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New diphosphinite ligands derived from mannitol for rhodium catalyzed enantioselective hydrogenation of ketones

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Abstract

We have developed new electron rich chiral bisphosphinites from mannitol. The new ligands have been found to be efficient chiral auxiliaries for rhodium catalyzed hydrogenation of functionalized ketones leading to hydroxy compounds in up to 86% ee.

Keywords: enantioselective hydrogenation; rhodium; diphosphanes; ketones.

Chiral phosphorous containing chelates occupy a special position among the chiral ligands applied in catalytic processes in the synthesis of optically active compounds.[1] In this context, chelates possessing diaryl substituted phosphorous ends associated to a great variety of chiral backbones have been very efficient for the asymmetric hydrogenation of C=C and C=O bonds.[1] If generally diphosphines have been utilized preferentially as stereodirecting auxiliaries for the latter reaction, there has been an increasing interest in diphosphinites for the same purpose.[2] In the latter class of ligands, carbohydrate diphosphinites constitute attracting chiral modifiers because they are easy to synthesize from readily available starting materials and have already led to important applications.[3,4]

In our continuous effort to develop easily accessible chiral diphosphanes, we have reported on the synthesis and use of the aminophosphine phosphinites (AMPP)[5] derived from amino and amido alcohols, which are highly enantioselective auxiliaries for the rhodium based asymmetric hydrogenation. Such ligands are not following the strategy consisting of incorporating a C_2-symmetry into the ligand design in order to restrict the number of diastereomeric transition states of the enantioselective catalytic process. Nevertheless, the basic cycloalkyl substituted AMPP ligands are particularly well suited for the hydrogenation of functionalized ketones.[6] We have been interested in the use of sugars as the chiral source and explored the potential of the corresponding C_2-symmetrical basic diphosphanes. Even if, as

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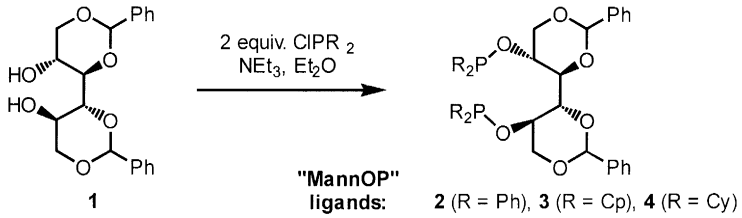
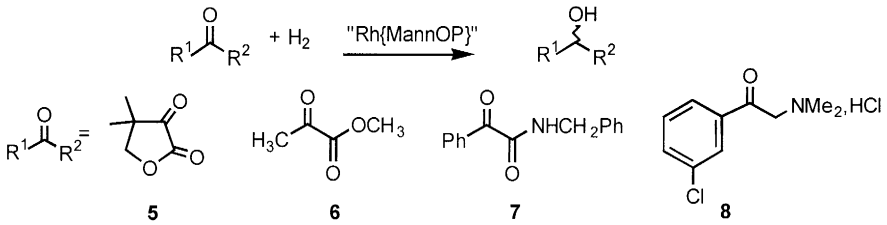
mentioned above, aryldiphosphinites based on sugar have been applied successfully in the asymmetric hydrogenation of enamides,[3,4] their behavior in the stereoselective hydrogenation of ketones has been reported only once[4c] and the synthesis and use of more basic peralkylated carbohydrate diphosphinites has not been reported yet. Herein, we describe the synthesis of new chiral carbohydrate diphosphinites and their use in the hydrogenation of functionalized ketones.

The mannitol derivative 1,3-4,6-di-*O*-benzylidene-D-mannitol **1** is readily prepared[7] and then reacted under nitrogen with two equivalents of chlorodiphenylphosphine, chlorodicyclopentylphosphine or chlorodicyclohexylphosphine in the presence of an excess of triethylamine in diethyl ether at room temperature for 18 h (Scheme 1).[8] Then, a chromatographic purification through basic alumina provided the C_2-symmetric Ph,Ph-MannOP **2**,[4c] Cp,Cp-MannOP **3**, and Cy,Cy-MannOP **4** ligands in 85–90% yields.[9]



Scheme 1.

These new ligands were then applied to the enantioselective hydrogenation of four functionalized ketones namely dihydro-4,4-dimethyl-2,3-furadione **5**, methylpyruvate **6**, *N*-benzyl benzoylformamide **7**, and *N*,*N*-dimethylamino-*m*-chloro-benzophenone **8** in the presence of rhodium catalysts (Scheme 2). The latter are prepared in situ by reacting two equivalents of the ligand with one equivalent of $[Rh(COD)Cl]_2$ or $[Rh(COD)(OCOCF_3)]_2$[10] in the solvent used for the catalytic reaction.



Scheme 2.

Results of the hydrogenation reactions are listed in Table 1. The series of investigated ketones underwent smooth hydrogenation leading to the corresponding hydroxy derivatives with modest to high enantioselectivities (40–86% ee). The electronic properties of the MannOP ligands influenced greatly the performances of the catalysts. Thus, the electron-donating alkyl substituted ligands induce higher ee than the corresponding phenyl substituted derivatives and they are also providing catalysts presenting higher activities (entry 11 versus 10 for example).[11] Generally, the bulkier cyclohexyl is most effective for asymmetric induction with respect to the cyclopentyl analogue (entry 21 versus 20 for example). On the other side, the dependency of the enantioselectivity and activity on the non-chiral ligand is also remarkable. Thus, the adequate association between the substrate to hydrogenate and the non-chiral ligand leads to the most effective catalysts i.e. **5** and **6** with CF_3COO (entries 9 and 14, respectively) and **7** with Cl (entry 18). Ethanol as solvent, necessary to dissolve the chlorohydrate **8**, affords most probably a cationic catalytic species in which the non-chiral ligand (Cl) has been removed. Thus, only the properties of the chiral ligands involved influences the activity and the enantioselectivity of the catalyst (entries 20 and 21). The replacement of phenyl by cycloalkyl substituents led to an opposite absolute

configuration for the hydrogenation in only one case (substrate **5**) (entry 3 versus 1).[12] This is attributed to the coordination of opposite enantiofaces for substrate **5** that result from different conformations of the catalytic intermediates including ligands **2** and **3**. Such a trend was not observed for the other substrates while being hydrogenated by catalytic systems involving identical ligands.[12]

Table 1
Asymmetric hydrogenation of ketones catalyzed by 'Rh-MannOP' complexes[a]

Entry	Substrate	Catalyst precursor	P_{H2} (bar)	Temp. (°C)	time (hr)	$t_{1/2}$ (min)[b]	conv. (%)[c]	ee (%) Config.[d]
1	**5**	[Rh{**2**}Cl]$_2$	50	20	19	nd	20	40 (*S*)
2		"	"	50	"	"	60	44 (*S*)
3		[Rh{**3**}Cl]$_2$	50	20	18	"	100	66 (*R*)
4		"	1	"	"	150	"	62 (*R*)
5	[e]	"	50	"	24	nd	100	70 (*R*)
6		[Rh{**3**}(OCOCF$_3$)]$_2$	"	"	4	25	"	80 (*R*)
7		[Rh{**4**}Cl]$_2$	50	"	18	nd	"	60 (*R*)
8		"	1	"	"	165	"	62 (*R*)
9		[Rh{**4**}(OCOCF$_3$)]$_2$	"	"	2	18	"	**84 (*R*)**
10	**6**	[Rh{**2**}Cl]$_2$	50	20	56	nd	70	48 (*R*)
11		[Rh{**3**}Cl]$_2$	"	"	3	"	100	76 (*R*)
12		[Rh{**3**}(OCOCF$_3$)]$_2$	"	"	"	"	"	78 (*R*)
13		[Rh{**4**}Cl]$_2$	"	"	"	"	"	82 (*R*)
14		[Rh{**4**}(OCOCF$_3$)]$_2$	"	"	"	"	"	**86 (*R*)**
15	**7**	[Rh{**2**}Cl]$_2$	50	50	48	nd	100	43 (*S*)
16		[Rh{**3**}Cl]$_2$	"	20	18	"	"	65 (*S*)
17		[Rh{**3**}(OCOCF$_3$)]$_2$	"	"	"	"	"	50 (*S*)
18		[Rh{**4**}Cl]$_2$	"	"	"	"	"	**76 (*S*)**
19		[Rh{**4**}(OCOCF$_3$)]$_2$	"	"	"	"	"	65 (*S*)
20	**8**[f]	[Rh{**3**}Cl]$_2$	50	50	24	nd	90	58 (*S*)
21		[Rh{**4**}Cl]$_2$	"	"	"	"	95	**78 (*S*)**

[a]The reactions were carried out by using 2 mmol of substrate, 0.1 M in dry degassed toluene unless otherwise stated. Substrate/Rh : 200/1. [b]Time required for 50% conversion; nd: not determined. [c]Determined by GC for **5** and **6** and by ^{1}H NMR of the crude product for **7** and **8.** For complete reactions, the times reported are not necessarily optimized. [d]Determined by GC analysis (FS-Cyclodex β-I/P) for the hydrogenated product of **5** and **6**, based on the specific rotation value $[\alpha]_D^{26}$ = +82.2 (*c* 1.09, $CHCl_3$) for (*S*)-(+)-*N*-benzylmandelamide, determined by HPLC analysis (Chiralcel OD (Daicel), hexane/*i*PrOH 95/5) for the free aminoalcohol obtained from **8**. [e]Substrate/rhodium = 1000/1. [f]EtOH as solvent.

The MannOP ligands reported here provide nine-membered chelates that are more prone to flexibility than five- or seven-membered chelates. In addition, they might also provide *trans*-coordinated ligands. Consequently, they may induce lower selectivities. Nevertheless, the degree of enantioselectivity obtained here suggests that the overall structure of the ligand confer a particular control of the chiral environment. The latter is keeping the phosphorous ends in space with a bite angle most appropriate for a *cis* chelation to the rhodium center. As a matter of fact, the nature of the derivatizing group on the sugar (here benzylidene) and the presence of several chiral centers are certainly important factors that influence significantly the conformational properties of the catalysts. The space arrangement of such ligands could be perceived from the examination of molecular mechanics optimized structures. From a reactivity

standpoint, these ligands are not superior to the previously reported AMPP analogues. However, from a tuning standpoint, they may offer attractive features when considering the modular approach to their synthesis. As such, the combination of the various derivatizing possibilities with the conversion of the remaining OH groups of the starting sugar into phosphinite species will lead to attractive structures.

In conclusion, we have demonstrated the applicability of such sugar based electron-donating ligands in asymmetric catalysis. Even though these ligands are not chiral vicinal diaryl or dialkyl phosphinites, they are quite effective for the hydrogenation of ketones. Research is under way to investigate both areas of new synthesis and applications of such ligands.

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References

1. (a) Noyori, R. In *Asymmetric Catalysis in Organic Synthesis*; Wiley: New York, 1994. (b) *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH Publishers, Inc.: New York, 1993. (c) Brunner, H.; Zettlmeier, W. *Handbook of Enantioselective Catalysis with Transition Metal Compounds*; VCH: Weinheim, 1993; Vol. I and II.
2. Lead references to diphosphinite ligands. (a) Hayashi, T.; Tanaka, M.; Ogata, I. *Tetrahedron Lett*. **1977**, *3*, 295–296. (b) Johnson, T. H.; Rangarajan, G. *J. Org. Chem*. **1980**, *45*, 62–65. (c) Zhu, G.; Zhang, X. *J. Org. Chem*. **1998**, *63*, 3133–3136. (d) Chan, A. S. C.; Hu, W.; Pai, C.-C.; Lau, C.-P. *J. Am. Chem. Soc*. **1997**, *119*, 9570–9571.
3. Examples of carbohydrate diphosphinites. (a) Selke, R.; Pracejus, H. *J. Mol. Catal*. **1986**, *37*, 213–225 and references cited therein. (b) Selke, R. *ibid*. **1986**, *37*, 227–234. (c) Selke, R.; Schwarze, M.; Baudish, H.; Grassert, I.; Michalik, M.; Oehme, G.; Stoll, N.; Costisella, B. *ibid*. **1993**, *84*, 223–237. (d) Selke, R. *J. Organomet. Chem*. **1989**, *370*, 241–248. (e) Cullen, W. R.; Sugi, Y. *Tetrahedron Lett*. **1978**, *19*, 1635–1636. (f) Kreutzfeld, H.-J.; Döbler, C.; Krause, H. W.; Facklam, B. *Tetrahedron: Asymmetry*, **1993**, *4*, 2047–2051. (g) RajanBabu, T. V.; Ayers, T. A.; Casalnuovo, A. L. *J. Am. Chem. Soc*. **1994**, *62*, 6012–6028. (h) RajanBabu, T. V.; Radetich, B.; You, K. K.; Ayers, T. A.; Casalnuovo, A. L.; Calabrese, J. C. *J. Org. Chem*. **1999**, *64*, 3429–3447.
4. For examples of open chain sugar based diphosphanes. (a) Yamashita, M.; Naoi, M.; Imoto, H.; Oshikawa, T. *Bull. Soc. Chem. Jpn.* **1989**, *62*, 942–944. (b) Chen, Y.; Li, X.; Tong, S.-k.; Choi, M. C. K.; Chan, A. S. C. *Tetrahedron Lett.* **1999**, *40*, 957–960. (c) Bendaya, A.; Masotti, H.; Peiffer, G.; Siv, C.; Archalvis, A. *J. Organomet. Chem*. **1993**, *444*, 41–46. (d) Choudary, B. M.; Ravichandra Sarma, M.; Dyurga Prasad, A.; Narender, N. *Indian J. Chem*. **1994**, *33B*, 152–155.
5. (a) Agbossou, F.; Carpentier, J.-F.; Hapiot, F.; Suisse, I.; Mortreux, A. *Coord. Chem. Rev.* **1998**, *180*, 1615–1645.
6. (a) Agbossou, F.; Carpentier, J.-F.; Hatat, C.; Kokel, N.; Mortreux, A.; Betz, P.; Goddard, R.; Krüger, C. *Organometallics* **1995**, *14*, 2480–2489. (b) Roucoux, A.; Thieffry, L.; Carpentier, J.-F.; Devocelle, M.; Méliet, C.; Agbossou, F.; Mortreux, A. *Organometallics* **1996**, *15*, 2440–2449. (c) Pasquier, C.; Naili, S.; Pelinski, L.; Brocard, J.; Mortreux, A.; Agbossou, F. *Tetrahedron: Asymmetry* **1998**, *9*, 193–196. (d) Devocelle, M.; Agbossou, F.; Mortreux, A. *Synlett* **1997**, 1306–1308.
7. Baggett, N.; Striblehill, P. *J. Chem. Soc., Perkin Trans. 1* **1977**, 1123–1126.
8. The chlorodiphenylphosphine and chlorodicyclohexylphosphine were commercially available. The chlorodicyclopentylphosphine was synthesized following the procedure reported in Ref. 6b. ^{31}P NMR always assayed that the reactions went to completion over the course of 18 h at room temperature.
9. $^{31}P\{^{1}H\}$ NMR of the ligands (CD_2Cl_2, δ ppm) **2**, 116; **3**, 142; **4**, 146.
10. Synthesis of $[Rh(COD)Cl]_2$: Giordano, G.; Crabtree, R. *Inorg. Synth*. **1979**, *19*, 218–220. Synthesis of $[Rh(COD)(OCOCF_3)]_2$: Lahoz, F.; Martin, A.; Esteruelas, M. A.; Sola, E.; Serrano, J. L.; Oro, L. A. *Organometallics* **1991**, *10*, 1794–1799.
11. This behavior is following what is generally observed with AMPP ligands as well.
12. Such a trend has been observed twice with AMPP ligands, see: Roucoux, A.; Suisse, I.; Devocelle, M.; Carpentier, J.-F.; Agbossou, F.; Mortreux, A. *Tetrahedron: Asymmetry* **1996**, *7*, 379–382 and Ref. 6a.