantioselectivities with mostly quantitative conversion of the substrates when used in asymmetric hydrogenation reactions. This makes them a promising class of ligands.

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Notes and references

† 0.081 ml (0.127 g, 0.929 mmol) PCl_3 dissolved in 30 ml toluene were cooled to −78 °C before 0.53 ml (0.384 g, 3.79 mmol) triethylamine were added. To this solution 200 mg (0.77 mmol) of 6,6′-[(1*S*)-1-methylethyl]dioxy(a*R*)-1,1′-biphenyl-2,2′-diol **2** were added as solid over a period of 30 min. After another 30 min of stirring at −78 °C the reaction mixture was allowed to warm to room temperature and stirred for 2 h. The solution was separated from solid triethylammonium chloride by filtration and the solvent was removed *in vacuo*. After dissolving the white residue in 20 ml of toluene and addition of 0.162 ml (0.117 g, 1.16 mmol) triethylamine, 0.06 ml (0.046 g, 0.77 mmol) isopropanol were added *via* a syringe. The reaction mixture was stirred for 12 h at room temperature before it was filtered and the solvent was removed under vacuum yielding 181 mg (68%) of a sticky white solid.

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6 These latter phosphite comopounds are currently also under inverstigation as ligands for hydrogenation reactions.