Highly Enantioselective Rhodium-Catalyzed Hydrogenation with Monodentate Ligands

Michel van den Berg, a Adriaan J. Minnaard, a Ebe P. Schudde, b Jan van Esch, a André H. M. de Vries, a, c Johannes G. de Vries, a, c and Ben L. Feringa a, d

Department of Organic and Molecular Inorganic Chemistry, University of Groningen, Nijenborgh 4, 9747 AG Groningen, The Netherlands

DSM Research, Life Sciences-Chemistry & Catalysis, P.O. Box 18, 6160 MD Geleen, The Netherlands

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The homogeneous enantioselective hydrogenation of functionalized prochiral olefins is one of the most frequently studied and most efficient transition-metal-catalyzed reactions. In the first reports using chiral Wilkinson type catalysts, low enantiomeric excesses (ee’s) were obtained using monodentate phosphines as ligands. All attempts to develop monodentate ligands which would afford high ee’s in this reaction met with limited success, the best result being reached with CAMP, already published in 1972, giving ee’s up to 90% in the hydrogenation of dehydroamino acids 8a.

Although new monodentate phosphorus ligands 4 play a significant role in other transition metal-catalyzed reactions, highly enantioselective hydrogenations are exclusively based on bidentate phosphorus ligands. Starting with Kagan’s diop 5 a large number of bidentate ligands with excellent selectivities was designed. Among the most successful are DIPAMP 6, which gives superior results compared to its monodentate analogue PAMP, the frequently used BINAP ligand, the ferroceny1-based ligands 6 and the DuPHOS, BPE, and FerroTANE ligands, the latter showing extremely high enantioselectivities and broad scope 6d, 10.

To date, not only phosphines (phosphines) are used but also bidentate aminophosphines, 11 phosphites, 12 phosphinites, 13 phosphonites, 14 and hybrid ligands such as phosphe-phosphine, 15 aminophosphine-phosphinite, 16 and phosphine-phosphinite, 17 whereas very recently phosphine-phosphoramidite 18 and phosphinite-phosphite 19 ligands were reported.

It is assumed that the use of bidentate ligands results in rigidity in the catalyst which leads to more effective chiral induction. 6a A similar conclusion has been drawn from the general trend of decreasing enantioselectivity with increasing conformational flexibility of the bidentate ligand. 20 This does not, however, preclude the possibility that rhodium catalysts based on monodentate ligands could show the same high selectivity, especially when the two ligands on rhodium strongly restrict each other’s conformational freedom. Encouraging is a recent report by Pringle and co-workers on a monodentate phosphonite ligand which leads to 92% ee at 73% conversion in the rhodium-catalyzed hydrogenation of methyl 2-acetamido acrylate. 21

Herein we report monodentate phosphoramidites as new ligands for the enantioselective rhodium-catalyzed hydrogenation of olefins with unprecedented high ee’s up to 99.8%.

Phosphoramide ligands have not been used in asymmetric hydrogenation but showed excellent enantioselectivities in copper-catalyzed dialkylzinc additions to enones. 22 With Rh(COD)2BF4 as the catalyst precursor and monodentate ligand (S)-14 (equiv with respect to rhodium) 25 we obtained quantitative conversion under ambient conditions (rt, 1 bar H2, 20 h) and a


were converted into their corresponding methyl esters in CH2Cl2 and EtOAc under ambient pressure at room temperature or 0 °C (Table 2). Optimum ee's were obtained in EtOAc as solvent at 0 °C without prehydrogenation of the substrate (0.2 mmol, 0.04 M), while 100% conversion was observed unless mentioned otherwise. \(^a\) See Supporting Information. \(^b\) Due to poor solubility of the catalyst the reaction was very slow and did not go to completion.

Table 2. Asymmetric Hydrogenation of Dehydroamino Acid and Itaconic Acid Derivatives

<table>
<thead>
<tr>
<th>substrate</th>
<th>solvent</th>
<th>% ee</th>
<th>0 °C</th>
<th>25 °C</th>
<th>conf.</th>
</tr>
</thead>
<tbody>
<tr>
<td>5: R = H, R' = Me</td>
<td>CH2Cl2</td>
<td>95</td>
<td>R</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5: R = H, R' = Me</td>
<td>EtOAc</td>
<td>97</td>
<td>R</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5: R = Ph, R' = Me</td>
<td>CH2Cl2</td>
<td>99</td>
<td>R</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5: R = Ph, R' = Me</td>
<td>EtOAc</td>
<td>99</td>
<td>R</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5: R = p-OAc-m-OMePh, R' = Me</td>
<td>CH2Cl2</td>
<td>97</td>
<td>R</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5: R = p-OAc-m-OMePh, R' = Me</td>
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<td>97</td>
<td>R</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7: R = Me</td>
<td>CH2Cl2</td>
<td>94</td>
<td>S</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7: R = H</td>
<td>CH2Cl2</td>
<td>98</td>
<td>S</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7: R = H</td>
<td>EtOAc</td>
<td>95</td>
<td>S</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) For conditions, see Table 1, 100% conversion was observed in all cases. \(^b\) See Supporting Information. \(^c\) For ee determination, products were converted into their corresponding methyl esters.

High pressures accelerate the hydrogenation reaction, but with a number of bidentate ligands a sharp decrease in ee is encountered.\(^6\) Hydrogenation experiments were performed at 5 bar of H2 pressure with a decreased amount of catalyst (0.5 mol%), showing only slight differences in ee compared to the hydrogenation under ambient pressure (Table 3). In addition the hydrogenation of \(5\) was carried out at a pressure of 60 bar (0.9 mol % catalyst)\(^28\) in EtOAc giving a very fast reaction (100% conversion in 4 min) with a slight increase in enantioselectivity (97% ee).

In conclusion, excellent ee's are obtained in the rhodium-catalyzed hydrogenation using a simple and readily available monodentate phosphoramidite chiral ligand. Notable features are the levels of enantioselectivity (>99%) reached, comparable with those of bidentate ligands, and the very fast and enantioselective hydrogenation under high pressure with only negligible effects on the levels of stereocontrol.

The easy preparation of ligand \(1\) from commercially available starting materials will strongly reduce catalyst costs, thus greatly enhancing prospects of industrial application. Extension of the scope of this reaction and mechanistic studies are currently under investigation.

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Supporting Information Available: Experimental and chromatographic details (PDF). This material is available free of charge via the Internet at http://pubs.acs.org

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