Synthesis, Characterization, and Applicability of Neutral Polyhydroxy Phospholane Derivatives and Their Rhodium(I) Complexes for Reactions in Organic and Aqueous Media

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Abstract: Two different protocols for the preparation of water-soluble, enantiomerically pure polyhydroxybisphospholanes from acid-labile acetal and *tert*-butyldimethylsilyl-protected derivatives are reported. These procedures circumvent two of the commonly encountered limitations in the synthesis of these potentially important ligands: (a) formation of phosphonium salts from the highly basic phosphine under acidic conditions, and (b) the need to start with preformed, fully protected cationic metal complex. Thus, cationic Rh complexes of these ligands have been prepared in a separate step, and they have been found to be excellent catalysts for organic and aqueous phase hydrogenation of dehydroamino acids. The viability of catalyst recovery has been demonstrated in three different systems, including two cases where > 99% ee can be achieved under recycling conditions.

Introduction

A number of different strategies have been employed to increase the solubility of phosphine ligands and their complexes in aqueous media.[1] The majority of successful applications of these reagents in aqueous homogeneous catalysis involve compounds that carry sulfonate (anionic) or quaternary ammonium (cationic) groups. Nonionic, chiral ligands with hydrophilic groups *designed to improve aqueous solubility* are beginning to receive increasing attention,[2−8] principally because biphasic reactions of poorly soluble organic substrates can be expected to benefit from these ligands. In addition, such neutral ligands may find applications for metal-catalyzed reduction of membrane lipids where the catalyst transport into the bilayer may be precluded by highly charged groups which lead to accumulation of the catalysts at the water−organic interface.[4] In their original work, Selke and co-workers used vicinal diarylphosphinite−Rh complexes derived from phenyl β-D-glucopyranoside (**1**) for asymmetric hydrogenation of dehydroamino acids in water.[5] They also showed that enhanced selectivity in the asymmetric hydrogenation of sparingly soluble substrates could be achieved by the use of surfactants. In an attempt to circumvent the limited solubility of monosaccharide derived ligands, we[7]and others[6] have resorted to disaccharides such as trehalose (**2**)[7a] (or ligands with quaternary ammonium groups derived from D-salicin such as **3**[7b]) as ligand precursors with the expectation that an increased number of hydroxyl groups would improve solubility in water.[8] Indeed, very high enantioselectivities can be achieved with Rh complexes of these ligands, especially in the presence of surfactants.[6b] Besides the need for surfactants, which have to be removed at the end of the reaction, two other problems are inherent with the diarylphosphinite system. Our investigations of the partition coefficient for the Rh complexes between organic and water phases

(1) For general reviews on the subject of organic chemistry in aqueous media, see: (a) Sinou, D. *Bull. Soc. Chim. Fr.* **1986**, 480. (b) Kunz, E. G. *Chemtech* **1987**, *17*, 570. (c) Kalck, P.; Monteil, F. *Adv. Organomet. Chem.* **1992**, *34*, 219. (d) Herrmann, W. A.; Kohlpaintner, W. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1524. (e) *Aqueous Organometallic Chemistry and Catalysis*; Horváth, I. T., Joó, F., Eds.; Kluwer: Dodrecht, 1995. (f) For thematic issues dedicated to applications of water-soluble organometallic compounds see: *J. Mol. Catal. A: Chem.* **1997,** *116 (1, 2)*, 1−309. *Catal. Today*, **1998**, *42* (4), 371−478. (g) Nagel, U.; Kinzel, E. *Chem. Ber.* **1986**, *119*, 1731.

(2) Börner and co-workers have published extensively on the use of hydroxyphosphines, most of them for applications in organic solvents. While our studies were in progress, the Börner group published the first report dealing with a water-soluble tetrahydroxyphospholane (see ref 2c). (a) Holz, J.; Quirmbach, M.; Börner, A. *Synthesis* **1997**, 983. (b) Selke, R.; Holz, J.; Riepe, A.; Börner, A. *Chem.—Eur. J.* **1998**, *4*, 769 and references therein. (c) Holz, J.; Quirmbach, M.; Schmidt, U.; Heller, D.; Stürmer, R.; Börner, A. *J. Org. Chem.* **1998**, *63*, 8031. (d) Holz, J.; Heller, D.; Stürmer, R.; Börner, A. *Tetrahedron Lett.* **1999**, *40*, 7059. (e) Börner, A. *Eur. J. Inorg. Chem.* **2001**, 327.

(3) For other reports of the synthesis of polyhydroxyphospholanes see: (a) Li, W.; Zhang, Z.; Xiao, D.; Zhang, X. *Tetrahedron Lett.* **1999**, *40*, 6701. (b) Li, W.; Zhang, Z.; Xiao, D.; Zhang, X. *J. Org. Chem.* **2000**, *65*, 3489. (c) Our investigations reveal that the hydroxyphospholane ligands described in these publications are most likely phosphonium salts (vide infra).

(4) (a) Quinn, P. J.; Taylor, C. E. *J. Mol. Catal.* **1981**, *13*, 389. (b) Madden, T. D.; Peel, W. E.; Quinn, P. J.; Chapman, D. *J. Biochem. Biophys. Methods* **1980**, *2*, 19. (c) For biomedical applications of hydroxyphosphines, see: Katti, K. V.; Gali, H.; Smith, C. J.; Berning, D. E. *Acc. Chem. Res.* **1999**, *32*, 9.

(5) (a) Kumar, A.; Oehme, G.; Roque, J. P.; Schwarze, M.; Selke, R. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2197 and references therein. (b) Selke, R. *J. Organomet. Chem.* **1989**, *370*, 241 and 249. (c) Graseert, I.; Paetzold, E.; Oehme, G. *Tetrahedron* **1993**, *49*, 6605. (d) Selke, R.; Ohff, M.; Riepe, A. *Tetrahedron* **1996**, *52*, 15079.

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

(7) (a) Shin, S.; RajanBabu, T. V. *Org. Lett.* **1999**, *1*, 1229. (b) Yan, Y.; RajanBabu, T. V. *J. Org. Chem.* **2001**, *66*, 3277.

(8) 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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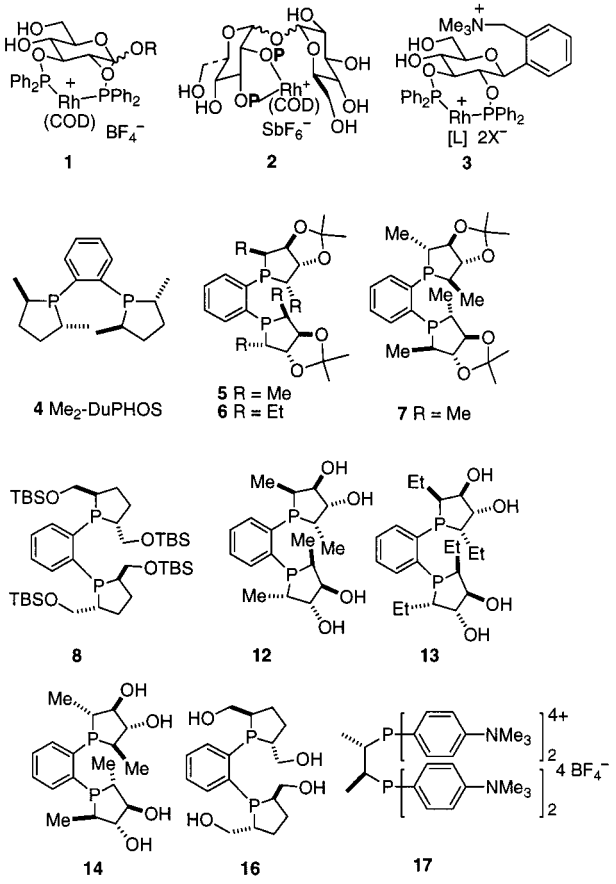
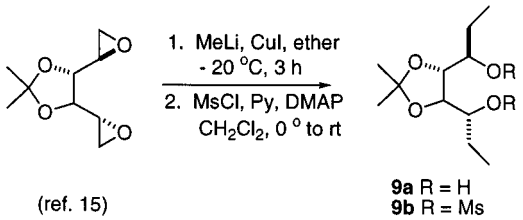
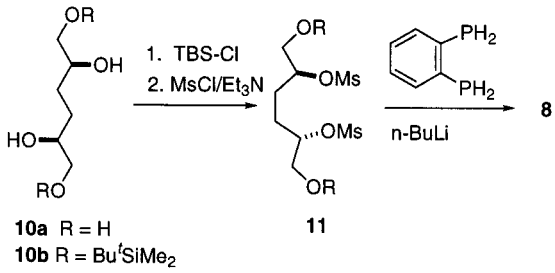


(by the inductively coupled plasma spectroscopy method) revealed that, despite the increased number of hydroxyl groups, the Rh(I)-complexes still possessed considerable solubility in the organic medium. Ohe, Uemura, and co-workers have noticed significant deterioration of catalytic activity upon reuse of the aqueous phase for subsequent reactions.[6a] One possible explanation of such decrease in activity could be the hydrolytic degradation of the P−O bond, as we have seen in the case of related salicin-derived diarylphosphinite complexes (**3**).[7b] We believe that an attractive solution to the dual problems of hydrolytic instability and hydrophobicity can be addressed through the use of polyhydroxyphosphines bearing robust P−C bonds (vis-á-vis P−O bonds) and a reduced number of aryl substituents on the phosphorus atom. The latter should help to decrease the hydrophobicity of the catalyst. With these goals in mind,[9] we chose the C_2-symmetric phospholane system, which forms the backbone of the enormously successful DuPhos ligands (e.g., **4**), discovered by Burk[10] and co-workers. Last year we reported a general route for synthesis of several highly functionalized phospholane derivatives **5**−**7** from readily available D-mannitol.[11a] Some of these are superb catalysts for

Scheme 1. Synthesis of Mesylate Precursor for **7**



Scheme 2. Synthesis of Bishydroxymethylphospholane **8**



prototypical Pd-catalyzed allylation[11b] and allylic amination[11c] reactions in organic media. In this paper, we report new protocols for the direct conversion of these ketal derivatives and of other silyl-protected compounds (for example, **8**) to the corresponding fully deprotected polyhydroxyphosphines. In the past, direct acid hydrolysis has been found to be problematic,[3a−c,12] and successful syntheses of such ligands bearing electron-rich phosphorus atoms have relied on either the formation of the corresponding BH_3 adducts[9c] or precomplexation with Rh(I).[2d,5−7,11b] We also record the complete characterization (C, H analysis and ^{1}H, ^{13}C, and ^{13}P NMR) of these potentially important ligands and their applications in asymmetric hydrogenation in aqueous and organic media. The reuse of an aqueous solution of the catalyst (up to four cycles) with no deleterious effects on the enantioselectivity will also be demonstrated for the first time.

Results and Discussion

(a) Synthesis of the Ligands. The syntheses of protected derivatives **5**[3a,11a] and **7**[11a] from D-mannitol have been reported.[13] Minor modifications of the procedures used for the synthesis of these compounds enabled the preparation of **6** and **8**[14] from the corresponding diols **9a** and **10a**. Diol **9a** was synthesized from 1:2;5:6-dianhydro-3,4-*O*-isopropylidene-D-mannitol[15] (Scheme 1) and bis(Bu^tMe_2Si)ether, **10b**, was prepared from the tetrahydroxy compound **10a.** Phospholane **8** was synthesized from **10b** in very good yield as shown in Scheme 2.

Because base-sensitive OH-protecting groups such as esters[8c,d] are incompatible with the highly nucleophilic phosphide anion used in the synthesis of the phospholanes, synthesis of the polyhydroxyphospholanes is a nontrivial problem, especially when the phosphine is electron-rich. Use of acid-sensitive

(9) For other reports of the synthesis and utility of functionalized phospholanes, see: (a) Hitchcock, P. B.; Lappert, M. F.; Yin, P. *J. Chem. Soc., Chem. Commun.* **1992**, 1598. (b) See ref 2c. (c) Carmichael, D.; Doucet, H.; Brown, J. M. *J. Chem. Soc., Chem. Commun.* **1999**, 261. (d) For the initial report from the Zhang group, see ref 3a.

(10) (a) Burk, M. J.; Feaster, J. E.; Harlow, R. L. *Tetrahedron: Asymmetry* **1991**, *2*, 569. (b) Burk, M. J.; Feaster, J. E.; Nugent, W. A.; Harlow, R. L. *J. Am. Chem. Soc.* **1993**, *115*, 10125. (c) Burk, M. J.; Harper, T. G. P.; Kalberg, C. S. *J. Am. Chem. Soc.* **1995**, *117*, 4423. (d) Burk, M. J.; Kalberg, C. S.; Pizzano, A. *J. Am. Chem. Soc.* **1998**, *120*, 4345. (e) Burk, M.; Gross, M. F.; Harper, T. G. P.; Kalberg, C. S.; Lee, J. R.; Martinez, J. P. *Pure Appl. Chem.* **1996**, *68*, 37 and references therein.

(11) (a) Yan, Y.; RajanBabu, T. V. *J. Org. Chem.* **2000**, *65*, 900. (b) Yan, Y.; RajanBabu, T. V. *Org. Lett.* **2000**, *2*, 199. (c) Yan, Y.; RajanBabu, T. V. Unpublished results.

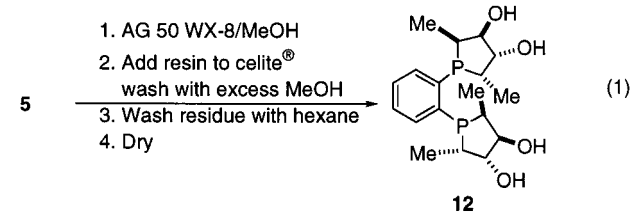
(12) Direct hydrolysis of acetals with a less basic diphenylphosphino group is known: (a) Börner, A.; Holz, J.; Ward, J.; Kagan, H. B. *J. Org. Chem.* **1993**, *58*, 6814. (b) Börner, A.; Ward, J.; Kortus, K.; Kagan, H. B. *Tetrahedron: Asymmetry* **1993,** *4*, 2219. (c) Tamao, K.; Nakamura, K.; Shigehiro, Y.; Shiro, M.; Saito, S. *Chem. Lett.* **1996**, 1007. (d) See also ref 8a.

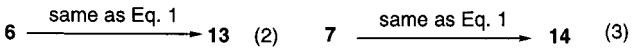
(13) For synthesis of other derivatives see refs 2c,d and 9c.

(14) Originally synthesized in 1999 by S. Shin of our group from **10a**. For **10a**, see: Corey, E. J.; Hopkins, P. B. *Tetrahedron Lett.* **1982**, *23*, 1979. (b) Marzi, M.; Misiti, D. *Tetrahedron Lett.* **1989**, *30*, 6075. (c) Machinaga, N.; Kibayashi, C. *J. Org. Chem.* **1992**, *57*, 5178.

(15) Le Merrer, Y.; Duréault, A.; Greck, C.; Micas-Languin, D.; Gravier, C.; Depezay, J.-C. *Heterocycles* **1987**, *25*, 541.

protecting groups is often the only alternative, and this procedure is fraught with problems.[16] For example, acid hydrolysis of DIOP (*trans*-4,5-bis[(diphenylphosphino)methyl]-2,2-dimethyl-1,3-dioxolane) derivatives with aqueous mineral acids gave considerable amounts of quaternary phosphonium salts.[17] Börner has reported that methanesulfonic acid in aqueous methanol can be used to liberate hydroxyphosphines from the corresponding tetrahydropyranyl (THP) derivatives, as long as the phosphine carried aromatic substituents (in the case cited, diphenylphosphino groups).[12] In most cases reported to date, including one example of a hydroxymethyl bisphospholane system,[2d] the hydroxyl protecting groups are removed after the formation of the cationic Rh chelate.[5−7] This protocol, while perfectly acceptable for Rh-catalyzed reactions, imposes serious limitations if other metals are to be considered for catalysis in aqueous media. Therefore, we thought that it would be highly desirable to have a direct route to the metal-free polyhydroxyphosphine ligands, and our initial efforts were directed toward this goal. While our early attempts to use strong acids in aqueous and alcoholic media to liberate the hydroxyl groups from **5**, **7**, and **8** were facing considerable difficulties, Zhang et al. reported[3a,b] what appeared to be a simple solution to the problem. These workers reported that ligand **5**, upon treatment with excess methanesulfonic acid in refluxing aqueous methanol (10 h), gave the deprotected derivative **12** in 90% yield as an oil! However, the proton, and especially the phosphorus-31 NMR data (broad peak at δ +11.9), suggested that the product of this reaction was most likely a phosphonium salt (**15**), and not the free hydroxyphospholane as claimed (vide infra).

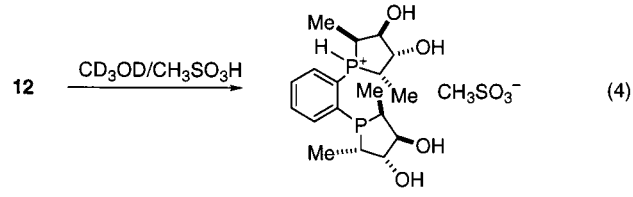


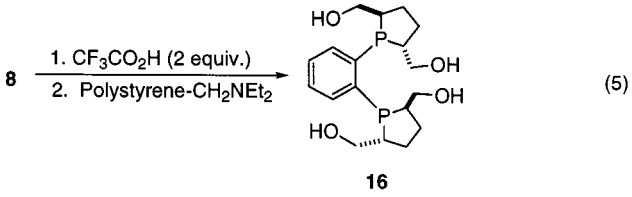


We have since discovered two separate procedures for the synthesis of the polyhydroxyphospholanes, depending on the protecting groups on the alcohol. The ketal protecting groups from **5**−**7** are removed by treatment with acidic resin (AG 50 WX-8) in anhydrous methanol (eqs 1−3). Best yields are obtained when the resin is carefully washed with and then swollen in methanol overnight at room temperature. It is subsequently washed with methanol three times and dried before use for hydrolysis. At the end of the reaction, the insoluble residue is filtered with the aid of Celite. The solvent is removed, the residue is washed with hexane, and the product is dried. In each case, the hydroxyphospholanes **12**−**14** are obtained as a white solid in 75−80% isolated yield (eqs 1−3). These potentially important ligands were fully characterized by elemental analysis (C, H) and ^{1}H, ^{13}C, and ^{31}P NMR. For example, ligand **12**, synthesized according to our protocol, is a white solid whose ^{31}P NMR spectrum in CD_3OD is characterized by a sharp singlet at δ −3.77. The corresponding phosphonium salt (**15**) prepared by treatment of **12** with 3 equiv of methanesulfonic acid in CD_3OD has a characteristic broad absorption at δ +15 (eq 4), suspiciously similar to that of the product obtained under aqueous hydrolysis conditions reported by Zhang.[3] We also noticed significant differences in the ^{13}C and ^{1}H NMR spectra of the two compounds. For example, the chemical shifts of the protons in the phosphonium salt, as expected, are in general at lower fields compared to those of the neutral ligand (see Experimental Section for details). Neutral ligands **13** and **14**, prepared by a similar route, also show characteristic ^{31}P NMR chemical shifts (CD_3OD) at δ −10.36 and −14.24. The cationic Rh complexes (Rh^+[**L**][COD] BF_4^-] prepared from these ligands show clean doublets for the J_{Rh-P} (**L** = **12**, 151.6 Hz; **L** = **13**, 151.2 Hz; **L** = **14**, 152.7 Hz), confirming the C_2-symmetric nature of the ligands.

Table 1. Hydrogenation of Dehydroamino acids Using [**L**]Rh^+[Cod] BF_4^-

entry	substrate (R in eq 6)	**L**	solvent	% ee (GC)
1	3-F-$C_6H_4^-$	**12**	MeOH	91
2	H	**12**	MeOH	>99
3	3-F-$C_6H_4^-$	**13**	MeOH	97
4	H	**13**	MeOH	>99
5	H	**13**	1:1 MeOH/H_2O	>99
6	H	**13**	H_2O	>99
7	3-F-$C_6H_4^-$	**14**	MeOH	95
8	H	**14**	MeOH	97



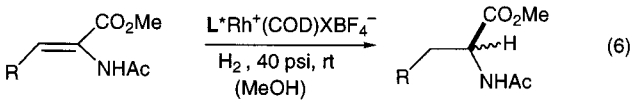


An alternate procedure was used for the synthesis of **16**. The use of AG 50 WX-8 for the deprotection of **8** gave poor yields of the expected product, primarily because of low recovery of the highly polar tetrahydroxyphosphine from the resin. However, the desilylation can be accomplished by reaction of **8** with CF_3CO_2H in MeOH (eq 5). After evaporation of the solvent, the residue (a solid which, by NMR, appears to be a mixture of phosphonium salts) is dissolved in methanol, and the methanol solution is passed through a short bed of diethylaminomethyl polystyrene. Evaporation of the filtrate gives the expected product in 84% yield. A very sharp peak at δ −12.4 (CD_3OD) is characteristic of the free phosphine. Further confirmation of the structure comes from detailed analysis of the ^{1}H, ^{13}C, and HETCOR spectra (see Experimental Section and Supporting Information for details and spectra).

(b) Hydrogenation Studies: Organic and Aqueous Media. Contrary to an earlier report,[3a] isopropylidene derivative **5** was found to be an excellent ligand for Rh-catalyzed asymmetric hydrogenation, delivering high ee's for prototypical substrates shown in eq 6. The diastereomeric phospholane, **7**, as expected, gave opposite selectivity in the hydrogenation of methyl acetamidoacrylate.

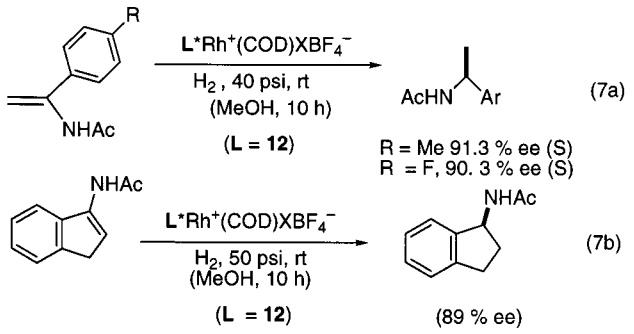
The cationic Rh complexes of the fully deprotected hydroxyphospholanes are excellent catalysts for hydrogenation of

(16) See also footnote 10 in ref 3a.
(17) Deschenaux, R.; Stille, J. K. *J. Org. Chem.* **1985**, *50*, 2299.



(6)

R	Ligand (L)	%ee
H	**5**	90.5 (S)
H	**7**	97.4 (R)
3-Br-C_6H_4	**5**	94.7 (S)
3-F-C_6H_4	**5**	92.8 (S)



(7a)

(7b)

dehydroamino acids (Table 1) and simple enamides (eq 7a,b) in methanol.[18] For these studies and the subsequent hydrogenations in aqueous media, we chose methyl acetamidoacrylate as the substrate, because this substrate is freely soluble in water, and its recovery by extractive workup would be a good indication of how effectively the aqueous phase containing the catalyst can be recycled in repeated operations (vide infra). Of special note in Table 1 is the complex prepared from 1,5-diethylphospholane **13** which gave >99% ee in neat water (entry 6). *Such high selectivity in the absence of added surfactants has seldom been achieved in purely aqueous medium, especially using neutral ligands.*[19] Phosphine ligands with quaternary ammonium groups structurally related to chiraphos (**17**) have been reported to give up to 94% ee in neat water when the reaction is done in a slurry.[20]

The enantioselectivity of the reaction is highly dependent on the structure of the catalyst and the solvent. For example, Table 2 shows the effect of water on the enantioselectivity of hydrogenation of acetamidoacrylate using ligand **12**. While near 100% ee is observed *reproducibly* in neat methanol, often a capricious reaction is observed in MeOH/H_2O mixtures, with enantioselectivity dropping off as the proportion of water increases (99% ee in neat methanol to 21% in 1:3 methanol/water). At the end of the reaction in several runs, precipitation of metallic Rh was noticed, which suggested that nonselective Rh-mediated processes might be responsible for such behavior. The problems of reproducibility and precipitation of rhodium can be alleviated by using an extra equivalent of the ligand (entry 4, Table 2). Using this protocol, it is now possible to recycle the aqueous solution of the catalyst without loss of selectivity.

(c) Catalyst Recovery and Reuse. An often stated, yet rarely achieved, goal of developing water-soluble ligands is to find conditions where the aqueous layer containing the catalyst can be recycled with *no loss of activity or selectivity*. While a number of examples of such recovery of catalysts containing ionic ligands are known, most notably phosphine ligands carrying ionic ($-SO_3^-$ or Me_3N^+) side chains,[1,20] ligands **12**−**14** are among the *first nonionic ligands where this has been possible with no apparent loss of selectivity*. The results for methyl acetamidoacrylate reductions are shown in Tables 3−5. The reaction is typically carried out in 1:1 methanol/water with 1 mol % of the isolated cationic Rh complex as the precatalyst with one mol % of extra ligand added to suppress precipitation of the metal. The product is separated at the end after each run by extraction into ether. The aqueous layer containing the catalyst is reused in subsequent hydrogenations. The results of hydrogenation using (COD)Rh^+[**14**] BF_4^- are shown in Table 3. Figure 1 shows the corresponding chromatograms. We have noticed a small, but discernible, increase in selectivity with each run. The diastereomeric complex (COD)Rh^+[**12**] BF_4^- also behaves in a similar fashion, even though the selectivity is lower (Table 4). Finally, Table 5 shows results with diethylphospholane **13**, *which is one of only two ligands (the other one being* ***16****, vide infra), which gave consistently high selectivities (>99% ee) in both neat methanol as well as water*. This catalyst can be recycled three times in 1:1 MeOH/H_2O, albeit with significant loss of reactivity during the last run (only 35% conversion under identical conditions). Most gratifyingly, the enantioselectivity remains unaltered. It is tempting to speculate that the loss of reactivity is related to the increased hydrophobicity of diethyl derivative **13** (vis-á-vis dimethyl derivative **12**) and the attendant loss of the catalyst in ether which is used to extract the product after the second run.

Table 2. Hydrogenation of Dehydroamino Acids Using [**12**]Rh^+[Cod] BF_4^- in MeOH: Effect of Water on the Hydrogenation of Methyl Acetamidoacrylate

entry	MeOH:water	conversion	% ee
1	1:0	100	>99
2	1:1	100	69
3	1:2	38	21
4	1:3 (+ 1 equiv **L**)	100	67

Table 3. Catalyst Recovery and Reuse in Hydrogenation of Methyl Acetamidoacrylate Using 1 Mol % of [**14**]Rh^+[Cod] BF_4^- (1:1 MeOH/water with 1 Mol % of Added Ligand)[a]

entry	run number	conversion	% ee
1	1	100	83
2	2	100	86
3	3	100	87
4	4	100	90

[a] See Figure 1 for chromatograms.

Among the ligands we prepared, **16** gave the best results in hydrogenation in 100% water. The enantioselectivity and recyclability is outstanding with the catalyst derived from this ligand as shown in Table 6 and Figure 1. In four sequential runs, ~99% ee and >90% isolated yield (100% conversion) were obtained for the hydrogenation of methyl acetamidoacrylate in *neat water*. The recycling was repeated for up to seven runs with a small loss of selectivity. The catalytic efficiency suffers in runs beyond the fourth cycle. For example, in the seventh cycle, it is approximately 50%, as judged by the 12 h needed to complete the reaction instead of the usual 6 h. A surprisingly high enantioselectivity of 95% was observed even for this run (Figure 1).

Summary and Conclusions

We record two different protocols for the preparation of water-soluble, enantiomerically pure polyhydroxybisphos-

(18) Zhang has also reported similar results in methanol. See ref 3b.

(19) For a notable exception see Börner et al., ref 2d. Excellent ee's using a surfactant (sodium dodecyl sulfate) in an aqueous medium have been recorded; see for example refs 5a and 6b.

(20) Toth, I.; Hanson, B. E.; Davis, M. E. *Tetrahedron: Asymmetry* **1990,** *1*, 913 and references therein. The recovery and reuse of the catalyst has also been demonstrated with this catalyst.

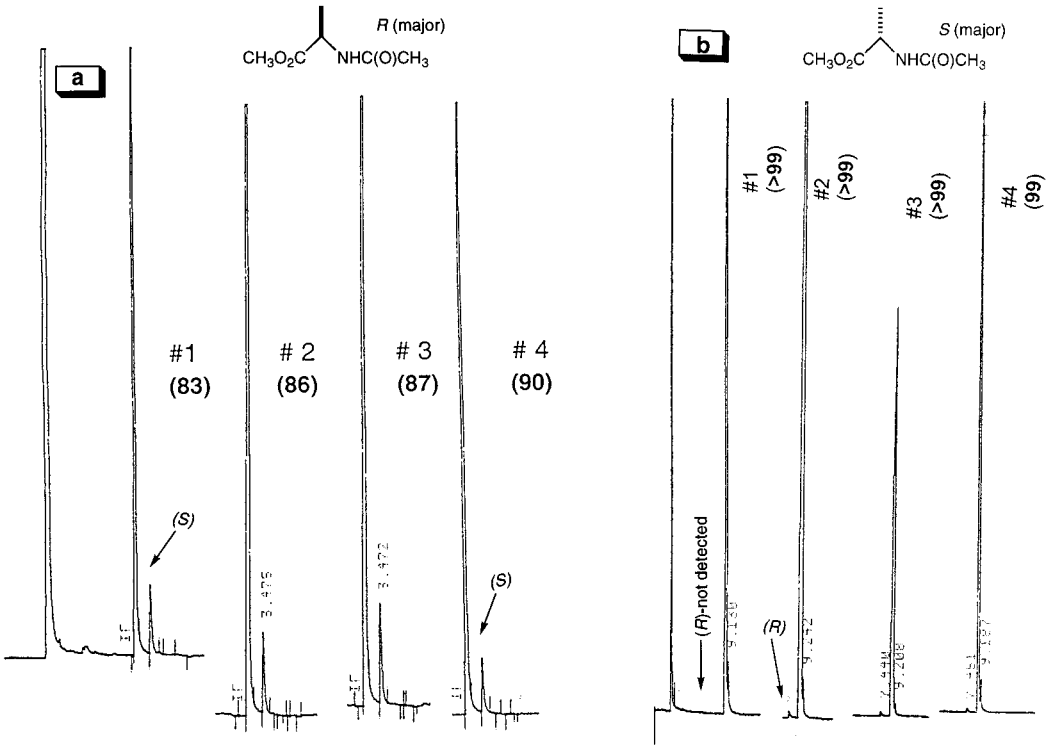


Figure 1. GCs of hydrogenation products (ee's in brackets) from successive runs using *recycled* aqueous solutions of (a) [**14**]Rh^+[COD] BF_4^- (Table 3) and (b) [**16**]Rh^+[NBD] SbF_6^- (Table 6).

Table 4. Catalyst Recovery and Reuse in Hydrogenation of Methyl Acetamidoacrylate Using 1 Mol % of [**12**]Rh^+[Cod] BF_4^- (1:1 MeOH/water with 1 Mol % of Added Ligand)

entry	run number	conversion	% ee
1	1	100	66
2	2	100	80
3	3	100	81
4	4	100	84

Table 5. Catalyst Recovery and Reuse in Hydrogenation of Methyl Acetamidoacrylate Using 1 Mol % of [**13**]Rh^+[Cod] BF_4^- (1:1 MeOH/water with 1 Mol % of Added Ligand)

entry	run number	conversion	% ee
1	1	100	>99
2	2	100	>99
3	3	35	>99

Table 6. Hydrogenation of Methyl Acetamidoacrylate Using 1 Mol % of [**16**]Rh^+[NBD] SbF_6^- in Water. Catalyst Recovery and Reuse in 100% Water with 1 Mol % of Added Ligand.[a]

entry	run number	conversion	% ee
1	1	100	>99
2	2	100	>99
3	3	100	>99
4	4	100	>99
5	5	100	~97

[a] See Figure 1 for chromatograms.

pholanes from acid-labile protected derivatives. These procedures circumvent two of the commonly encountered limitations in the synthesis of these potentially important ligands: (a) formation of phosphonium salts from the highly basic phosphine under acidic conditions, and (b) the need to start with preformed fully protected cationic metal complex. Thus, cationic Rh complexes, (and presumably other metal complexes) can be prepared in a separate step, and they have been found to be excellent catalysts for aqueous phase hydrogenation of dehydro-amino acids. The viability of catalyst recovery has been demonstrated in three different systems, including two cases where >99% ee can be achieved under recycling conditions. We are currently exploring applications of these ligands in other catalytic processes.

Experimental Section

General Methods. All anaerobic reactions were carried out in an inert atmosphere of nitrogen in a Vacuum Atmospheres drybox or by using Schlenk techniques. Methylene chloride was distilled from calcium hydride under nitrogen and stored over 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; coupling values are reported in hertz. Gas chromatographic analyses were performed using an HP-ultra-1 cross-linked methyl silicone capillary column (25 m length × 0.2 mm i.d.).

The hydrogenation reactions were carried out as follows. In a drybox, a Fischer−Porter tube was charged with the enamide substrate (0.1 mmol), the appropriate solvent (2 mL), and preformed [COD]Rh^+**L**X^- (1 mol %). After sealing, the tube was removed from the drybox and placed behind proper shielding. After five vacuum-refilling cycles with hydrogen, the tube was brought to the appropriate pressure (40 psi) of H_2, and the mixture was vigorously stirred for 3−6 h. After removing the catalyst on a plug of silica gel, the ee's of the product were determined by chiral GC (Chirasil-L-Val on WCOT fused silica 25 m × 0.25 mm). Baseline separation of the enantiomers is observed, and the ee's are reproducible within ± 0.5%.

Hydrogenation in aqueous media was also carried out as described in the previous paragraph. Water used for these experiments was degassed by a repeated freeze−thaw procedure. In the recycling experiments, the Fischer−Porter tube was taken inside the drybox, and the product was extracted into ether (5 mL each, three times). To the aqueous layer was added an additional 0.5 mL degassed water to

facilitate the separation of the two layers in the subsequent runs. Fresh substrate was added to the aqueous solution of the recovered catalyst, and the hydrogenation was continued at 40 psi of hydrogen. The ether layer was concentrated and analyzed by gas chromatography as mentioned earlier.

Syntheses of precursors **5**[3a,11a] and **7**[11a] from D-mannitol have been reported.

Synthesis of the Mesylate Precursor 9b. The title compound was prepared in two steps from 1,2:5,6-dianhydro-3,4-*O*-isopropylidene-D-mannitol (Scheme 1). A 1.4 M solution of MeLi in ether (89 mL, 124.6 mmol) was added to a suspension of CuI (11.8 g, 62 mmol) in ether (25 mL) at −20 °C. After 2 h at −10 °C, the mixture was cooled to −30 °C, and a solution of the diepoxide (3.86 g, 20.7 mmol) in ether (10 mL) and THF (10 mL) was added. After stirring at −20 °C for 3 h, the reaction mixture was poured into cold saturated NH_4Cl, and the product was extracted with ether. The extract was washed with brine, dried over $MgSO_4$, and evaporated on a rotary evaporator to leave an oil, which was chromatographed on silica gel with ethyl acetate/hexane as eluant to get **9a** as a colorless oil (4.38 g, 97%, crude). ^{1}H NMR ($CDCl_3$): δ 1.00 (t, J = 7.4, 6H), 1.35 (s, 6H), 1.82 (m, 2H), 3.52 (m, 4H), 3.66 (dd, J = 1.9 and 6.0, 2H); ^{13}C NMR: δ 9.24, 26.82, 26.99, 74.28, 82.83, 108.66.

To a mixture of 2.0 g (9.16 mmol) of diol **9a** and 30 mg of DMAP in 10 mL of pyridine and 5 mL of CH_2Cl_2 was added, slowly, 1.95 mL (3 equiv) of methanesulfonyl chloride at 0 °C. After stirring for 6 h at that temperature, the reaction mixture was poured into 100 mL of ice-cold 2 N HCl, and the product was extracted with CH_2Cl_2 (3 × 30 mL). The combined extracts were successively washed with 30 mL of water and saturated $NaHCO_3$ solution and then dried with anhydrous $MgSO_4$. Removal of the solvent on a rotary evaporator gave the crude product which was purified by column chromatography on silica gel (elution with ethyl acetate/hexane, 70/30). Dimesylate **9b** was obtained in 87% yield as an oil. ^{1}H NMR: δ 1.07 (t, J = 7.4, 6H), 1.42 (s, 6H), 1.87 (m, 4H), 3.10 (s, 6H), 4.19 (dd, J = 1.5 and 3.9, 2H), 4.71 (m, 2H). ^{13}C NMR: δ 9.02, 23.73, 27.10, 38.86, 78.57, 82.80, 111.07.

Synthesis of Bisphospholane 6. To a solution of 1,2-bisphosphanobenzene (142.1 mg, 1.0 mmol) in 5 mL of THF was added *n*-BuLi (1.4 mL of 1.6 M solution in hexane) via a syringe at −78 °C. The solution was warmed to room temperature and was stirred for an additional 1 h. After cooling to 0 °C, a solution of **9b** (749.4 mg, 2.0 mmol) in 4 mL of THF was added, and the mixture was stirred for 2 h. Then, 2.2 equiv of *n*-BuLi (1.4 mL) were added dropwise at 0 °C, and the orange suspension was stirred overnight. After 14 h, 8 mL of water was added, and the THF layer was separated. The aqueous phase was extracted with ether (2 × 15 mL). The combined organic extracts were dried over sodium sulfate, and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography on silica gel inside the drybox (elution with 5:95 v/v ether/hexane) to obtain 115 mg (23%) of diphospholane **6** as a white solid. ^{1}H NMR ($CDCl_3$): δ 0.77 (t, J = 7.0, 6H), 0.86 (m, 2H), 0.97 (t, J = 7.3, 6H), 1.32 (m, 4H), 1.47 (s, 12H), 2.00 (m, 2H), 2.20 (m, 2H), 2.62 (m, 2H), 4.40 (dd, J = 6.6 and 10.4, 2H), 4.47 (dd, J = 7.4, 10.4, 2H), 7.37 (m, 4H). ^{13}C NMR: δ 13.08 (t, J = 6.1), 14.57 (t, J = 2.2), 21.15 (t, J = 14.4), 21.39, 27.25, 27.36, 32.85 (t, J = 9.7), 32.98 (t, J = 2.6), 81.37 (t, J = 6.1), 82.30, 117.05, 129.15, 131.05, (t, J = 2.7), 141.29 (t, J = 6.0). ^{31}P NMR ($CDCl_3$): δ 35.63. Elemental analysis for $C_{28}H_{44}O_4P_2$ Calcd: C, 66.38; H, 8.75. Found: C, 66.35; H, 8.79.

Deprotection of 7: Synthesis of Tetrahydroxyphospholane 14 [(*R*,*S*,*S*,*R*)]. In a drybox, to a solution of 90 mg (0.20 mmol) of bisphospholane **7** in 3 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, washed three times with methanol, and dried 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 hexane and dried under high vacuum to get 59 mg (80%) of **14** [*(R,S,S,R)*] as a white solid**.** ^{1}H NMR (CD_3OD): 0.89 (m, 6H), 1.33 (m, 6H), 2.06 (m, 2H), 2.46 (m, 2H), 3.48 (m, 4H), 7.42 (dd, J = 3.3 and 5.7, 2H), 7.62 (m, 2H). ^{13}C NMR (CD_3OD): 15.73 (t, J = 3.1), 18.18 (t, J = 17.0), 34.24, 34.73 (t, J = 6.3), 83.67 (t, J = 5.1), 83.84, 130.11, 133.34 (t, J = 3.1), 143.35 (d, J = 4.0). ^{31}P NMR (CD_3OD): δ −14.24 (s).

Deprotection of 6: Synthesis of Tetrahydroxyphospholane 13 [(*S*,*S*,*S*,*S*)]. The title compound was prepared by a route similar to that of the previous experiment for the synthesis of **14**, except starting with the bisphospholane of **6** instead of the bisphospholane of **7** (yield: 74%). ^{1}H NMR (CD_3OD): δ 0.91 (t, J = 7.3, 6H), 0.93 (t, J = 7.3, 6H), 1.27 (m, 2H), 1.44 (m, 4H), 1.71 (m, 2H), 1.92 (m, 2H), 2.58 (m, 2H), 2.87 (m, 2H), 3.38 (m, 2H), 4.31 (m, 4H), 7.28 (dd, J = 3.2 and 5.4, 2H), 7.97 (dd, J = 3.0 and 5.7, 2H). ^{13}C NMR (CD_3OD): δ 14.45 (t, J = 4.0), 14.81 (t, J = 5.2), 21.32, 23.20 (t, J = 16.1), 43.56 (t, J = 7.8), 46.98, 79.40, 80.23, 129.01, 134.89, 144.38 (t, J = 6.0). ^{31}P NMR (CD_3OD): δ −10.36 (s). Elemental analysis for $C_{22}H_{36}O_4P_2$ Calcd: C, 61.96; H, 8.51. Found: C, 62.22; H, 8.42.

Deprotection of 5: Synthesis of Tetrahydroxyphospholane 12 [(*S*,*S*,*S*,*S*)]. The title compound was prepared by a route similar to that of the previous experiment for the synthesis of **14**, except starting with the bisphospholane of **5** instead of the bisphospholane of **7** (yield: 82%). ^{1}H NMR (CD_3OD): δ 0.83 (m, 6H), 1.27 (m, 6H), 2.77 (m, 2H), 2.91 (m, 2H), 4.13 (m, 4H), 7.28 (dd, J = 3.3 and 5.6, 2H), 7.70 (m, 2H). ^{13}C NMR (CD_3OD): δ 13.07, 14.32 (t, J = 17.4), 34.77 (t, J = 6.7), 35.28, 80.72, 80.83, 129.34, 133.13, 143.54 (t, J = 4.9). ^{31}P NMR (CD_3OD): δ −3.77 (s). Elemental analysis for $C_{18}H_{28}O_4P_2$ Calcd: C, 58.37; H, 7.62. Found: C, 56.69; H, 7.46.

^{31}P NMR of the Cationic Rh Complexes. [COD]Rh$^+$[**7**] BF_4^-: ^{31}P NMR (CD_3OD) 65.03 (d, J_{Rh-P} = 152.7 Hz). [COD]Rh$^+$[**5**] BF_4^-: ^{31}P NMR (CD_3OD) 77.66 (d, J_{Rh-P} = 151.8 Hz). [NBD]Rh$^+$[**8**] SbF_6^-: ^{31}P NMR (CD_3OD) 63.0 ppm (d, J_{Rh-P} = 154.4 Hz). [COD]Rh$^+$[**12**] BF_4^-: ^{31}P NMR (CD_3OD) 77.66 (d, J_{Rh-P} = 151.6 Hz). [COD]Rh$^+$-[**13**] BF_4^-: ^{31}P NMR (CD_3OD) 70.99 (d, J_{Rh-P} = 151.2 Hz). [COD]-Rh$^+$[**14**] BF_4^-: ^{31}P NMR (CD_3OD) 65.02 (d, J_{Rh-P} = 152.7 Hz). [NBD]Rh$^+$[**16**] SbF_6^-: ^{31}P NMR (CD_3OD) 66.0 (d, J_{Rh-P} = 155.4 Hz).

1,6-Di-*O*−*t*-Butyldimethylsilyl-3,4-dideoxy-D-mannitol (10b). To a solution of tetrol **10a** (0.500 g, 3.33 mmol) and imidazole (0.567 g, 8.32 mmol) in 3 mL of *N*,*N*-dimethylformamide was added, at 0 °C, a solution of *tert*-butyldimethylsilyl chloride (1.104 g, 7.32 mmol) in 3 mL of DMF. The mixture was stirred at 0 °C for 2.5 h. The reaction mixture was subsequently diluted with 100 mL of ether and was washed with brine (50 mL × 2) and water (50 mL). The organic layer was dried ($MgSO_4$), and the solvent was removed to give 0.890 g (71%) of white crystalline solid, mp 79−81 °C (lit. 78 °C).

(2*S*,5*S*)-1,6-Di(*tert*-butyldimethylsilyloxy)-2,5-di(methanesulfonyloxy)hexane (11). To a stirred solution of diol **10b** (258 mg, 0.681 mmol) and triethylamine (380 uL, 2.725 mmol) in 3 mL of CH_2Cl_2 at −20 °C was added dropwise methanesulfonyl chloride (158.2 μL, 2.044 mmol). After complete addition, the mixture was stirred at −20 °C for 30 min longer and was diluted with 20 mL of ether. The solution was washed with water (3 mL × 2) and dried ($MgSO_4$), and the solvent was removed. The residue was purified on a silica gel column (ethyl acetate/hexane = 1:4) to give a colorless oil, which became a crystalline solid (322.0 mg, 88%) upon keeping in a refrigerator overnight. Mp 74−76 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.00 (s, 6H, Me−Si × 2), 0.01 (s, 6H, Me−Si × 2), 0.82 (s, 18H, *t*-Bu × 2), 1.71 (m, 4H, C3/C4−H), 3.00 (s, 6H, CH_3 in Mesyl), 3.66 (d, J = 5.2 Hz, 4H, C1/C6−H), 4.66 (t, br, J = 5.4 Hz, 2H, C2/C5−H). ^{13}C NMR (100 MHz, $CDCl_3$): δ −5.0, 18.8, 26.3, 26.8, 39.0, 65.5, 83.6.

Preparation of Bisphospholane 8. To a solution of 1,2-bisphosphinobenzene (34.0 mg, 0.24 mmol) in 2 mL of THF was added *n*-BuLi (0.21 mL of 2.5 M solution in hexane, 2.2 equiv) via syringe at −30 °C, and the mixture was stirred at that temperature for 1.5 h. To the resulting orange solution was added, dropwise, dimesylate **11** (256.1 mg, 0.48 mmol) in 2 mL of THF at −30 °C, and the mixture was slowly warmed to room temperature over 1 h. After cooling the mixture to −30 °C, an additional 2.2 equiv of *n*-BuLi was added, and the reaction mixture was allowed to stir overnight. After 16 h, the reaction mixture was filtered through a Celite pad, and the pad was rinsed with ether. The crude product was purified by flash chromatography on silica gel inside the drybox (elution with 5:95 v/v ether/hexane) to give 98.3 mg (50%) of pure bisphospholane **8** as colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.13 (s, 6H), −0.10 (s, 6H), 0.04 (s, 6H), 0.06 (s, 6H), 0.77 (s, 18H), 0.90 (s, 18H), 1.64 (m, 2H, C3−H), 1.72 (m, 2H,

C4−H), 2.10 (m, 2H, C4′−H), 2.25 (m, 2H, C3′−H), 2.50 (m, 2H, C5−H), 2.82 (m, 2H, C2−H), 2.86 (t, J = 10.3, 2H, C6−H), 3.63 (m, 2H, C1−H), 3.68 (dd, J = 4.2, 10.3 Hz, 2H, C6′−H), 3.82 (m, 2H, C1′−H), 7.23 (m, 2H), 7.39 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 4.94, −4.88, −4.81, −4.79, 18.66, 18.81, 26.33, 26.39, 30.1, 30.5, 41.4 (J_{P-C} = 7.1), 42.1, 65.7 (J_{P-C} = 4.8), 67.2 (J_{P-C} = 27.2), 128.6, 131.9, 141.8. ^{31}P NMR (200 MHz, $CDCl_3$): δ −13.4 ppm (s). ^{31}P NMR (200 MHz, CD_3OD) for cationic rhodium complex [Rh(**8**)(NBD)]BF_4: δ 63.0 ppm (d, J_{Rh-P} = 154.4).

Hydrolysis of the *tert*-Butyldimethlsilyl Ethers. Tetrahydroxyphospholane 16. To a mixture of **8** (64.2 mg, 0.078 mmol) and 2 mL of MeOH was added CF_3CO_2H (44 mg, 0.38 mmol, 5.0 equiv), and the mixture was stirred at room temperature for 10 h. The progress of deprotection can be checked by TLC (THF as eluent, R_f = 0.45). The reaction was stirred for 10 h. After evaporation of solvent to dryness, the residue was redissolved in MeOH and was filtered through a 2 cm pad of polystyrene−CH_2NEt_2 resin to remove residual acid. The solvent was removed, and the resulting white solid was purified by flash chromatography using THF as eluent to give **16** as a white solid. Unprotected phospholane and partially deprotected phospholane were combined, and the mixture was treated with CF_3CO_2H in MeOH to give complete deprotection. The combined yield after chromatography was 24.1 mg (84%). ^{1}H NMR (500 MHz, CD_3OD): δ 1.55 (m, 2H, C4−H), 1.64 (m, 2H, C3−H), 2.08 (m, 2H, C3′−H), 2.30 (m, 2H, C4′−H), 2.41 (m, 2H, C2−H), 2.80−2.92 (m, 4H, C5−H, C1−H), 3.49 (dd, J = 5.4 and 11.1, 2H, C1′−H), 3.55−3.72 (m, 4H, C6−H, C6′−H), 7.31 (m, 2H), 7.46 (m, 2H). ^{13}C NMR (125 MHz, CD_3OD): δ 29.6 (C4), 30.5 (C3), 42.1 (C5), 42.4 (J_{P-C} = 6.8 Hz, C2), 64.0 (J_{P-C} = 3.9 Hz, C1), 65.7 (J_{P-C} = 22 Hz, C6), 128.8, 132.1, 141.6 (J_{P-C} = 4.8 Hz). ^{31}P NMR (202 MHz, CD_3OD): δ −12.4 ppm (s).

Procedure for Formation of Rh Complexes. To a solution of tetrahydroxybisphospholane **16** (12.4 mg, 33.5 μmol) in 1 mL of MeOH-d_4 was added $[Rh(NBD)_2]^+$ SbF_6^- (15.9 mg, 30.4 μmol) [NBD = norbornadiene], and the resulting bright orange solution was stirred for 30 min at room temperature. [Rh (**16**)(NBD)]SbF_6 ^{31}P NMR (200 MHz, CD_3OD) : δ 66.0 ppm (d, J_{Rh-P} = 155.4).

Typical Hydrogenation Procedure using [Rh(16)(NBD)]$^+$ SbF_6^-. Inside a vacuum atmosphere drybox, the Rh complex (1.6 mg, 2.0 μmol) and free ligand **16** (0.7 mg, 2.0 μmol) in 2 mL of neat water (degassed as described earlier) were placed in a Fisher−Porter bottle, and methyl 2-acetamidoacrylate (28.6 mg, 0.200 mmol) was added. The bottle was sealed and then taken outside the drybox. The bottle was charged with 50 psi of H_2 and then was evacuated under house vacuum. This cycle was repeated five times before it was finally charged with 50 psi of H_2. With efficient stirring, the mixture was hydrogenated at room temperature for 5−7 h. After this period, the bottle was brought inside the drybox. The aqueous layer (2 mL) was extracted with 4 mL of Et_2O with vigorous magnetic stirring. This extraction was repeated 3−4 times, and then the ethereal layer was dried ($MgSO_4$) and evaporated to give methyl *N*-acetylalanate (isolation: ∼90%). The GLC analysis 100 °C (isothermal run at 100 °C) of the product was done on a chiralsil L-Val column.

Recycling and Reuse of the Catalyst ([Rh(16)(NBD)]$^+$ SbF_6^-). To the aqueous layer above was added 28.6 mg of methyl 2-acetamidoacrylate (28.6 mg, 0.200 mmol). The same procedure was repeated for hydrogenation. After the fourth cycle, more water was added because of loss of water during extraction.

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Supporting Information Available: NMR spectra (^{1}H, ^{13}C, and ^{31}P) of **8**, **12**−**14**, **16** (PDF). This material is available free of charge via Internet at http://pubs.acs.org.

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