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

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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.

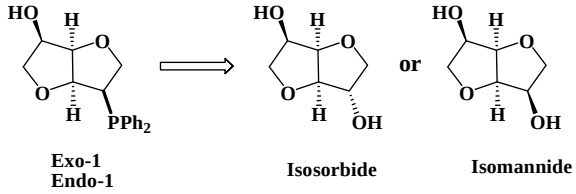
The development of available, inexpensive, modular and innovative catalysts from biomass products is expected to be one of the key procedures for expanding the reaction scope and the synthetic potential of metal-catalyzed enantioselective catalysis.

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.

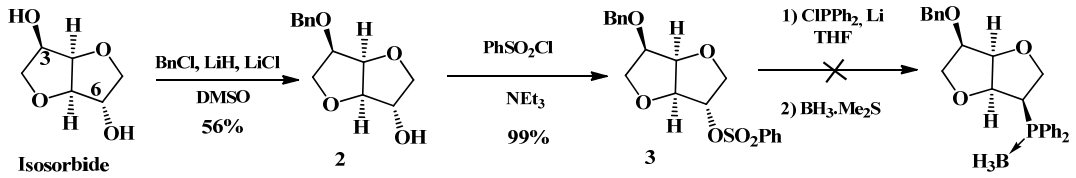
Although isosorbide or isomannide were described as starting materials for the synthesis of phosphorus ligands, essentially bidentate ligands such as diphosphines, diphosphites, bisdiaminophosphites or diamidophosphites,[6] no example of monophosphine derived from 1,4 : 3,6-dianhydrohexitol has been reported so far. Presently, the application field of monophosphine in organometallic catalysis has received much attention, particularly for

organocatalysis.[7] 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).



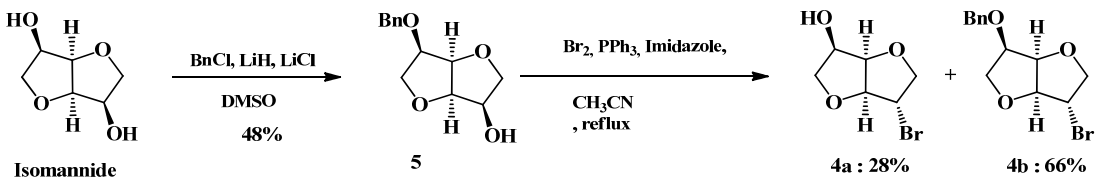
Scheme 1. Structure of monophosphines.

First, our synthesis was inspired by our previous work on the synthesis of aminoalcohol ligands[5] 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**.



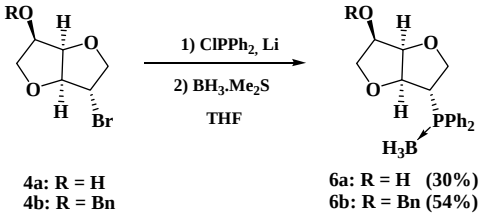
Scheme 2. Synthesis of monophosphine from isosorbide.

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).



Scheme 3. Synthesis of bromo derivatives from isomannide.

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).



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

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.[6a] It was demonstrated that the choice of solvent had an important effect on stereochemistry. The presence of Et_2O favors the *endo* product, whereas THF gave the *exo* as the major product.

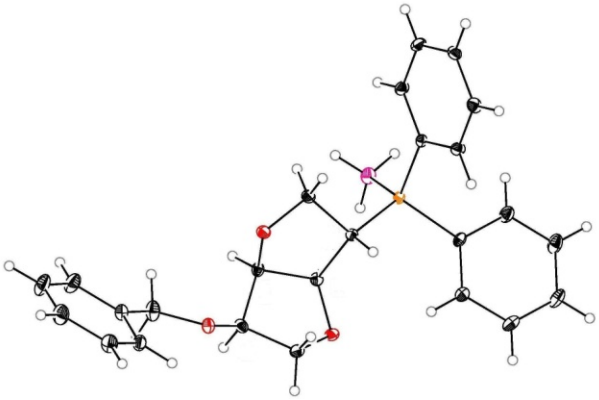
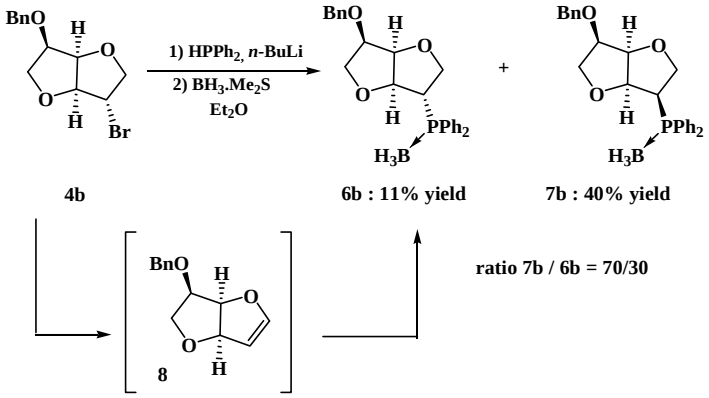


Figure 1. ORTEP drawing of **6b**. Ellipsoids are drawn at the 50 % probability level.

By adding $LiPPh_2$ formed by addition of *n*-BuLi on $HPPh_2$ in diethylether following by addition of $BH_3.Me_2S$, 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.

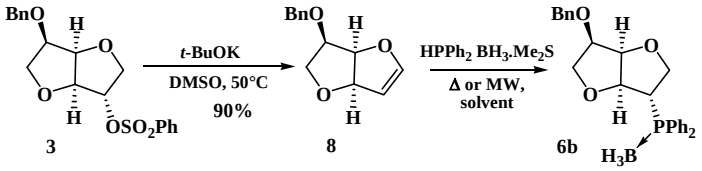


Scheme 5. Synthesis of monophosphines **6b** and **7b**.

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 $LiPPh_2$ (Scheme 5).[8] The stereoselectivity could be easily explained by the attack of PPh_2 anion on the less hindered face of the alkene **8**. However, when performing the reaction of diphenylphosphine and alkene **8**[9] in Et_2O at 20°C for 96h, no conversion was observed (Table 1). In THF, only a trace of hydrophosphination product was detected by ^{31}P 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.[10] 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.

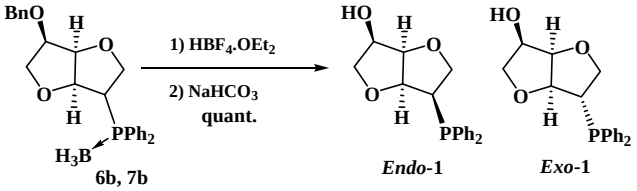
Hydrophosphination of 8.



Conditions[a]	solvent	*T* (°C)	*T* (h)	Conv. (%)[b]	Isolated yield (%)
-	Et_2O	20	96	0	-
-	THF	20	145	≤5	-
Oil bath	$PhCH_3$	60	72	< 10	nd[c]
MW	$PhCH_3$	50	5	> 95	47

[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).

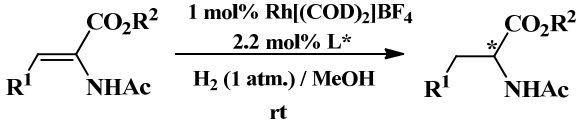


Scheme 6. Obtaining of momophosphines *endo*-and *exo*-**1**.

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.

Hydrogenation of activated olefins.[a]



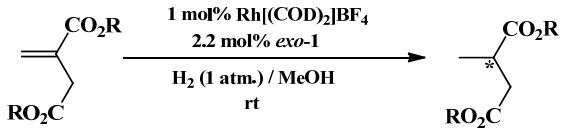
L*	R^1	R^2	$T_{1/2}$	Conversion (%)[b]	Ee (%)[c]
Exo-**1**	Ph	Me	8 min	>95	(*S*)-57
Exo-**1**	Ph	Me	24h	85	(*S*)-71[d]
Exo-**1**	Ph	H	17 min	>95	(*S*)-30
Exo-**1**	H	Me	4 min	>95	(*S*)-72
Exo-**1**	H	H	6 min	>95	(*S*)-70
Endo-**1**	Ph	Me	No reaction		

[a] Reactions were carried out at room temperature under atmospheric pressure of dihydrogen with 1mol% of $Rh(COD)_2BF_4$ 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.

Hydrogenation of itaconic acid derivatives[a]



R	$T_{1/2}$ (min)	Conversion (%)[b]	Ee (%)[c]
H	47	>95	(*S*)-32
Me	55	>95	(*S*)-96

[a] Reactions were carried out under 1 atm of hydrogen at room temperature.
[b] Determined by ^{1}H NMR. [c] Determined by chiral HPLC analysis.

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

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