Synthesis of novel chiral monophosphine ligands derived from isomannide and isosorbide. Application to enantioselective hydrogenation of olefins.

Houssein Ibrahim and Giang Vo-Thanh*

Institut de Chimie Moléculaire et des Matériaux d’Orsay, ICMMO. UMR 8182. Laboratoire de Catalyse Moléculaire. Université Paris-Sud 11, 91405 Orsay Cedex, France. Fax: (+) 33 169154680, E-mail: giang.vo-thanh@u-psud.fr

Abstract: A new class of monophosphine ligands has been prepared from naturally chirality renewable source, 1,4:3,6-dianhydrohexitol compounds, via a nucleophilic substitution process or a hydrophosphination reaction involving microwave activation. These ligands have been evaluated for the rhodium-catalyzed enantioselective hydrogenation of olefins giving good conversion and enantioselectivity up to 95% and 96% ee, respectively

Keywords: Monophosphine ligands, isosorbide, isomannide, hydrogenation.

The development of available, inexpensive, modular and innovative catalysts from biomass products is expected to be one of the key procedures for expanding the reaction scope and the synthetic potential of metal-catalyzed enantioselective catalysis.

Isosorbide and isomannide, industrially obtained by dehydration of D-sorbitol or D-mannitol, represent commercially available and low cost chiral starting materials for the synthesis of sophisticated molecules including chiral ionic liquids,\(^1\) phase-transfer catalysts\(^2\) and ligands (amino alcohols, amines, diphosphines, diphosphites, bis diaminophosphites, diamidophosphites).\(^3,4\)

We have recently shown that this starting material provides easy and cost effective access to optically pure functionalized and stable amino alcohol, or diamine ligands.\(^5\) The structure modification could be easily and efficiently obtained by classical organic transformations of diol groups.

Although isosorbide or isomannide were described as starting materials for the synthesis of phosphorus ligands, essentially bidentate ligands such as diphosphines, diphosphites, bisdiaminophosphites or diamidophosphites,\(^6\) no example of monophosphine derived from 1,4:3,6-dianhydrohexitol has been reported so far. Presently, the application field of monophosphine in organometallic catalysis has received much attention, particularly for
organocatalysis. We report herein the synthesis of chiral monophosphines 1 derived from isosorbide and isomannide and their use as ligand for enantioselective hydrogenation of olefins (Scheme 1).

Scheme 1. Structure of monophosphines.

First, our synthesis was inspired by our previous work on the synthesis of aminoalcohol ligands including the selective monobenzylation of the hydroxyl group at the endo position C3 of isosorbide and the activation of the free hydroxyl group at the exo position C6 as its sulfonate 3 (Scheme 2). However, the substitution of 3 with the diphenylphosphine anion failed and produced only the alcohol 2.

Scheme 2. Synthesis of monophosphine from isosorbide.

We then chose the isomannide as starting material. Indeed, benzylation of isomannide gave the monobenzylated compound 5 in 48% yield. Bromination of 5 afforded a mixture of 4a and 4b in 28% and 66% yield respectively. 4d 4a and 4b were easily separated by flash chromatography on silica gel. At this point, the exo configuration of the carbon C6 for compound 4b was confirmed by X-ray analysis (Scheme 3).

Introduction of phosphine group consists of the nucleophilic substitution of 4a or 4b. Phosphine-borane complexes 6a and 6b were obtained from 4a or 4b respectively after protection with borane dimethylsulfide complex (Scheme 4).

Surprisingly, X-ray analysis of pure crystals from 6b and 6a confirms an exo position of phosphine group due to a total retention of configuration during the substitution step (Figure 1). This was already observed by Dervisi et al. when they carried out the synthesis of isomannide-based diphosphine from the corresponding dibromide. It was demonstrated that the choice of solvent had an important effect on stereochemistry. The presence of Et₂O favors the endo product, whereas THF gave the exo as the major product.

By adding LiPPh₂ formed by addition of n-BuLi on HPPh₂ in diethyl ether following by addition of BH₃.Me₂S, we obtained a mixture of endo-7b/exo-6b (70/30) of desired phosphine boranes (Scheme 5). Endo-phosphine borane 7b and exo-phosphine borane 6b were isolated in 40% and 11% yield respectively.

---

**Scheme 4.** Synthesis of monophosphines 6a and 6b.

**Figure 1.** ORTEP drawing of 6b. Ellipsoids are drawn at the 50% probability level.
Scheme 5. Synthesis of monophosphines 6b and 7b.

We thought that the obtaining of the compound 6b with the unexpected ‘exo’ configuration could be explained by a hydrophosphination of the alkene 8 which could be obtained in situ from 4b by an elimination process in the presence of LiPPh₂ (Scheme 5). The stereoselectivity could be easily explained by the attack of PPh₂ anion on the less hindered face of the alkene 8. However, when performing the reaction of diphenylphosphine and alkene 8 in Et₂O at 20°C for 96h, no conversion was observed (Table 1). In THF, only a trace of hydrophosphination product was detected by ³¹P NMR analysis after 145h. On the other hand, using toluene as solvent in classical heating conditions, very low conversion was observed (<10%) after 72h of reaction. We turned our attention to the use of microwave irradiation (MW). This technique was widely developed in our laboratory and in other research groups. Under microwave activation, an excellent conversion was obtained after only 5h affording the regioselective exo phosphine 6b in 47% yield after purification by flash chromatography.

Table 1.

Hydrophosphination of 8.
<table>
<thead>
<tr>
<th>Conditions(^a)</th>
<th>solvent</th>
<th>(T) (°C)</th>
<th>(T) (h)</th>
<th>Conv. (%)(^b)</th>
<th>Isolated yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Et(_2)O</td>
<td>20</td>
<td>96</td>
<td>0</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>- THF</td>
<td>20</td>
<td>145</td>
<td>≤5</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Oil bath PhCH(_3)</td>
<td>60</td>
<td>72</td>
<td>&lt; 10</td>
<td>nd(^c)</td>
<td></td>
</tr>
<tr>
<td>MW PhCH(_3)</td>
<td>50</td>
<td>5</td>
<td>&gt; 95</td>
<td>47</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) Reaction was carried out using an oil bath or in a CEM microwave reactor. \(^b\) Determined by \(^1\)H NMR. \(^c\) Not determined.

Treatment of the phosphines-borane 6b and 7b with an excess of tetrafluoroboric acid dimethylether complex resulted in quantitatively formation of the phosphines exo-1 and endo-1 (Scheme 6).

\[
\begin{align*}
\text{BnO} & \quad \text{H} & \quad \text{H} & \quad \text{H}_3\text{B} \\
\text{O} & \quad \text{O} & \quad \text{HO} & \quad \text{PPh}_2
\end{align*}
\]

Scheme 6. Obtaining of momophosphines endo- and exo-1.

Complexes formed in situ from Rh[(COD)\(_2\)]BF\(_4\) and exo-1 or endo-1 ligand were examined as catalysts for the enantioselective hydrogenation of activated olefins (Table 2).

Table 2.

<p>| Hydrogenation of activated olefins.(^a) |</p>
<table>
<thead>
<tr>
<th>L*</th>
<th>R(^1)</th>
<th>R(^2)</th>
<th>(T_{1/2})</th>
<th>Conversion (%)(^b)</th>
<th>Ee (%)(^c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exo-1</td>
<td>Ph</td>
<td>Me</td>
<td>8 min</td>
<td>&gt;95</td>
<td>(S)-57</td>
</tr>
<tr>
<td>Exo-1</td>
<td>Ph</td>
<td>Me</td>
<td>24h</td>
<td>85</td>
<td>(S)-71(^d)</td>
</tr>
<tr>
<td>Exo-1</td>
<td>Ph</td>
<td>H</td>
<td>17 min</td>
<td>&gt;95</td>
<td>(S)-30</td>
</tr>
<tr>
<td>Exo-1</td>
<td>H</td>
<td>Me</td>
<td>4 min</td>
<td>&gt;95</td>
<td>(S)-72</td>
</tr>
<tr>
<td>Exo-1</td>
<td>H</td>
<td>H</td>
<td>6 min</td>
<td>&gt;95</td>
<td>(S)-70</td>
</tr>
<tr>
<td>Endo-1</td>
<td>Ph</td>
<td>Me</td>
<td>No reaction</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) Reactions were carried out at room temperature under atmospheric pressure of dihydrogen with 1mol% of Rh(COD)\(_2\)BF\(_4\) and 2.2mol% of ligand. \(^b\) Determined by \(^1\)H NMR. \(^c\) Determined by chiral HPLC analysis. \(^d\) Reaction at \(-10°C\) for 24h.
1H NMR analysis showed that complete conversions were obtained in most of cases in few minutes at room temperature under atmospheric pressure of dihydrogen. The products were obtained with satisfactory enantioselectivities when the catalyst was prepared with Exo-1 ligand. Surprisingly, no hydrogenation occurred in the presence of Endo-1 ligand. On the other hand, in the presence of Rh- Exo-1 catalyst, itaconic acid was hydrogenated quantitatively, but with a modest enantiomeric excess (32% ee), whereas, in the same reaction conditions, its corresponding dimethyl itaconate conducted to a good enantioselectivity up to 96% ee (Table 3).

Table 3.

<table>
<thead>
<tr>
<th>R</th>
<th>T½ (min)</th>
<th>Conversion (%)</th>
<th>Ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>47</td>
<td>&gt;95</td>
<td>(S)-32</td>
</tr>
<tr>
<td>Me</td>
<td>55</td>
<td>&gt;95</td>
<td>(S)-96</td>
</tr>
</tbody>
</table>

Table 3. Hydrogenation of itaconic acid derivatives

In summary, we have developed a synthesis of new monophosphine ligands derived from isosorbide and isomannide, naturally renewable sources. The initial results in asymmetric catalysis such as hydrogenation of olefins showed good catalytic activity and enantioselectivity, up to 96% ee for dimethyl itaconic ester. Although the results are certainly still quite modest with respect to what can be achieved by using well-developed enantioselective hydrogenation catalysts, this represents the highest enantioselectivity to date for hydrogenation catalysts incorporating a monophosphine ligand. During our work, we have also reported a new way to conduct the phosphines using microwave-assisted olefin hydrophosphination. Development of theses phosphorus compounds as ligands or organocatalysts in asymmetric catalysis are currently underway in our laboratory.

Acknowledgments

We wish to thank the French Ministry of Education and Research (MENESR), the CNRS and the University Paris-Sud 11 for financial supports.
References and notes


9. Compound 8 was prepared from 3 by an elimination process in the presence of t-BuOK as base.