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Water-Soluble Organometallic Catalysts from Carbohydrates. 1. Diphosphinite–Rh Complexes

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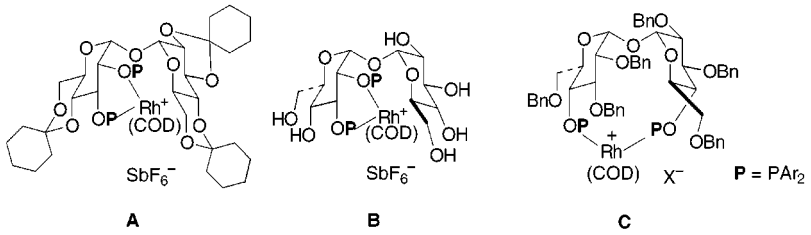
ABSTRACT



Cyclohexylidene-protected diphosphinite-Rh complex A derived from α,α′-trehalose was treated with acidic resin in methanol to get the unprotected complex B, which is water soluble. Preparation of complexes A–C and their applications for hydrogenations show the problems and prospects of using water as a solvent for these reactions.

Ever since the introduction of the Ruhrchemie/Rhône-Poulenc hydroformylation process, which uses a water-soluble sulfonated triphenylphosphine complex of Rh, homogeneous catalysis in aqueous medium has attracted considerable attention.[1] While the use of water as an environmentally friendly solvent is a debatable issue, for a homogeneously catalyzed process running in a biphasic system, the advantages offered by way of separation of catalysts and organic products cannot be overemphasized. In addition, there are several documented instances of reactions where water shows beneficial (also in some cases detrimental) effects in terms of activity and selectivity, as compared to the counterparts run in organic media. Selective functionalization of large water-soluble biomolecules is an area of increasing importance in connection with a number of biotechnology problems, and here, water-soluble catalysts have distinct advantages and often are the only alternatives except for the use of enzymes.[2] Substrate dependence and volumetric productivity are two principal limitations of the use of enzymes, even when a biochemical alternative to the target structure can be identified.

Simple carbohydrates are the most abundantly available water-soluble natural products, and their use as ligand precursors for asymmetric synthesis has been on the rise.[3] In previous work, we have shown that carbohydrate phosphinite complexes catalyze a wide variety of reactions such as hydrocynation (Ni), hydrogenation (Rh), hydroformylation

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(2) (a) Casalnuovo, A. L.; Calabrese, J. C. *J. Am. Chem. Soc.* **1990**, *112*, 4324. (b) Chaloner, P. A.; Esteruelas, M. A.; Joó, F.; Oro, L. A. *Homogeneous Hydrogenation*; Kluwer: Dodrecht, 1994.

(3) Sugar phosphinites have been used as ligands since 1978. For recent references, see: (a) Selke, R.; Holz, J.; Riepe, A.; Börner, A. *Chem. Eu. J.* **1998,** *4*, 769 and references therein. (b) RajanBabu, T. V.; Casalnuovo, A. L.; Ayers, T. A. Ligand Tuning in Asymmetric Catalysis. In *Advances in Catalytic Processes*, JAI Press: Greenwich, 1997; Vol. 2, pp 1−41.

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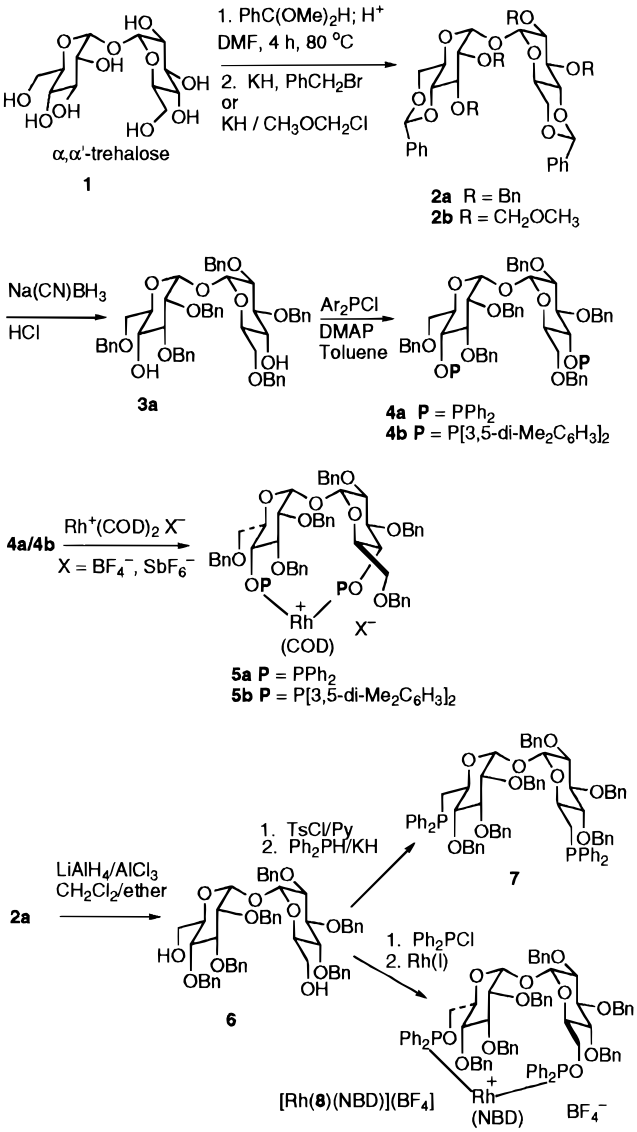
(Rh), and allylation (Ni and Pd).[4] While the carbohydrate backbone provided the necessary stereochemical diversity, substitution patterns around phosphorus were used to vary the steric and electronic properties of the ligand. One salient property of carbohydrates that has not been fully exploited is their water solubility due to the polyhydroxylic nature. Pioneering studies conducted by the Selke and Oehme[5] have amply demonstrated that even phosphinite ligands derived from monosaccharides have some solubility in water. They also showed impressive enhancement of enantioslectivity in the presence of micelle-forming amphiphiles when sparingly soluble substrates are used. The high ee of these reactions notwithstanding, anecdotal evidence seems to suggest that these monosaccharide-derived ligands have only limited aqueous solubility. In connection with the asymmetric hydrocyantion project, in 1992 we first reported a number of bisphosphinite ligands from disaccharides including a few from α,α′-trehalose.[6] We wondered ever since how the enantioselectivity of the Rh-catalyzed hydrogenation using the corresponding fully deprotected ligands will be affected by the incorporation of four more hydroxyl groups (vis-á-vis monosaccharide ligands) and the attendant greater solubility in water.[7] Here we record the details of the relevant chemistry for the selective functionalization of α,α′-trehalose for the synthesis of novel bisphosphinites. In addition, we have studied the stability, solubility properties, and applicability of the Rh-complexes of these ligands for hydrogenation of dehydroamino acids.

Synthesis of a series of C_2-symmetric phosphine and phosphinite ligands from α,α′-trehalose is shown in Scheme 1.[8] The 4,6:4′,6′-benzylidene acetal **2a** (or **2b**) is a key intermediate, which can be readily prepared from trehalose in two steps. Selective cleavage of the benzylidene acetal using either $Na(CN)BH_3/HCl$[9] or $LiAlH_4/AlCl_3$[10] gives 4,4′- and 6,6′-unprotected trehalose derivatives **3** or **6**, respectively. Treatment of these compounds with diarylchlorophosphines in the presence of a base gives the corresponding bisphosphinites (e.g., **4a** or **4b**). The 6,6′-diol **6** is a useful precursor for the synthesis of bisphosphine **7**, a compound that has been prepared by an alternate route before.[8a] All bisphosphinites were fully characterized by ^1H, ^{13}C and ^{31}P spectroscopy.[11]

Scheme 1. Selective Functionalization of α,α′-Trehalose for the Synthesis of Macrocyclic Bisphosphinite Ligands



The bisphosphinites are excellent ligands for Ni(0)-catalyzed asymmetric hydrocyanation[3b] and Rh(I)-catalyzed hydrogenation. The Rh complexes of the bisphosphinite (**5a**/**5b**) are readily prepared by treating the ligands with $Rh^+(COD)_2\ SbF_6^-$ in CH_2Cl_2 or $CDCl_3$ at room temperature. The C_2-symmetric nature of the complex is evident from the ^{31}P NMR spectrum. The major ^{31}P signal appears as a doublet in **5a** at $\delta = 122.2$ ($J_{P-Rh} = 181$ Hz). In addition, the ^{31}P NMR spectrum of **5a** shows broad signals between δ 152 and 158. The intensity ratio of the major doublet to the broad signal(s) is highly dependent on the temperature (<10% at 37 °C, and increasing as the temperature is decreased), suggesting that the latter arises from a mixture of complexes in which the benzyloxy group is probably coordinated to Rh.[12] Lack of coupling between the two phosphorus atoms

(5) See, for example: Kumar, A.; Oehme, G.; Roque, J. P.; Schwarze, M.; Selke, R. *Angew. Chem., Int. Ed. Engl.* **1994,** *33*, 2197 and references therein.

(6) (a) RajanBabu, T. V.; Casalnuovo, A. L. *J. Am. Chem. Soc.* **1992,** *114*, 6265, footnote 10. Also ref 3b and: Casalnuovo, A. L.; RajanBabu, T. V. U.S. Patent 5 175 335, 1992.

(7) For other recent reports dealing with the use of carbohydrates for solubilizing an organometallic catalyst, see: (a) Beller, M.; Krauter, J. G. E.; Zapf, A. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 772. (b) Sawamura, M.; Kitayama, K.; Ito, Y. *Tetrahedron: Asymmetry* **1993**, *4*, 1829. (c) Mitchell, T. N.; Heesche-Wagner, K. *J. Organomet. Chem.* **1992**, *436*, 43.

(8) For the synthesis of *phosphine* ligands from trehalose see: (a) Brown, J. M.; Cook, S. J.; Kent, A. G. *Tetrahedron* **1986**, *42*, 5097.; Gilbertson, S. R.; Chang, C. T. *J. Org. Chem*. **1995**, *60*, 6226. (b) Just prior to the submission of this manuscript (7/30/1999) a report dealing with the syntheis and applications of phosphinites related to **14** has appeared. Yonehara, K.; Hashizume, T.; Mori, K.; Ohe, K.; Uemura, S. *J. Org. Chem.* **1999**, *64*, 5593. Our work was presented at the Central Regional ACS Meeting, Columbus, OH, June 21−23, Abstract No. 129. (c) Wallace, P. A.; Minnikin, D. E. *J. Chem. Soc., Chem. Commun.* **1993**, 1292.

(9) Garegg, P.; Hultberg, H. *Carbohydr. Res.* **1981**, *93*, C10.

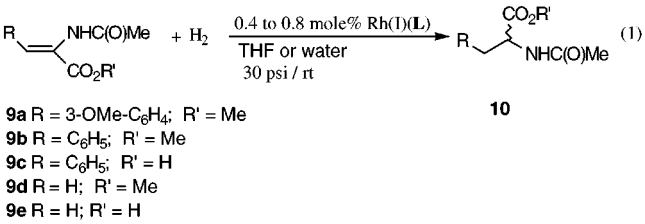
(10) Lipták, A.; Jodál, I.; Nánási, P. *Carbohydr. Res.* **1975**, *44*, 1.

(11) See the Supporting Information for details.

(12) Borns, S.; Kadyrov, R.; Heller, D.; Baumann, W.; Spannenberg, A.; Kempe, R.; Holz, J.; Börner, A. *Eur. J. Inorg. Chem.* **1998,** 1291.

in the major complex is clearly an indication of the symmetry of the molecule that renders the two phosphorus atoms equal. The complex **5b** has the ^{31}P signal at $\delta = 127.0$ ($J_{P-Rh} =$ 174 Hz) with the minor broad signals appearing at δ 121−118 (<5% at 25 °C), and complex Rh[**8**](NBD)(BF_4) has a doublet at $\delta = 123.1$ ($J_{Rh-P} = 184$ Hz).

Hydrogenation of *(Z)-N*-acetylacrylic acid derivatives (eq 1) were carried out using these complexes, and the results are shown in Table 1 (entries 1−5). As with other



phosphinites,[4b] high yields of hydrogenation can be achieved in THF at room temperature and 30−40 psi of H_2, even though the enantioselectivity of the reaction remains marginal. These ligands are insoluble in water, and in each case the starting material was recovered unchanged under typical

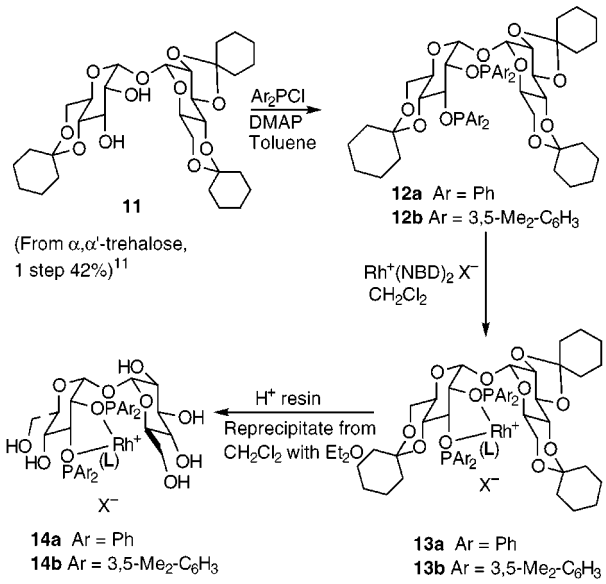
Table 1. Hydrogenation of Dehydroamino Acids with Trehalose-Derived Phosphinites in THF[11]

entry	catalyst[a]	substrate	% ee
1	**5a**	**9a**	70 *(R)*
2	**5a**	**9b**	35 *(R)*
3	**5b**	**9a**	40 *(R)*
4	**5b**	**9b**	30 *(R)*
5	**8**	**9b**	25 *(R)*
6	**13a**	**9a**	70 *(S)*
7	**13a**	**9b**	69 *(S)*
8	**13a**	**9d**	65 *(S)*
9	**13b**	**9a**	92 *(S)*
10	**13b**	**9b**	87 *(S)*
11	**13b**	**9d**	83 *(S)*

hydrogenation conditions. Repeated attempts to remove the protecting groups via hydrogenolysis (Pd/C, Pearlman's catalyst, Ni in the case of the benzyl derivatives and acidic resin in the case of the methoxymethyl derivatives) failed, and we turned our attention to the more hydrolytically unstable cyclohexylidene derivatives shown in Scheme 2.[8b,c]

The tris-cyclohexylidene derivative **11** was synthesized according to the procedure reported in the literature.[8c] This diol was easily converted to the vicinal bisphosphinites **12a** and **12b** and subsequently to the corresponding Rh(I) complexes **13a** and **13b**. As shown in the table (Table 1, entries 6−11), these are excellent catalysts for hydrogenation giving isolated yields near 100% and ee's up to 92%. Note that in accordance with our previous observations the electron-rich 3,5-dimethylphenyl-phosphinite ligand **13b** is clearly superior to the simple phenylphosphinite **13a** (entries 6 vs 9 and 7 vs 10).

Scheme 2. Water-soluble ligands from an Acid-Labile Trehalose Derivative



The cyclohexylidene protecting group in **13a** (or **13b**) is easily removed (96% yield) by treatment of the Rh(I) complex dissolved in thoroughly degassed methanol with carefully prepared AG 50 WX-8 resin.[11] The progress of the reaction was monitored by ^{31}P NMR. The crude product can be further purified by dissolving it in minimum amout of CH_2Cl_2 followed by reprecipitation with excess ether. We also found that the corresponding BF_4^- complex can be deprotected in degassed methanol using 50 mol % recrystallized *p*-TsOH·H_2O.

The deprotected complexes **14a** and **14b** are readily soluble in water and can be used for hydrogenation of α-acetamidoacrylic acids (Table 2). Methyl α-acetamidoacrylate is reduced quantitatively by **14a** in water at 40 psi of hydrogen in 55% ee (*S*) using a substrate-to-catalyst ratio of 125. Under identical conditions, **14b** gave 49% ee for the *S* isomer. However, hydrogenation in aqueous medium is less selective in comparison to organic medium (for **13a**/**14a**, 65% vs 55% or **13b**/**14b** 83% vs 49%). One

Table 2. Hydrogenation of Dehydroamino Acids with Water-Soluble Trehalose-Derived Phosphinites[a]

entry	solvent	catal/subst	% ee *(S)*
1	H_2O	**14a**/**9d**	55
2	H_2O	**14a**[b]/**9e**	59
3	H_2O/THF 1:1	**14a**[c]/**9c**	65
4	THF	**14a**/**9c**	70
5	H_2O	**14b**/**9d**	49
6	H_2O/EtOAc	**14a**/**9e**	65[d]

[a] All (COD)(SbF_6)$^-$ salts; substrate/catalyst (S/C) 125; 40 psi H_2; 2 h; ∼100% yield. [b] Reaction in a slurry. [c] 12% conversion in 24 h. [d] 100% conversion in 20 h, 25% product, and rest polymeric material.

of the possible explanations for this deterioration of enantioselectivity is the intervention of protonolysis of the putative Rh−C bond before the final reductive elimination.[13] When the substrate is more hydrophobic, and hence less soluble in water, the complex **14a** is a poor catalyst for the hydrogenation. For example, *(Z)*-acetamidocinnamic acid (**9c**), which has only limited solubility in water, is reduced in a yield of only 12% (65% ee) by 24 h in 1:1 THF/water, as compared to 67% yield (70%ee) in neat THF. Water clearly slows down the reaction.

One of the purported goals in developing water-soluble catalysts is the ease of recovery of the catalyst from the aqueous layer. Further, we and others[8b] have shown that catalysts such as **14a** can be used in biphasic media. Yet there are few reports in the literature where the actual distribution of the catalyst in biphasic medium has been measured *under the reaction conditions*. The traditional way of demonstrating the viability of the recovery option has been to separate the organic phase and to reuse the aqueous phase containing the catalyst for subsequent reactions. Arguably, for highly efficient catalysts such as the Rh(I)-bisphosphinites,[4b] unless careful quantitative rate studies are done with the recovered catalyst solution, this is *not* a satisfactory way of demonstrating the practicality of this approach, since residual amounts of the Rh complex can still facilitate the hydrogenation. Hence, we have sought to determine the distribution of the cationic Rh complexes between water and several common organic solvents by the ion-coupled plasma (ICP) method, which gives more quantitative information on the Rh-distribution under typical reaction conditions. The distribution of complex **14a** between water and CH_2Cl_2, ethyl acetate, and ether are shown in Table 3. Surprisingly even the most water-soluble complex we have prepared has significant solubility in all these organic solvents. Ether appears to be the best solvent if the catalyst is to be recovered after the first hydrogenation, and even in this solvent up to 4% of the Rh will lost after each subsequent cycle. Careful choice of the solvent therefore is important if recovery of the catalyst is desired. It is our view that despite the attraction of water as a solvent, the hydrogenation of substrates other than the most soluble ones are best carried out in organic medium. Practical problems associated with degassing (repeated freeze−thaw cycles) water, especially when the reaction is to be carried out on a large scale, partial loss of enantioselectivity, and the limited prospects of recovering the catalyst are limitations that have to be carefully considered in this context.

Table 3. Partition of Complex **14a** (NBD)(BF_4) between Water and Organic Solvents in Dilute Solutions

entry	solvent	total Rh[a] (mg)	ratio[b]
1	CH_2Cl_2/water	0.32	1.05
2	EtOAc/water	0.17	0.63
3	ether/water	0.24	0.04

[a] In 9.0 mL each of solvent mixture. [b] Determined by ICP-MS, error limit in estimation ±4%. In our estimation, it is highly unlikely that complexes of this type have the solubilities (>4.0 g/100 mL) reported in the literature.[8b]

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Supporting Information Available: Synthetic procedures and spectral data for compounds **5**, **8**, **13**, and **14**, ^{31}P and ^{1}H NMR spectra for typical compounds, and the procedure for determining partition coefficients. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) For example, in the reduction of **9d**, using 0.8 mol % of the catalyst **14b,** 50% α-deuteration was observed at 30% conversion when the reaction was carried out in D_2O. The exact mechanism of this reaction and its stereochemical consequences remain unknown. For related observations, see: Lecomte, L.; Sinou, D.; Bakos, J.; Tóth, I.; Heil, B. *J. Organomet. Chem.* **1989,** *370*, 277−284. Laghmari, M.; Sinou, D. *J. Mol. Catal.* **1991,** *66*, L15−L18.