Carbohydrate Phosphinites as Practical Ligands in Asymmetric Catalysis: Electronic Effects and Dependence of Backbone Chirality in Rh-Catalyzed Asymmetric Hydrogenations. Synthesis of *R*- or *S*-Amino Acids Using Natural Sugars as Ligand Precursors

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Vicinal diarylphosphinites derived from carbohydrates are excellent ligands for the Rh(I)-catalyzed enantioselective asymmetric hydrogenation of dehydroamino acid derivatives, producing the highest enantioselectivity of any ligands directly prepared from natural products. The enantioselectivity can be enhanced by the appropriate choice of substituents on the aromatic rings of the phosphinites. For example, the use of phosphinites with electron-donating bis(3,5-dimethylphenyl) groups on phosphorus provides ee's up to 99% for a wide range of amino acids including some with easily removable N-protecting groups. Electron-withdrawing aryl substituents, on the other hand, decrease the enantioselectivity. Sense of chiral induction in the amino acid product depends on the relative juxtaposition of the vicinal diphosphinites on a given sugar backbone. When readily available D-glucopyranosides are used as the starting sugars, 2,3-phosphinites give the *S*-amino acids and 3,4-phosphinites give the *R*-amino acids. In the case of aromatic and heteroaromatic amino acids, enantioselectivities > 95% are consistently obtained. Practical considerations such as the ease of ligand synthesis, rates of reactions, catalyst turnover, and scope and limitations in terms of substrates are discussed. A possible explanation for the enhancement of enantioselectivity by electron-rich phosphinites is offered.

Introduction

Catalytic asymmetric synthesis using organometallic reagents is currently one of the most active areas of research in organic chemistry.[1] Despite the enormous progress in this area, our inability to predict, a priori, the type of ligands required to achieve useful levels of enantioselectivity severely limits the rational development of highly selective catalysts. With a few notable exceptions, models which adequately predict the stereochemical outcomes rely on spatial orientation of groups in the chiral environment around the metal.[2] Such models are especially useful for designing catalysts for reactions where the precise structure of the catalytically relevant intermediate is known and its absolute configuration can be related to that of the final product.[3−8] In these instances model building can be a useful tool for the design of better catalysts, provided there is sufficient flexibility in the synthesis of the ligands. For other reactions such as the Rh(I)-catalyzed hydrogenation of acetamidoacrylates[9−11] or the Ni(0)-catalyzed hydrocyanation of olefins,[12] where the relative reactivities of transiently-formed, often undetectable intermediates dictate the overall stereochemical outcome, the predictive value of such models is tenuous at best. Recently, increasing number of examples of electronic tuning of asymmetric catalysts are beginning to appear in the literature.[12−19] A clear understanding of the origin of the

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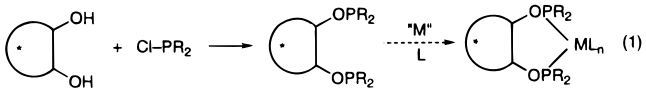
pronounced dependence of enantioselectivities on the electronic properties of ligands is still lacking, and this further impedes the de novo design of useful ligands. Such inadequacies notwithstanding, steric and electronic tuning of ligands has been successfully employed in developing efficient asymmetric reactions.



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In light of the foregoing discussion, it is apparent that an empirical approach to ligand design remains a powerful option, especially when dealing with an asymmetric reaction for which the details of the mechanism and of the origin of asymmetric induction are poorly understood. In practical terms, such an approach is limited only by the ability to make systematic structural changes in a ligand scaffolding to produce the broadest possible electronic and stereochemical diversity. We were first confronted with such a situation in our attempts to find an asymmetric variant for the Ni(0)-catalyzed hydrocyanation of vinylarenes, for which no synthetically useful precedent existed.[20−22] Initial experiments with ligands (including BINAP, DIOP, CHIRAPHOS, BPPFA, DUPHOS)[23] which were known to give excellent selectivities in other asymmetric reactions resulted in disappointingly low reactivity and/or selectivity in the hydrocyanation reaction. A careful analysis of the various syntheses of these and a number of other well-known ligand systems quickly revealed that making structural changes even within a given scaffolding could be prohibitively time consuming for two reasons: (a) the number of synthetic steps involved; (b) need of a resolution process which in many cases has to be optimized for each substituted derivative. Thus we embarked on a search for easily tunable ligands which could be prepared in a few steps from readily available natural products. In reviewing the literature we were particularly attracted to chiral vicinal diaryl and dialkyl phosphinites because of the inherent simplicity in their synthesis (eq 1) from carbohydrates and amino acids.[24] In addition, the use of diarylchlorophosphine as the source of phosphorus in this modular construction allows for easy manipulation of the electronic and steric properties of the chelating atom(s). In the study of the Ni(0)-catalyzed asymmetric hydrocyanation of vinyl arenes (eq 2) using carbohydrate-derived phosphinites, we have since demonstrated that ligand optimization is indeed a powerful strategy to develop new asymmetric processes.[12,19] During this study, we discovered two crucial control elements: (a) chirality of the sugar backbone; (b) the electronic properties of the chelating atoms. Thus, 2,3-bis-*O*-(diarylphosphinite)s

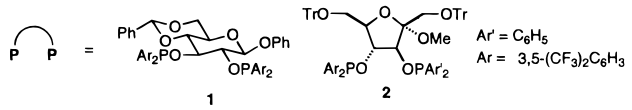
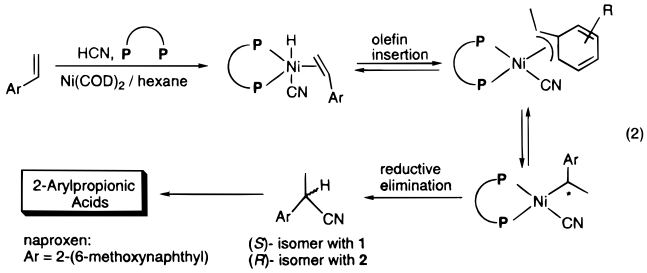


Figure 1. Prototypical sugar phosphinite ligands giving opposite enantioselectivities.

from phenyl β-D-glucopyranoside (**1**) gave the (*S*)-2-arylpropiononitrile as the major isomer whereas the 3,4-bis-*O*-(diarylphosphinite)s from methyl α-D-fructofuranoside (**2**) gave the opposite enantiomer (Figure 1). The enantioselectivity of the reaction increases dramatically when D-glucose-derived 2,3-bis(diarylphosphinite)s (Figure 1) contain electron-withdrawing *P*-aryl substituents, and enantiomeric excesses (ee) up to 91% were realized for the hydrocyanation of 2-methoxy-6-vinylnaphthalene, a precursor for the antiinflammatory drug, naproxen (eq 2, Ar = 2-(6-methoxynaphthyl). In a detailed mechanistic investigation that involved kinetic as well as deuterium labeling studies we have provided convincing evidence that the amplification of enantioselectivity by the electron-withdrawing *P*-aryl sustituents is related to an increase in the rate of *reductive elimination* of the product from the penultimate (η^3-benzyl)nickel cyanide intermediate (eq 2).[12] At the time of our initial report[15] dealing with the hydrocyanation of vinyl arenes, with a few notable



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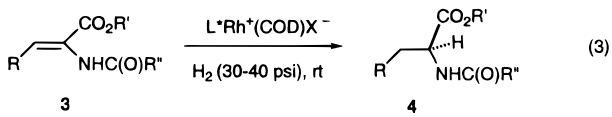
exceptions,[13a,14] electronic tuning of ligands had seldom been employed as a control element in asymmetric catalysis. Since the sugar phosphinite system was especially amenable to electronic tuning, we wondered how a reaction where *oxidative addition* to the metal center is a key step would respond to electronic effects in the ligand. For this we chose the well-known Rh-catalyzed asymmetric hydrogenation of α-(acylamino)acrylic acid derivatives (eq 3), a reaction which has been studied extensively because of its great synthetic potential for the synthesis of amino acids.[9,25−29] In sharp contrast to the Ni(0)-catalyzed asymmetric hydrocyana-



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tion reaction, electron-donating substituents on the *P*-aryl groups of vicinal phosphinites enhance the enantioselectivity of the Rh(I)-catalyzed asymmetric hydrog-

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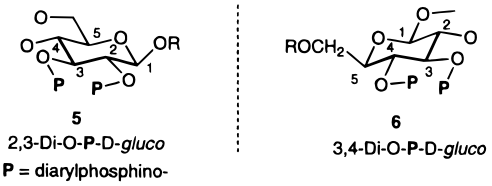


Figure 2. Pseudoenantiomeric relation between 2,3- and 3,4-disubstituted glucopyranosides.

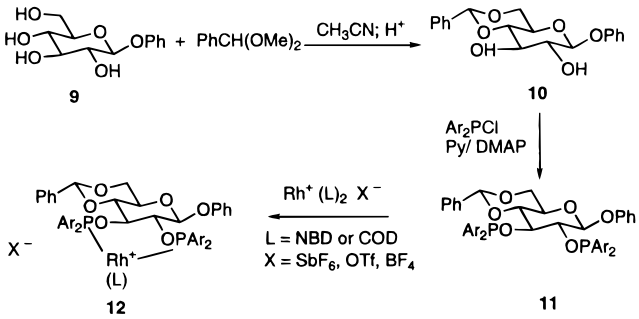
enation reaction.[30] In this paper we provide the details of this study.[31]

One of the perceived limitations of using natural products as a source of chiral ligands is that often only one of the enantiomeric series (in the case of carbohydrates and amino acids D- and L-series, respectively) is readily available, and thus synthesis of only one enantiomer of the product is economically viable. For example, while D-glucose is available for less than $1.00/kg, the corresponding L-sugar costs about $1.00/g. A solution to this problem can be found if one examines the stereochemical relationships between the C-2, C-3, and C-4 carbon atoms of the glucopyranoside ring system in a pairwise fashion. The C-2:C-3-bis-phosphinite is pseudoenantiomeric with respect to the C-3:C-4 phosphinite (Figure 2). Admittedly, there is no perfect matching of all the groups in the periphery of the sugar ring. *Now if one makes the basic assumptions that the enantioselectivity of the reaction depends only on the local chirality, i. e., the chirality of the two vicinal carbons to which the chelating phosphorus atoms are attached, and that there is no large scale disruption of the equatorial arrangement of the rest of the groups on the sugar backbone, it should be possible to make both enantiomers of a product using the D-sugar backbone.* These assumptions have been borne out for the first time in the context of asymmetric hydrogenation, making it possible to develop a series of readily available ligands for the synthesis of *R*- and *S*-amino acids by choosing the appropriate ring carbons for the attachment of the diarylphosphino groups to the D-sugar backbone. In the hydrogenation of α-(*N*-acylamino)acrylic acid derivatives, the cationic Rh-complexes of 2,3- and 3,4-bis(diarylphosphinite)s derived from sugars with the D-*gluco*- configuration give *S*- and *R*-amino acid derivatives, respectively. In nearly all cases, the electronic amplification of enantioselectivity is key to obtaining practical levels of asymmetric induction.

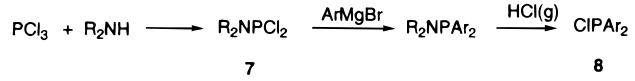
Results and Discussion

Sugar Phosphinites as Ligands in Rh-Catalyzed Asymmetric Hydrogenation. Phosphinites have been used as ligands since 1975,[32] and almost invariably their use has been limited to Rh-catalyzed hydrogenations.[24,33,34] Based on the work of the Selke group,[24,35a] a commercial process for the manufacture of L-DOPA has been developed.[35b] During the course of our investigations two limitations of the use of simple diphenylphosphinites became apparent: (1) for a number of heteroaromatic and aromatic amino acids with substituents on the ring, diphenylphosphinites gave relatively low enantioselectivities; (2) we (vide infra) and others[36] have observed low enantioselectivities in the reduction of dehydroamino acids with protecting groups other than acetyl on the nitrogen. The latter is an important limitation since it has been found that removal of the acyl protecting group may lead to low yields and occasionally significant racemization at the α-carbon.[37] It is desirable to have a catalyst that gives high enantioselectivity for amino acids carrying easily removable protecting groups such as N-Cbz or N-Boc.[38]

Scheme 1. Synthesis of "D-Gluco" 2,3-Diarylphosphinite Rhodium Complexes



Scheme 2. Preparation of Diarylchlorophosphines



Among the chelating phosphines, arguably, the sugar phosphinite ligand system appeared to be the most easily accessible, and overcoming the above-mentioned limitations using these ligands would be of practical significance. Toward this goal, we decided to examine the role of ligand electronic effects on the course of this reduction. Accordingly, we prepared a variety of phenyl 2,3-bis-*O*-(diarylphosphino)-β-D-glucopyranosides with electronically different aryl groups by slight modifications of procedures described in the literature (Scheme 1).[12,35a] The requisite chlorodiarylphosphines were prepared from dichloro(diethylamino)phosphine[39] and a Grignard reagent followed by treatment of the resulting diarylaminophosphine with anhydrous HCl (Scheme 2).[40] The chlorodiarylphosphines can also be prepared by the

(30) Anecdotal evidence of electronic effects in Rh-catalyzed hydrogenation dates back to some of the original studies done by Kagan. See for example: (a) Dang, T. P.; Poulin, J. C.; Kagan, H. B. *J. Organomet. Chem.* **1975**, *91*, 105. (b) Hengartner, U.; Valentine, D., Jr.; Johnson, K. K.; Larscheid, M. E.; Pigott, F.; Scheidl, F.; Scott, J. W.; Sun, R. C.; Townsend, J. M.; Williams, T. H. *J. Org. Chem.* **1979**, *44*, 3741. (c) Yamagishi, T.; Yatagai, M.; Hatakeyama, H.; Hida, M. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 1897. (d) Inoguchi, K.; Morimoto, T.; Achiwa, K. *J. Organomet. Chem.* **1989**, *370*, C9. (e) Werz, U.; Brune, H. A. *J. Organomet. Chem.* **1989**, *365*, 367. (f) Morimoto, T.; Chiba, M.; Achiwa, K. *Chem. Pharm. Bull.* **1992**, *40*, 2894.

(31) A preliminary account of this work has been published; see reference 16.

(32) Tanaka, M.; Ogata, I. *J. Chem. Soc., Chem. Commun.* **1975**, 735.

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(34) Nomura, N.; Mermet-Bouvier, Y. C.; RajanBabu, T. V. *Synlett* **1996**, 745.

(35) (a) Selke, R.; Pracejus, H. *J. Mol. Catal.* **1986**, *37*, 213. (b) Vocke, W.; Hänel, R.; Flöther, F.-U. *Chem. Tech. (Leipzig)* **1987**, *39*, 123.

(36) (a) Kreuzfeld, H.-J.; Döbler, C.; Krause, H. W.; Facklam, C. *Tetrahedron: Asymmetry* **1993**, *4*, 2047. See also: (b) Döbler, C.; Kreuzfeld, H.-J.; Krause, H. W.; Michalik, M. *Tetrahedron: Asymmetry* **1993**, *4*, 1833. (c) Ojima, I.; Yoda, N.; Yatabe, M.; Tanaka, T.; Kogure, T. *Tetrahedron* **1984**, *40*, 1255. (d) Achiwa, K. *Chem. Lett.* **1977**, 777.

(37) Taudien, S.; Schinkowski, K.; Krause, H. W. *Tetrahedron: Asymmetry* **1993**, *4*, 73.

(38) Use of DUPHOS ligands is another solution to this problem; see reference 29.

(39) Perich, J. W.; Johns, R. B. *Synthesis* **1988**, 142.

(40) Unruh, J. D.; Christenson, J. R. *J. Mol. Catal.* **1982**, *14*, 19.

reaction of 2 equiv the corresponding arylmagnesium bromide with tri-*n*-butyl phosphite followed by treatment of the resulting phosphinic acid with a halogenating agent such as PCl_3.[12] Treatment of various diols with the chlorodiarylphosphines gave high yields of the phosphinites. The corresponding cationic Rh-complexes were prepared by treating the ligand with $Rh^+(\mathbf{L})_2\ X^-$ where **L** is either 1,4-cyclooctadiene or norbornadiene and X is SbF_6, OTf, or BF_4.[41] The structures of ligands used in this study are shown in Figure 3.

1. (*S*)-Aromatic and -Heteroaromatic Amino Acids. The best substrates for the sugar-derived phosphinites are the aromatic and heteroaromatic dehydroamino acids. The hydrogenation of various (*Z*)-*N*-acyl dehydroamino acid substrates using cationic Rh-complexes were carried out at 30−40 psi of hydrogen at room temperature in a Fischer−Porter tube. The results of hydrogenation using ligands **11a**−**h** (Figure 3) are shown in Table 1. Seven-membered Rh-chelates of electron-rich vicinal phosphinites are very efficient catalysts,[35a] and typically, 1 mmol of a dehydroamino acid or the corresponding methyl ester dissolved in 4 mL of THF is quantitatively hydrogenated in less than 15 min using 0.004 mol of Rh^+(**11b**)(NBD) SbF_6^-. In general, the scouting experiments were run for 2−3 h using 0.05−0.1 mol% of the catalyst. The ee's were determined by capillary gas chromatographic analysis of the crude product using Chirasil-L-Val column under conditions where a base-line separation of the enantiomers was observed for the *N*-acetyl methyl esters of all the amino acids reported here. In reactions where the acid was used as the substrate, the methyl esters were prepared by reaction of the hydrogenation product with diazomethane. In several instances the enantiomeric purity were corroborated with HPLC analysis using Chiralcel OJ or OB column and optical rotation. The gas chromatographic data is reproducible within ±0.2%, and the HPLC data within ±0.5%. Several typical chromatograms are included in the Supporting Information.

The most conspicuous result in the table is the remarkable electronic effect of the aryl substituents of the chelating phosphorus atom. In the case of methyl (*Z*)-*N*-acetylcinnamate, the enantioselectivity varies from 2% ee for the electron-deficient 3,5-difluorophenyl derivative to 99% ee for the electron-rich 3,5-bis(trimethylsilyl)phenyl derivative[42] (Table 1, entry 1). The same general trend is seen for other substrates. Under otherwise identical conditions, the acid substrates gave slightly better selectivity as compared to the esters. Significant differences in ee's between the unsubstituted (**11e**) and 3,5-dimethylphenyl (**11b**)-substituted phosphinites were noticed, and the difference is highly substrate dependent. By some estimates the trimethylsilyl group is 1.25 times as electron-donating as a methyl substituent[43] and as expected the corresponding phosphinites (**11a**) gave excellent ee's. However, in practical terms, 3,5-dimethyl derivatives are preferred because of the ease of preparation. Reduction of the Cbz-protected dehydroamino acid ester (Scheme 3) in entry 6 (Table 1) is particularly noteworthy since this substituent has been shown to give low selectivities under other catalytic hydrogenation conditions.[36] Thus use of the diphenylphosphinite **11e**

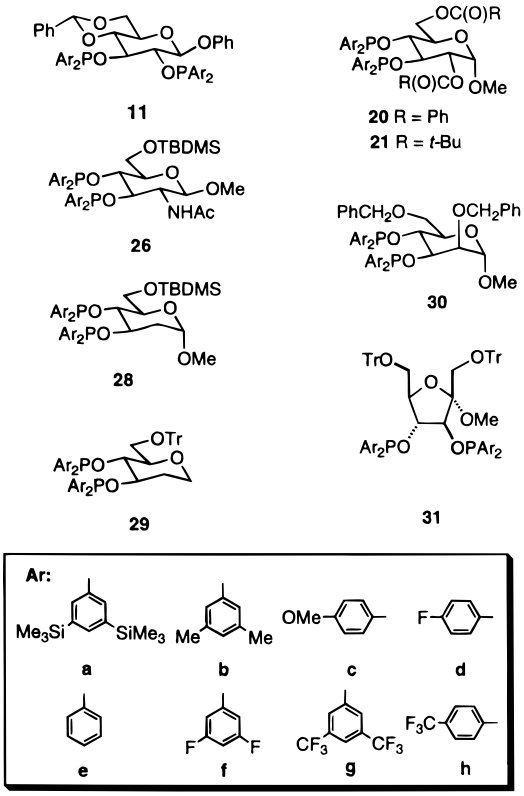


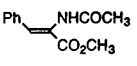
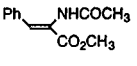
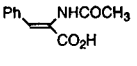
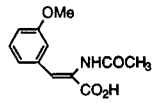
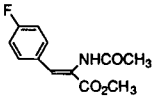
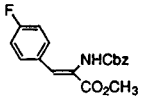
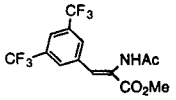
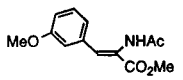
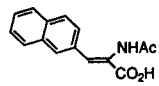
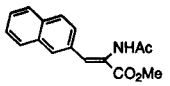
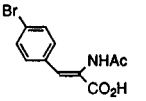
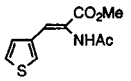
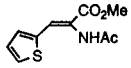
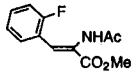
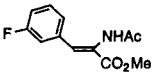
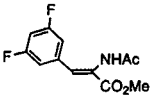
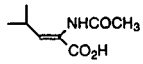
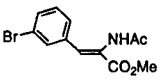
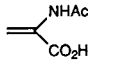
Figure 3. Carbohydrate-derived ligands for amino acid synthesis.

gave only 62.0% ee where as the bis(dimethylphenyl) derivative **11b** gave 96% ee. The Cbz amino acid ester did not give satisfactory separation on any of the chiral columns, so the analysis of the product was conducted on the *N*-acetyl derivative **15**, which was prepared by hydrogenolysis of the Cbz group in acetic anhydride (Scheme 3). Alternatively, the ester can be reduced to a primary alcohol **16** and the N-Cbz-protected alcohol(s) can be analyzed by HPLC on Chiralcel OJ column. Heterocyclic amino acids such as 2- and 3-thienylalanine are also formed with excellent selectivity (entries 12 and 13) using the ligands **11a** and **11b**. The counterion appears to have a small, yet discernible effect on the enantioselectivity. For example, in THF, SbF_6^- generally gave a slightly better selectivity than BF_4^- (Table 1, entries 1, 2, 5, 7, and Table 2, entries 1, 3, 5, 11). By simple recrystallization of the crude hydrogenation product (entries 3, 7, and 12), optically pure derivatives of phenylalanine (99.7% ee), 3,5-bis(trifluoromethyl)phenylalanine (99.3% ee), and 3-thienylalanine (99.5% ee) were prepared in excellent yields. Optical antipodes of two of the corresponding amino acids are shown in Table 2, entries 4 and 13. It should be noted that, in general, none of the experimental protocols have been optimized.

2. Effect of the Sugar Backbone on the Sense of Asymmetric Induction: (*R*)-Amino Acids. The high selectivity and the ease of ligand synthesis notwithstanding, a serious limitation of this approach for the synthesis of (*R*)-amino acids is the scarcity of L-glucose. The highest selectivity recorded for the preparation of an (*R*)-amino acid using a carbohydrate-derived ligand prior to this work is only 63%.[44,45] A solution to this problem might be the use of sugars such as arabinose which are available in both enantiomeric forms. However, the realization that in the context of the β-D-glucopyranoside

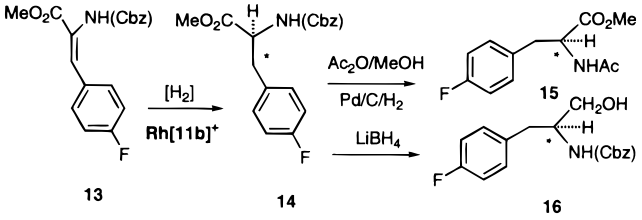
(41) Schrock, R. R.; Osborn, J. A. *J. Am. Chem. Soc.* **1971**, *93*, 2397.
(42) For the preparation of bis[3,5-bis(trimethylsilyl)phenyl]diethylaminophosphine, see: Trost, B. M.; Murphy, D. J. *Organometallics* **1985**, *4*, 1143.
(43) Gassman, P. G.; Deck, P. A.; Winter, C. H.; Dobbs, D. A.; Cao, D. H. *Organometallics* **1992**, *11*, 959.
(44) Habuš, I.; Raza, Z.; Šunjić, V. *J. Mol. Catal.* **1987**, *42*, 173.

Table 1. Enantioselectivity in Hydrogenations Using Catalysts [11a−h]Rh^{+}(L) X^{-}

Entry	Substrate	X	3,5-$(TMS)_2$	3,5-Me_2	4-(MeO)	H	4-F	4-CF_3	3,5-F_2	3,5-$(CF_3)_2$
1.		SbF_6	99.0	97.4	--	90.2	81.0	2.0	2.0	--
2.		BF_4	98.2	94.4	--	84.7	--	9.8	6.2	7.2
3.		SbF_6	97.6	99.0 (99.7)*	93.0 (96.0 with OTf)	94.0	91	--	60.0	--
4.		SbF_6	--	97.0	--	91.0	--	--	53.0	5.0
5.		SbF_6	98.7	97.2	89	85.0 (84 with BF_4^-)	81.0	--	13.0	9.0
6.		SbF_6	--	95.7	85	62	--	--	<3	<5
7.		SbF_6	97.1 (96.9 with BF_4)	95.8 (99.3)*	--	85.2	--	--	--	--
8.		SbF_6	98.8	96.8	--	88.0	--	--	21.0	--
9.		SbF_6	--	98.0	--	94.0	--	--	22.0	26.6
10.		SbF_6	--	97.1	--	86.5	--	--	--	10.8
11.		SbF_6	--	98	--	--	--	--	47	--
12.		SbF_6	98.8	96.7 (99.5)*	--	86.6	--	--	--	--
13.		SbF_6	97.2	95.6	--	85.2	--	--	--	--
14.		SbF_6	97.8	96.8	--	89.1	--	--	--	--
15.		SbF_6	--	97.1	--	88.9	--	--	--	--
16.		SbF_6	98.4	97.0	--	88.3	--	--	--	--
17.		SbF_6	83.6 (Me ester 87.2)	91.0	--	90.0	--	--	64.4	26.0
18.		SbF_6	--	96.8	--	89.2	--	--	--	--
19.		SbF_6	--	96.9	--	--	--	--	--	--

(* ee's upon recrystallization)

Scheme 3. Hydrogenation of N-Cbz Dehydroamino Acids



scaffolding, the 2,3-phosphinite is psuedoenantiomeric with the 3,4-phosphinite (Figure 2), prompted us to investigate this substitution pattern for ligand synthesis. We initially chose α-methyl D-glucopyranoside because of the availability of the starting sugar and ease of synthesis of the corresponding 2,6-di-*O*-protected derivatives. A series of 3,4-*O*-bis(diarylphosphinite)s of these derivatives were synthesized from the corresponding diols, which in turn were prepared using chemistry reported by Ogawa et al.[46] Thus α-methyl D-glucopyranoside **17** upon treatment with bis(tri-*n*-butyltin) ether in refluxing toluene followed by reaction with either benzoyl chloride or pivaloyl chloride selectively yielded the 2,6-di-*O*-protected glucosides **18** and **19**, respectively (Scheme 4). The dibenzoyl derivatives are highly crystalline and easily prepared in large quantities.[47] Preparation of bis-phosphinites **20** and **21** and the corresponding Rh-complexes were accomplished as described earlier. The results of hydrogenation of a variety of substituted dehydroamino acids using the Rh complexes of **20** and **21** are shown in Table 2.

A careful inspection of the data reveals several important points. The electronic effect of the phosphinites are just as pronounced in this ligand system as in the 2,3-bis-*O*-(diarylphosphinite) system **11**. As compared to **11**, where the 4,6-oxygens form a conformationally locked acetal, the manifestation of the electronic effect appears to be more pronounced and systematic across the various aryl substituents in the more flexible 3,4-bis(diarylphosphinite) **20**.[64] Electron-deficient phosphinites carrying F or CF_3 substituents uniformly gave very low selectivities (Table 2, entries 1−5). As expected methyl 2,6-benzoyl-3,4-bis-*O*-[bis(3,5-dimethylphenyl)phosphino]-α-D-glucopyranoside (**20b**) gave the best results. As before, we observed that when the reaction is done in THF solvent, use of SbF_6 as a counteranion appears to be slightly beneficial, especially if the dehydroamino acid rather than the methyl ester is the substrate. Highly enriched products can be recrystallized to get optically pure (*R*)-amino acid derivatives. 3,5-Bis(trifluoromethyl)phenylalanine (99.4% ee) and 3-thienylalanine (99.5% ee) (entries 4 and 13, Table 2) are illustrative.

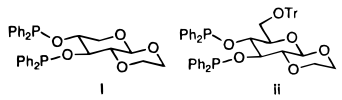
The ligands derived from the 2,6-*O*-benzoyl pyranoside **20** are better than those from the pivaloyl derivative **21**. For comparison, the syntheses of several amino acids using the 2,6-pivaloyl complex [**21b**]Rh^+[COD] BF_4^- were carried out, and the results are shown in Table 2, entries 1, 3, 5 and 11 (the numbers in parentheses). In THF solution, %ee's of 92.4, 92.0, 93.1, and 93.0 were obtained for these substrates. This should be compared to %ee's of 93, 96.2, 95.9, and 96.0 for the corresponding 2,6-di-*O*-benzoyl ligands. The importance of electronic effect is illustrated by the complexes of [**21e**] and [**21g**] which gave ee's of 84% and 11%, respectively (entry 1, Table 2), for example, for methyl (*Z*)-*N*-acetylcinnamate.

Excellent enantioselectivity for (*R*)-amino acid was also observed with ligands derived from 2-amino-2-deoxy-D-glucose, a sugar abundantly available from chitin. The preparation of methyl *N*-acetyl-2-amino-2-deoxybis-3,4-*O*-(diarylphosphino)-α-D-glucopyranoside (**26**) is shown in Scheme 5. Table 3 lists the results of hydrogenation of selected dehydroamino acids using the ligands **26**. Note that the enantioselectivity in these reactions using the vicinal (3,5-dimethylphenyl)phosphinites are among the highest reported for these substrates,[29] and even an aliphatic amino acid such as alanine (entry 6) is produced in high ee (vide infra).

Dependence of the chirality of the product on the chirality of the vicinal carbons carrying the phosphinite groups was examined with four other sugar backbones (**28**, **29**, **30**, and **31**). Synthesis of these ligands are shown in Schemes 6, 7, 8, and 9, respectively. The relative stereochemistry of the two phosphorus-carrying carbon atoms, coincidentally C-3 and C-4 in both the pyranose and furanose cases, is the same as that in **20**, and the major enantiomer is, as expected, the (*R*)-amino acid. The enantioselectivities observed for the prototypical substrate, (*Z*)-methyl *N*-acetylcinnamate and a corresponding 4-fluoro derivative, are shown in Table 4. Even a 3,4-bis-*O*-(diarylphosphino)fructofuranoside (**31**) produces the (*R*)-amino acid. A similar switching of enantioselectivity between 2,3-bis-*O*-gluco- and 3,4-bis-*O*-fructo-diarylphosphinites has been observed before in the asymmetric hydrocyanation of vinyl arenes.[19] The effect of an axial substituent is examined with the mannose-derived ligand **30**. Note that enantioselectivity is considerably lower than that observed when the corresponding C_2-equatorial substituted ligands (e.g., **20** or **21**) are used. Removal of the axial methoxy group from **28** produces a ligand (**29**) which gives reasonably good enantioselectivity. Comparing the selectivities observed with ligands **28** and **29**, it is conceivable that the axial methoxy group in **28** is partly responsible for the lower ee's seen with this ligand. Thus, a pyranose system with all equatorial substituents appears to be necessary for high enantioselectivity in hydrogenation reactions.[48]

3. Limitations of the Carbohydrate-Derived Ligands: Aliphatic Amino Acids. The sugar phosphinite ligand system thus appears to be among the most practical ligands for the synthesis of (*S*)- and (*R*)-*aromatic* and -*heteroaromatic* alanine derivatives. One of the serious limitations of this ligand system that needs further attention is in its utility for the synthesis of aliphatic amino acids. The results with prototypical ligands described in the previous sections are shown in Table 5. The only amino acid that is amenable to the currently available catalysts is alanine, the (*S*)-isomer of which is produced in 96.9% ee with the Rh-complex of

(45) After our initial communication[16] appeared, R. Selke informed us of the use of conformationally restricted phosphinites **i** and **ii** for the syntheis of D amino acids (presented at the International Conference on Circular Dichroism, Bochum, Germany, 1991, Abstracts p 305). We thank Dr. Selke for this private communication. See also reference 24d.



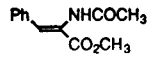
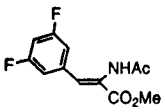
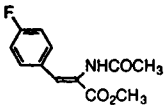
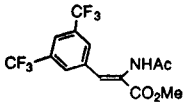
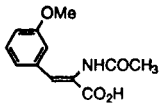
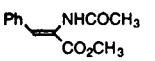
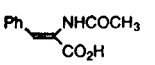
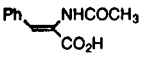
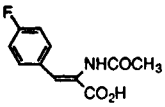
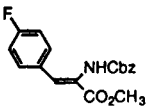
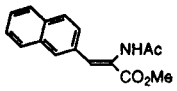
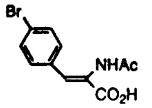
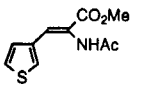
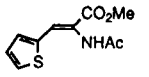
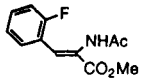
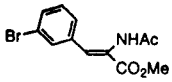
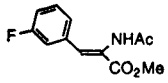
I ii

(46) Ogawa, T.; Matsui, M. *Tetrahedron* **1981**, *37*, 2363.

(47) It has since been found that for large scale synthesis of **18** low temperature benzoylation of α-methyl D-glucopyranose using 3-picoline as a base can be employed, thereby avoiding the use of the toxic tin derivatives (unpublished results with R. Shapiro).

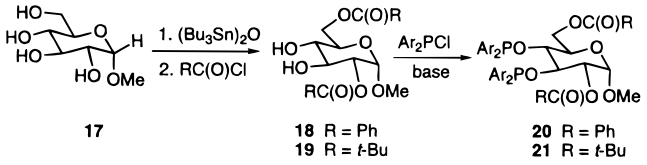
(48) Selke, R.; Schwarze, M.; Baudisch, H.; Grassert, I.; Michalik, M.; Oehme, G.; Stoll, N.; Costisella, B. *J. Mol. Catal.* **1993**, *84*, 223. For related observations see: Selke, R. *J. Prakt. Chem.* **1987**, *329*, 717.

Table 2. Enantioselectivity of Hydrogenations Using Catalysts [20/21]Rh^{+}(L) X^{-}

Entry	Substrate	X	3,5-Me_2	4-(MeO)	H	4-CF_3	3,5-F_2	3,5-$(CF_3)_2$
1.		BF_4	93.0 (92.4)[a]	84.7	87.4 (84)[a]	2.0	1.0	2.3 (11.0)[a]
2.		SbF_6	96.2	85.1	73.0	2.7	3.0	5.6
3.		SbF_6	96.2 (92.0)[a]	87.0	73.5	<1	<1	11.0
4.		SbF_6	97.4 (99.4)*	83.9	77.9	<1	3.2	<1
5.		SbF_6	95.9 (93.1)[a]	85.3	73.4	2.1	<1	2.3
6.		SbF_6	96.3	--	--	--	--	--
7.		BF_4	95.8	--	--	--	--	--
8.		SbF_6	97.0	--	--	--	--	--
9.		SbF_6	96.4	--	--	--	--	--
10.		SbF_6	90	--	--	--	--	--
11.		SbF_6	96.0 (93.0)[a]	--	--	--	--	--
12.		SbF_6	96.4	--	--	--	--	--
13.		SbF_6	97.0 (99.5)*	--	--	--	--	--
14.		SbF_6	96.0	--	--	--	--	--
15.		SbF_6	95.6	--	--	--	--	--
16.		SbF_6	96.4	--	--	--	--	--
17.		SbF_6	96.3	--	--	--	--	--

* ee's upon recrystallization; [a] [21]Rh^{+}(L) BF_4^{-} catalyst see text.

Scheme 4. Synthesis of "D-Gluco" 3,4-Diarylphosphinites



Scheme 5. Synthesis of Methyl 2-Acetamido-2-deoxy-3,4-bis0*O*-(diarylphosphino)-6-*O*-(*t*-butyldimethylsilyl)-α-D-glucopyranoside

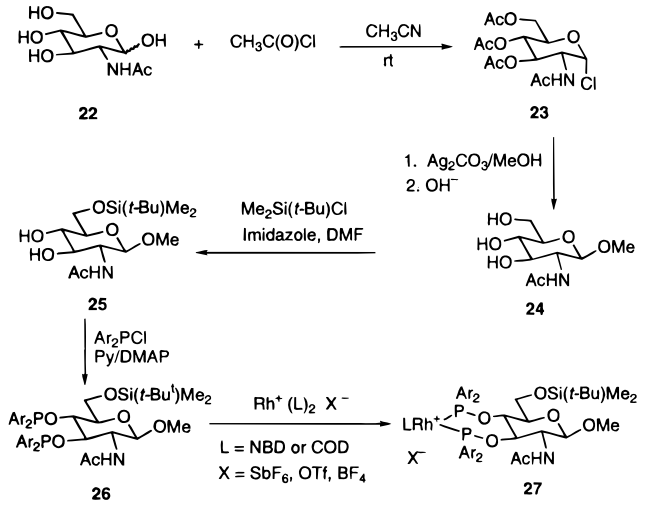
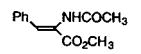
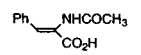
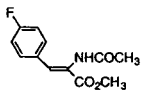
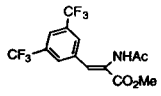
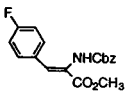
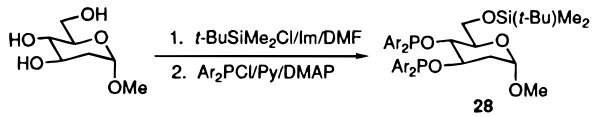


Table 3. Hydrogenations Using Catalysts [26]Rh$^+$(COD) X$^-$

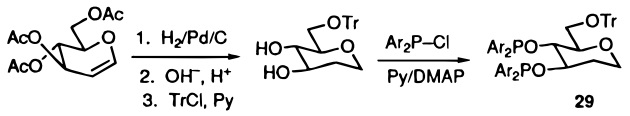
Entry	Substrate	X$^-$	3,5-$Me_2C_6H_4$	H
1.		BF_4^- SbF_6^-	98.3 98.4	-- 94.9
2.		SbF_6 BF_4	-- 94.5	94.5 --
3.		BF_4^-	97.8	--
4.		BF_4^-	93.7	--
5.		BF_4^-	96.0	--
6.		BF_4^-	95.0	--

Scheme 6. Synthesis of Ligands from 2-Deoxyglucopyranoside

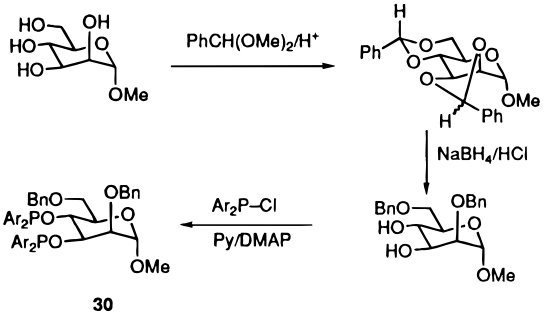


11b (Table 5, entry 1). The corresponding (*R*)-enantiomer is produced in a respectable 95.0% ee using the 3,4-bis(phosphinite) derived from *N*-acetylglucosamine (**27b**). It is interesting to note that (*Z*)-*N*-acetyl dehydroamino acids are reduced with higher enantioselectivity as compared to the corresponding (*E*)-isomers (entry 2). Thus using Rh$^+$(**11b**)(COD) SbF_6^-, 92.0% ee was observed

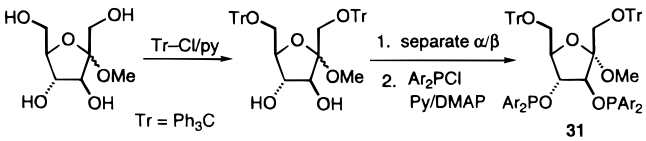
Scheme 7. Synthesis of 3,4-Diarylphosphinites from 1,5-Anhydro-2-deoxyglucitol



Scheme 8. Synthesis of "D-Manno" 3,4-Diarylphosphinites



Scheme 9. Synthesis of "D-Fructo" 3,4-Diarylphosphinites



for the (*Z*)-dehydrovaline whereas the corresponding (*E*)-isomer gave only 73.3% ee. A mixture of (*Z*) and (*E*) (ratio 90/10) dehydro-precursors gave 86.5% ee. Likewise, *β*,*β*-disubstituted α-acetamidoacrylates[49,50] and a homophenylalanine precursor gave unacceptably low selectivities with both the 2,3- and the 3,4-bis(diarylphosphinite)s (Table 5, under **11b** and **20b**, entries 4 and 5).

4. Some Practical Considerations in Using the Sugar-Derived Phosphinites as Ligands for Amino Acid Synthesis. It is widely accepted that a seven-membered chelate intermediate can undergo reorganizations within its coordination sphere faster than in a five-membered one. For this reason catalytic processes that involve seven-membered chelates are relatively faster.[51] Such flexibility has to be balanced against the conformational rigidity at critical stages in the catalytic cycle if high enantioselectivity is desired. In the case of the best sugar-derived vicinal diarylphosphinites both these conditions are met, and the corresponding Rh chelates are extremely active catalysts. Qualitative measurements of the half-lives of the reactions done at room temperature with 0.01 mmol of catalyst/mmol of substrate in 5 mL of THF at 30−40 psi of hydrogen gives a value of less than 10 min for the best catalyst **11b**. For a direct comparison, we chose one of the best five-membered chelates viz., [Me-DUPHOS][COD]Rh$^+$ complex,[29] and the results are shown in Scheme 10. Using THF as the solvent, at 0.001 equiv of the respective precatalysts, the hydrogenation of (*Z*)-*N*-acetyl 3,5-bis-(trifluoromethyl)phenylalanine methyl ester was carried

(49) For a solution to this problem see: Burk, M. J.; Gross, M. F.; Harper, G. P.; Kalberg, C. S.; Lee, J. R.; Martinez, J. P. *Pure Appl. Chem.* **1996**, *68*, 37.

(50) Sawamura, M.; Kuwano, R.; Ito, Y. *J. Am. Chem. Soc.* **1995**, *117*, 9602.

(51) Oliver, J. D.; Riley, D. P. *Organometallics* **1983**, *2*, 1032. For a study of rates of hydrogenation using five-, six-, and seven-membered rhodium chelates see also: Landis, C. R.; Halpern, J. *J. Organomet. Chem.* **1983**, *250*, 485. Descotes, G.; Lafont, D.; Sinou, D.; Brown, J. M.; Chaloner, P. A.; Parker, D. *Nouv. J. Chim.* **1981**, *5*, 167.

Table 4. Dependence of Chirality of Phosphinooxy Carbons and the Sugar Backbone in Rh-Catalyzed Hydrogenations (all *R*-amino acids)

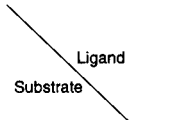
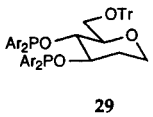
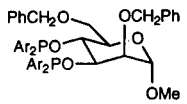
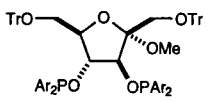
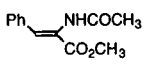
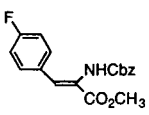
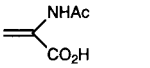
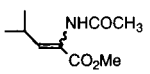
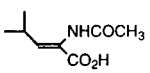
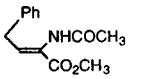
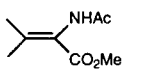
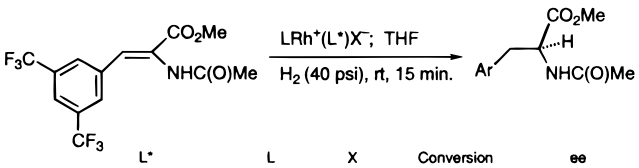
Substrate \ Ligand	 **28**	 **29**	 **30**	 **31**
	65.1 (BF_4^-) Ar = 3,5-Me_2-C_6H_3	83.2 (SbF_6^-) Ar = 3,5-Me_2-C_6H_3	72.2 (BF_4^-) Ar = 3,5-Me_2-C_6H_3	49.0 (SbF_6^-) Ar = Ph
	--	--	--	53.0 (SbF_6^-) Ar = Ph 57.0 (SbF_6^-) Ar = 4-MeO-C_6H_4 56.8 (SbF_6^-) Ar = 3,5-di-Me_2-C_6H_3

Table 5. Synthesis of Aliphatic Amino Acids

		Ligands for Rh^+					
Entry	Substrate	**11a**	**11b**	**11e**	**11g**	**20b**	**20a**
1		--	96.9	--	--	90.8 (*R*) (95.0 using **27b**)	--
2		87.2	92.0 (Z) 73.3 (E) 86.5 (E/Z)	--	5.6(*R*)	86.9(*R*)	86.5(*R*)
3		83.6	91.0	90.0	--	89.2(*R*)	--
4		--	40.6	--	--	67.0(*R*)	--
5		racemic	15.5 (28.4)*	--	7.8(*R*)	10.1(*R*)	--

All *(S)*-amino acids unless stated otherwise. * in propylene carbonate

Scheme 10. Relative Rates of Hydrogenation of a Dehydroamino Acid Ester Using [11b]Rh^+(NBD) SbF_6^- and [(*R,R*)-Me-DUPHOS]Rh^+(COD) TfO^- in THF



L*	L	X	Conversion	ee
11b	NBD	SbF_6	100	96.1
(*R,R*)-Me-DUPHOS	COD	OTf	10.7	96.2

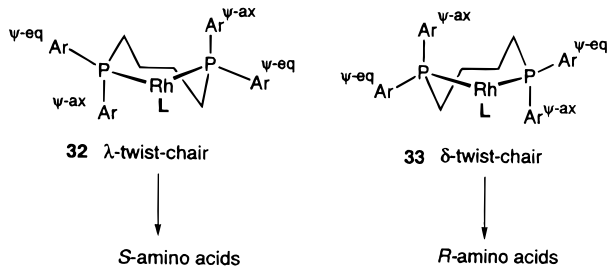
out for 15 min, and the reaction was terminated by releasing the hydrogen and refilling the reaction vessel with nitrogen. Conversion and ee's were measured by gas chromatography. While the phosphinite-catalyzed reaction proceeded to completion giving 96.1% ee, the Me-DUPHOS-mediated reaction was only 10.7% complete (96.2% ee). However, in making this comparison, it should be noted that in the original studies with the DUPHOS catalysts, the reactions were carried out in alcoholic solvents even though it has been reported that there is little difference between various solvents.[29] The enantioselectivity for DUPHOS ligands are in general 1−3% higher for *aromatic* amino acids. This marginal difference in selectivity is more than offset by the ease of preparation of the sugar-derived ligands. In addition, as mentioned earlier, a single recrystallization usually gave nearly optically pure (~99.5% ee) product in cases where we attempted such purifications. There is no reason to doubt that this is the case with other solid amino acids. For *aliphatic* amino acids the sugar-derived ligands are still not competitive with the DUPHOS series, except for alanine. Another important advantage of the DUPHOS ligands is that they are able to reduce both (*Z*)- and (*E*)-isomers of dehydroamino acids with equal facility. Therefore, a mixture of the stereoisomers of these substrates can be used for the production of aliphatic amino acids. For the sugar-derived phosphinites further optimizations are needed before this can be accomplished. Such studies are in progress.

5. Origin of Enantioselectivity. Asymmetric hydrogenation of α-acetamidoacrylic acid derivatives is arguably the most extensively studied catalytic asymmetric reaction. Details of the kinetic and thermodynamic aspects of the key steps under a variety of reaction conditions are known[9,28] and a number of intermediates have been isolated.[27,52−55] Several models have been advanced to explain the sense, if not the level, of

(52) McCulloch, B.; Halpern, J.; Thompson, M. R.; Landis, C. R. *Organometallics* **1990**, *9*, 1392.

(53) Brown, J. M.; Chaloner, P. A. *J. Chem. Soc., Chem. Commun.* **1978**, 321.

Scheme 11. Conformation of Seven-Membered Cationic Rh Chelates and the Sense of Asymmetric Induction in Hydrogenation



asymmetric induction.[56] In the case of five- and seven-membered chelates, there exists a good empirical correlation between the λ- and δ-conformations (represented in their limiting forms by **32** and **33** in Scheme 11) of the starting Rh-catalyst. These conformations present an asymmetric, alternating axial−equatorial array of *P*-aryl groups around the metal to an approaching substrate. Effect of such asymmetry can be seen even on a coordinated cyclooctadiene,[51,57,58] and the clockwise or anticlockwise skewing of this ligand with respect to the P−Rh−P plane can be related to the sense of asymmetric induction. The same forces responsible for the skewing of the diene are thought to be responsible for the enantioselective recognition and the subsequent selective hydrogenation of prochiral olefins.[59] From a large body of work it is well-known that the seven-membered chelates (with a P−Rh−P bite angle of 96° vs 82° for five-membered chelates) are more flexible, and a number of energetically similar conformations of the chelate are available in this coordination geometry. This makes modeling of intermediates difficult. Nonetheless seven-membered chelates, by virtue of their flexibility and the attendant ability to undergo facile reorganization during the catalytic cycle, generally promote faster reactions.[51] Occasional dramatic reversal of the sense of asymmetric induction[60−62] can also be attributed to such flexibility in the seven-membered chelates. Yet

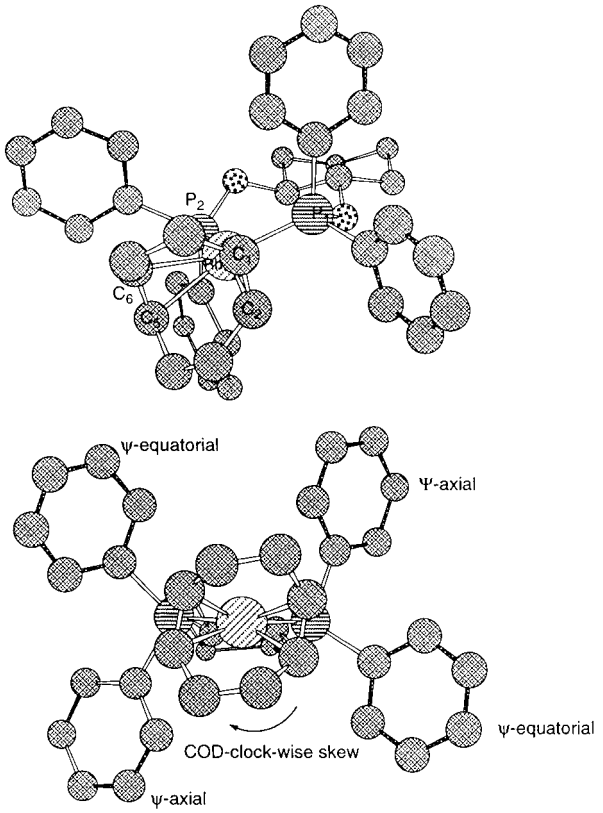


Figure 4. Chem3D version of the crystal structure of cationic **34**. Hydrogens and the SbF_6^- counterion have been omitted for clarity.

another consequence of such flexibility is a better manifestation of the electronic effects (see Tables 1 and 2). Preliminary observations seem to suggest that a conformationally labile system is capable of imparting better substituent electronic effects.[63,64]

After repeated attempts, we have been able to grow single crystals of the complex **34** (Figures 4 and 5) derived from (1*S*,2*S*)-1,2-bis[(diphenylphosphino)oxy]cyclohexane, stereochemically related to the 2,3-bis-*O*-(diarylphosphino)-D-glucopyranoside.[65] The diphosphinites gave high ee's in the hydrogenation of acetamidocinnamic acid derivatives (74.2 and 82.0, respectively for the diphenylphosphinite and the bis[bis(3,5-dimethylphenyl)phosphinite].[66] Two perspectives of a Chem3D rendition of the crystal structure of the cationic Rh species of **34** are shown in Figure 4.[66] A schematic representation based on the X-ray crystal structure is shown in Figure 5. This corresponds approximately to a λ-twist-chair conformation, and as predicted by the correlations, (*S*)-amino acid is the major product of hydrogenation with this catalyst. Note that the COD ligand is skewed in a clockwise direction as has been seen for other cationic Rh complexes that give the (*S*)-enantiomer.[51,57,58] Selected interatomic distances and intramolecular angles are shown in Table

(54) Brown, J. M.; Chaloner, P. A. *J. Chem. Soc., Chem. Commun.* **1980**, 344.

(55) Bircher, H.; Bender, B. R.; von Philipsborn, W. *Magn. Res. Chem.* **1993**, *31*, 293.

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(59) However, caution should be excercised in applying these correlations because several cationic Rh complexes exist as different polymorphs which can have widely different conformations. See reference 51. We have obtained crystal structures of (1*S*,2*S*)-bis[(diphenylphosphino)oxy]cyclohexane−Rh^+ (**L**) $SbF6^-$ with **L** as COD and NBD. While the former has a well-defined λ-twist-chair conformation (**34**), in the crystals of the latter, two kinds of conformations can be identified, a λ-twist-chair and a λ-twist-boat (unpublished results with T. A. Ayers and J. Calabrese). Both these conformations exhibit a clockwise skewed rotation of the diene ligands as expected of the catalysts that give the (*S*)-enantiomers.

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(64) We have seen similar behavior in catalytic enantioselective alkylation of π-allylpalladium compounds by stabilized carbanions. Rigid backbones even with seven-membered chelates tend to diminish the electronic effects. Conformationally flexible ligands show more pronounced and generally predictable trends in electronic effects. At present, more examples are needed before this hypothesis can be fully verified (see reference 34).

(65) For the structure of a related complex see: Kempe, R.; Schwarze, M.; Selke, R. *Zeit. Krystall.* **1995**, *210*, 555.

(66) A more detailed NMR and modeling study of this simplified system is forthcoming (unpublished results with C. Hadad, B. Radetich, and K. You).

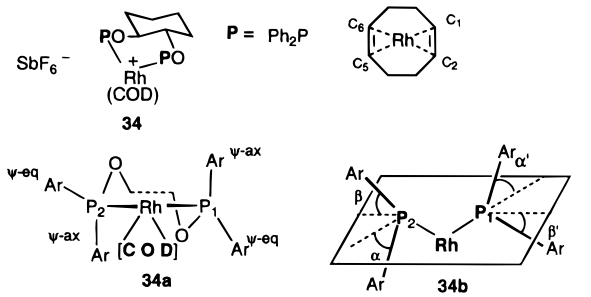

Figure 5. λ-Twist-chair conformation of cationic Rh complex **34**.

Table 6. Selected Interatomic Distances and Angles for 34 (See Figures 4 and 5)

distances, Å		angles (degrees)	
Rh−P(1)	2.250	α	75.2 (rear)
Rh−P(2)	2.239	*ν*	46.6 (front)
P(1)−P(2)	3.179	α′	89.9 (rear)
Rh(1)−C(1)	2.279	*β*′	31.1 (front)
Rh(1)−C(2)	2.290	P_1−Rh−P_2	90.2°
Rh(1)−C(5)	2.266		
Rh(1)−C(6)	2.286		

6. The dihedral angles are depicted using **34b**, adapted from Seebach et al.[67] The front/rear designations refer to the positioning of the *P*-aryl groups with respect to a plane perpendicular to the P_1−Rh−P_2 plane which passes through P_1 and P_2.

The origin of the enhancement of enantioselectivity as a function of the electronic nature of the *P*-aryl groups remains speculative at this point. Assuming the Halpern mechanism[9] holds good for the catalysis by the vicinal bis(phosphinite) Rh complexes, under ambient conditions, the enantioselectivity arises primarily as a consequence of the increased rate of oxidative addition of H_2 to the minor diastereomer that is formed between the dehydroamino acid (or ester) and the cationic catalyst. This oxidative addition of hydrogen to d^8 metal complex, which is the rate-determining step in the hydrogenation, has been extensively studied. A pronounced role of electronic effects on the course of H_2 addition to a number of Rh and Ir complexes including Vaska's complex (*trans*-$IrCl(CO)(PPh_3)_2$) has been documented.[68−71] The major interactions between the d^8 metal and the hydrogen molecules involve (i) σ donation from the hydrogen bonding orbital into the empty p_z or a p_z-d_z^2 hybrid orbital, (ii) transfer of electron density from one of the filled d_π orbitals (d_{xz} or d_{yz}) into the hydrogen antibonding orbitals, and (iii) repulsive interaction between the filled σ bonding orbital of hydrogen and the d_z^2 orbital of the metal. Of these, the last one is likely to be the major contributor for the activation barrier toward addition of H_2.[72] Any electronic effect that optimizes these orbital interactions in the minor complex vis-á-vis the major one should affect the enantioselectivity. Such an approach to catalyst optimization was suggested by a timely publication that appeared from the laboratory of von Philipsborn.[73] After an extensive study of the ^{103}Rh NMR chemical shifts of the major and minor diastereomers of the dehydroamino acid−Rh(I) complexes, these workers concluded that there is considerable difference in the Rh-shielding parameters for the two initially formed complexes. On further analysis, the data seem to suggest that a remote substituent on the olefin can create substantial and disproportionately different ^{103}Rh shielding between the major and minor complexes. For example, the differences ($\Delta\delta$) between the ^{103}Rh chemical shifts of the major and minor enamide complexes from the 4-nitro, 4-H, and 4-OH acetamidocinnamic acid are 247, 108, and 47, respectively. Enantioselectivity of related enol acetate reductions seemed to be affected by remote substituent, electron-rich double bond getting reduced with higher selectivity.[26] Taken together these data suggest that the electron density at rhodium may be related to the enantioselectivity of the reaction, presumably brought about by the differences in relative rates of oxidative addition of hydrogen to the major and minor Rh^+ [enamide] complexes. It is thus conceivable that one could also affect the electronic character of Rh by making changes in the ligand, rather than the olefin as in the above-mentioned cases. Would this result in enhanced reactivity in the minor isomer resulting in higher ee's? Our results seem to suggest that this might be the case with the vicinal bis(phosphinite)s. Thus, we propose that the *P*-aryl substituents on our ligand system change the reactivity patterns of the major and minor complexes, presumably by increasing the electron density on the central Rh atom, thereby affecting the relative rates of oxidative additions.[74] Admittedly, at this point it is not clear whether this difference is due to an increased reactivity of the minor isomer or a decreased reactivity of the major isomer when the ligand is changed from a vicinal bis(diphenylphosphinite) to a more electron-rich system. Enhancement of rate of oxidative addition of H_2 to d^8 metals by electron-rich ligands as well as stereoelectronic effects on such additions[70,75] have been documented and therefore it is possible that the latter (i.e., increased rate of addition to the minor complex) is the source of higher enantioselectivity. Since the enantioselectivity is also affected, albeit to a lesser extent, by the ratio of major to minor diastereomeric acetamidocinnamate−Rh complexes, yet another scenario is that this equilibrium is affected in favor of the kinetically important minor isomer.[74] Hydrogenation studies under non-equilibrium, non-Curtin−Hammett conditions (at higher pressures and low temperatures, for example) should shed some light on this possibility. Further experiments including pressure and temperature dependence on enantioselectivity and ^{103}Rh NMR studies of the intermediate complexes to probe this possibility in the vicinal phosphinite system are underway.

Experimental Section

General Methods. Manipulations of air and moisture sensitive materials were conducted in a nitrogen atmosphere by using either Schlenk techniques or a Vacuum Atmospheres

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(74) At this time we cannot rule out the *unlikely* possibility that a remote substituent might be bringing about conformational changes in key intermediates. This possibility has been suggested by two experiments involving a reversal of sense of induction under modified reaction conditions: (i) when the hydrogenation reaction was done under widely diffent solvents (ref 61); (ii) when 4-(dimethylamino)phenyl substituent was used in the DIOP series (ref 60). For related observations in Pd-catalyzed allylation of stabilized carbanions, see reference 34.

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dry box. Tetrahydrofuran (THF), ether, dimethoxyethane (DME), hexane, and pentane were distilled from sodium benzophenone ketyl under nitrogen. Benzene and toluene were distilled from lithium aluminum hydride and stored over activated 4 Å molecular sieves. Methylene chloride, dimethylformamide (DMF), and acetonitrile were distilled from calcium hydride and stored over activated 3 Å molecular sieves. Flash column chromatography[76] was carried out on 230−400 (0.040−0.063 mm) silica (EM Reagents). NMR spectra were recorded on C_6D_6 or $CDCl_3$ solutions using a General Electric QM-300 spectrometer (^{1}H at 300 MHz, ^{31}P at 121.7 MHz). Gas chromatographic (GC) analysis was performed with a Hewlett-Packard (HP) Model 5890 GC fitted with a HP3396A integrator. Conversions were determined using an HP cross-linked methyl silicone capillary column (30 m × 0.530 mm). Chiral gas chromatographic (GC) separations were accomplished using Chirasil L-Val on WCOT fused silica (25 m × 0.25 mm, 0.12 μm film thickness) capillary GC column purchased from Chrompack (1130 Route 202 South, Raritan, NJ 08869). HPLC separations were carried out on Chiralcel OJ or Chiralcel OB HPLC column (25 cm × 4.6 mm) from Daicel (Chiral Technologies, Inc., 730 Springdale Drive, Drawer 1, Exton, PA 19341). Phenyl α-D-glucopyranoside, tri-acetyl-D-glucal, methyl α-D-glucopyranoside, methyl β-D-glucopyranoside, methyl α-D-mannopyranoside, and the aryl bromide precursors for the diarylchlorophosphines were purchased from Aldrich. 2-Deoxy-D-glucose, D-fructose, and *N*-acetyl-D-glucosamine were purchased from Pfanstiehl Laboratories (1219 Glenrock Avenue, Waukegan, IL 60085-0439). Acetamidoacrylate derivatives,[77] $(COD)_2$ Rh^+ SbF_6^- [41], and $(COD)_2$ Rh^+ BF_4^- [41] were synthesized according to literature procedures.

Example of Synthesis of a Cationic Bis-(COD)−Rh Complex.[41] In a dry box 2.00 g (4.06 mmol) of $[(COD)RhCl]_2$ was dissolved in 40 mL of CH_2Cl_2 and 4 mL of 1,5-cyclooctadiene. With the room lights turned off, 2.79 g (8.11 mmol) of $AgSbF_6$ was added in one lot, and the mixture was stirred for 10 min. The solution was filtered through Celite, and the Celite pad was washed with CH_2Cl_2. The filtrate was concentrated to 10 mL, and 12 mL of ether was added to precipitate $(COD)_2Rh$ SbF_6 (1.09 g, 48%). Anal. C 34.69; H 4.42; F 19.80; calcd for $RhC_{16}H_{24}$ SbF_6 C 34.63; H 4.36; F 20.54. This analytically pure complex was used for subsequent steps for the formation of the Rh-complexes. The compounds $(COD)_2Rh^+$ OTf^- and $(COD)_2Rh^+$ BF_4^- were prepared in a similar manner.

Example of Synthesis of Diarylchlorophosphines: Bis-(3,5-dimethylphenyl)chlorophosphine. Preparation of 3,5-Dimethylphenylmagnesium Bromide. A three-necked flask fitted with a mechanical stirrer, thermocouple adapter, and an addition funnel was charged with 4.6 g (189 mmol) of magnesium turnings in 60 mL each of THF and ether. A crystal of iodine was added to facilitate the initiation of the reaction. To this suspension was added 35.44 g (180 mmol) of bromo-3,5-dimethylbenzene in 35 mL of ether at such rate that the temperature is kept around 22−28 °C. The reaction was stirred overnight, and the contents were transferred into dry addition funnel via a cannula. Additional 60 mL of THF was used to facilitate quantitative transfer of the Grignard reagent. Based on the unreacted Mg, the yield of the Grignard reagent was estimated as 99.4%.

A 500 mL three-necked round-bottomed flask fitted with a mechanical stirrer and thermocouple adapter was charged with 12.6 mL (15.0 g, 86.4 mmol) of Et_2NPCl_2[39] in 80 mL of THF. The addition funnel containing the Grignard solution from the previous step was attached to the third neck. The reaction flask was cooled to 0−5 °C, and the Grignard reagent was added over 1 h. The mixture was stirred overnight at 5−10 °C.

The mixture was transferred into a 1 L dry flask, and it was further concentrated to ~150 mL on a vacuum pump. To the mixture was added sieve-dried cyclohexane (300 mL), the solution was filtered through dry Celite under nitrogen using a pressure funnel, and the filtrate was collected in a 500 mL flask. A ^{31}P NMR (benzene-d_6) of the product at this stage showed only a single peak at δ 63.3 corresponding to the (diethylamino)diarylphosphine.

A Claisen adaptor was attached to the flask, and dry HCl gas (dried by bubbling through concd H_2SO_4) was passed through the solution for 45 min at a copious rate. The reaction was mildly exothermic. The mixture was degassed by bubbling nitrogen, and the solid precipitate (diethylamine hydrochloride) was filtered off using a pressure funnel. The precipitate was washed with 100 mL of cyclohexane. The filtrate was concentrated and distilled on a kugelrohr oven. ^{1}H NMR (C_6D_6) 1.85 (4 s, 12 H), 6.62 (s, 2 H), 7.25 (m, 4 H); ^{31}P NMR (C_6D_6) 84.0. Yield 83−88%.

For the synthesis of diphosphinites which can be recrystallized (for example **20b**), there is no need to distill the chlorophosphine. A crude NMR (^{1}H NMR and ^{31}P NMR) showed that the crude chlorophosphine is at least 90% pure. This may be used in subsequent steps provided ca. 10% excess is used for phosphinylation.

Diethylaminobis[3,5-bis(trimethylsilyl)phenyl]phosphine was prepared according to the procedure of Trost et al.,[42] and it was converted into the chlorophosphine by treatment with anhydrous HCl. ^{1}H NMR (C_6D_6) 0.10 (s, 36 H), 7.81 (m, 2 H), 8.05 (dd, J = 1.1, 8.0 Hz, 4 H); ^{31}P NMR (C_6D_6) 84.4.

Preparation of Chlorophosphines via the Corresponding Diarylphosphinic Acid. An alternate preparation of diarylchlorophosphines and their spectral data have been described elsewhere.[12]

Synthesis of the Diol Precursors. Phenyl 4,6-*O*-benzylidene-β-D-glucopyranoside (10). A dry 2 L round-bottomed flask was charged with 50 g (195 mmol) of phenyl β-D-glucopyranoside in 1 L of distilled acetonitrile. To the heterogeneous mixture was added 1.37 g of *p*-toluenesulfonic acid followed by 35.1 mL (234 mmol) of dimethoxytoluene. After 2 h, a homogeneous solution was formed. Neat triethylamine (1.2 mL) was added to neutralize the acid, and the solvent was removed on the rotary evaporator. Recrystallization from neat ethyl acetate gave 58.9 g (88%) of product: mp 154−160 °C; lit.[78] 162−165 °C.

Methyl 2,6-Di-*O*-benzoyl-α-D-glucopyranoside (18). A solution of 2.2 g (14 mmol) of methyl α-D-glucopyranoside and 12.5 g (21 mmol) of $(Bu_3Sn)_2O$ in 100 mL of toluene was heated to reflux with azeotropic removal of water. When the volume reached 10 mL of toluene, an additional 100 mL of toluene was added. Distillation was continued until the volume reached ca. 50 mL. After cooling to room temperature, 4.2 g (30 mmol) of PhC(O)Cl in 5 mL of toluene was added dropwise. After 2 h, 10 mL of a saturated KF solution and 100 mL of ether were added. The resulting white solids were removed by filtration through Celite. The organic phase was dried ($MgSO_4$) and concentrated. Recrystallization from ethyl acetate/hexane gave 3.6 g (64%) of methyl 2,6-di-*O*-benzoyl-α-D-glucopyranoside.[46]

Modified Procedure for the Preparation of Methyl 2,6-Di-*O*-benzoyl-α-D-glucopyranoside (18). In a Dean−Stark set-up, a suspension of 40 g (0.21 mol) of dry methyl α-D-glucopyranoside and 184.0 g (157 mL, 0.31 mol) of di-*n*-butyltin ether in 1 L toluene was brought to reflux. About 800 mL of toluene and water was azeotopically removed, and the mixture was cooled to 0 °C. To the above solution was added 87 g (72 mL, 0.62 mol) of benzoyl chloride, and the solution was brought to room temperature. The mixture was stirred overnight, and to the white solid formed was added 40 mL of glacial acetic acid followed by 100 mL of toluene. The low boiling components were removed on a rotary evaporator at 60 °C over 2 h. The solid residue was taken up in an extraction thimble and continuously extracted with boiling hexane (1500 mL) for 3 h. The remaining white solid (55.52 g, 67%) in the extraction thimble was dried under vacuum overnight at 0.1 mm. TLC and NMR showed the material to be essentially pure. Further

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purification was achieved by recrystallizing from ethyl acetate and hexane or diisopropyl ether: mp 141−144 °C (lit.[46] 140−142 °C).

Methyl 2,6-Di-*O*-pivaloyl-α-D-glucopyranoside (19). Prepared in a route similar **18**, except for substitution of pivaloyl chloride in the place of benzoyl chloride: mp 91−94 °C. Anal. C 56.34; H 8.65. Calcd for $C_{17}H_{30}O_8$ C 56.34; H 8.34.

Methyl 2-Deoxy-6-*O*-(*tert*-butyldimethylsilyl)-α-D-glucopyranoside (Scheme 6). To a solution of 100 mg (0.56 mmol) of methyl 2-deoxy-α-D-glucopyranoside, 41 mg (0.60 mmol) of imidazole, and 5 mg of DMAP in 1 mL of DMF was added 90 mg (0.60 mmol) of *tert*-butyldimethylchlorosilane in 1 mL of DMF. After 18 h, the mixture was concentrated. Flash chromatography using 50% hexane/ethyl acetate as eluant gave 98 mg (60%) of the title compound: mp 49−50 °C; ^{1}H NMR 0.07 (2 s, 6 H), 0.88 (s, 9 H), 1.61 (m, 1 H), 2.05 (m, 1 H), 3.29 (s, 3 H), 3.35 (m, 1 H), 3.46−3.55 (m, 2 H), 3.85−3.78 (m, 4 H), 4.73 (d, J = 3, 1 H). Anal. C 53.58; H 9.34. Calcd for $C_{13}H_{28}O_5Si$ C 53.49; H 10.04.

Methyl 2-Acetamido-2-deoxy-6-*O*-(*tert*-butyldimethylsilyl)-β-D-glucopyranoside (25, Scheme 5). Prepared by silylation of methyl 2-acetamido-2-deoxy-β-D-glucopyranoside, which in turn was prepared from 2-amino-2-deoxyglucose via 2-acetamido-2-deoxy-3,4,6-tri-*O*-acetyl-β-D-glucopyranosylchloride. **(a) 2-Acetamido-2-deoxy-3,4,6-tri-*O*-acetyl-β-D-glucopyranosyl Chloride (23).** In a 500 mL flask, 25 g of *N*-acetylglucosamine and 75 mL of distilled acetyl chloride was combined, and the mixture was stirred for 24 h under nitrogen. Methylene chloride (150 mL) was added, and the organic layer was washed with water (4 × 50 mL) and then saturated sodium bicarbonate (2 × 100 mL). After the solution was concentrated to 100 mL, 300 mL of ether was added, and the solution was allowed to stand overnight. The fine crystals formed (58% yield) were filtered off with the aid of a pressure funnel with exclusion of moisture, and the crystals were dried in a vacuum desiccator overnight at <0.01 mm vacuum. **(b) Methyl 2-Acetamido-2-deoxy-3,4,6-tri-*O*-acetyl-β-D-glucopyranoside.** In a dry flask 3.067 g (8.38 mmol) of the chloride was dissolved in 4 mL of CH_2Cl_2. A separate flask was charged with 6.46 g (8.38 mmol) of silver carbonate and 0.8 g of 4 Å molecular sieves in 30 mL of 2:1 CH_2Cl_2/MeOH. The chloride solution was carefully added to the methanol solution under nitrogen, and the mixture was stirred overnight. The insoluble precipitates were removed by filtration and further washed with CH_2Cl_2. The pure product (2.423 g, 78%) was collected by column chromatography on silica gel using neat ethyl acetate as a solvent. **(c) Methyl 2-Acetamido-2-deoxy-β-D-glucopyranoside (24).** To a solution of 1 g of the triacetate from the previous experiment in 20 mL of anhydrous methanol was added 100 mg of Biorad AGMP (OH^-) resin, and the mixture was stirred at room temperature overnight. Since the reaction was incomplete, an additional 200 mg of resin was added, and the stirring was continued until all the starting material disappeared as judged by TLC on silica gel using 10% methanol in CH_2Cl_2 employing 5% H_2SO_4 for spot visualization. The resin was filtered off in a pressure funnel, and it was then washed with hot methanol. The methanol solution was evaporated to get 619 mg (95%) of an off white solid which was used for the subsequent silylation reaction. **(d) Methyl 2-Acetamido-2-deoxy-6-*O*-*tert*-butyldimethylsilyl-β-D-glucopyranoside (25).** The triol from the previous step was silylated using *tert*-butyldimethylchlorosilane in DMF in the presence of imidazole, and the product was purified by column chromatography on silica gel using ethyl acetate/hexanes as solvent: mp 151−155 °C; ^{1}H NMR 0.00 (2 s, 6 H), 0.80 (2 s, 9 H), 1.98 (s, br, 3H), 3.20−3.32 (m, 1 H), 3.32−3.50 (s, superimposed on m, 5 H), 3.59 (dd, J = 12, 8, 1 H), 3.76, 3.84 (ABX, J_{AB} = 18, 2 H), 4.28 (d, J = 8, 1 H), 6.42 (d br J = 4, 3 H). Anal. C 51.23; H 9.20. Calcd for $C_{15}H_{31}NO_6Si$ C 51.55; H 8.94.

Methyl 2,6-Di-*O*-benzyl-α-D-mannopyranoside (Scheme 8). A 2:1 mixture of exo- and endo-isomers of bis[(2,3-*O*),(4,6-*O*)]benzylidene-α-D-mannopyranoside[79] was prepared by the reaction of methyl α-D-mannopyranoside with 2.2 equiv of α,α-dimethoxytoluene and catalytic *p*-toluenesulfonic acid in acetonitrile. This compound was treated with $NaBH_4$ and HCl[80] to provide a mixture of products from which the methyl 2,6-di-*O*-benzyl-α-D-mannopyranoside was isolated by flash chromatography. The assignment of this isomer was confirmed by ^{1}H decoupling experiments on the corresponding bis(3,4-*O*-(diphenylphosphino) derivative **30e**. ^{1}H NMR 7.42−7.24 (m, aromatic), 4.81 (d, J = 1, 1 H), 4.75−4.54 (m, 4 H), 3.78−3.71 (m, 6 H), 3.36 (s, 3) H, 2.83 (s, br, 1 H), 2.43 (s, br, 1 H).

1,5-Anhydro-2-deoxy-6-*O*-(triphenylmethyl)-D-glucitol (Scheme 7). To 1 g of tri-*O*-acetyl-D-glucal dissolved in 10 mL of ethyl acetate and 5 mL of ethanol was added 100 mg of 10% Pd/C, and the solution was hydrogenated in a Fischer−Porter tube at 30 psi of hydrogen. After vigorous stirring overnight, the catalyst was filtered off with the aid of Celite. The Celite bed was washed with excess ethyl acetate. The combined filtrate was concentrated, and the reduced triacetate was collected by column chromatography on silica gel using 50% ethyl acetate/hexanes as solvent. ^{1}H NMR 2.00−2.10 (3 s, 9 H), 3.40−3.60 (m, 2 H), 4.00−4.30 (m, 5 H), 4.95−5.03 (m, 2 H). The crude product was used for the subsequent reaction.

To a solution of the triacetate (4.56 g) in 50 mL of distilled methanol was added 1.50 g of Biorad AGMP(OH^-) resin was added. The reaction was stirred at room temperature until all of the starting material disappeared (TLC, 10% methanol in CH_2Cl_2, 18 h). The resin was filtered off, and the methanolic filtrate was concentrated on a rotary evaporator. The last traces of the solvent was removed high vacuum at 0.01 mm to get quantitative yield of the expected triol. This analytically pure crude product was used for the subsequent tritylation. ^{1}H NMR (D_2O) 1.60 (dddd, J = 12, 12, 12, 6, 1 H), 1.97 (dd, br, J = 12, 6, 1 H), 3.21 (d m, 2 H), 3.50 (dt, J = 12, 2, 1 H), 3.60−3.70 (m, 2 H), 3.90 (dd, J = 10, 2, 1 H), 3.95 (dd, J = 12, 5, 1 H). Anal. C 48.26; H 8.36. Calcd for $C_6H_{12}O_4$ C 48.64; H 8.16.

The triol (148 mg) was converted into the corresponding 6-*O*-trityl derivative by treatment with 307 mg (1.1 equiv) of trityl chloride and 6 mg of 4-(dimethylamino)pyridine in 3 mL of pyridine. After 5 days, 30 mL each of of cold water and methylene chloride were added, and the organic layer was separated. The aqueous layer was further extracted with methylene chloride (30 mL × 2). The combined organic layer was washed with ice-cold 1 N HCl followed by saturated $NaHCO_3$. It was further dried and concentrated. Chromatography on silica yielded 103 mg (26%) of desired product. ^{1}H NMR 1.70 (dddd, J = 12, 12, 12, 6, 1 H), 1.90 (dm, 12, 1 H), 2.50 (s, br, exch OH), 2.90 (s, br, OH, exch 1 H), 3.30−3.50 (m, 5 H), 3.59−3.70 (m, 1 H), 3.90 (ddd, J = 12, 6, 2, 1 H), 7.20−7.50 (aromatic).

Methyl 1,6-Bis-*O*-(triphenylmethyl)-α- and β-D-fructofuranosides (Scheme 9). These compounds were prepared by tritylation of a mixture of methyl α- and β-fructofuranosides with trityl chloride in pyridine at 50 °C and separating these isomers by column chromatography on silica gel using 10−30% ethyl acetate in hexane as eluant. The α-anomer eluted first. The α-anomer: mp 92−93 °C; ^{1}H NMR 3.05 (s, 3 H), 3.07 (d, J = 10 , 1 H), 3.24, 3.48 (ABX, J_{AB} = 10, 2 H), 3.34, 3.50 (AB, J_{AB} = 10 , 2 H), 3.57 (d, J = 10 Hz, 1 H), 3.87 (d, br, J = 11, 1 H) 4.05 (m, 1 H), 4.19 (d, J = 10, 1 H), 7.20−7.60 (m, aromatic). Anal. C 78.85; H 6.37. Calcd C 79.62; H 6.24. The β-anomer: mp 195−199 °C; ^{1}H NMR 2.15 (d, J = 4, 1 H, exch with D_2O), 2.65 (d, br, J = 8, exch with D_2O, 1 H), 3.05 (s, 3 H), 3.07−3.27 (m, 4 H), 3.97 (m, 1 H), 4.17−4.22 (m, 2 H), 7.20−7.55 (m, aromatic). Anal. C 78.85; H 6.36. Calcd C 79.62; H 6.24.

The stereochemistry of the two fructosides were established by conversion to the known[81,82] methyl 3,4-anhydro-derivatives by Mitsunobu reaction and examination of the ^{13}C NMR spectrum. For the α-anomer, the methoxy signal consistently has the lower chemical shift. In the case of the triphenylmethyl fructofuranosides, the α-methoxy carbon appears at δ 49.20 and the β-derivative at 52.30 ($CDCl_3$).

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(80) Horne, D. A.; Jordan, A. *Tetrahedron Lett.* **1978**, *19*, 1357.

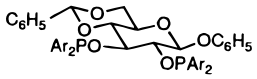
(81) Guthrie, R. D.; Jenkins, I. D.; Yamasaki, R. *J. Chem. Soc., Perkin Trans. 1* **1981**, 2328.

(82) RajanBabu, T. V.; Nugent, W. A. *J. Am. Chem. Soc.* **1994**, *116*, 986.

A Typical Procedure for the Synthesis of a Diarylphosphinite.[12] To a solution of 300 mg (0.75 mmol) of methyl 2,6-*O*-dibenzoyl-α-D-glucopyranoside and 10 mg of DMAP in 5 mL of pyridine was added 430 mg (1.56 mmol) of bis(3,5-dimethylphenyl)chlorophosphine in 5 mL of CH_2Cl_2. After 16 h, the mixture was concentrated to dryness. Benzene was added to the residue, and this mixture was filtered and concentrated. Recrystallization from hexane/benzene gave 600 mg (91%) of **20b**: ^{1}H NMR 1.73 (s, 6 H), 1.88 (s, 6 H), 1.91 (s, 6 H), 2.02 (s, 6 H), 2.75 (s, 3 H), 3.90 (dd, J = 4, 12, 1 H), 4.04 (dd, J = 4, 10, 1 H), 4.42 (d, J = 12, 1 H), 4.89 (m, 1 H), 5.00 (d, J = 3, 1 H), 5.23 (m, 1 H), 5.51 (dd, J = 4, 10, 1 H), 6.03 (s, 1 H), 6.32 (s, 1 H), 6.46 (s, 1 H), 6.63 (s, 1 H), 6.70−7.30 (m, aromatic), 7.80 (m, aromatic), 8.13 (m, aromatic); ^{31}P NMR 124.7, 118.8. Anal. C 72.30; H 6.82; P 6.58. Calcd for $C_{53}H_{56}O_8P_2$: C 72.10; H 6.39; P 7.02.

Preparation of Rh-Complexes: General Procedure. In a dry box under nitrogen, a solution of 0.50 mmol of phosphinite in 5 mL of CH_2Cl_2 was added to 0.49 mmol of $Rh(COD)_2^+ X^-$ (X = SbF_6, BF_4, OSO_2CF_3) in 5 mL of CH_2Cl_2 at room temperature. The mixture was stirred for 30 min to 3 h and the solvent was carefully removed under vacuum. A fine powder of the Rh-complex may be obtained by redissolving the complex in 8 mL of benzene and freeze-drying the sample under high vacuum.

Ligands and Catalysts from Phenyl 4,6-*O*-Benzylidene-β-D-glucopyranoside (10).



Phenyl 4,6-*O*-benzylidene-2,3-bis-*O*-(diarylphosphino)-β-D-glucopyranosides (11a−11h). The synthesis of these ligands and their spectral properties have been described elsewhere.[12]

[(11a)Rh(COD)]$^+$ SbF_6^-. ^{31}P NMR (C_6D_6) ABX (= P_1P_2Rh), ν_A = 129.9, ν_B = 131.3, J_{PP} = 24, J_{RhP} = 176.

[(11a)Rh(COD)]$^+$ BF_4^-. ^{31}P NMR (C_6D_6) ABX (= P_1P_2Rh), ν_A = 125.6, ν_B = 128.3, J_{PP} = 38, J_{AX} = J_{BX} (= J_{RhP}) = 175.

[(11b)Rh(COD)]$^+$ SbF_6^-. ^{31}P NMR ($CDCl_3$): ABX (= P_1P_2Rh), ν_A = 136.6, ν_B = 136.8, J_{PP} = 27, J_{AX} = J_{BX} (= J_{RhP}) = 177; in C_6D_6 ABX (= P_1P_2Rh), ν_A = 134.0, ν_B = 136.0, J_{PP} = 29, J_{AX} = J_{BX} (= J_{RhP}) = 175.

[(11b)Rh(COD)]$^+$ BF_4^-. ^{31}P NMR ($CDCl_3$): ABX (= P_1P_2Rh), ν_A = 133.6. ν_B = 129.3, J_{PP} = 31, J_{AX} = J_{BX} (= J_{RhP}) = 177.

[(11c)Rh(COD)]$^+$ SbF_6^-. ^{31}P NMR (C_6D_6) ABX (= P_1P_2Rh), ν_A = 139.5, ν_B = 140.1, J_{PP} = 24 , J_{AX} = J_{BX} (= J_{RhP}) = 182.

[(11c)Rh(COD)]$^+$ OTf $^-$. ^{31}P NMR (C_6D_6) ABX (= P_1P_2Rh), ν_A = 136.8, ν_B = 138.5, J_{PP} = 28 , J_{AX} = J_{BX} (= J_{RhP}) = 181.

[(11d)Rh(COD)]$^+$ SbF_6^-. ^{31}P NMR ($CDCl_3$): ABX (= P_1P_2Rh), ν_A = 134.7, ν_B = 137.9, J_{PP} = 28, J_{AX} = J_{BX} (=J_{RhP}) = 182.

[(11d)Rh(COD)]$^+$ BF_4^-. ($CDCl_3$) ABX (= P_1P_2Rh), ν_A = 131.4, ν_B = 135.9, J_{PP} = 30, J_{AX} = J_{BX} (= J_{RhP}) = 180.

[(11e)Rh(COD)]$^+$ SbF_6^-. ^{31}P NMR ($CDCl_3$): ABX (= P_1P_2Rh), ν_A = 137.5, ν_B = 138.6, J_{AB} = 27, J_{AX} = J_{BX} (=J_{RhP}) = 176.

[(11e)Rh(COD)]$^+$ BF_4^-. ^{31}P NMR: ABX (= P_1P_2Rh), ν_A = 134.6,ν_B = 137.5, J_{PP} = 28, J_{AX} = J_{BX} (= J_{RhP}) = 179.

[(11f)Rh(COD)]$^+$ SbF_6^-. ^{31}P NMR ($CDCl_3$): multiplet superimposed on an ABX 8-line pattern with further small coupling presumably due to long range interaction with fluorines. δ 126.5, 126.8, 128.0, 128.3, 129.2, 129.5, 130.8, 131.1 (insoluble in benzene).

[(11f)Rh(COD)]$^+$ BF_4^-. ^{31}P NMR: ABX (= P_1P_2Rh), ν_A = 125.4, ν_B = 120.3, J_{AB} = 38, J_{AX} = J_{BX} (= J_{RhP}) = 179.

[(11g)Rh(COD)]$^+$ SbF_6^-. ^{31}P NMR (C_6D_6): ABX (= P_1P_2Rh), ν_A = 126.8, ν_B = 130.5, J_{PP} = 36, J_{AX} = J_{BX} (= J_{RhP}) = 182. In addition this complex shows another minor component (10−15%) with similar 8-line ^{31}P spectrum. Seven of these lines appear at δ 124.2, 124.6, 126.5, 138.4, 138.8, 140.3, and 140.7. The 8th line could not be located. It is possibly under the peak at 126.1.

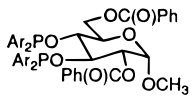
[(11g)Rh(COD)]$^+$ BF_4^-. (C_6D_6) ν_A = 122.9, ν_B = 126.8, J_{PP} = 39 , J_{RhP} = 179. Minor component (30%) ν_A = 123.9, ν_B = 139.9, J_{PP} = 48, J_{RhP1} = 234, J_{RhP2} = 240.

[(11g)Rh(COD)]$^+$ OTf$^-$. (C_6D_6) ν_A = 122.4, ν_B = 125.9, J_{PP} = 44 , J_{RhP} = 180.

[(11h)Rh(COD)]$^+$ BF_4^-. ^{31}P NMR (C_6D_6): ν_A = 125.0, ν_B = 117.3, J_{PP} = 36 Hz, J_{RhP} = 173.

Methyl 4,6-*O*-Benzylidene-2,3-bis-*O*-[bis(3,5-dimethylphenyl)phosphino]-α-D-glucopyranoside. ^{1}H NMR 7.34−6.42 (m, aromatic), 5.13 (s, 1 H), 5.03 (m, 1 H), 4.49−4.42 (m, 2 H), 4.02 (dd, J = 5, 10, 1 H), 3.88 (m, 1 H), 3.56 (t, J = 9, 1 H), 3.37 (t, J = 10, 1 H), 2.75 (s, 3 H), 1.95 (s, 6 H), 1.94 (s, 6 H), 1.91 (s, 6 H), 1.90 (s, 6 H); ^{31}P NMR 119.6, 118.9.

Ligands and Catalysts from Methyl 2,6-Di-*O*-benzoyl-α-D-glucopyranoside (18).



Methyl 2,6-Di-*O*-benzoyl-3,4-bis-*O*-[bis(3,5-dimethylphenyl)phosphino]-α-D-glucopyranoside (20b) (for preparation see Typical Procedure for the Synthesis of a Phosphinite).

[(20b)Rh(COD)]$^+$ BF_4^-. ^{31}P NMR (C_6D_6): ABX (= P_1P_2Rh), ν_A = 129.0, ν_B = 130.4, J_{PP} = 10, J_{AX} = J_{BX} (= J_{RhP}) = 175.

[(20b)Rh(COD)]$^+$ SbF_6^-. ^{31}P NMR (C_6D_6): ABX (= P_1P_2Rh), ν_A = 132.8, ν_B = 134.2, J_{PP} = 30, J_{AX} = J_{BX} (= J_{RhP}) = 151.

[(20b)Rh(COD)]$^+$ OTf$^-$. ^{31}P NMR (C_6D_6): ABX (= P_1P_2Rh), ν_A = 130.5, ν_B = 131.8, J_{PP} = 34, J_{AX} = J_{BX} (= J_{RhP}) = 174.

Methyl 2,6-Di-*O*-benzoyl-3,4-bis-*O*-[bis(4-methoxyphenyl)phosphino]-α-D-glucopyranoside (20c). ^{1}H NMR 3.02 (s, 3 H), 3.19 (s, 3 H), 3.32 (s, 3 H), 3.34 (s, 3 H), 3.41 (s, 3 H), 4.19 (m, 1 H), 4.29 (m, 1 H), 4.65 (dd, J = 2, 12, 1 H), 4.93 (m, 1 H), 5.27 (d, J = 4, 1 H), 5.45 (m, 1 H), 5.69 (dd, J = 4, 10, 1 H), 6.46−8.40 (m, aromatic); ^{31}P NMR 120.5 (d, 1, J_{PP} = 5), 117.8 (d, 1, J_{PP} = 5). Anal. C, 65.33; H, 5.58; P 6.99. Calcd for $C_{49}H_{48}O_{12}P_2$ C 66.06; H 5.43; P 6.95.

[(20c)Rh(COD)]$^+$ BF_4^-. ^{31}P NMR (C_6D_6): ABX (= P_1P_2Rh), ν_A = 134.4, ν_B = 136.1, J_{PP} = 28, J_{AX} = J_{BX} (= J_{RhP}) = 181 Hz.

Methyl 2,6-Di-*O*-benzoyl-3,4-bis-*O*-(diphenylphosphino)-α-D-glucopyranoside (20e). ^{1}H NMR 2.78 (s, 3 H), 3.91 (dd, J = 4, 12, 1 H), 4.04 (dd, J = 4, 10, 1 H), 4.39 (d, J = 12, 1 H), 4.70 (m, 1 H), 5.08 (d, J = 3, 1 H), 5.22 (m, 1 H), 5.40 (dd, J = 4, 12, 1 H), 6.49−7.50 (m, aromatic), 7.85 (m, 2 H, aromatic), 8.12 (m, 2 H, aromatic); ^{31}P NMR 120.0 (d, J_{PP} = 4), 116.0 (d, J_{PP} = 4).

[(20e)Rh(COD)]$^+$ BF_4^-. ^{31}P NMR (C_6D_6): ABX (= P_1P_2Rh), ν_A = 130.8, ν_B = 133.7, J_{PP} = 32, J_{AX} = J_{BX} (= J_{RhP}) = 176.

[(20e)Rh(COD)]$^+$ SbF_6^-. ^{31}P NMR (C_6D_6): ABX (= P_1P_2Rh), ν_A = 136.3, ν_B = 133.1, J_{PP} = 28 Hz, J_{AX} = J_{BX} (= J_{RhP}) = 177 Hz.

Methyl 2,6-Di-*O*-benzoyl-3,4-bis-*O*-[bis(3,5-difluorophenyl)phosphino]-α-D-glucopyranoside (20f). ^{1}H NMR 2.81 (s, 3 H), 3.86 (m, 2 H), 4.23 (m, 1 H), 4.46 (m, 1 H), 4.82 (m, 1 H), 4.99 (d, 1, 4 H), 5.24 (dd, J = 4, 10, 1 H), 5.71 (m, 1 H), 6.10−6.34 (m, 3 H), 6.58−8.20 (m, aromatic); ^{31}P NMR 113.3, 109.8.

[(20f)Rh(COD)]$^+$ BF_4^-. ^{31}P NMR (C_6D_6): ABX (= P_1P_2Rh), ν_A = 126.7, ν_B = 127.6, J_{PP} = 39, J_{AX} = J_{BX} (= J_{RhP}) = 179.

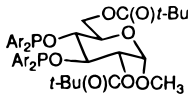
Methyl 2,6-Di-*O*-benzoyl-3,4-bis-*O*-[bis[3,5-bis(trifluoromethyl)phenyl]phosphino]-α-D-glucopyranoside (20g). ^{1}H NMR 2.93 (s, 3 H), 3.98 (dd, J = 5 12, 1 H), 4.11 (dd, J = 5, 10, 1 H), 4.28 (d, J = 12, 1 H), 4.52 (m, 1 H), 5.11 (d, J = 4, 1 H), 5.19 (m, 1 H), 5.45 (dd, J = 4, 10, 1 H), 6.89−8.22 (m, aromatic), ^{31}P NMR 113.0, 107.5. Anal. C 48.38; H, 2.79; P 4.65. Calcd for $C_{53}H_{32}F_{24}O_8P_2$ C, 48.42; H, 2.45; P 4.71.

[(20g)Rh(COD)]$^+$ BF_4^-. ^{31}P NMR (C_6D_6/CD_2Cl_2): 127.6 (d, J_{RhP} = 181).

Methyl 2,6-Di-*O*-benzoyl-3,4-bis-*O*-[bis[4-(trifluoromethyl)phenyl]phosphino]-α-D-glucopyranoside (20h). ^{1}H NMR (C_6D_6) 2.80 (s, 3 H), 3.85 (dd, J = 13, 4, 1 H), 4.06 (ddm, J = 8, 4, 1 H), 4.28 (dd, J = 13, 2, 1 H), 4.60 (dt, J = 12, 12 1 H), 5.00 (m, 1 H), 5.03 (d, J = 4, 1 H), 5.28 (dd, 12, 4, 1 H), 6.70−7.60 (m, aromatic). Anal. Calcd for $C_{49}H_{36}F_{12}O_8P_2$ C 56.44; H 3.48; P 5.94. Found C 56.36; H 3.75; P 5.92.

[(20h)Rh(COD)]$^+$ BF$_4^-$. ^{31}P NMR (C_6D_6): ABX (= P_1P_2Rh), ν_A = 125.2, ν_B = 127.4, J_{PP} = 37, $J_{AX} = J_{BX}$ (= J_{RhP}) = 177. Also seen is a minor (<5%) isomer with an 8-line pattern in the ^{31}P NMR spectrum between δ 130 and 138.

Ligands and Catalysts from Methyl 2,6-Bis-*O*-(trimethylacetyl)-α-D-glucopyranoside (19).



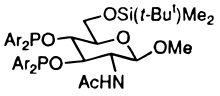
Methyl 2,6-Bis-*O*-(trimethylacetyl)-3,4-bis-*O*-[bis(3,5-dimethylphenyl)phosphino]-α-D-glucopyranoside (21b). ^{1}H NMR 0.93 (s, 9 H), 1.14 (s, 9 H), 1.90 (s, 6 H), 1.93 (s, 6 H), 1.98 (s, 6 H), 1.99 (s, 6 H), 2.88 (s, 3 H), 3.72 (m, 1 H), 3.95 (m, 1 H), 4.12 (dm, 1, J = 12, 1 H), 4.50 (m, 1 H), 4.89 (m, 1 H), 5.08 (m, 1 H), 5.30 (m, 1 H), 6.33 (s, 1 H), 6.47 (s, 1 H), 6.53 (s, 1 H), 6.64 (s, 1 H), 6.85−6.95 (m, 2 H), 7.18−7.35 (m, aromatic); ^{31}P NMR 122.1, 117.9.

[(21b)Rh(COD)]$^+$ BF$_4^-$. ^{31}P NMR (C_6D_6): ABX (= P_1P_2Rh), ν_A = 129.0, ν_B = 135.2, J_{PP} = 30 Hz, $J_{AX} = J_{BX}$ (= J_{RhP}) = 176.

Methyl 2,6-Bis-*O*-(trimethylacetyl)-3,4-bis-*O*-(diphenylphosphino)-α-D-glucopyranoside (21e). ^{1}H NMR 0.93 (s, 9 H), 1.14 (s, 9 H), 2.97 (s, 3 H), 3.75 (dd, J = 5, 12, 1 H), 3.94 (ddd, J = 2, 5, 10, 1 H), 4.17 (dd, J = 2, 12, 1 H), 4.44 (m, 1 H), 5.00 (d, J = 3, 1H), 5.05 (m, 1 H), 5.25 (dd, J = 4, 10, 1 H), 6.78−7.50 (m, aromatic); ^{31}P NMR 118.0 (d, 1, J_{PP} = 5), 114.8 (d, 1, J_{PP} = 5).

[(21e)Rh(COD)]$^+$ BF$_4^-$. ^{31}P NMR (C_6D_6): ABX (= P_1P_2Rh), ν_A = 134.0, ν_B = 136.5, J_{PP} = 30, $J_{AX} = J_{BX}$ (= J_{RhP}) = 178.

Ligands and Catalysts from Methyl 2-Acetamido-2-deoxy-6-*O*-(*tert*-butyldimethylsilyl)-β-D-glucopyranoside (25).



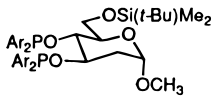
Methyl 2-Acetamido-6-*O*-(*tert*-butyldimethylsilyl)-2-deoxy-3,4-*O*-bis[bis-(3,5-dimethylphenyl)phosphino]-β-D-glucopyranoside (26b). This compound was purified by column chromatography inside the dry box using 40% ether/hexanes on silica gel. ^{1}H NMR 0.15 (s, 3 H); 0.16 (s, 3 H), 1.12 (s, 9 H), 2.10−2.35 (4 s, total 27 H), 3.49 (s, 3 H), 3.80 (m, 4 H), 4.42 (m, 1 H), 4.73 (m, 1 H), 5.13 (d, J = 8, 1 H), 5.26 (m, 1 H), 6.59−6.86 (m, aromatic), 7.22−7.55 (m, aromatic); ^{31}P NMR 120.4 (d, J_{PP} = 4), 115.7 (d, J_{PP} = 4).

[(26b)Rh(COD)]$^+$ BF$_4^-$. ^{31}P NMR (C_6D_6) ABX (= PPRh),ν_A = 118.9, ν_B = 126.6, J_{PP} = 34, J_{RhP} = 170.

Methyl 2-Acetamido-6-*O*-(*tert*-butyldimethylsilyl)-2-deoxy-3,4-*O*-bis(diphenylphosphino)-β-D-glucopyranoside (26e). ^{1}H NMR (C_6D_6) −0.08 (s, 3 H), −0.02 (s, 3 H), 0.90 (s, 9 H), 2.11 (s, 3 H), 3.30 (s, 3 H), 3.35−3.55 (m, 4 H), 4.48 (q, J = 8, 1 H), 4.72 (d, J = 8, 1 H), 5.05 (d, J = 8, 1 H), 5.15 (q, J = 8, 1 H), 6.70−7.60 (m, aromatic); ^{31}P NMR (C_6D_6) 112.70 (d, J_{PP} = 5), 117.17 (d, J_{PP} = 5).

[(26e)Rh(COD)]$^+$ SbF$_6^-$. ^{31}P NMR (C_6D_6) ABX (= PPRh), ν_A = 122.5, ν_B = 129.2, J_{PP} = 35, J_{RhP} = 173.

Ligands (28) and Catalysts from Methyl 6-*O*-(*tert*-Butyldimethylsilyl)-2-deoxy-α-D-glucopyranoside.

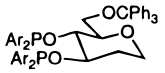


Methyl 2-Deoxy-3,4-bis-*O*-[bis(3,5-dimethylphenyl)phosphino]-α-D-glucopyranoside (28b). ^{1}H NMR inter alia 0.11−0.12 (2 s, 3 H each), 1.11 (s, 9 H), 2.12 (s, 6 H), 2.14 (s, 6 H), 2.16 (s, 6 H), 2.21 (s, 6 H), 3.14 (s, 3 H), 4.45 (d, J = 3, 1 H), 4.64 (m, 1 H), 5.20 (m, 1 H), 6.60−7.61 (m, aromatic); ^{31}P NMR 121.1 (d, J_{PP} = 2), 113.1 (d, J_{PP} = 2).

[(28b)Rh(COD)]$^+$ OTf$^-$. ^{31}P NMR (C_6D_6) ABX (= PPRh),ν_A = 123.6, ν_B = 128.2, J_{PP} = 34, J_{RhP} = 173.

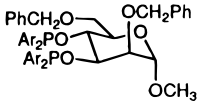
[(28b)Rh(COD)]$^+$ BF$_4^-$. ^{31}P NMR (C_6D_6) ABX (= PPRh) ν_A = 124.9, ν_B = 127.4, J_{PP} = 33, J_{RhP} = 173.

1,5-Anhydo-2-deoxy-3,4-bis-*O*-[bis(3,5-dimethylphenyl)phosphino]-6-*O*-(triphenylmethyl)-D-glucitol (29b). ^{1}H NMR (C_6D_6) 1.80−2.04 (m), 2.82−2.96 (m, 1 H), 3.22−3.58 (m, 4 H), 4.30−4.50 (m, 2 H), 6.30−7.60 (m, aromatic); ^{31}P NMR 110.89 (d, J_{PP} = 4), 115.88 (d, J_{PP} = 4).



[(29b)Rh(COD)]$^+$ SbF$_6^-$. ^{31}P NMR (CD_3COCD_3) 129.3 (dd), 132.9 (dd), J_{RhP} = 176, J_{PP} = 30.

Ligands (30) and Catalysts from Methyl 2,6-Di-*O*-benzyl-α-D-mannopyranoside.



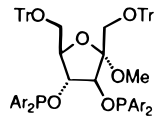
Methyl 2,6-Di-*O*-benzyl-3,4-bis-*O*-[bis(3,5-dimethylphenyl)phosphino]-α-D-mannopyranoside (30b). ^{1}H NMR 1.87 (s, 6), 1.93 (s, 6 H), 1.94 (s, 6 H), 1.96 (s, 6 H), 3.00 (s, 3 H), 3.43−3.57 (m, 2 H), 3.74 (m, 1 H), 4.00−4.23 (m, 5 H), 4.56 (m, 1 H), 5.02−5.20 (m, 2 H), 6.40−7.50 (m, aromatic); ^{31}P NMR 120.5, 115.7.

[(30b)Rh(COD)]$^+$ BF$_4^-$. ^{31}P NMR (C_6D_6) ν_A = 124.8, ν_B = 133.9, J_{PP} = 30; J_{RhP} = 176.

Methyl 2,6-Di-*O*-benzyl-3,4-bis-*O*-(diphenylphosphino)-α-D-mannopyranoside (30e). ^{1}H NMR 3.13 (s, 3 H), 3.55 (m, 2 H), 4.02 (m, 1 H), 4.11 (m, 1 H), 4.22 (m, 4 H), 4.72 (d, J = 2, 1 H), 4.95 (m, 1 H), 5.09 (m, 1H), 6.80−7.78 (m, aromatic); ^{31}P NMR 117.3, 110.4.

[(30e)Rh(COD)]$^+$ BF$_4^-$. ^{31}P NMR (C_6D_6) ν_A = 129.2, ν_B = 137.2, J_{PP} = 27, J_{RhP} = 177.

Ligands (31) and Catalysts from Methyl 5,6-*O*-Bis-(triphenylmethyl)-α-D-fructofuranoside.



Methyl 1,6-Bis-*O*-(triphenylmethyl)-3,4-bis-*O*-[bis(3,5-dimethylphenyl)phosphino]-α-D-fructofuranoside (31b). ^{1}H NMR 1.85, 1.91, 1.94, 2.05 (4 s, 3H each), 3.10 (s, 3H), 3.45−3.60 (ABX, J_{AB} = 9, $J_{AX} = J_{BX}$ = 5, 2H), 3.67, 3.80 (ABq, J_{AB} = 10, 2H), 4.47 (q m, br, 1H), 5.63 (d, J = 11 Hz, 1 H), 5.20 (m, 1 H), 6.50−7.80 (m, aromatic); ^{31}P NMR (C_6D_6) 116.41 (d, J_{PP} = 8), 118.53 (d, J_{PP} = 8).

[(31b)Rh(COD)]$^+$ BF$_4^-$. ^{31}P NMR (C_6D_6): 114.2 (d), 131.5 (dd), J_{RhP} = 169, J_{PP} = 28.

Methyl 1,6-Bis-*O*-(triphenylmethyl)-3,4-bis-*O*-[bis(4-methoxyphenyl)phosphino]-α-D-fructofuranoside (31c). ^{1}H NMR (C_6D_6) 3.05−3.30 (4 s total 15 H), 3.40, 3.50 (ABX, J_{AB} = 10, J_{AX} = 7, J_{BX} = 6, 2 H), 3.61, 3.79 (AB, J_{AB} = 10, 2 H), 4.58 (dd m, br, 1H), 4.90 (m, 1H), 5.05 (d, J = 10, 1 H), 6.42−7.61 (m, aromatic); ^{31}P NMR (C_6D_6) 115.0 (d), 115.2 (d), J_{PP} = 7.

[(31c)Rh(COD)]$^+$ SbF$_6^-$. ^{31}P NMR (C_6D_6) ABX (= PPRh), ν_A = 121.8, ν_B = 122.1, J_{PP} = 27, J_{RhP} = 167.

[(31c)Rh(COD)]$^+$ OTf$^-$. ^{31}P NMR (C_6D_6) ABX (= PPRh), ν_A = 121.3, ν_B = 121.9, J_{PP} = 28, J_{RhP} = 166.

Methyl 1,6-Bis-*O*-(triphenylmethyl)-3,4-bis-*O*-(diphenylphosphino)-α-D-fructofuranoside (31e). ^{1}H NMR (C_6D_6) 3.10 (s, 3H), 3.35, 3.45 (ABX, J_{AB} = 10, J_{AX} = 7, J_{BX} = 6, 2 H), 3.60, 3.78 (AB, J_{AB} = 10, 2 H), 4.50 (ddm, br, 1H), 4.88 (m, 1H), 5.00 (d, J = 10, 1 H), 6.80−7.80 (m, aromatic); ^{31}P NMR (C_6D_6) 114.2, 115.1, J_{PP} = 9.

[(31e)Rh(COD)]$^+$ SbF$_6^-$. ^{31}P NMR (C_6D_6) ABX (= PPRh), ν_A = 119.7, ν_B = 122.8 J_{PP} = 29, J_{RhP} = 166.

Ligands and Catalysts from (1*S*,2*S*)-*trans*-1,2-cyclohexanediol. (1*S*,2*S*)-1,2-Bis-*O*-(diphenylphosphino)cyclohexane. To 200 mg (1.72 mmol) of azeotropically dried (1*S*,2*S*)-*trans*-1,2-cyclohexanediol, 11 mg (0.05 equiv) of 4-(dimethylamino)pyridine, and 1 mL of pyridine in 2 mL of CH_2Cl_2 at 0 °C and under nitrogen was added 0.836 g (3.788 mmol) of

chlorodiphenylphosphine dissolved in 2 mL of methylene chloride. An additional 2 mL of methylene chloride was used to facilitate transfer of the chlorophosphine quantitatively. The mixture was slowly allowed to come to room temperature and was stirred for 18 h. The precipitated solids were filtered off with the aid of a cotton-plugged disposable pipette. The NMR spectrum of this solid showed that it was pyridine hydrochloride. The vials were washed with 2 mL of 1:1 ether/hexanes, and the solid in the disposable pipette was washed with this solvent. The filtrate was concentrated to get a white solid. The product was recrystallized from benzene. ^{1}H NMR (C_6D_6) 0.70−0.95 (m, 2 H), 1.10−1.45 (m, 4 H), 1.90−2.05 (m, 2 H), 4.05 (m, 2 H), 6.70−7.15 (m, aromatic), 7.45−7.70 9 (m, aromatic); ^{31}P NMR 108.7.

[(1*S*,2*S*)-1,2-[(Diphenylphosphino)oxy]cyclohexane] Rh$^+$(COD) SbF$_6^-$. The complex was prepared by adding a CH_2Cl_2 solution of the bis(phosphinite) to a solution of $(COD)_2$ Rh^+ SbF_6 in CH_2Cl_2 at room temperature and stirring the solution overnight. The low-boiling components were removed and the NMR spectra were recorded in $CDCl_3$. ^{1}H NMR 0.70−1.15 (m, 4 H), 1.35−1.60 (d, br, 2H), 1.78 (d, br, 2 H), 2.10−2.30 (m, 4 H), 2.32−2.60 (m, 4 H), 3.82−4.02 (m, 2 H), 4.42 (q, br, 2 H), 4.90 (s, br, 2 H), 7.00 −7.80 (m, aromatic); ^{31}P NMR 131.0 (d, J = 177). Minor peaks (together <2%) at 121.7 (d) and 123.1 (d) were also observed. The compound was recrystallized from benzene by slow evaporation. X-ray structure analysis on this compound confirmed the structure.

X-ray Crystallography. An orange prism of **34** grown from benzene by slow evaporation with dimensions 0.35 × 0.19 × 0.37 mm was mounted in a glass capillary under argon and placed on an Enarf-Nonius CAD4 diffractometer equipped with a Mo Kα source. The data was collected at −55 °C.

Crystal data: $SbRhP_2F_6O_2C_{50}H_{54}$; monoclinic-b, 12 a = 19.333(3), b = 12.042(2), c = 20.920(3) Å, β = 94.94(1)°, T = −55 °C, V = 4852.3 Å^3, Z = 4, FW =1087.59, D_c = 1.489g/mL, μ(Mo) = 10.18 cm^{-1}.

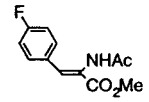
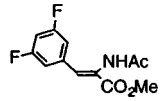
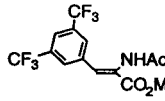
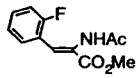
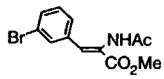
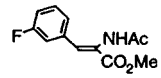
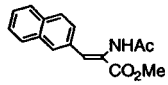
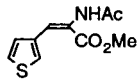
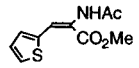
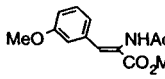
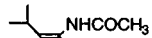
Data collection: Enarf-Nonius CAD4 diffractometer equipped with a Mo Kα source, 6577 data collected, 2.8° ≤ 2θ ≤ 55.0°, maximum h,k,l = 25 15 27, data octants = +++, −++, ω scan method, scan width = 1.20−2.20° ω, scan speed = 1.70−5.00°/min, typical half-height peak width = 0.12° ω, 2 standards collected 30 times, 1% fluctuation, 13.3% variation in azimuthal scan, no absorption correction, 156 duplicates, 1.6% R-merge, 3629 unique reflections with $I \geq 3.0\sigma(I)$.

Solution and refinement: Structure was solved by automated Patterson analysis (PHASE). The asymmetric unit consists of one cation in a general position, with two half SbF_6 anions on special positions, and two partially occupied benzene solvate molecules. Hydrogen atoms were idealized with C−H = 0.95 Å, refinement by full-matrix least squares on F, scattering factors from *International Tables for X-ray Crystallography*, Vol. IV, including anomalous terms for Sb, Rh, P, biweight ∝ $[\sigma^2(I) + 0.00091^2]^{-1/2}$ (excluded 5), refined anisotropic: Sb, Rh, P, F, O, C, isotropic: F, C, fixed atoms: H, 498 parameters, data/parameter ratio = 7.28, final R = 0.051, R_w = 0.044, error of fit = 1.40, maximum Δ/σ = 0.12. The SbF_6 disorder was modeled with partial F positions to yield a correct formula unit, while the benzene occupancies were adjusted to yield reasonable thermal parameters. The absolute configuration corresponds to the enantiomorph with the lowest R-value (5.09 vs 5.14%). Largest residual density = 0.58 e/Å^3, near Rh1.

Fractional coordinates, isotropic and anisotropic thermal parameters and a complete listing of bond angles and bond lenths are given in the Supporting Information.

Typical Scouting Procedure for the Hydrogenation of Acetamidoacrylate Derivatives (3, eq 3). In the dry box, a 150 mL Fischer−Porter tube was loaded with 0.25 mmol of methyl acetamidoacrylate, 1 mg (0.4 mol %) of **11b**, and 2 mL of THF or glyme. After sealing, the tube was removed from the dry box and placed behind proper shielding. With adequate stirring of the solution at room temperature, the tube was first charged with 40 psi of H_2 gas and was subsequently evacuated. This procedure of filling and evacuation was repeated twice more. The tube was charged with 30 to 40 psi of H_2 before stirring for 3 h. The conversion was quantitative in most instances as judged by gas chromatographic analysis. When a methyl ester of an *N*-acetylamino acid derivative of **3** was used, the crude mixture was analyzed directly by gas chromatography (Chirasil S-Val, 170 °C/20 min, programmed for 10 °C/min increase to 195 °C, 195 °C/30 min. (See Table 7 for retention times. See also the attached chromatograms in the Supporting Information). However, when an *N*-acetylamino acid acid was employed, the crude mixture was treated with excess diazomethane (Caution: diazomethane is known to be explosive, Aldrich mini-Diazald kit was used to prepare the diazomethane) to convert the acid to the corresponding methyl ester for GC analysis. See Tables 1−5 for results. The assignments of structures for all compounds were confirmed by comparison with authentic samples.[29]

Table 7. GC Retention Times (min) of Selected Amino Acid Derivatives[a]

Dehydroamino acid	*R*-isomer	*S*-isomer
	8.2	8.6
	6.8	7.3
	4.9	5.4
	6.8	7.4
	19.2	20.3
	7.2	7.9
	33.8	34.2
	7.9	8.8
	7.0	7.4
	11.0[b]	11.6[b]
	8.8[c]	10.5[c]

[a] Chirasil L-Val, conditions: initial temp 170 °C / 20 min, rate: 10 °C / min, final temp. 195 °C / 30 min. [b] initial temp 180 °C / 20 min, rate: 10 °C / min, final temp. 195 °C / 30 min. [c] Initial temp 120 °C / 20 min, rate: 10 °C / min, final temp. 195 °C / 30 min.

Examples of Laboratory Scale Preparations: (*S*)-*N*-Acetylphenylalanine Methyl Ester. In the dry box, a 150 mL Fischer−Porter tube was loaded with 1.0 g (4.9 mmol) of (*Z*)-acetamidocinnamic acid (Aldrich, recrystallized), 0.62 mg of the catalyst (0.00048 mmol; 1/5000 equiv of catalyst, measured by using 206 μL of a freshly prepared stock solution of 30 mg of **[(11b)Rh(COD)]$^+$ SbF$_6^-$** in 5.0 mL of THF), and 8 mL of THF. After sealing, the tube was removed from the dry box and placed behind proper shielding. With adequate stirring of the solution at room temperature, the tube was charged with 30 psi of H_2 gas and vented. This procedure was repeated twice. The tube was charged with 30 psi of H_2 and recharged as necessary to maintain 30 psi. After 16 h, the tube was vented. A small sample of the crude mixture was treated with diazomethane giving *N*-acetyl S-phenylalanine methyl ester in 97.8% ee. The remainder was recrystallized from 95% ethyl acetate/hexane to give 881 mg (88%) of (*S*)-

N-acetylphenylalanine with 99.7% ee (determined by GC on the methyl ester).

The reaction is sensitive to the purity of the starting dehydroamino acid precursor. The same reaction repeated on different batches of starting material (Interchem) with 1/10000 equiv of the catalyst (51 μL of the above solution) at room temperature and 40 psi hydrogen on a scale of 0.500 g provided (*S*)-*N*-acetylphenylalanine of 99.0% ee. Depending upon the purity of the starting material, we have observed variations as much as 81.0 to 99.0% ee for this and other hydrogenations. Purification of the starting dehydroamino acid derivatives by recrystallization/column chromatography is highly recommended.

Preparation of Either Antipode of *N*-Acetyl-3-(3-thienyl)alanine Methyl Ester: Hydrogenation of Methyl (*Z*)-*N*-Acetyl-3-(3-thienyl)-2-propenoate. The (*S*)-isomer (prepared using ligand **11b**): crude ee 96.7% (GC) and 99% (HPLC); $[\alpha]^{20}_D$ ($CHCl_3$, *c* 1) 99 ± 0.8°; HPLC (Chiralcel OJ, 10% 2-propanol/hexanes, 1 mL/min) 13.00 min. Recrystallized ee 99.5%; mp 114 °C; $[\alpha]^{20}_D$ 100 ± 0.8° (*c* 1, $CHCl_3$). Anal. C 53.33; H 5.72; N 5.96; S 14.01. Calcd C 52.85; H 5.77; N 6.16; S 14.11.

The (*R*)-isomer (prepared using ligand **20b**): crude ee 97.0%; Recrystallized ee 99.5%; mp 107−109 °C (reported[36b] 106−108 °C); $[\alpha]^{20}_D$ −15.6 ± 0.8° (EtOH, *c* 1; reported[36b] −14.66); −95.0 ± 0.8° ($CHCl_3$, *c* 1); HPLC (Chiralcel OJ, 10% 2-propanol/hexanes, 1 mL/min) 10.6 min.

Hydrogenation of Methyl (*Z*)-*N*-Acetyl-3-[3,5-bis(trifluoromethyl)phenyl]-2-propenoate: *N*-Acetyl-3-[3,5-bis-(trifluoromethyl)phenyl]alanine Methyl Ester. The (*R*)-isomer (prepared using ligand **20b**): crude ee 97.4%; ee of recrystallized (10% ethyl acetate/hexane) sample: 99.4%; mp 107−109 °C (reported[29] 111−112 °C); $[\alpha]^{25}_D$ −78.8 ± 0.8° ($CHCl_3$, *c* 1) reported[29] −75.6°.

The (*S*)-isomer (prepared using ligand **11b**): crude ee 95.8%; recrystallized (from 10% ethyl acetate/hexane) 99.3% ee; $[\alpha]^{25}_D$ −74.4 ± 0.8° ($CHCl_3$, *c* 1).

Example of Hydrogenation of a Dehydroamino Acid with a Cbz Protecting Group on Nitrogen. In the dry box, a 150 mL Fischer−Porter tube was loaded with 50 mg (0.15 mmol) of methyl (*Z*)-2-[*N*-(benzyloxycarbonyl)amino]-3-(4-fluorophenyl)prop-2-enoate, 1 mg of **11b**, and 2 mL of THF. After sealing, the tube was removed from the dry box and placed behind proper shielding. With adequate stirring of the solution at room temperature, the tube was charged with 30 psi of H_2 gas and vented. This procedure was repeated twice. The tube was charged with 30 psi of H_2 and recharged as necessary to maintain 30 psi. After 16 h, the tube was vented. The crude mixture concentrated provided an oil in nearly quantitative yield. HPLC columns Chiralcel OJ or OB did not separate the two enantiomers using an 2-propanol/hexane solvent system.

Purification by column chromatography on silica gel using 30% ethyl acetate/hexanes as solvent gave 44 mg (89%) of a clear oil identified as the desired product from the following data and its subsequent reactions. ^{1}H NMR ($CDCl_3$) 3.08 (d, AB, J = 6, J = 13, 2 H), 3.72 (s, 3 H), 4.65 (ddd, J = 7, 7, 6, 1 H), 5.10 (AB, J = 12, 2 H), 5.21 (d, br, 1 H), 6.90−7.10 (m, 4 H), 7.20−7.42 (m, 5 H). $[\alpha]^{25}_D$ = +47.2 ± 0.8° ($CHCl_3$, *c* 1). Enantiomeric purity was established on the corresponding alcohol obtained via $LiBH_4$ reduction or from the *N*-acetyl derivative as described below.

To the crude product obtained from the above reaction using 0.1 g of starting dehydro derivative was added 0.25 mL of a 2.0 M solution of $LiBH_4$ in THF. After 2 h, 5 mL of water was added, and the mixture was stirred until gas evolution stopped. The product was extracted into ether. The organic phase was washed with water and dilute $NaHCO_3$, dried ($MgSO_4$), and concentrated. The crude mixture was passed through a short column of silica using 40% ethyl acetate/hexane as eluant, and the product was collected. GC retention time on an HP methylsilicone column under conditions reported earlier at 180 °C was 11.43 min. Chiral GC on chirasil-L-Val showed two incompletely separated peaks at retention times 25.2 and 25.7 min, respectively, with the (*R*)-isomer appearing first. HPLC analysis on the Chiralcel OJ column using 92.5% hexane/*i*-PrOH at 1 mL/min as eluant showed 97% ee [retention time (min): (*S*)-isomer 24.4 min, (*R*)-isomer 27.8 min]. 2-[*N*-(Benzyloxycarbonyl)amino]-3-(4-fluorophenyl)-1-propanol: mp 95−96 °C; $[\alpha]^{25}_D$ = −24.6 ± 0.8° ($CHCl_3$, *c* 1); ^{1}H NMR ($CDCl_3$) 2.10−2.30 (s, br, 1 H), 2.83 (d, 2, J = 7, 2 H), 3.55, 3.68 (ABX, J_{AB} = 13, J_{AX} = 4, J_{BX} = 5, 2 H), 3.90 (m, br 1 H), 5.01 (s, br, 1H), 5.16 (s, 2), 6.90−7.50 (m, aromatic); IR ($CHCl_3$) 3630, 3438, 1716 cm^{-1}. Anal. C 67.10; H 6.04; N 4.64. Calcd for $C_{17}H_{18}FO_3N$ C 67.31; H 5.98; N 4.62.

The enantioselectivity was confirmed by converting the N-Cbz derivative to the corresponding N-Ac derivative. For this, the Cbz derivative was hydrogenated at 30 psi using 10% Pd/C in 5:1 methanol/acetic anhydride. The solvents were removed on the pump, and the product was analyzed by NMR, GC, and HPLC. Chiral GC (Chirasil-L-Val column, 160 °C) and Chiral HPLC (Chiralcel OJ, 7.5% *i*-PrOH/hexane) gave base-line separations of the N-Ac derivative, and the ee was ascertained to be 96% by HPLC and 95.7% by GC.

For this reduction, the following selectivities were observed for various catalysts: [**11b**]Rh^+(COD) SbF_6^- 96% (*S*); [**11c**]Rh^+(COD) SbF_6^- 85% (*S*); [**11e**]Rh^+(COD) SbF_6^- 62% (*S*); [**11f**]Rh^+(COD) SbF_6^- <3% (*S*); [**11g**]Rh^+(COD) SbF_6^- <5% (*S*); [**20b**]Rh^+(COD) SbF_6^- 90% (*R*); [**27b**]Rh^+(COD) BF_4^- 96% (*R*).

Relative Rates of Hydrogenation of a Dehydroamino Acid Ester Using [11b]Rh^+(NBD) SbF_6^- and [(*R*,*R*)-Me-DUPHOS] Rh^+(COD) TfO^- in THF. In a dry box, two Fischer−Porter tubes were charged with methyl (*Z*)-*N*-acetyl-3-[3,5-bis(trifluoromethyl)phenyl]-2-propenoate (75 mg, 0.211 mmol) in 3 mL of THF. To one was added 0.25 mg (0.0002 mmol, as a THF solution of known concentration) of [**11b**]Rh^+(NBD) SbF_6^- and to the other 0.14 mg (0.0002 mmol, as a THF solution of known concentration) of [(*R*,*R*)-Me-Duphos]Rh^+(COD) TfO^-. The tubes were brought outside the box and were connected to a hydrogen cylinder. The catalytic hydrogenation was accomplished as described before at 40 psi of hydrogen after three cycles of purging and evacuation. The tubes were evacuated at 15 min and refilled with nitrogen. The contents were analyzed by gas chromatography to determine the extent of reaction and enantioselectivities. The results are shown in Scheme 10.

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Supporting Information Available: Conditions for chromatographic analysis, typical chromatograms of *R* and *S* amino acid derivatives, and X-ray diffraction data for **34** including fractional coordinates, isotropic and anisotropic thermal parameters, and a complete listing of bond angles and bond lengths (19 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from ACS; see any current masthead page for ordering information.

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