Highly Enantioselective Rhodium-Catalyzed Hydrogenation with Monodentate Ligands

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

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

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

Received July 10, 2000

The homogeneous enantioselective hydrogenation of functionalyzed prochiral olefins is one of the most frequently studied and most efficient transition metal-catalyzed reactions.1 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 acid.2

Although new monodentate phosphorus ligands4 play a significant role in other transition metal-catalyzed reactions, highly enantioselective hydrogenations are exclusively based on bidentate phosphorus ligands.5 Starting with Kagan’s diop ligand, a large number of bidentate ligands with excellent selectivities was designed.6 Among the most successful are DIPAMP,7 which gives extremely high enantioselectivities and broad scope.6d,10

The best results were obtained using monodentate phosphoramidite7a ligands.8 Although new monodentate phosphorus ligands4 play a significant role in other transition metal-catalyzed reactions, highly enantioselective hydrogenations are exclusively based on bidentate phosphorus ligands.5 Starting with Kagan’s diop ligand, a large number of bidentate ligands with excellent selectivities was designed.6 Among the most successful are DIPAMP,7 which gives extremely high enantioselectivities and broad scope.6d,10

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%. Phosphoramidite ligands have not been used in asymmetric hydrogenation22 but showed excellent enantioselectivities in copper-catalyzed dialkylzinc additions to enones.23 With Rh(COD)2BF4 as the catalyst precursor and monodentate ligand (S)-1 (2 equiv with respect to rhodium)25b we obtained quantitative conversion under ambient conditions (rt, 1 bar H2, 20 h) and a

* University of Groningen.
† DSM Research, Life Sciences-Chemistry & Catalysis.
† University of Groningen.
The hydrogenation of dehydroamino acid and itaconic acid derivatives was examined in CH$_2$Cl$_2$ and EtOAc under ambient pressure at room temperature or 0 °C (Table 2). Optimum ee's are obtained in EtOAc as solvent at 0 °C without prehydrogenation. The reaction was performed at room temperature under ambient H$_2$ pressure for 20 h [substrate (0.2 mmol, 0.04 M):Rh(COD)$_2$BF$_4$:ligand (S)-1 = 1:0.05:0.11], 100% conversion was observed unless mentioned otherwise. See Supporting Information. Due to poor solubility of the catalyst the reaction was very slow and did not go to completion.

For ee determination, products were converted into their corresponding methyl esters.

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

<table>
<thead>
<tr>
<th>Solvent</th>
<th>% ee$^b$</th>
<th>conf.$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH$_2$Cl$_2$</td>
<td>95</td>
<td>R</td>
</tr>
<tr>
<td>CICH$_2$CH$_2$Cl</td>
<td>89</td>
<td>R</td>
</tr>
<tr>
<td>MeOH</td>
<td>75</td>
<td>R</td>
</tr>
<tr>
<td>CH$_3$(CH$_2$)$_2$OCH$_2$CH$_2$OH</td>
<td>77</td>
<td>R</td>
</tr>
<tr>
<td>THF</td>
<td>93</td>
<td>R</td>
</tr>
<tr>
<td>Acetone</td>
<td>97</td>
<td>R</td>
</tr>
<tr>
<td>EtOAc</td>
<td>97</td>
<td>R</td>
</tr>
<tr>
<td>MeOAc</td>
<td>96</td>
<td>R</td>
</tr>
<tr>
<td>toluene</td>
<td>95$^c$</td>
<td>R</td>
</tr>
</tbody>
</table>

$^a$ For conditions, see Table 1, 100% conversion was observed in all cases. See Supporting Information. 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. Hydrogenation experiments were performed at 5 bar of H$_2$ 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 3 was carried out at a pressure of 60 bar (0.9 mol % catalyst) in EtOAc giving a very fast reaction (100% conversion in 4 min) with a slight increase in enantioselectivity (97%).

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 stereocenters.

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.

Acknowledgment. We thank Mr. M. B. van Gelder, Ms. L. Bleijlevens, and Dr. L. Duchateau for carrying out the GC and HPLC measurements. Financial support from the Dutch Ministry of Economic Affairs, Grant EETK97107, administered through the EET program for the development of clean technology is gratefully acknowledged.

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

JA002507F

(26) Preliminary semiempirical calculations (PM3) on an anticipated rhodium complex containing two ligands (S)-1 and a substrate molecule show favorable conformations which correspond with the observations of Pringle et al. cf. ref 21. The least stable diastereomer leads to the main product in accordance with the Halpern mechanism, cf. Halpern, J. Science 1982, 217, 401.

(27) Phosphoramidites, such as 1, are stable in protic solvents.

(28) Rh(NBD)$_2$BF$_4$ was used as the catalyst precursor.

(29) After submission of this manuscript Reetz et al. reported on monodentate phosphonite ligands in rhodium-catalyzed enantioselective hydrogenation resulting in 94% ee; Reetz, M. T.; Sell, T. Tetrahedron Lett. 2000, 41, 6333