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Chiral Monophosphites Derived from Carbohydrate: Conformational Effect in Catalytic Asymmetric Hydrogenation

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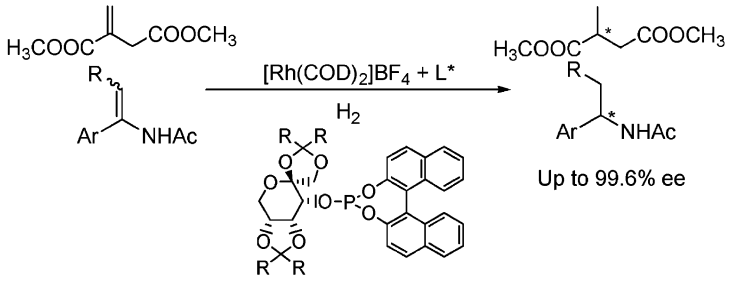
ABSTRACT



The carbohydrate-derived chiral monophosphites with additional groups have been synthesized and used for asymmetric hydrogenation of dimethyl itaconate and enamides. Up to 99.6% ee and 98.5% ee have been obtained, respectively.

The design and synthesis of efficient chiral phosphorus ligands has played an important role in the development of transition-metal-catalyzed asymmetric hydrogenation reactions.[1] In general, most of the effective chiral phosphorus ligands are bidentate. While the synthesis of monophosphorus ligands is usually simpler than that of diphosphorus compounds, it is often difficult to develop effective catalysts using chiral monophosphines as ligands, which may be due to some extent to free rotation of M−P bond.

Recently, some easily prepared and efficient chiral monophosphorus ligands such as **1** have been developed by Pringle,[2] Reetz,[3] and Feringa,[4] and these have exhibited high enantioselectivity in asymmetric hydrogenation.[5] The X-ray structure of the Pt−**1a** complex gave some insights into why the high enantioselectivities are achieved with this system; it is because rotation of the ligand around Pt−P bond is hindered which reduces the number of rotameric forms.[2]

To further expand the range of ligands and enantioselectivity of this asymmetric hydrogenation process, we designed a new class of chiral monophosphorus ligands **2**, which contain additional groups in the proper spatial configuration

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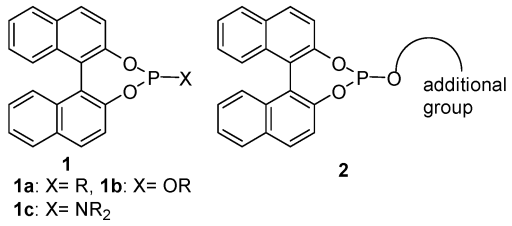


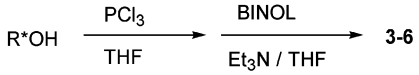
Figure 1.

to effectively restrain the rotation of the M−P bond by secondary interactions (Figure 1).[6]

For many years, carbohydrates have been extensively explored as backbones for chiral ligands due to their easy modification and ready availability. These features are beneficial for systematically modifying the structure of the ligands. Excellent results have been obtained with carbohydrate-based bidentate ligands in asymmetric hydrogenation.[7,8] However, few good monodentate chiral ligands have been reported based on carbohydrates.[9]

Herein, we report the synthesis of a new series of monophosphite ligands **3**−**6** based on D-fructose and D-glucose, and their applications in asymmetric hydrogenation reactions. To ascertain the importance of the monosaccharide[10] component affected enantioselectivity and yield of the asymmetric hydrogenation process, we evaluated a wide range of ketalated[11] carbohydrate derivatives.

The new ligands **3**−**6** were synthesized very efficiently from BINOL and the corresponding monosaccharide alcohols, which were synthesized on large scale from D-fructose and D-glucose (Figure 2).[12] The RO−PCl_2 intermediates were prepared by the reaction of alcohols with PCl_3 in the absence of Et_3N. These were then directly reacted with BINOL in the presence of Et_3N to afford the desired product. Ligands **3**−**6** were easily purified through a short silica gel plug and were stable in the solid state.



The catalytic performance of ligands **3**−**6** was initially explored in the enantioselective Rh-catalyzed hydrogenation reaction of dimethyl itaconate. The catalyst was prepared in situ by mixing $[Rh(COD)_2]BF_4$ and the monophosphite ligands in CH_2Cl_2. All the hydrogenation reactions were typically carried out at room temperature under 10 atm pressure of H_2 and with a substrate, Rh, and ligand ratio of 1.0/0.01/0.022. Although a standard reaction time of 12 h was chosen, most of the reactions were complete within 3 h.

The results of the Rh-catalyzed hydrogenation reactions are summarized in Table 1 and show that the carbohydrate-derived monophosphites we have created are efficient ligands for asymmetric hydrogenation. However, the enantioselectivities proved to be influenced dramatically by the structure of the ligands. Comparison of the results in Table 1 shows that the enantiomeric excess depends strongly on the absolute configuration of carbon atom at C-3 in the carbohydrate backbone. In general, fructose-derived ligands **4a**−**d**, with *R* configuration on carbon atom C-3, produced much higher enantioselectivities than ligands **3a**−**d** with opposite configuration on C-3. For the ligands **3a**−**d**, (*S*)-BINOL is matched cooperatively to the corresponding carbohydrate backbone, while for ligands **4a**−**d**, (*R*)-BINOL and the carbohydrate components are matched. With ligand **4a** the

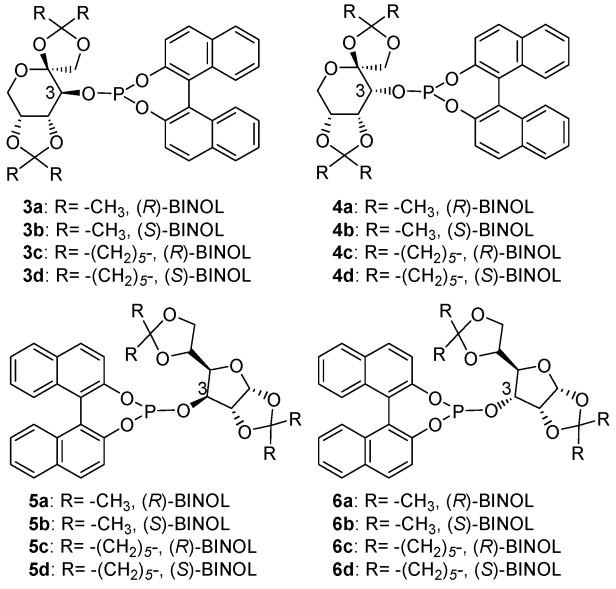


Figure 2.

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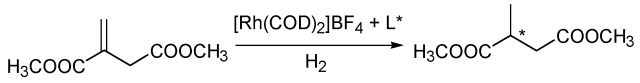
Table 1. Enantioselective Hydrogenation of Dimethyl Itaconate Catalyzed by Rh-**3**−**6**[a]



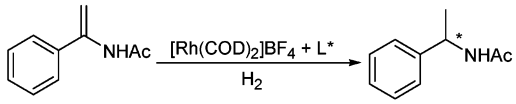
entry	ligand	ee (%) (config)[b]	entry	ligand	ee (%) (config)[b]
1	**3a**	49.7 (*R*)	9	**5a**	92.8 (*R*)
2	**3b**	82.5 (*S*)	10	**5b**	99.1 (*S*)
3	**3c**	18.5 (*R*)	11	**5c**	92.9 (*R*)
4	**3d**	91.5 (*S*)	12	**5d**	96.9 (*S*)
5	**4a**	99.6 (*R*)	13	**6a**	93.6 (*R*)
6	**4b**	99.1 (*S*)	14	**6b**	77.5 (*S*)
7	**4c**	99.4 (*R*)	15	**6c**	84.3 (*R*)
8	**4d**	90.3 (*S*)	16	**6d**	81.0 (*S*)

[a] The reactions were carried out in CH_2Cl_2 at room temperature for 12 h, $P(H_2) = 10$ atm, substrate/$[Rh(COD)_2]BF_4$/ligand = 1.0/0.01/0.022. 100% conversion in all cases. [b] Determined by GC with γ-DEX-225 capillary column, and the absolute configuration was determined by comparing the sign of specific rotation.

highest ee value (99.6%) was obtained (Table 1, entry 5). Similar observations were made with **5** and **6**.

To expand the utility of these monophosphite ligands and further investigate the influence of the carbohydrate component, we examined the Rh-catalyzed enantioselective hydrogenation of 1,1-disubstituted-α-arylenamides (Table 2).

Table 2. Rh-Catalyzed Asymmetric Hydrogenation of *N*-Acetylphenylethenamine with **3**−**6** as Chiral Ligands[a]



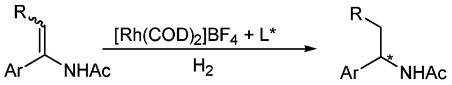
entry	ligand	ee (%) (config)[b]	entry	ligand	ee (%) (config)[b]
1	**3a**	16.3 (*S*)	9	**5a**	**93.9** (*S*)
2	**3b**	44.7 (*S*)	10	**5b**	85.5 (*R*)
3	**3c**	19.5 (*R*)	11	**5c**	**91.7** (*S*)
4	**3d**	39.7 (*S*)	12	**5d**	**95.1** (*R*)
5	**4a**	**87.7** (*S*)	13	**6a**	49.1 (*R*)
6	**4b**	4.7 (*S*)	14	**6b**	87.1 (*S*)
7	**4c**	**95.0** (*S*)	15	**6c**	49.1 (*R*)
8	**4d**	10.3 (*S*)	16	**6d**	67.9 (*R*)

[a] The reactions were carried out in CH_2Cl_2 at room temperature for 12 h, $P(H_2) = 10$ atm, substrate/$[Rh(COD)_2]BF_4$/ligand = 1.0/0.01/0.022. 100% conversion in all cases. [b] Determined by GC with chiral select 1000 capillary column, the absolute configuration was determined by comparing the sign of specific rotation.

The results in Table 2 show that the observed enantioselectivity of the reaction was again sensitive to the configuration of carbon atom C-3 of the carbohydrate moiety, which further confirmed the function of additional groups in the Rh-complex of these monophosphite ligands. On the other hand, the absolute configuration of BINOL also influenced the enantioselectivity of these ligands. The best enantioselectivity (95% ee) was obtained with **4c** and **5d** using (*R*)-BINOL and (*S*)-BINOL matched with the carbohydrate backbone (Table 2, entries 7 and 12).

We subsequently applied the new efficient monophosphite **4c** in the Rh-catalyzed hydrogenation of other α-arylenamides; the results are summarized in Table 3.

Table 3. Rh-Catalyzed Asymmetric Hydrogenation of Various *N*-Acetyl α-Arylenamides with **4c** as Chiral Ligand[a]



entry	substrate (Ar, R)	ee (%) (config)[b]
1	(Ph, H)	95.0 (*S*)
2	(p-FC_6H_4, H)	96.5 (*S*)
3	(p-BrC_6H_4, H)	98.5 (*S*)
4	(p-ClC_6H_4, H)	98.5 (*S*)
5	(p-$CH_3OC_6H_4$, H)	95.9 (*S*)
6	(p-$CF_3C_6H_4$, H)	98.5 (*S*)
7	(*2*-naphthyl, H)	96.9 (*S*)
8	(Ph, Me)	96.7 (*S*)

[a] The reactions were carried out in CH_2Cl_2 at room temperature for 12 h, $P(H_2) = 10$ atm, substrate/$[Rh(COD)_2]BF_4$/ligand = 1.0/0.01/0.022. 100% conversion in all cases. [b] Determined by GC with chiral select 1000 and CP-Chiralsil-L-Val capillary column; the absolute configuration was determined by comparing the sign of specific rotation.

In all cases, the ligand **4c** exhibited good to excellent enantioselectivities (95.0−98.5% ee). The electronic nature of the para substituents in α-arylenamides appeared to affect the enantioselectivity observed. Hydrogenation of α-arylenamides with electron-withdrawing substituents (entries 2, 3, 4, and 6) on the phenyl ring gave higher enantioselectivity than those with electron-donating substituents (entry 5). A mixture of *E*- and *Z*-α-arylenamide (entry 8) was also reduced with high enantioselectivity. It is noteworthy that the ee values of 95.0−98.5% obtained with monophosphite ligand **4c** are higher than that obtained from MonoPhos[4] and Reetz's monophosphites[5e] derived from simple alcohols or comparable to the result of modified MonoPhos.[5b]

In conclusion, a new class of monphosphite ligands containing additional groups derived from D-fructose and D-glucose have been synthesized and applied in the Rh-catalyzed hydrogenation of dimethyl itaconate and enamides. Excellent ee values up to 99.6% and 98.5% have been achieved. The superb enantioselectivities and the pronounced effect of carbohydrate backbones in these ligands indicates that the additional groups orientated in a proper spatial configuration contained in monophosphites are beneficial for improvement of enantioselectivity observed. More detailed studies on the structure of these ligands as well as synthesis of other new effective chiral monophosphorus ligands containing additional groups and their applications in asymmetric catalysis are in progress.

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Supporting Information Available: Experimental details, spectra of new ligands **3**−**6,** and ee value determination conditions of GC. This material is available free of charge via the Internet at http://pubs.acs.org.

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