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 carbohydrates4 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 bicarbazole-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.

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

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Chart 1

Scheme 1 Reagents and conditions: i. TBDMSI, 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.
TBDMS-ethers. N,N-dialkylation was achieved after deprotonation using KHDMDS as the base followed by treatment of the resulting potassium amides with 2-(2-(methoxyethoxy)ethoxy)ethyl 2-bromoacetate. TBAF mediated liberation of the hydroxy 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)2BF4 in CH2Cl2 and subsequent removal of the solvent. As a representative substrate N-acetyl dehydroalanine was chosen. The hydrogenation reactions were performed in a semi-automated eight reactor by reaction of two equivalents of the ligand with Rh(COD)2BF4 in MonoPhos which proved highly effective in the asymmetric phosphoramidite PegPhos.

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

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>PegPhos*</th>
<th>TOF/h⁻¹</th>
<th>MonoPhos*⁺⁺</th>
<th>TOF/h⁻¹</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>CH₂Cl₂</td>
<td>57</td>
<td>133</td>
<td>90 (82)</td>
<td>400 (133)</td>
</tr>
<tr>
<td>2</td>
<td>MeOH</td>
<td>90</td>
<td>1200</td>
<td>95 (94)</td>
<td>600 (600)</td>
</tr>
<tr>
<td>3</td>
<td>MeOH–H₂O</td>
<td>89</td>
<td>1200</td>
<td>65 (54)</td>
<td>20 (55)</td>
</tr>
<tr>
<td>4</td>
<td>H₂O</td>
<td>82</td>
<td>55</td>
<td>16 (9)</td>
<td>20 (25)</td>
</tr>
<tr>
<td>5</td>
<td>MeOH + 10% SDS</td>
<td>74</td>
<td>2000</td>
<td>89 (83)</td>
<td>63 (300)</td>
</tr>
<tr>
<td>6</td>
<td>MeOH–H₂O + 10% SDS</td>
<td>82</td>
<td>750</td>
<td>80 (47)</td>
<td>20 (92)</td>
</tr>
<tr>
<td>7</td>
<td>H₂O + 10% SDS</td>
<td>89</td>
<td>600</td>
<td>83 (79)</td>
<td>50 (44)</td>
</tr>
</tbody>
</table>

* Ee’s in %, * Products were analysed as their corresponding methyl ester. † Values in parentheses are results from in situ formed catalyst.

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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References


