PegPhos: a monodentate phosphoramidite ligand for enantioselective rhodium-catalysed hydrogenation in water†

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A BICOL derived monodentate phosphoramidite ligand gives ee's up to 89% in the enantioselective Rh-catalysed hydrogenation of *N*-acyl dehydroalanine using water as the solvent.

Water is a very attractive solvent for organic synthesis from an economical as well as an environmental point of view.[1] Extensive research has been done on the use of water as solvent for (stereoselective) organic reactions. Also hydrogenation reactions in water are well documented.[2] On the other hand, only limited reports have appeared describing asymmetric hydrogenations in an aqueous environment. In general, the low water solubility of the catalysts and substrates cause a decrease in reaction rate. The obvious way to avoid this problem is to make the ligands water-soluble.

In general, chiral ligands used for these reactions are water-soluble analogues of well known bidentate phosphines (*e.g.* BINAP, DIOP, BDPP and BIFAP)[3] as well as ligands based on carbohydrates[4] or amino acids.[5] The use of biphasic systems makes it possible to recycle these water soluble ligands. An alternative method to increase the reaction rate of catalysts in aqueous media is by adding surfactants. A variety of surfactants were introduced by Oehme and Selke for the rhodium-catalysed asymmetric hydrogenation of different substrates.[6] Good enantioselectivities and high reaction rates were obtained.

In this communication we want to disclose the, to the best of our knowledge, first monodentate phosphoramidite ligand providing high ee's in the Rh-catalysed enantioselective hydrogenation of a dehydroamino acid in water.

Currently, BINOL-derived monodentate phosphoramidite ligands such as MonoPhos (Chart 1) are among the cream of the crop for the enantioselective hydrogenation of a variety of *N*-acyl dehydroamino acids, enamides and enol carbamates.[7] Unfortunately, modification of BINOL to render the ligand water-soluble, is not straightforward. To overcome this problem, the BINOL related biscarbazole-derived BICOL was developed allowing facile introduction of functional moieties at both nitrogen atoms enabling fine-tuning of the catalytic and physical properties.[8]

Enantiopure BICOL derived phosphoramidite ligands have been prepared functionalised with carbosilane dendritic wedges at both nitrogen atoms. This allows easy recovery after the Rh-catalysed asymmetric hydrogenation of dehydro aminoesters that gave ee's up to 95%.[9] These results also show that carbazole-*N* functionalisation is possible without affecting the catalytic efficiency. We envisioned that attachment of neutral tetraethylene glycol units at both nitrogen atoms of BICOL renders the ligand soluble in water. Further elaboration into the corresponding phosphoramidite would afford PegPhos (see Chart 1), a potential ligand for the Rh-catalysed enantioselective hydrogenation in water.

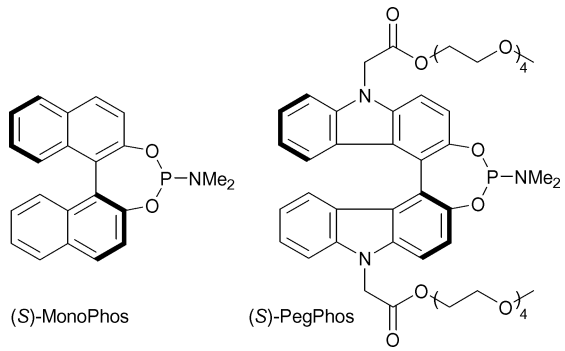
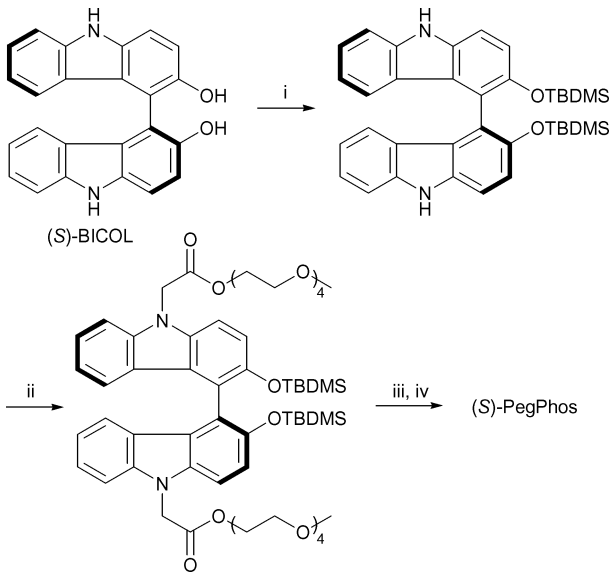


Chart 1

The synthesis of (*S*)-PegPhos was achieved in just four steps from (*S*)-BICOL (Scheme 1). To allow selective *N*,*N*-dialkylation, the phenolic hydroxyl groups of (*S*)-BICOL were protected as



Scheme 1 *Reagents and conditions*: i. TBDMSCl, imidazole, DMF, 65 °C, 4 h. ii. KHDMS, DMF, 0 °C, 1 h, followed by addition of the bromide, RT, 12 h. iii. TBAF, THF. iv. HMPT, MeCN, reflux, 4 h.

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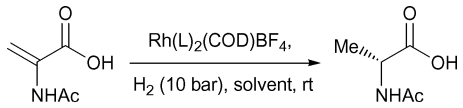
Table 1 Asymmetric hydrogenation of *N*-acyl dehydroalanine with PegPhos and MonoPhos in various solvents



Entry	Conditions	PegPhos[a,b]	TOF/h^{-1}	MonoPhos[a,b,c]	TOF/h^{-1}
1	CH_2Cl_2	57	133	90 (82)	400 (133)
2	MeOH	90	1200	95 (94)	600 (600)
3	MeOH–H_2O	89	1200	65 (54)	20 (55)
4	H_2O	82	55	16 (0)	20 (25)
5	MeOH + 10% SDS	74	2000	89 (83)	63 (300)
6	MeOH–H_2O + 10% SDS	82	750	80 (47)	20 (92)
7	H_2O + 10% SDS	89	600	83 (79)	50 (44)

[a] Ee's in %. [b] Products were analysed as their corresponding methyl ester. [c] Values in parentheses are results from *in situ* formed catalyst.

TBDMS-ethers. *N*,*N*-dialkylation was achieved after deprotonation using KHDMS as the base followed by treatment of the resulting potassium amides with 2-(2-(2-methoxyethoxy)ethoxy)ethyl 2-bromoacetate. TBAF mediated liberation of the hydroxyl groups and subsequent reaction with HMPT provided the water soluble phosphoramidite PegPhos.

The catalytic performance of PegPhos was compared with MonoPhos which proved highly effective in the asymmetric hydrogenation of dehydroamino acids. The catalyst was obtained by reaction of two equivalents of the ligand with $Rh(COD)_2BF_4$ in CH_2Cl_2 and subsequent removal of the solvent. As a representative substrate *N*-acyl dehydroalanine was chosen. The hydrogenation reactions were performed in a semi-automated eight reactor Endeavor™ autoclave pressurized with 10 bar of hydrogen.

Initial experiments in CH_2Cl_2 (Table, Entry 1) gave full conversion and ee's of 57% and 90% for PegPhos and MonoPhos, respectively, both in favour of the *R*-product and with TOF's of 133 h^{-1} and 400 h^{-1}.

By switching to the more polar solvent MeOH (Entry 2), especially PegPhos showed a remarkable 9-fold reaction rate increase and also the ee now reached 90%. The addition of water (Entry 3) slowed down the activity of MonoPhos drastically (30-fold) together with a significant drop in ee, in sharp contrast with PegPhos that fully maintained its high rate and enantioselectivity. In pure water (Entry 4) PegPhos still gave a respectable 82% ee but at the expense of a 22-fold rate decrease while under the same conditions MonoPhos almost lost its enantioselectivity and activity. Also, it is clear that the phosphoramidite moiety is fully compatible with water showing no sign of hydrolysis.

The addition of surfactants is known to influence the activity and selectivity of homogeneous catalysts in highly polar solvents (*vide supra*). Regarding the ee, no beneficial effect could be seen after addition of SDS to MeOH (Entry 5) or a water–MeOH mixture (Entry 6). By adding SDS to water, the ee obtained with MonoPhos increased from 16% to 83% together with a more than 2-fold increase of the TOF. Under these conditions PegPhos clearly outperformed MonoPhos by reaching an ee of 89% as well as a 12-fold higher rate.

In conclusion, we have shown that the versatile biscarbazole based BICOL skeleton may be functionalized with polyethylene glycol units at the nitrogen atoms to render this highly apolar moiety soluble in water. The resulting PegPhos ligand showed to be superior to the parent MonoPhos ligand, in activity as well as in selectivity, in the enantioselective Rh-catalysed hydrogenation of dehydroamino acids in polar solvents, especially in water.

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