Water-Soluble Organometallic Catalysts from Carbohydrates. 2. A Strategy for the Preparation of Catalysts with Pendant Quaternary Ammonium Groups Using D-Salicin

Yuan-Yong Yan and T. V. RajanBabu*

Department of Chemistry, The Ohio State University, 100 W. 18th Avenue, Columbus, Ohio 43210

rajanbabu.1@osu.edu

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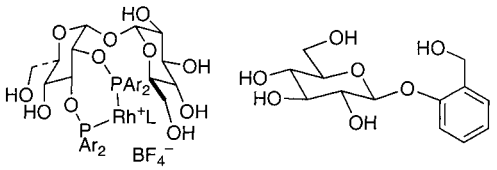
A series of water-soluble chelating bis-phosphinite ligands have been prepared from D-salicin (2-(hydroxymethyl)phenyl β-D-glucopyranoside). The 4- and 6-hydroxyl groups of salicin were protected as a cyclic ketal. Mitsunobu reaction with phthalimide at the benzylic position was used to install the aminomethyl side-chain in the C_1-aromatic substituent. Formation of the bis-2,3-*O*-diarylphosphinite was accomplished by reaction of the resulting diol with chlorodiarylphosphine. Quaternization with Meerwein's salt (Me_3O^+ BF_4^-) followed by reaction with $Rh^+(COD)_2$ BF_4^- gave precatalysts with limited aqueous solubility. Deprotection of the ketal group with acidic resin in methanol gave water-soluble cationic Rh complexes that are competent to carry out highly efficient hydrogenation of acetamidoacrylic acid derivatives in organic, aqueous, or biphasic media. However, enantioselectivities of these reactions in neat aqueous or biphasic media are generally lower than those observed in organic medium.

Introduction

Of the various strategies for solubilizing an organometallic catalyst in water, use of a carbohydrate scaffolding for the attachment of the metal has the distinct advantage that the backbone incorporates easily tunable chiral elements.[1] Consequently, under optimum conditions, reactions catalyzed by such complexes can be expected to be stereoselective. Use of the highly hydrophilic, polyhydroxylic backbone also helps circumvent some of the problems associated with the sulfonation protocol often used to prepare water-soluble ligands.[2] A number of different procedures have been used to attach catalytically active metal ions to carbohydrates.[3−7] In their pioneering work, Selke and co-workers used vicinal diarylphosphinite−Rh complexes derived from phenyl β-D-glucopyranoside for asymmetric hydrogenation of dehydroamino acids in water.[4] In an attempt to circumvent the limited solubility of monosaccharide-derived ligands we[5] and others[6] have resorted to disaccharides such as trehalose (1-glucopyranosyl glucopyranoside) as ligand precursors, with the expectation that increased number of hydroxyl groups would improve solubility in water. Indeed very high enantioselectivities were achieved for such a catalyst in the Rh-catalyzed asymmetric hydrogenations in aqueous medium. Our investigations of the partition coefficient for these Rh-complexes between organic solvents and water (by ion-coupled plasma method) also revealed that despite the increased number of hydroxyl groups, the disaccharide-derived Rh(1) complexes (e.g., **1**) still possessed considerable solubility in organic solvents.[5] Alternatively, use of tetraalkylammonium moiety for the preparation of chiral water-soluble phosphine ligands have been explored by Nagel[8a] and Hanson,[8b] and some of the resulting quaternized derivatives of Rh^+-complexes of BDDP, Chiraphos, and DIOP have been described as having "unlimited water solubility". We wondered whether such a strategy could be



1 Ar = Ph; L = COD, NBD **2** D-Salicin

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(3) For other examples of the use of carbohydrates for the preparation of water-soluble phosphines, see: (a) Mitchell, T. N.; Heesche-Wagner, K. *J. Organomet. Chem.* **1992**, *436*, 43. (b) Sawamura, M.; Kitayama, K.; Ito, Y. *Tetrahedron: Asymmetry* **1993**, *4*, 1829. (c) Beller, M.; Krauter, J. G. E.; Zapf, A. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 772. See also: (d) Ferrara, M. L.; Orabona, I.; Ruffo, F.; Funicello, M.; Panunzi, A. *Organometallics* **1998**, *17*, 3832.

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(5) Shin, S.; RajanBabu, T. V. *Org. Lett.* **1999**, *1*, 1229.

(6) Yonehara, K.; Hashizume, T.; Ohe, K.; Uemura, S. *J. Org. Chem.* **1999**, *64*, 5593, 9381.

(7) Some more recent examples: (a) Holz, J.; Heller, D.; Stürmer, R.; Börner, A. *Tetrahedron Lett.* **1999**, *40*, 7059. (b) Selke, R.; Holz, J.; Riepe, A.; Börner, A. *Chem. Eur. J.* **1998**, *4*, 769. (c) Li, W.; Zhang, Z.; Xiao, D.; Zhang, X. *J. Org. Chem.* **2000**, *65*, 3489.

(8) (a) Nagel, U.; Kinzel, E. *Chem. Ber.* **1986**, *119*, 1731. (b) Tóth, I.; Hanson, B. E. *Tetrahedron Asymmetry* **1990**, *1*, 895.

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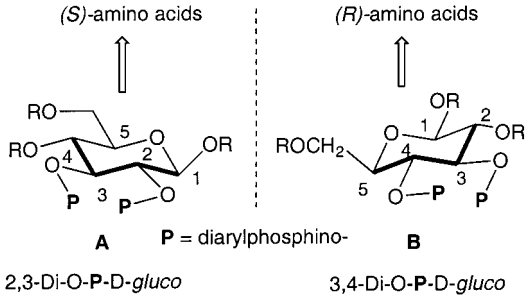
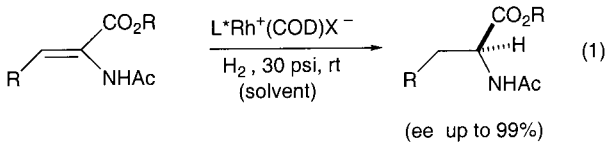
Scheme 1. D-Glucose-Derived Phosphinites for the Synthesis of Amino Acids[9b,c]



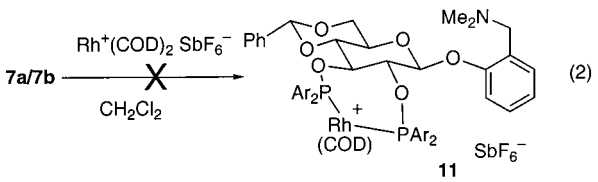
employed in connection with the remarkably successful sugar phosphinite ligands which have been found to have wide applications in asymmetric catalysis.[9] For example, we have shown that cationic Rh-complexes of D-glucose-derived ligands can be used to prepare both *R* and *S* amino acid derivatives in (ee 97−99%) depending on the juxtaposition (2,3 or 3,4) of the diarylphosphinoxy groups (Scheme 1).[9b,9c] Highest recorded enantioselectivity for asymmetric hydrocyanation reaction of olefins was achieved using Ni(0)-complexes of structurally related sugar phosphinites.[9d,9e] In this paper we report the details of the synthesis of bis-phosphinite ligands with pendant quaternary ammonium groups starting with a readily available monosaccharide, D-salicin (2-hydroxymethylphenyl *β*-D-glucopyranoside, **2**). Preliminary results on the applications of these ligands in Rh-catalyzed hydrogenation of acetamidoacrylic acid derivatives are also reported.



(1)

Results and Discussion

Functionalization of D-Salicin. A general route to convert salicin to the 4,6-dialkylidene-protected derivative with a dimethylaminomethyl side-chain is shown in Scheme 2. Treatment of salicin with 1,1-dimethoxytoluene under acidic conditions produced the acetal **3a** which was readily converted into the phthalimido-derivative **4a** by a selective Mitsunobu reaction at the more reactive benzylic position. The amino group was liberated by treatment of **4a** with hydrazine hydrate. Installation of the dimethylamino group is accomplished by reaction of **5a** with formic acid and formaldehyde. The diol **6a** thus produced was readily converted into the bis-diarylphosphinites through the dipotassium salt. The first huddle in projected synthesis of the Rh complex appeared when the diphosphinite **7a** was treated with $Rh^+(COD)_2\ SbF_6^-$. Instead of the expected Rh complex **11**, a mixture of products was obtained as indicated by the ^{31}P NMR (eq 2). Instead of the doublet of doublet (J_{Rh-P} and J_{P-P}) usually observed for *each* of the phosphorus atoms in a typical bis-phosphinite chelate, a multitude of peaks, including one large doublet (J_{Rh-P} = 172 Hz), were observed. As subsequent experiments (vide infra) would show, the presence of the dimethylamino group, which can act as a chelating group is most probably responsible for this complication. Quaternization of the amine with Meerwien's salt produces **8**, which was converted into the Rh complex **9** without any problems. However, the robust benzylidene protecting group, which survives the formaldehyde/formic acid reaction for the dimethylamine synthesis, could not be removed without destroying the complex, and alternate protecting group strategy[4,5] was developed for the synthesis of the unprotected precatalyst **10**.



(2)

The replacement of the 4,6-*O*-benzylidene protecting group with a more labile isopropylidene group was carried out by substituting 2,2-dimethoxypropane for dimethoxytoluene in the initial protection scheme. The isopropylidene derivative **3b** was converted into the benzylamine **5b** as described before. Reductive amination with formaldehyde and $NaB(CN)H_3$ gave the tertiary amine **6b**. Formation of the bis-diarylphosphinites and the corresponding Rh(1)-complexes (**13a**, **13b**, and **13c**) proceeded without any complications (Scheme 3). The isopropylidene group is easily removed by treatment with acidic resin (AG 50 WX-8) in methanol[5] to liberate the unprotected complexes **10a**, **10b**, and **10c** which were subsequently used for catalytic studies.

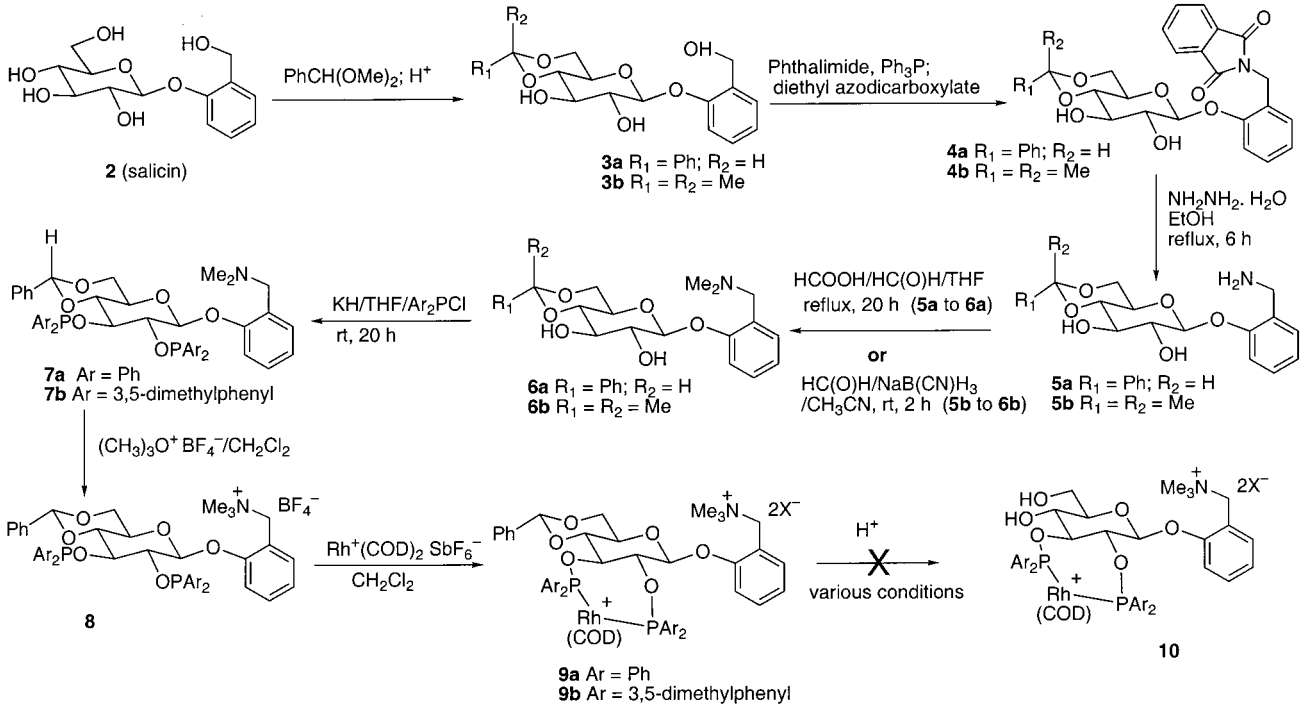
Hydrogenation Studies. Since the Rh-catalyzed hydrogenation of dehydroamino acid derivatives has received more attention than any other asymmetric reactions conducted in an aqueous medium, we chose this system for our initial study.[4−8,9a−c,10] Hydrogenation reactions of a variety of methyl α-acetamidoacrylic acid derivatives were conducted as described in our earlier publications,[9c] and the results are shown in Tables 1−4. The substrates chosen for this study have generally been found to give lower selectivities compared to the more commonly studied methyl α-acetamidocinnamate.[9a−c] In addition, use of the bis-diarylphosphinite ligands with these substrates permits an examination of the effect of *P*-Ar substituents on the hydrogeantion selectivity. Recall that we had established a strong electronic effect of the ligands on the enantioselectivity of these reactions.[9b,11] Typically 0.1 mmol of the substrate was dissolved in the solvent in a Fischer−Porter tube, and to this was added 0.01 equiv of the preformed cationic Rh-catalyst. The tube was sealed while inside the drybox and it was degassed thoroughly. The reaction vessel was charged with ∼40

(9) Applications of sugar phosphinites in asymmetric catalysis. Rh-catalyzed hydrogenations: (a) Selke, R. *React. Kinetic. Catal. Lett.* **1979**, *10*, 135. (b) RajanBabu, T. V.; Ayers, T. A.; Casalnuovo, A. L. *J. Am. Chem. Soc.* **1994**, *116*, 410. (c) RajanBabu, T. V.; Ayers, T. A.; Halliday, G. A.; You, K. K.; Calabrese, J. C. *J. Org. Chem.* **1997**, *62*, 6012. Ni-catalyzed hydrocyanation: (d) Casalnuovo, A. L.; RajanBabu, T. V.; Ayers, T. A.; Warren, T. H. *J. Am. Chem. Soc.* **1994**, *116*, 9869. (e) RajanBabu, T. V.; Casalnuovo, A. L. *J. Am. Chem. Soc.* **1996**, *118*, 6325. Hydroformylation: (f) RajanBabu, T. V.; Ayers, T. A. *Tetrahedron Lett.* **1994**, *35*, 4295. Hydrovinylation: (g) Park, H.; RajanBabu, T. V. Unpublished results. Pd-catalyzed allylation: (h) Clyne, D.; Mermet-Bouvier, Y. C.; Nomura, N.; RajanBabu, T. V. *J. Org. Chem.* **1999**, *64*, 7601.

(10) For a comprehensive review, see: Chaloner, P. A.; Esteruelas, M. A.; Joó, F.; Oro, L. A. In *Homogeneous Hydrogenation*; Noels, A. F., Grazini, M., Hubert, A. J., Ed.; Kluwer Academic: Dordrecht, 1994; p 183.

(11) RajanBabu, T. V.; Radetich, B.; You, K.; Ayers, T. A.; Casalnuovo, A. L.; Calabrese, J. C. *J. Org. Chem.* **1999**, *64*, 3429.

Scheme 2. Functionalization of Salicin



Scheme 3. Synthesis of Water-Soluble Rh−Phosphinite Complexes from Salicin

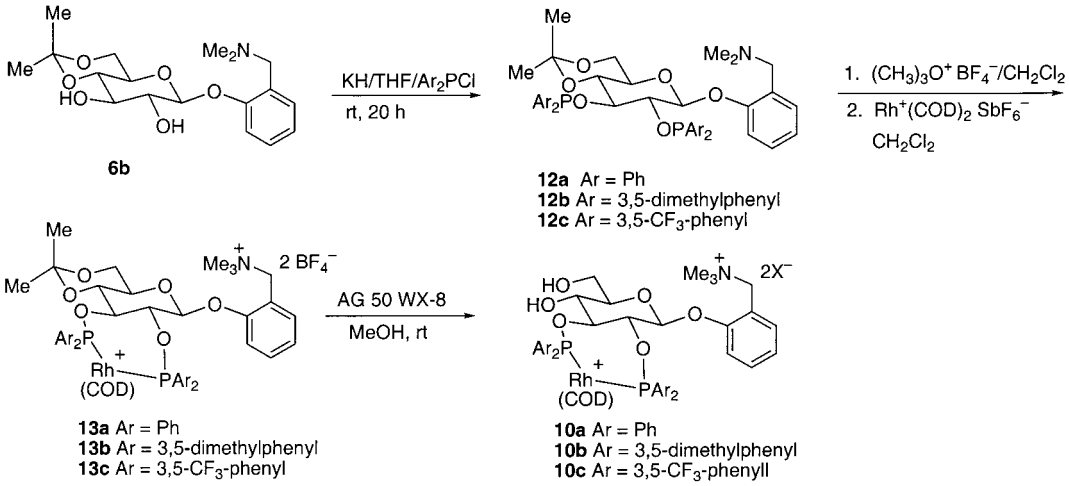


Table 1. Asymmetric Hydrogenation of Acetamidoacrylates Using Catalysts 9a and 9b[a]

entry	solvent	substrate (R in eq 1)	conversion	enantioselectivity[e] catalyst **9a** (**9c**)	enantioselectivity[e] catalyst **9b** (**9d**)
1	THF	2-F-C_6H_4	100	66 (89)	94 (97)
2	THF	3-F-C_6H_4	100	63 (89)	96 (97)
3	THF	3-Br-C_6H_4	100	74 (89)	95 (97)
4	THF	2-thienyl	—[b]	26 (85)	80 (96)
5	THF	3-thienyl	—[c]	28 (87)	92 (97)
6	THF	H	100	86 (—)	90 (97)
7	H_2O	H	100[d]	14 (—)	—

[a] Conditions: 2 mL solvent/0.1 mL substrate, 40 psi H_2, rt, 3 h. [b] For catalyst **9a** and **9b**, 91% and 28% conversions, respectively. [c] 86% and 68%, respectively. [d] Reaction time 19 h. [e] Determined by GC; in brackets are ee's for **9c** and **9d**, the Rh complexes without the $[CH_2NMe_3]^+$ side-chain in the aglycone.

Table 2. Hydrogenation of Acetamidoacrylates Using Catalysts 13a, 13b, and 13c[a]

entry	substrate R in eq 1	solvent	enantioselectivity/sub:cat ratio **13a**	**13b**	**13c**
1	H	THF	87/150	93/100	0/150
2	H	MeOH	54/150	37/100	—
3	H	EtOH	—	89/100	—
4	H	H_2O	53/150	2/100[b]	—
5	H	H_2O/EtOAc[c]	6/100	2/100	—
6	Ph	THF	—	97/150	—
7	Ph	H_2O/EtOAc[c]	—	7/100	—
8	3-Br-C_6H_4	THF	—	96/100	—
9	3-F-C_6H_4	THF	—	95/100	2/100

[a] Conditions: 2 mL solvent/0.1 mL substrate, 40 psi H_2, rt. [b] At 35% conversion (12 h) % ee is 57.8. [c] 1:1 ratio.

psi of hydrogen and was subsequently evacuated. This operation of filling and evacuation was done three times. Finally the tube was charged with 40 psi of hydrogen, and the mixture was stirred vigorously at room temperature for the times indicated. At the end of the reaction, the tube was vented, and the product was extracted into

Table 3. Effect of Water Content in Asymmetric Hydrogenation of Methyl α-Acetamidoacrylate (R = H in eq 1) Using Catalysts 13b[a]

entry	solvent	sub./cat.	time (h)	conv	ee %
1	THF	100	3	100	93
2	EtOH	150	1	100	89
3	H_2O/THF (3:1)	100	2	100	87
4	MeOH	100	3	100	37
5	MeOH/ H_2O (1:1)	100	7	100	90
6	MeOH/ H_2O (1:3)	100	3	100	74
7	MeOH/ H_2O (1:20)	150	3	100	57
8	H_2O	100	21	100	2
9	H_2O	150	12	35	58
10	H_2O/EtOH (1:1)	150	1	100	85

[a] Conditions: 2 mL solvent/0.1 mL substrate, 40 psi H_2, rt, 3 h.

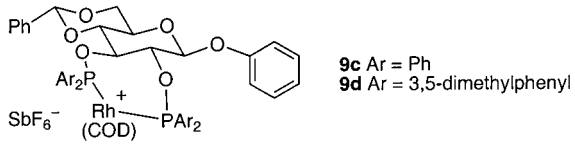
Table 4. Asymmetric Hydrogenation of Methyl α-Acetamidoacrylate (R = H in eq 1) Using Catalysts 10b[a]

entry	solvent	sub./cat.	time (h)	conversion	ee %
1	H_2O	150	1	100	61
2	H_2O (run 1)	100	3	99	8
3	H_2O (run 2)	100	3	95	5
4	THF	150	1	100	86

[a] Conditions: 2 mL solvent/0.1 mL substrate, 40 psi H_2, rt.

ether or chloroform and analyzed by gas chromatography. The ee's reported are based on chiral GC analysis where baseline separation of the two isomers was observed. The reproducibility of the measurements of ee's based on the integration of the areas under the appropriate peaks is ±0.3%. Accordingly, only two significant figures are reported for the ee's.

The enantioselectivity for the hydrogenation of several dehydroamino acids using the 4,6-benzylidene-protected precatalysts **9a** and **9b** are shown in Table 1. Shown in brackets in the last column are the values for the corresponding Rh-complexes (**9c** and **9d**)[9b] without the



9c Ar = Ph
9d Ar = 3,5-dimethylphenyl

$Me_3N^+CH_2$ side-chain of the aglycone. In all cases a quantitative reaction ensues giving the α-amino acid ester. As expected from our previous studies,[9c] in each case, the catalyst carrying the 3,5-dimethyl substituents on the *P*-aryl groups shows an increased selectivity. The pendant quaternary ammonium group appears to have some effect on the enantioselectivity of the Rh-catalyzed hydrogenation reaction, the effect being dependent on the nature of the *P*-aromatic substituent. In general the ee's are lower for the ammonium derivatives. The difference is more pronounced in the case of simple diphenylphosphinite ligands (**9a** vs **9c**) as compared to the 3,5-dimethylphenylphosphinite derivatives (**9b** vs **9d**). The catalyst **9a** has sufficient solubility in water to be able to effect the hydrogenation of α-acetamidocinnamate in quantitative yield (entry 7). However, the reactivity (19 h to complete the reaction) and enantioselectivity remains unacceptably poor.

Rhodium complexes **13a**, **13b**, and **13c** (Scheme 3) with the 4,6-di-*O*-isopropylidene protecting groups behave similarly. Hydrogenations of methyl α-acetamidoacrylate and various α-acetamidocinnamates in THF (Table 2, entries 1, 6, 8, and 9) using **13b** give ee's comparable to **9b**. Use of these complexes in methanol, water, or ethyl acetate/water mixtures leads to significant deterioration of enantioselectivity (Table 2, column 5), even though quantitative conversions are still observed. The surprising observation that methanol is a better solvent than the biphasic combinations of water and ethyl acetate has been made before,[2,5,6] and this observation does not portend well for the use of this technique for immobilization of the catalyst. Use of the bis(3,5-bis(trifluoromethyl)phenyl)phosphinite−Rh complex **13c**, even in THF gave nearly racemic products (entries 1 and 9). In previous studies of the electronic effects of phosphinite ligands we had noticed this remarkable trend with the CF_3-substituent.[9c,11]

The enantioselectivities of these reactions were found to depend on the solvent and reaction time. We were intrigued by this variation of selectivities observed with **13b**. Results of a study of solvent effect using this ligand are shown in Table 3. Reactions done in THF gave the highest ee, with ethanol a close second. Aqueous THF is an acceptable solvent, where as neat methanol or water are not. Selectivity in methanol appears to be a function of the amount of water present; as the mole fraction of water increases the ee drops from 90% to 57% (entries 5−8). When reactions have to be run longer to effect higher conversions in water, nearly racemic products (entry 8) are obtained. At low conversions (short reaction times) higher ee of the product (up to 58%) is observed (entry 9). One possibility is that the primary product undergoes racemization in water (vide infra, Table 4). As for the longer reaction times in water, even with the quaternary ammonium group, it is likely that these complexes with the hydrophobic 4,6-benzylidene or isopropylidene protecting groups are not completely soluble in water,[12] and hence the need for longer reaction times.

The solubility of the catalyst can be improved by removing the isopropylidene protecting group from **13b**. When the protecting group is completely removed, making the catalyst totally soluble in water, the hydrogenation can be completed in less than 60 min and consequently higher ee's can be realized (entry 1, Table 4, compare to entry 8 in Table 3). However, if the product is left in contact with water for longer periods of time under the reaction conditions, enantioselectivity drops off precipitously (entries 3 and 4), another indication that some racemization is possible in water. The completely deprotected derivative **10b** has sufficient solubility in THF to effect complete reduction of acetamidoacrylic acid (ee 86%) in ∼60 min at 1 mol % catalyst loading (entry 4, Table 4). Note that the corresponding protected derivative under similar conditions gives an ee of 93% (entry 1, Table 3). One possible explanation for the deterioration of enantioselectivity in water is the intervention of protonolysis of the putative Rh−C bond before the final reductive elimination.[13] Since significant α-deuterium incorporation has been observed in reactions run in D_2O-containing media,[13,5] it has been suggested that Rh−H/Rh−D exchange could also take place in the penultimate intermediate in the catalytic cycle. The exact mechanism

(12) Even though we have not carried out any quantitative studies on the solubilities of these and related compounds in water, an indication of the solubility can be gleaned from the attempts to run ^{31}P NMR spectra of **10a** (the completely deprotected complex). Compared to **13a** (in $CDCl_3$) a saturated solution of **10a** in water takes a minimum of 5 times longer to provide a satisfactory ^{31}P NMR of with similar signal-to-noise ratio. Even the deprotected derivatives therefore appear to have limited solubility in water.

(13) Laghmari, M.; Sinou, D. *J. Mol. Catal.* **1991**, *66*, L15.

of this reaction and its stereochemical consequences remain unknown. A further complication in the resolution of this issue is that the extent of D-incorporation is dependent on the ligand and solvent.[14]

Stability of Diarylphosphinite Complex 10a in Water. A saturated solution of **10a** in D_2O was prepared,[12] and the deterioration of the complex was followed by the disappearance of the characteristic doublet of doublets for each phosphorus signals (P_1: 124.40, dd, $J_{Rh-P1} = 174$; $J_{P1-P2} = 33$; P_2: 131.94, dd, $J_{Rh-P2} = 173$; $J_{P1-P2} = 33$. There was very little change in the spectrum in 24 h, clearly showing that under the hydrogenation reaction conditions, the Rh-complexes were surprisingly stable. Some discernible degradation (<10%) could be observed after 96 h. At the end of 216 h, more than 50% of the complex had undergone decomposition, with appearance of new signals in the ^{31}P NMR spectrum at δ 36.72 and 36.35.

Conclusions

We have discovered new synthetic routes to water-soluble, chiral vicinal bis-diarylphosphinite complexes starting with a readily available carbohydrate precursor, D-salicin. The Rh-complexes of these ligands are competent to carry out highly efficient asymmetric hydrogenation of acetamidoacrylic acid derivatives in organic, aqueous or biphasic media. However, enantioselectivities of these reactions in a neat aqueous or biphasic media are generally lower than those observed in organic medium, raising serious doubts about the viability of this technique for catalyst recovery. Reactions where such recovery of the catalyst is not an issue could still benefit from this new strategy for solubilizing organometallic reagents. Potential examples of this include reactions of substrates that are mostly soluble in water. Explorations along these lines will be reported in the future.

Experimental Section

General. All anaerobic reactions were carried out in an inert atmosphere of nitrogen in a Vacuum Atmospheres drybox, or using Schlenk techniques. Methylene chloride was distilled from calcium hydride under nitrogen and stored over 4 Å molecular sieves. Tetrahydrofuran (THF) and diethyl ether were distilled under nitrogen from sodium/benzophenone ketyl. All chemicals were purchased from Aldrich Chemical Co. unless otherwise noted. Analytical TLC was done on E. Merck precoated (0.25 mm) silica gel 60 F_{254} plates. Column chromatography was conducted by using silica gel 40 (Scientific Adsorbents Incorporated, Microns Flash). ^1H NMR spectra were recorded in $CDCl_3$ unless otherwise mentioned. Gas chromatographic (GC) analyses were performed on a chromatograph equipped with an HP-ultra-1 cross-linked methyl silicone capillary column (25 m length H 0.2 mm i.d.) and an FID detector with helium as carrier gas. The ee's of the products were determined by chiral GC (Chirasil-L-Val on WCOT fused silica 25m × 0.25 mm).

4,6-*O*-Phenylmethylidene-D-salicin (3a). A dry 100 mL round-bottomed flask was charged with 1.43 g (5.0 mmol) of D-salicin in 25 mL of distilled acetonitrile. To the heterogeneous mixture was added 30 mg of *p*-toluenesulfonic acid followed by 0.90 mL (6.0 mmol) of 1,1-dimethyoxytoluene. After 2 h, a homogeneous solution was formed. Neat triethylamine (28 μL) was added to neutralize the acid, and the solvent was removed on a rotary evaporator. The crude product was purified by silica gel column chromatography, eluting with EtOAc:hexane (5:1) to get 1.326 g (71%) of **3a** as a white powder. Mp: 203−204 °C. ^1H NMR ($CDCl_3$): δ 2.36 (b s, 3H), 3.56−3.67 (m, 2H), 3.78−3.90 (m, 3H), 4.38−4.45 (m, 2H), 4.86−4.94 (m, 2H), 5.56 (s, 1H), 7.04−7.32 (m, 4H), 7.34−7.40 (m, 3H), 7.48−7.52 (m, 2H).

4,6-*O*-(1-Methylethylidene)-D-salicin (3b). A dry 150 mL round-bottomed flask was charged with 2.86 g (10.0 mmol) of D-salicin in 80 mL of distilled acetonitrile. To the heterogeneous mixture was added 68 mg of *p*-toluenesulfonic acid followed by 1.47 mL (12 mmol) of 2,2-dimethyoxypropane. After 2 h, a homogeneous solution was formed. Neat triethylamine (56 μL) was added to neutralize the acid, and the solvent was removed on a rotary evaporator. The crude product was purified by silica gel column chromatography eluting with EtOAc:hexane (3:1) to get 2.335 g (72%) of **3b** as a white powder. ^1H NMR (DMSO-d_6): δ 1.34 (s, 3H), 1.45 (s, 3H), 3.42 (m, 4H), 3.70 (t, J = 10.1 Hz, 1H), 3.83 (dd, J = 5.0, 10.4 Hz, 1H), 4.47 (dd, J = 6.1, 14.4 Hz, 1H), 4.65 (dd, J = 5.5, 14.3 Hz, 1H), 4.97 (m, 2H), 5.25 (d, J = 4.3 Hz, 1H), 5.55 (d J = 4.3 Hz, 1H), 7.04 (m, 2H), 7.20 (ddd, J = 1.6, 7.7, 15.4 Hz, 1H), 7.38 (dd, J = 1.0, 7.4 Hz, 1H). ^{13}C NMR(DMSO-d_6): δ 19.13, 29.09, 48.65, 58.16, 61.48, 66.81, 73.09, 74.38, 98.85, 101.55, 114.72, 121.97, 127.27, 127.66, 131.64, 154.32.

2-(Phthalimidomethyl)phenyl 4,6-*O*-(Phenylmethylidene)glucopyranoside (4a). In a drybox, to a solution of 4.97 g of **3a**, 1.95 g of phthalimide, and 3.48 g of triphenylphosphine in 80 mL of anhydrous THF was slowly added a solution of 2.31 g of diethyl azodicarboxylate (abbreviated as DEAD) in 20 mL of the same solvent. The orange color of DEAD disappeared after each drop, and a thick white precipitate formed. The mixture was stirred at room temperature for 24 h and then brought out of drybox. The solvent was removed on a rotary evaporator. The residue was dissolved 350 mL of hot ethyl acetate, filtered, washed three times with ethyl acetate, and dried under high vacuum overnight. After column chromatography eluting with $CHCl_3/CH_3OH$ (40:1), the product was obtained **4a** as a white solid (5.40 g, 83%). ^1H NMR ($CDCl_3$): δ 3.69 (m, 2 H), 3.83 (m, 2 H), 3.97 (m, 1 H), 4.42 (dd, J = 4.4, 10.4 Hz, 1 H), 4.49 (m, 3 H), 5.58 (s, 1 H), 7.08 (m, 2 H), 7.27 (m, 1 H), 7.37 (m, 3 H), 7.52 (m, 2 H), 7.60 (m, 1 H), 7.72 (m, 2 H), 7.81 (m, 2 H). Anal Calcd for $C_{28}H_{25}NO_8$: C 66.79; H 5.00; N 2.78. Found, C 63.24; H 4.98; N 2.61.

2-(Phthalimidomethyl)phenyl 4,6-*O*-(1-Methylethylidene)glucopyranoside (4b). In a drybox, to a solution of 2.51 g (7.69 mmol) of **3b**, 1.13 g of phthalimide, and 2.02 g of triphenylphosphine in 50 mL of anhydrous THF was added dropwise a solution of 1.34 g of DEAD in 5 mL of the same solvent. The orange color of DEAD disappeared after each drop. The mixture was stirred at room-temperature overnight and then brought out of drybox. The solvent was removed on a rotary evaporator. The residue was purified by column chromatography on silica gel, eluting with EtOAc/Hexanes (6:4), to get 3.24 g (93%) of **4b** as a white solid. ^1H NMR ($CDCl_3$): δ 1.46 (s, 3H), 1.52 (s, 3H), 3.46 (m, 1H), 3.76 (m, 4H), 3.96 (dd, J = 5.3, 10.7 Hz, 1H), 4.87 (m, 3H), 7.03 (m, 2H), 7.24 (m, 1H), 7.55 (dd, J = 1.6, 7.5 Hz, 1H), 7.65 (m, 2H), 7.78 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 19.22, 29.20, 37.17, 62.21, 67.79, 73.05, 73.24, 74.65, 77.44, 100.04, 102.36, 115.03, 123.12, 123.58, 124.88, 130.02, 132.06, 132.40, 134.32, 155.41, 168.71.

2-(Aminomethyl)phenyl 4,6-*O*-(Phenylmethylidene)-glucopyranoside (5a). A 15 mL glass autoclave was charged with 0.503 g of **4a**, 99 μL of hydrazine monohydrate (98%), and 6 mL of anhydrous ethanol. The mixture was stirred in 120 °C oil bath for 5 h. The crude product was dissolved in 50 mL of warm ethanol and then filtered. The filtrate was evaporated, and the residue was purified by column chromatography eluting with $CHCl_3/CH_3OH/Et_3N$ (100:10:1), to get 0.298 g (68%) of **5a** as a white powder. ^1H NMR ($CDCl_3$): δ 2.75 (s, 4H), 3.68−3.75 (m, 3H), 3.82−3.93 (m, 3H), 4.13−4.17 (m, 1H), 4.44−4.47 (m, 1H), 4.85−4.88 (m, 1H), 5.59 (s, 1H),

(14) Other studies of the solvent effects on Rh-catalyzed asymmetric hydrogenation: Lecomte, L.; Sinou, L.; Bakos, J.; Tóth, I.; Heil, B. *J. Organomet. Chem.* **1989**, *370*, 277. See also: Bakos, J.; Karaivanov, R.; Laghmari, M.; Sinou, D. *Organometallics* **1994**, *13*, 2951. Sinou, D.; Amrani, Y. *J. Mol. Catal.* **1986**, *36*, 319.

7.02−7.06 (m, 1H), 7.14−7.21 (m, 2H), 7.26−7.30 (m, 1H), 7.36−7.38 (m, 3H), 7.50−7.52 (m, 2H).

2-(Aminomethyl)phenyl 4,6-*O*-(1-Methylethylidene)-glucopyranoside (5b). A 15 mL glass autoclave was charged with 0.455 g (1.0 mmol) of **4b**, 99 μL of hydrazine monohydrate (98%), and 6 mL of anhydrous ethanol. The mixture was stirred in a 115 °C oil bath for 5 h. The crude product was dissolved in 50 mL of warm ethanol and then filtered. The filtrate was evaporated, and the residue was purified by column chromatography eluting with $CHCl_3/CH_3OH$ (10:1), to get 0.280 g (86%) of **5b** as a white powder. ^{1}H NMR ($CDCl_3$): δ 1.43 (s, 3H), 1.48 (s, 3H), 3.31 (m, 1H), 3.59−3.97 (m, 6H), 4.21 (d, J = 12.4 Hz, 1H), 4.67 (d, J = 7.4 Hz, 1H), 6.56 (s, 2H), 6.87−7.03 (m, 2H), 7.13−7.23 (m, 2H), 7.48 (b s, 1H), 7.90 (b s, 1H).

2-(Dimethylaminomethyl)phenyl 4,6-*O*-(Phenylmethylidene)glucopyranoside (6a). To a 25 mL of round-bottom flask was added 0.220 g of **5a** in 2 mL of THF. The flask was cooled in an ice bath and 87 μL of formic acid was slowly added followed by 150 μL of formaldehyde. The flask was equipped with a magnetic stirrer and a condenser and placed in a 78 °C oil bath for 24 h. The mixture was cooled and made basic with 25% aqueous sodium hydroxide, and the product was extracted three times with 15 mL portions of ether. The ether layers were combined, washed with brine (3 mL), and then dried over anhydrous magnesium sulfate. The solvent was removed under rotary evaporator. The crude product was purified by silica gel column chromatography eluting with $CHCl_3/CH_3OH$ (20:1), to obtain 0.175 g (76%) of **6a** as a white solid. MP. 158−160 °C; ^{1}H NMR ($CDCl_3$): δ 2.21 (s, 6 H), 2.87 (d, J = 11.8 Hz, 1 H), 3.63 (m, 2 H), 3.75 (t, J = 8.2 Hz, 1 H), 3.84 (t, J = 8.6 Hz, 1 H), 3.88 (t, J = 9.9 Hz, 1 H), 4.11 (d, J = 11.9 Hz, 1 H), 4.44 (dd, J = 4.4, 10. 4 Hz, 1 H), 4.80 (d, J = 7.5 Hz, 1 H), 5.58 (s, 1 H), 7.03 (t, J = 7.4 Hz, 1 H), 7.11 (d, J = 7.2 Hz, 1 H), 7.18 (d, J = 8.1 Hz, 1 H), 7.31 (t, J = 7.7 Hz, 1 H), 7.36 (m, 3 H), 7.51 (t, J = 3.7 Hz, 2 H). ^{13}C NMR ($CDCl_3$): δ 44.60, 60.22, 67.08, 68.71, 72.97, 75.07, 80.23, 101.85, 106.20, 117.33, 123.21, 126.28, 127.06, 128.18, 129.10, 129.95, 131.76, 137.04, 157.82. Anal Calcd for $C_{22}H_{27}NO_6$: H 6.78; C 65.82; N 3.49. Found: H 6.83; C 66.09; N 3.45.

2-(Dimethylaminomethyl)phenyl 4,6-*O*-(1-Methylethylidene)glucopyranoside (6b). To a stirred solution of **5b** (1.43 g, 4.39 mmol) and 1.7 mL (22.6 mmol) of 37% aqueous formaldehyde in 10 mL of acetonitrile was added 0.442 g (7.0 mmol) of sodium cyanoborohydride. A vigorous exothermic reaction ensued, and a yellow white residue separated. The reaction mixture was stirred for 20 min, and then glacial acetic acid was added dropwise until the solution tested neutral on a wet pH paper. Stirring was continued for an additional 2 h, glacial acetic acid being added occasionally to maintain the pH near neutrality. The solvent was evaporated under reduced pressure, and 20 mL of 2 N KOH was added to the residue. The resulting mixture was extracted with three 10 mL portions of ether. The combined ether extract was washed with 20 mL of 0.5 N KOH and then dried over K_2CO_3. The solvent was removed on a rotary evaporator. The crude product was purified by silica gel column chromatography, eluting with $CHCl_3/CH_3OH$ (20:1), to get 0.884 g (57%) of **6b** as a white powder. ^{1}H NMR ($CDCl_3$): δ 1.45 (s, 3H), 1.53 (s, 3H), 2.25 (s, 6H), 2.91 (d, J = 11.9 Hz, 1H), 3.43 (m, 1H), 3.68 (m, 3H), 3.87 (t, J = 10.5 Hz, 1H), 4.02 (dd, J = 5.4, 10.8 Hz, 1H), 4.13 (d, J = 11.9 Hz, 1H), 4.75 (m, 1H), 7.01 (ddd, J = 1.1, 7.4, 14.7 Hz, 1H), 7.13 (m, 2H), 7.29 (ddd, J = 1.7, 7.7, 15.4 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 19.27, 29.24, 44.86, 60.37, 62.39, 68.20, 73.07, 73.75, 75.25, 99.99, 106.30, 117.50, 123.38, 126.95, 130.28, 132.02, 158.03. Anal. Calcd for $C_{18}H_{27}NO_6$: H 7.70; C 61.17; N 3.96. Found: H 7.20; C 57.56; N 3.87.

2-(Dimethylaminomethyl)phenyl 2,3-Bis-*O*-(diphenylphosphino)-4,6-*O*-(phenylmethylidene)glucopyranoside (7a). In a drybox, to a stirring solution of 0.223 g of **6a** in 2 mL of anhydrous THF was added slowly 45 mg of potassium hydride. After 1 h, a solution of 0.245 g of chlorodiphenylphosphine in 1 mL of the same solvent was added, and stirring was continued at room-temperature overnight. The solvent was removed under high vacuum. The residue was purified by flash chromatography, eluting with ether/hexane (1:1) and Et_3N (3%), to get 0.381 g (89%) of **7a** as a white powder. ^{31}P NMR ($CDCl_3$): δ 113.69 (d, J_{P-P} = 3 Hz), 116.59 (d, J_{P-P} = 3 Hz).

2-(Dimethylaminomethyl)phenyl 2,3-Di-*O*-(bis(3,5-dimethylphenyl)phosphino)-4,6-*O*-(phenylmethylidene)-glucopyranoside (7b). Compound **7b** was prepared by a route similar to the previous experiment for the synthesis of **7a** using bis(3,5-dimethylphenyl)chlorophosphine instead of chlorodiphenylphosphine. Yield: 76%. ^{31}P NMR ($CDCl_3$): δ 114.99 (d, J_{p-p} = 3 Hz), 120.34 (d, J_{P-P} = 3 Hz).

The Cationic Rhodium Complex, (COD)Rh$^+$[8] SbF_6^- (Ar = 3,5-dimethylphenyl) (9b). In a drybox, to a suspension of 17.7 mg (0.12 mmol) of trimethyloxonium tetrafluoroborate in 1 mL of anhydrous CH_2Cl_2 was added 105.8 mg (0.12 mmol) of **7b** in 1 mL of the same solvent and stirred overnight at room temperature. To the reaction mixture was added a solution of 66.6 mg (0.12 mmol) of $Rh^+(COD)_2$ SbF_6^- in 1 mL of CH_2Cl_2 and continued stirring for 3 h at room temperature. The solvent was removed under vacuum. The residue was collected, washed three times with Et_2O, and dried under high vacuum overnight. A fine powder of the Rh-complex was obtained (100%). ^{31}P NMR ($CDCl_3$): δ 130.58 (dd, J_{p-p} = 30 Hz, J_{P-Rh} = 173 Hz), 132.44 (dd, J_{P-P} = 30 Hz, J_{P-Rh} = 177 Hz).

The Cationic Rhodium Complex, (COD)Rh$^+$[8] SbF_6^- (Ar = phenyl) (9a). This complex was prepared in a quantitative yield by a route similar to the previous experiment for the synthesis of **9b**. ^{31}P NMR ($CDCl_3$): δ 130.44 (dd, J_{P-P} = 29 Hz, J_{P-Rh} = 176 Hz), 132.62 (dd, J_{P-P} = 29 Hz, J_{P-Rh} = 173 Hz).

2-(Dimethylaminomethyl)phenyl 2,3-Di-*O*-(bis(3,5-dimethylphenyl)phosphino)-4,6-*O*-(1-methylethylidene)-glucopyranoside (12b). In a drybox, to a stirring solution of 0.67 g (1.90 mmol) of **6b** in 4 mL of anhydrous THF was slowly added 0.183 g (2.4 equiv) of potassium hydride. After 1 h, a solution of 1.577 g (3.0 equiv) of bis(3,5-dimethylphenyl)-chlorophosphine in 3 mL of the same solvent was added, and the stirring was continued at room-temperature overnight. The solvent was removed under high vacuum. The residue was purified by flash chromatography, eluting with ether/hexane (3:2) containing Et_3N (1%), to obtain 1.22 g (77%) of **12b** as a white powder. ^{1}H NMR ($CDCl_3$): δ 0.82 (s, 3H), 1.10 (s, 3H), 1.94 (s, 6H), 2.06 (s, 6H), 2.12 (s, 6H), 2.17 (s, 6H), 2.26 (s, 6H), 2.80 (d, J = 14.0 Hz, 1H), 3.24 (d; J = 14.0 Hz, 1H), 3.38 (m, 1H), 3.65 (m, 2H), 3.85 (dd, J = 5.3, 10.8, Hz, 1H), 4.38 (m, 1H), 4.50 (m, 1H), 5.26 (d, J = 7.1 Hz, 1H), 6.55 (s, 1H), 6.63 (s, 1H), 6.80 (s, 1H), 6.84 (s, 1H), 6.92 (m, 6H), 7.05 (ddd, J = 1.8, 7.7, 15.5 Hz, 1H), 7.17 (m, 2H), 7.21 (m, 1H). ^{31}P NMR ($CDCl_3$): δ 115.40 (d, J_{P-P} = 3 Hz), 120.23 (d, J_{P-P} = 3 Hz). Anal. Calcd for $C_{50}H_{61}NO_6P_2$: H 7.37; C 72.01; N 1.68. Found: H 7.52; C 72.20; N 1.66.

2-(Dimethylaminomethyl)phenyl 2,3-Di-*O*-(diphenylphosphino)-4,6-*O*-(1-methylethylidene)glucopyranoside (12a). The title compound was prepared by a route similar to the previous experiment for the synthesis of **12b** using chlorodiphenylphosphine instead of bis(3,5-dimethylphenyl)chlorophosphine (yield, 87%). ^{1}H NMR ($CDCl_3$): δ 0.83 (s, 3H), 1.12 (s, 3H), 2.19 (s, 6 H), 2.97 (d, J = 13.9 Hz, 1H), 3.32 (d, J = 13.9 Hz, 1H), 3.40 (m, 1H), 3.69 (m, 2H), 3.86 (dd, J = 5.3, 10.7 Hz, 1H), 4.45 (m, 2H), 5.25 (d, J = 7.0 Hz, 1H), 6.63 (d, J = 8.0 Hz, 1H), 6.93 (t, J = 7.3 Hz, 1H), 7.05 (m, 10 H), 7.27 (m, 10 H), 7.56 (m, 2H). ^{31}P NMR ($CDCl_3$): δ 113.42 (s), 116.24 (s).

2-(Dimethylaminomethyl)phenyl 2,3-Di-*O*-(bis(3,5-ditrifluromethylphenyl)phosphino)-4,6-*O*-(1-methylethylidene)glucopyranoside (12c). The title compound was prepared by a route similar to the previous experiment for the synthesis of **12b** using bis(3,5-di(triflurometh)phenyl)chlorophosphine instead of bis(3,5-dimethylphenyl)chlorophosphine (yield, 78%). ^{1}H NMR ($CDCl_3$): δ 0.98 (s, 6H), 2.15 (s, 6H), 2.90 (d, J = 13.3 Hz, 1H), 3.22 (d, J = 13.2 Hz, 1H), 3.42 (m, 1H), 3.67 (t, J = 0.5 Hz, 1H), 3.77 (t, J = 9.2 Hz, 1H), 3.87 (dd, J = 5.4, 10.9 Hz, 1H), 4.55 (m, 2H), 5.25 (d, J = 7.1 Hz, 1H), 6.46 (dd, J = 0.8, 8.2 Hz, 1H), 6.91 (ddd, J = 1.1, 7.4,

14.8 Hz, 1H), 7.01 (ddd, J = 1.8, 7.8, 15.5 Hz, 1H), 7.13 (dd, J = 1.8, 7.4 Hz, 1H), 7.53 (d, J = 1.2 Hz, 2H), 7.57 (bs, 1H), 7.67 (d, J = 1.4 Hz, 2H), 7.69 (d, J = 1.5 Hz, 2H), 7.72 (bs, 1H), 7.74 (bs, 1H), 7.86 (d, J = 0.5 Hz, 1H), 7.93 (bs, 1H), 7.96 (d, J = 0.5 Hz, 1H). ^{31}PNMR ($CDCl_3$): δ 107.14(s), 109.47(s).

The Cationic Rhodium Complex 13b. In a drybox, to a suspension of 35.5 mg (0.24 mmol) of trimethyloxonium tetrafluoroborate in 2 mL of anhydrous CH_2Cl_2 was added 200 mg (0.24 mmol) of **12b** in 3 mL of the same solvent, and the mixture was stirred overnight at room temperature. To the reaction mixture was added a solution of 97.4 mg (0.24 mmol) of $Rh^+(COD)_2BF_4^+$ in 2 mL of CH_2Cl_2, and the stirring was continued for 3 h. The solvent was removed under vacuum. The residue was collected, washed three times with Et_2O, and dried under high vacuum overnight to get 0.28 g (95%) of a fine powder of the Rh-complex **13b**. ^{31}P NMR ($CDCl_3$): δ 131.14 (dd, J_{P-P} = 29 Hz, J_{Rh-P} = 144 Hz), 132.87 (dd, J_{P-P} = 29, J_{Rh-P} = 149 Hz). Anal. Calcd for $RhC_{59}H_{76}NO_6P_2B_2F_8$: H 6.21; C 57.44; N 1.14. Found H 5.95; C 54.13; N 1.13.

The Cationic Rhodium Complex 13a. The title compound was prepared by a route similar to the previous experiment for the synthesis of **13b** except starting with **12a** instead of **12b** (yield: 99%). ^{31}P NMR ($CDCl_3$): δ 131.36 (dd, J_{P-P} = 29 Hz, J_{Rh-P} = 163 Hz), 133.09 (dd, J = 29 Hz, J_{Rh-P} = 159 Hz).

The Cationic Rhodium Complex 13c. was prepared by a route similar to the previous experiment for the synthesis of **13b** except using **12c** instead of **12b** (yield: 97%). ^{31}P NMR (CD_3OD): δ 134.87 (dd, J_{P-P} = 70 Hz, J_{Rh-P} = 198 Hz), 137.16 (dd, J_{P-P} = 70 Hz, J_{Rh-P} = 201 Hz).

The Cationic Rhodium Complex 10b. In a drybox, to a solution of 140 mg (0.113 mmol) of **13b** in 4 mL of methanol was added 40 mg of resin (AG 50 WX-8). The resin had been previously swollen in methanol overnight at room temperature, filtered, and washed three times with methanol before use in this experiment. The reaction mixture was stirred at room-temperature overnight. The resin was filtered through Celite. The solvent was removed under high vacuum, and the residue was washed three times with Et_2O and dried under high vacuum to get 0.112 g (83%) of **10b** as a white powder. ^{31}P NMR(CD_3OD): δ 123.09 (dd, J_{P1-P2} = 31.5, J_{Rh-P1} = 173.9 Hz), 130.46 (dd, J_{P1-P2} = 32 Hz, J_{Rh-P2} = 172 Hz).

The Cationic Rhodium Complex 10a. This complex was prepared by a route similar to the previous experiment for the synthesis of **10b** (yield: 70%). ^{31}P NMR (CD_3OD): δ 125.25 (dd, J_{P-P} = 32 Hz, J_{Rh-P} = 176 Hz), 130.82 (dd, J_{P-P} = 32 Hz, J_{Rh-P} = 173 Hz), ^{31}P NMR (D_2O): δ 124.40 (dd, J_{P-P} = 34 Hz, J_{Rh-P} = 174 Hz), 131.94 (dd, J = 33 Hz, J_{Rh-P} = 173 Hz).

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