Preparation and Use of C_2-Symmetric Bis(phospholanes): Production of α-Amino Acid Derivatives via Highly Enantioselective Hydrogenation Reactions

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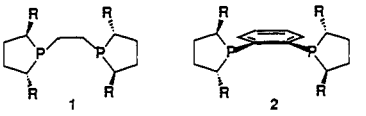
Abstract: A new class of chiral C_2-symmetric bis(phospholane) ligands has been prepared and used in rhodium-catalyzed asymmetric hydrogenation reactions. We describe a practical, one-pot procedure which utilizes enantiomerically pure 1,4-diol cyclic sulfates **4** for the preparation of a homochiral series of 1,2-bis(phospholano)ethanes **1** and 1,2-bis(phospholano)benzenes (DuPHOS) **2**. Cationic rhodium complexes bearing these new ligands behave as very efficient catalyst precursors for the asymmetric hydrogenation of a broad range of α-(*N*-acylamino)acrylate (enamide) substrates **5**. Significantly, a variety of unnatural and nonproteinaceous α-amino acid derivatives **6** were obtained *directly* with enantioselectivities approaching 100% ee when using the DuPHOS ligands **2**. Substrate-to-catalyst ratios of 10 000 were routinely used, and ratios as high as 50 000 were demonstrated in these reactions. Details of the DuPHOS–Rh-catalyzed hydrogenations are discussed.

Asymmetric phosphine ligands have played a dominant role in the development of novel transition-metal-catalyzed enantioselective syntheses.[1] Notwithstanding the high selectivities observed in certain applications using some of the more successful asymmetric phosphines such as DIPAMP,[2] CHIRAPHOS,[3] and BINAP,[4] there are many reactions of interest where catalysts bearing these phosphines perform rather poorly in terms of efficiency and enantioselectivity. Such failure indicates the need for alternative asymmetric ligands and/or catalysts.

Toward this goal, our research has been focused on the design of new chiral ligands for use in transition-metal-based asymmetric catalysis. We recently outlined our approach and described the synthesis of new electron-rich C_2-symmetric bis(phospholane) and C_3-symmetric tris(phospholane) ligands.[5-7] These studies indicated the potential utility of C_2-symmetric 1,2-bis(phospholano)ethane ligands of type **1**. The reported ligand preparation, however, was inefficient for cases other than the dimethyl-substituted diphospholane (i.e., **1a**, R = Me). We herein report details of an improved synthetic procedure that allows facile preparation of the homochiral series of C_2-symmetric 1,2-bis(phospholano)ethanes **1** (BPE, R = Me, Et, Pr, and *i*-Pr). The evolutionary nature of our ligand design subsequently led us to prepare the analogous homochiral series of 1,2-bis(phospholano)benzene ligands **2** (DuPHOS, R = Me, Et, Pr, and *i*-Pr).[8]

We have found that the new ligands **1** and **2** afford efficient catalysts for the highly enantioselective hydrogenation[5-9] and hydrosilylation[10] of various unsaturated substrates. In particular, enantioselectivities approaching 100% ee have been observed in the Rh-catalyzed hydrogenation of a wide range of α-(*N*-acylamino)acrylates. Importantly, the high efficiency, selectivity, and substrate generality exhibited by these catalysts provide a practical route to a variety of enantiomerically pure unnatural and nonproteinaceous α-amino acid derivatives. The details of these hydrogenation studies are described herein.



Results and Discussion

Bis(phospholano)ethane (BPE) Ligands 1. Ligand Preparation. We have uncovered a versatile synthetic route for the preparation of a new class of enantiomerically pure ligands based on the *trans*-2,5-dialkylphospholane moiety (Scheme I). The phosphine synthesis utilizes the homochiral 1,4-diols **3** (R = Me, Et, Pr, and *i*-Pr) which were prepared in a simple three-step procedure involving the Ru–BINAP-catalyzed asymmetric hydrogenation of β-keto esters to β-hydroxy esters, followed by hydrolysis to the corresponding β-hydroxy acids and subsequent electrochemical Kolbe coupling.[5,6] Importantly, this sequence allows the preparation of multigram quantities of both diol enantiomers in optically pure form. The crystalline diols **3** were readily converted to the corresponding 1,4-diol cyclic sulfates **4** (Scheme I) by reaction with thionyl chloride followed by ruthenium-catalyzed oxidation (0.1 mol % $RuCl_3/NaIO_4$) of the intermediate cyclic sulfites (not isolated).[11] The cyclic sulfates **4** were isolated in high yield (75–90%) as colorless crystalline solids. As a precautionary measure, the cyclic sulfates generally were recrystallized at least once from hexane or an ether/hexane mixture to ensure enantiomeric purity. The crystalline cyclic sulfates **4** thus obtained were then used directly in a simple one-pot phosphine synthesis.

1,2-Bis(phospholano)ethanes **1** (BPE; **a**, R = Me; **b**, R = Et; **c**, R = Pr; and **d**, R = *i*-Pr) were conveniently prepared at room

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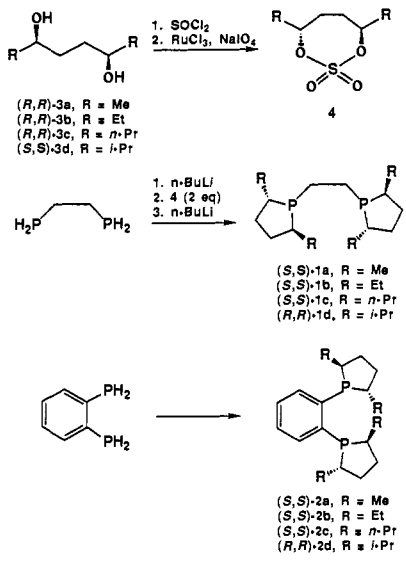
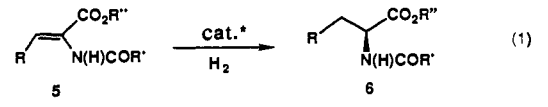
Scheme I



temperature by successive treatment of 1,2-bis(phosphino)ethane with 2 equiv of *n*-BuLi, followed by 2 equiv of cyclic sulfate **4**, and then followed by an additional 2 equiv of *n*-BuLi (Scheme I). The first *n*-BuLi treatment is known to deprotonate the diphosphine to generate dilithium bis(phosphido)ethane.[12] Subsequent reaction with **4** presumably leads to nucleophilic opening of one cyclic sulfate by each phosphide. The main advantage of cyclic sulfates **4** over seemingly comparable 1,4-electrophiles such as the corresponding bis(mesylates) is that, upon nucleophilic ring opening of **4**, a sulfate leaving group is produced. The anionic nature of the sulfate leaving group renders it kinetically less reactive than the starting cyclic sulfate. Thus, no competitive intramolecular phosphide attack leading to ring closure nor intermolecular attack leading to oligomerization occur prior to complete addition of **4**. The second *n*-BuLi addition allows deprotonation of each remaining PH and induces smooth closure to the five-membered phospholane rings. The series of 1,2-bis(phospholano)ethanes **1** was thus obtained in high yield and as essentially the only phosphorous-containing products formed.

As expected, in all cases, complete inversion of stereochemistry occurred at the stereogenic carbon centers of cyclic sulfates **4** to provide the phosphines of opposite absolute configuration. The enantiomeric purity of bis(phospholanes) **1** (and **2**, *vide infra*) should necessarily follow from the purity of the starting cyclic sulfates **4**. To ascertain this point, each phosphine was reacted with (*R*)-[dimethyl(α-methylbenzyl)aminato-*C*,*N*]palladium(II) chloride dimer[13] and the reaction monitored by ^{31}P NMR spectroscopy. In all cases, only a single diastereomeric complex (within limits of detection) was observed. Comparisons were made with the spectrum obtained with the opposite phosphine enantiomer. The corresponding Pd complex bearing the diphosphine (*R*,*R*)-**1d**, [(*R*)-[*N*,*N*-dimethyl(α-methylbenzyl)-aminato-*C*,*N*]palladium((*R*,*R*)-*i*-Pr-BPE)]$^+SbF_6^-$, was characterized by X-ray crystallography. The *R*,*R* absolute configuration of the ligand was confirmed.[14]

Asymmetric Hydrogenation with BPE Ligands. We next sought to evaluate the effectiveness of the new chiral diphosphines **1** in asymmetric catalysis. The asymmetric hydrogenation of (*Z*)-α-(*N*-acylamino)acrylates (enamides) **5** has been extensively investigated (eq 1), and relatively high enantioselectivities have been achieved with certain substrates using chiral diphosphine–Rh catalysts.[1-4] Thus, enamide hydrogenations have become a standard test reaction for new chiral phosphine ligands.



In addition to being a test reaction, it is a very important reaction in that it potentially provides one of the most efficient, cost effective methods for the production of valuable enantiomerically pure α-amino acid derivatives **6**. In particular, asymmetric hydrogenation could find extensive application in the production of a variety of unnatural and nonproteinaceous α-amino acids. Such α-amino acids are becoming increasingly important in pharmaceutical research as synthetic intermediates for the preparation of many biologically active compounds.[15] In particular, the use of nonproteinaceous α-amino acids in peptide and peptidomimetic drugs often has produced significant improvement in properties such as *in vivo* binding, transport, and bioavailability. Despite this importance, *no single asymmetric hydrogenation catalyst has yet been developed and shown to provide directly a wide range of α-amino acid derivatives with very high enantioselectivity* (≥99% ee).

For the series of 1,2-bis(phospholano)ethane ligands **1a–d**, we have examined the rhodium-catalyzed asymmetric hydrogenation of two different α-acetamidoacrylate methyl esters **5a** (R = H and R′, R″ = Me) and **5b** (R = Ph and R′, R″ = Me). Relatively high enantioselectivities were observed in these reductions (Table I); the catalyst derived from Et-BPE **1b** afforded products **6a** and **6b** in 98% ee and 93% ee, respectively. While these results do compare favorably with enantiomeric excesses obtained using known catalysts,[1c] the very high enantioselectivities (≥99% ee) that we were striving for were not attained. Significantly, however, these results did demonstrate that relatively efficient transfer of chirality from the phospholane moieties of **1** to the substrate could be achieved with this new class of diphosphine ligands.

X-ray Crystallography: (*R*,*R*)-Me-BPE–rhodium complex. To gain insight into the asymmetric environment imposed by the BPE ligands **1**, we examined the structure of the catalyst precursor [(COD)Rh((*R*,*R*)-Me-BPE)]$^+SbF_6^-$ (Me-BPE = **1a** and COD = 1,5-cyclooctadiene) by X-ray crystallography.[5] The ORTEP diagram (Figure 1) shows the two phospholane moieties extending to the left and right of the COD ligand as well as the C_2-symmetry of the coordinated diphosphine. Selected interatomic bond distances and angles are provided in Table II. The P–Rh–P angle of 83.25° is comparable to values observed in other rhodium complexes containing ethano-bridged diphosphines.[16] A large dihedral angles (24°) exists between the P–Rh–P plane and the plane defined by the COD olefin midpoints and Rh. Also, C1 and C5 of the COD ligand are closer to Rh than their double-bonded counterparts C2 and C6. Steric interactions between the phospholane methyl groups (C16 and C26) and the vinylic CH groups (C2 and C6) appear to be responsible for this distortion from the expected square-planar geometry at Rh. Similar distortions have been seen in other structurally characterized

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(14) Crystal data for [(*R*)-[dimethyl(α-methylbenzyl)-aminato-*C*,*N*]palladium((*R*,*R*)-*i*-Pr-BPE)]$^+SbF_6^-$ ($C_{32}H_{58}F_6NP_2PdSb$): orthorhombic, $P2_12_12_1$ (No. 19), a = 11.348(3) Å, b = 15.734(5) Å, c = 21.338(6) Å, T = −130 °C, V = 3809.9 Å^3, Mo Kα radiation, μ_{calcd} = 13.09 cm^{-1}, d_{calcd} = 1.497 g cm^{-3}, Z = 4, fw = 860.92. The structure was solved by direct methods (MULTAN) and refined by a full-matrix least-squares procedure to residuals of R = 0.068, R_w = 0.055, GOF = 1.20 for 4017 unique reflections with $I > 3.0\sigma(I)$ and 223 variables. Two octants of data were collected and used in the refinement. The *R* absolute configuration for all stereogenic carbon centers was confirmed. An ORTEP diagram and full structural details are given as supplementary material.

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Table I. Asymmetric Hydrogenations Using BPE Ligands **1**[a]

ligand	substrate (% ee)	
	5a	**5b**
1a	91.4	85
1b	98.1	93
1c	97.7	92
1d	96.4	93

[a] Reactions were carried out at 20–25 °C and an initial H_2 pressure of 30 psi (2 atm) with 0.25–0.35 M methanol solutions of substrate and the catalyst precursors $[(COD)Rh(P_2)]^+OTf^-$ (0.1 mol %). Reactions time allowed for complete (100%) conversion was 1 h.

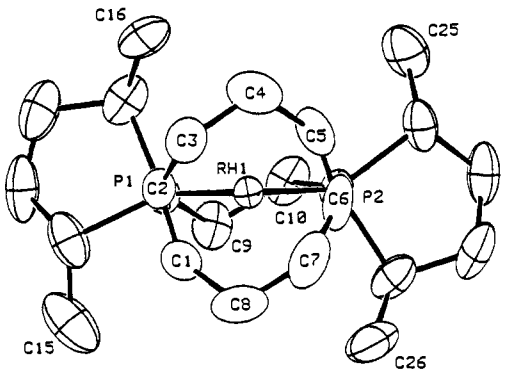

Figure 1. ORTEP diagram of catalyst precursor $[(COD)Rh((R,R)\text{-Me-BPE})]^+SbF_6^-$ (Me-BPE = **1a**). SbF_6^- counterion and hydrogen atoms have been omitted for clarity.

Table II. Selected Interatomic Distances and Intramolecular Angles for $[(COD)Rh((R,R)\text{-}\mathbf{1a})]^+SbF_6^-$

Interatomic Distances (Å)	
Rh(1)–P(1)	2.258(2)
Rh(1)–P(2)	2.276(2)
Rh(1)–C(1)	2.209(7)
Rh(1)–C(2)	2.268(6)
Rh(1)–C(5)	2.211(6)
Rh(1)–C(6)	2.273(7)
C(1)–C(2)	1.354(9)
C(5)–C(6)	1.338(11)
Intramolecular Angles (deg)	
P(1)–Rh–P(2)	83.25(6)
C(1)–Rh–C(5)	94.6(3)
C(1)–Rh–C(6)	80.6(3)
C(2)–Rh–C(5)	80.3(2)
C(2)–Rh–C(6)	86.7(2)
Rh(1)–P(1)–C(9)	108.9(2)
Rh(1)–P(2)–C(10)	110.3(2)
Intramolecular Nonbonded Distances (Å)	
C(2)–C(16)	3.671(11)
C(6)–C(26)	3.662(12)
C(3)–C(7)	3.038(11)

$[(COD)Rh(\text{chiral diphosphine})]^+X^-$ complexes.[17] A full quadrant of data was used in the refinement of the structure, and the enantiomorphic structure (containing (*S,S*)-Me-BPE) refined to *R* values which were more than 0.03 higher, consistent with the expected (*R,R*) absolute configuration of the phospholane moieties.

A subtle yet important structural feature which guided our subsequent ligand design was the conformation of the ethano bridge of the Me-BPE ligand complexed to Rh. In general, the 2-carbon bridge of (*R,R*)-**1a** can exist in two limiting conformations upon coordination to Rh. One backbone conformation is essentially as shown in Figure 1 (actually the ethano bridge is slightly distorted from the limiting conformation), while the two methylene groups would be transposed to opposite sides of the P–Rh–P plane in the other limiting conformation. Molecular modeling studies suggested that the backbone conformation of ligands **1** would dramatically influence the asymmetric environment around the metal. In one conformation, the phospholane methyl groups of **1a** are splayed back away from the metal center, while in the other conformation, the methyl groups of **1a** project out toward the metal coordination sites. In order to maximize stereochemical communication between the ligand and an incoming substrate, the latter conformation would appear to be desired. Unfortunately, at least in the solid state, we have accessed the wrong conformation. At worst, this conformation holds in solution and less than optimum interaction occurs between the methyl groups and the metal coordination sphere. At best, conformational mobility in solution is facile, leading to various different asymmetric environments around the metal. NMR measurements, in fact, have confirmed the dynamic nature of this ligand system. We, therefore, decided to prepare a class of ligands where conformational mobility was eliminated or at least restricted.

Bis(phospholano)benzene (DuPHOS) Ligands 2. Ligand Preparation. Using the same preparative protocol as described above for the BPE ligands, 1,2-(diphosphino)benzene was subjected to successive treatment with *n*-BuLi, followed by cyclic sulfate **4**, and then *n*-BuLi (Scheme I). Similarly, the 1,2-bis-(phospholano)benzene analogues **2** were obtained in high yield (**a**, Me-DuPHOS (R = Me); **b**, Et-DuPHOS (R = Et); **c**, Pr-DuPHOS (R = Pr); and **d**, *i*-Pr-DuPHOS (R = *i*-Pr)). Importantly, both enantiomers of the ligands were readily accessed, since both antipodes of 1,4-diol **3** and 1,4-cyclic sulfate **4** are available. The ligands Me-DuPHOS **1a** and *n*-Pr-DuPHOS **1c** are crystalline solids, while Et- and *i*-Pr-DuPHOS **1b** and **1d** are liquids or viscous oils. In the case of *i*-Pr-DuPHOS, a slight impurity was formed during the preparation, and the ligand was purified by simple short-path distillation (see the Experimental Section). The formation of a side product in this reaction is probably the result of steric encumbrance associated with the *i*-Pr groups in the starting 1,4-diol cyclic sulfate **4** and the bis-(phospholane) product **2**. All other DuPHOS ligands were obtained essentially pure as crude products.

Given that the DuPHOS ligands possess dialkyl-substituted phosphorous atoms, it is somewhat surprising that these diphosphines are relatively stable to air oxidation. No detectable (^{31}P NMR) oxidation of Et-DuPHOS occurred over 24 h in air, while the crystalline Me-DuPHOS was resistant to oxidation over a 10-day period! In solution (C_6D_6) over a 3-week period, ca. 65% conversion to the phosphine oxides of Me- and Et-DuPHOS was observed. Such air stability is useful in terms of handling ease and probably derives from the sterically hindered environment created by the phospholane moieties.

Ligand Design. From a design standpoint, the DuPHOS ligands **2** possess several unique and desirable features which we hoped would bestow advantages over the known asymmetric phosphine ligands. The most important properties embodied in these new ligands are as follows. **1. Electron-rich Phosphorus.** Ligand electronic properties are known to influence the reactivity and selectivity of transition-metal centers.[18] In particular, electronics play a large role in controlling relative rates for oxidative addition/reductive elimination reactions and in the bonding of π-ligands. The dialkyl substitution of the DuPHOS phosphorous atoms (and the trialkyl substitution of **1**) provides an electron-rich environment relative to metal complexes derived from the usual asymmetric diphosphines which posses two or three aryl substituents on phosphorus. We envisioned that complexes bearing DuPHOS may exhibit different types of reactivity and higher levels of enantioselectivity in certain reactions of interest. **2. Rigid Backbone.** Design of the DuPHOS ligands was based on the

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premise that the efficiency of chirality transfer can be enhanced by rigidity. The 1,2-phenylene backbone of **2** should reduce conformational mobility and confer added rigidity to these ligands, especially relative to the alkyl linkages of **1** and many known asymmetric diphosphine ligands. **3. Tight Binding.** The 1,2-bis(tertiary arsino)benzene and 1,2-bis(tertiary phosphino)-benzene ligand systems are known to be tightly binding chelates capable of stabilizing a wide variety of transition metals,[19] as well as lanthanide and actinide centers.[20] In transition-metal-based asymmetric catalysis, it is important to maintain the chirality, and thus the ligand, at the metal center. A tightly binding ligand should ensure this. **4. Ordered Asymmetric Environment.** The chirality of most asymmetric phosphines resides within the ligand backbone and is transferred to the metal coordination sphere through a chiral array of aryl groups on the phosphorus.[1,2] In contrast, the 1,2-phenylene unit of **2**, together with the chiral five-membered phospholane rings, provides an ordered C_2-symmetric environment which does not rely on potentially inefficient secondary transfer of chirality from the ligand backbone. **5. Variable Steric Environment.** The ability to access a series of DuPHOS ligands with various R substituents allows one to systematically vary the steric environment imposed by the phosphines without significantly varying the electronic nature of the metal center in a corresponding series of complexes. Such a situation is not possible with chiral diarylphosphines where changing the steric bulk will inevitably affect the ligand electronics. **6. Steric Optimization of Enantioselectivity.** By varying the steric nature of the DuPHOS ligands, we hoped to optimize enantioselectivities by matching the steric demand of the ligands to the steric demands of the particular substrates of interest, an approach we refer to as "steric matching". As described below, this approach has been fruitful.

X-ray Crystallography: (*S,S*)-Me-DuPHOS–Rhodium complex. The first indication that we may have solved our problem with backbone conformational mobility was provided by X-ray crystallography. The cationic complexes [(COD)Rh-(DuPHOS)]$^+X^-$ (DuPHOS = **2** and X = O_3SCF_3, PF_6, and SbF_6) were most conveniently prepared by reacting the ligand with the precursor complex $[(COD)_2Rh]^+X^-$ in THF.[21] Important information about the asymmetric environment created by the DuPHOS ligands was gleaned from the structure of the hydrogenation catalyst precursor [(COD)Rh((*S,S*)-Me-DuPHOS)]$^+SbF_6^-$. ORTEP diagrams are provided in Figure 2, and selected interatomic bond distances and angles are listed in Table III. Figure 2A shows the two phospholane moieties extending to the left and right of the COD ligand and depicts the C_2-symmetric nature of (*S,S*)-Me-DuPHOS. The Rh-P bond lengths are normal, and the P-Rh-P bond angle (85°) is similar to that observed in other bis(phosphino)benzene complexes.[19c,22] Figure 2B clearly displays the 1,2-bis(phospholane) unit as well as the relative orientation of the methyl groups on the phospholane rings. Significantly, the 1,2-phenylene unit remains essentially planar upon coordination of the phospholane moieties, and only a slight (5.95°) dihedral twist out of the P–Rh–P plane is observed. The rigidity of the 1,2-phenylene unit firmly positions the phospholane methyl groups of **2a** close to the Rh coordination sphere, thus allowing for more efficient stereochemical communication. As in the complex of **1a**, a large dihedral angle of 18° is observed between the P–Rh–P plane and the plane defined by the COD olefin midpoints and Rh. The enantiomorphic structure refined to slightly higher *R* values ((*S,S*)-enantiomorph, *R* = 0.046, R_w = 0.035; (*R,R*)-enantiomorph, *R* = 0.049, R_w = 0.039), consistent with the expected (*S,S*) configuration of the Me-DuPHOS phospholane moieties.

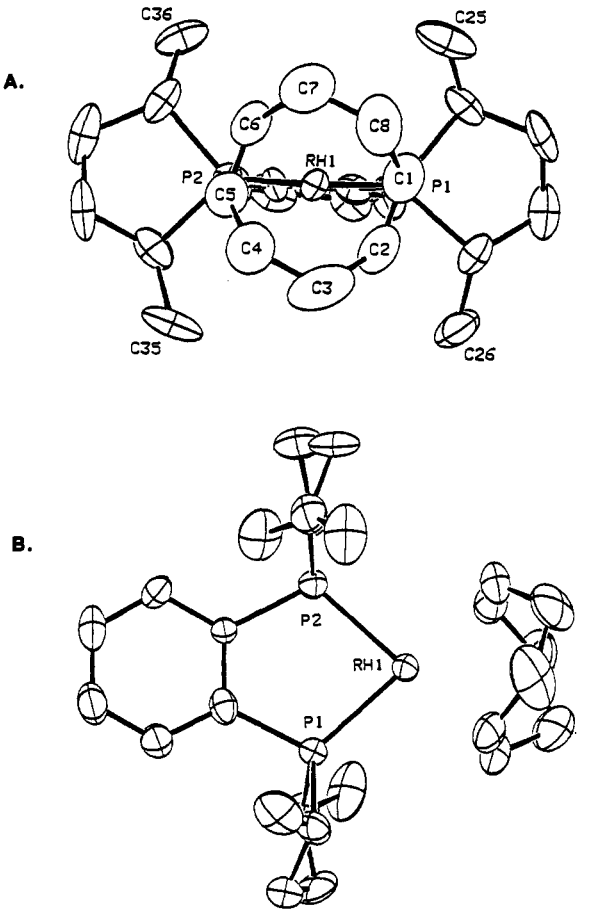


Figure 2. ORTEP drawings of catalyst precursor [(COD)Rh-((*R,R*)-Me-DuPHOS)]$^+SbF_6^-$ (Me-DuPHOS = **2a**): (A) front view, showing phospholane rings and planarity of the 1,2-phenylene moiety and (B) top view, showing 1,2-phenylene unit and orientation of the methyl groups. SbF_6^- counterion and hydrogen atoms have been omitted for clarity.

Table III. Selected Interatomic Distances and Intramolecular Angles for [(COD)Rh((*S,S*)-**2a**)]$^+SbF_6^-$

Interatomic Distances (Å)	
Rh(1)–P(1)	2.263(2)
Rh(1)–P(2)	2.273(2)
Rh(1)–C(1)	2.269(9)
Rh(1)–C(2)	2.235(8)
Rh(1)–C(5)	2.259(9)
Rh(1)–C(6)	2.214(9)
C(1)–C(2)	1.374(13)
C(5)–C(6)	1.365(12)
Intramolecular Angles (deg)	
P(1)–Rh–P(2)	84.73(7)
C(1)–Rh–C(5)	88.0(3)
C(1)–Rh–C(6)	80.3(3)
C(2)–Rh–C(5)	79.6(3)
C(2)–Rh–C(6)	93.2(3)
Rh(1)–P(1)–C(9)	111.0(3)
Rh(1)–P(2)–C(10)	109.6(2)
Intramolecular Nonbonded Distances (Å)	
C(13)–C(36)	3.444(13)
C(16)–C(26)	3.466(13)
C(5)–C(35)	3.721(14)
C(4)–C(8)	3.190(16)

Asymmetric Hydrogenations Using DuPHOS. α-Acetamidoacrylate Esters. That the added rigidity imparted by the 1,2-phenylene backbone of the DuPHOS ligands could be translated into higher selectivity was demonstrated by the rhodium-catalyzed

(19) (a) McAuliffe, C. A.; Levason, W. J. *Phosphine, Arsine, and Stibine Complexes of the Transition Elements*; Elsevier Scientific Publishing Col: Amsterdam, 1979. (b) Warren, L. F.; Bennett, M. A. *Inorg. Chem.* **1976**, *15*, 3126. (c) Liu, S.-T.; Chen, J.-T.; Peng, S.-M.; Hsiao, Y.-L.; Cheng, M.-C. *Inorg. Chem.* **1990**, *29*, 1169 and references there in.

(20) Professor Richard A. Andersen, U. C. Berkeley, personal communication.

(21) Schrock, R. R.; Osborn, J. A. *J. Am. Chem. Soc.* **1971**, *93*, 2397.

(22) (a) Appelt, A.; Ariaratnam, V.; Willis, A. C.; Wild, S. B. *Tetrahedron: Asymmetry* **1990**, *1*, 9. (b) Miedaner, A.; Haltiwanger, R. C.; DuBois, D. L. *Inorg. Chem.* **1991**, *30*, 417.

Table IV. Asymmetric Hydrogenations Using DuPHOS Ligands **2**[a]

ligand	substrate (% ee)	
	5a	**5b**
2a	99.0	98
2b	99.4	99
2c	99.8	>99
2d	95.4	87

[a] Reactions were carried out at 20–25 °C and an initial H_2 pressure of 30 psi (2 atm) with 0.25–0.35 M methanol solutions of substrate and the catalyst precursors $[(COD)Rh(P_2)]^+OTf^-$ (0.05 mol %). Reactions time allowed for complete (100%) conversion was 1 h.

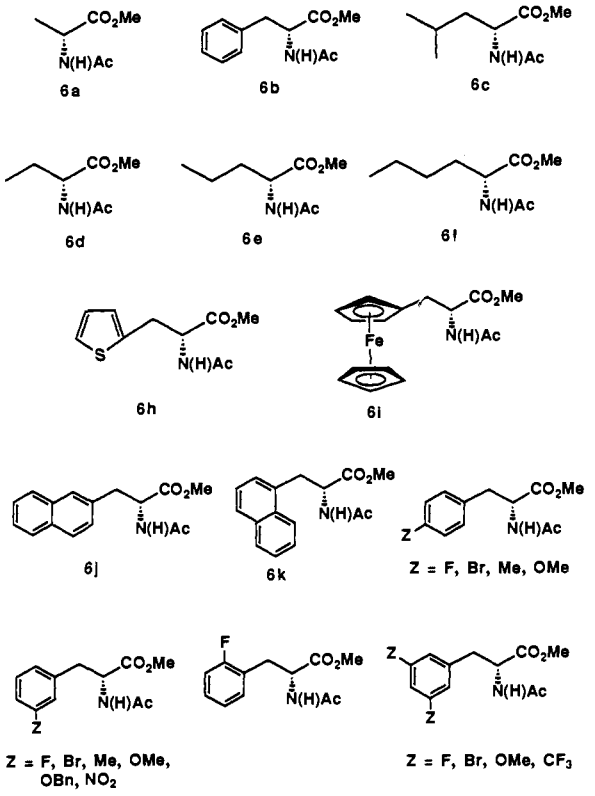


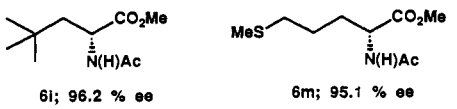
Figure 3. α-Amino acid derivatives produced in ≥99% ee using Et-DuPHOS–Rh or Pr-DuPHOS–Rh hydrogenation catalysts.

asymmetric hydrogenation of the two test substrates, α-acetamidoacrylate methyl esters **5a** (R = H and R′, R″ = Me) and **5b** (R = Ph and R′, R″ = Me).

The results of this study are shown in Table IV. As can be seen, very high enantioselectivities were achieved in these hydrogenations. The enantiomeric excesses smoothly increase and peak at the ligand Pr-DuPHOS, where selectivities approaching 100% were observed. In most cases examined thus far, Pr-DuPHOS provided slightly higher (0.2–0.6%) enantiomeric excesses relative to those of Et-DuPHOS. It appears that Pr-DuPHOS is the sterically optimum ligand for this class of substrates; the enantiomeric excesses decrease upon moving to the sterically more encumbered *i*-Pr-DuPHOS. Overall, the enantiomeric excesses we attained with the Et-DuPHOS–Rh and P-DuPHOS–Rh catalysts are generally higher than any previously reported for the hydrogenation of enamide esters.[1-4,23]

Other Enamide Substrates. The breadth of the DuPHOS–Rh catalysts is particularly noteworthy; extremely high enantioselectivities consistently were observed over a broad range of α-acetamidoacrylate substrates (Figure 3). *When either the Et-DuPHOS–Rh or Pr-DuPHOS–Rh catalyst was used, each of the listed products* **6** *was obtained directly with enantioselectivities ≥ 99% ee.* Like the high selectivities achieved in the hydrogenation of **5a** to afford (*R*)-*N*-acetylalanine methyl ester (**6a**; 99.8% ee with (*R,R*)-Pr-DuPHOS–Rh), the alkyl-substituted derivatives **6c–f** were obtained in 99.4% ee, 99.6% ee, 99.7% ee, and 99.6%% ee, respectively. A wide array of ring-substituted phenylalanine derivatives also were formed with high enantioselectivity regardless of the substituent or substitution pattern. Other aromatic amino acid derivatives such as 2-naphthylalanine **6j** and 1-naphthylalanine **6k** as well as 2-thienylalanine derivatives **6h** were each produced with similarly high enantiomeric excess. Particularly interesting is the redox-active ferrocenylalanine derivative **6i**.

Even notoriously difficult substrates were hydrogenated with high enantioselectivity when using the Pr-DuPHOS–Rh catalyst. The sterically encumbered *tert*-butyl-substituted enamide **5l** (R = *t*-Bu) was hydrogenated smoothly to yield **6l** in 96.2% ee. Hydrogenation of the methylthio-containing **5m** (R = $(CH_2)_2$-SMe) to the homomethionine derivative **6m** demonstrated that the catalyst can tolerate sulfur substituents. While the rate was diminished with this substrate (48 h at substrate-to-catalyst (S/C) ratio of 1000), the selectivity was again high at 95.1% ee.



Hydrogenation of the corresponding α-acetamidoacrylic acids **5a–c** (R″ = H) with the Et-DuPHOS–Rh catalyst proceeded smoothly and with virtually identical enantiomeric excesses to those obtained with the esters. The presence of added base such as NEt_3 had no noticeable influence on the rate or the selectivity in the hydrogenation of acids. Likewise, changing the enamide *N*-acetyl group to *N*-benzoyl (**5**, R′ = Ph and R″ = Me or H)) had no apparent effect on the selectivity.

***N*-Cbz-Protected Enamides.** The *N*-acyl group of enamides **5** has been shown to act as a ligand and allow chelation of the substrate to the cationic rhodium center in analogous hydrogenation systems.[1,24,25] In general, asymmetric hydrogenation of enamides has been restricted to the study of *N*-acetyl- or *N*-benzoyl-protected substrates. One drawback of the use of these substrates as amino acid precursors is that removal of the *N*-acyl group generally requires rather harsh acidic hydrolysis conditions. In certain cases, significant racemization has been shown to occur during the hydrolysis step.[26] Therefore, the enantioselective hydrogenation of enamides possessing more easily removed protecting groups would be desirable.[27]

(23) (a) Nagel, U.; Kinzel, E.; Andrade, J.; Prescher, G. *Chem. Ber.* **1986**, *119*, 3326. (b) Miyashita, A.; Takaya, H.; Souchi, T.; Noyori, R. *Tetrahedron* **1984**, *40*, 1245. (c) Selke, R.; Pracejus, H. *J. Mol. Cat.* **1986**, *37*, 213. (d) Riley, D. P.; Shumate, R. E. *J. Org. Chem.* **1980**, *45*, 5187. (e) Takahashi, H.; Achiwa, K. *Chem. Lett.* **1989**, 305. (f) Inoguchi, K.; Achiwa, K. *Chem. Pharm. Bull.* **1990**, *38*, 818.

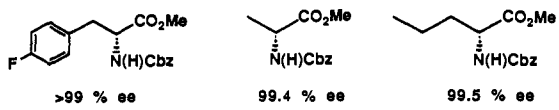
(24) (a) Halpern, J. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1985; Vol. 5, Chapter 2. (b) Landis, C. R.; Halpern, J. *J. Am. Chem. Soc.* **1987**, *109*, 1746. (c) Ojima, I.; Kogure, T.; Yoda, N. *J. Org. Chem.* **1980**, *45*, 4728. (d) Nagel, U.; Rieger, B. *Organometallics* **1989**, *8*, 1534.

(25) (a) Brown, J. M.; Chaloner, P. A. *J. Chem. Soc., Chem. Commun.* **1980**, 344. (b) Brown, J. M.; Murrer, B. A. *J. Chem. Soc., Perkin Trans. II* **1982**, 489. (c) Chan, A. S. C.; Pluth, J. J.; Halpern, J. *J. Am. Chem. Soc.* **1980**, *102*, 5952.

(26) (a) Krause, H.-W.; Kreuzfeld, H. J.; Dobler, C.; Taudien, S. *Tetrahedron: Asymmetry* **1992**, *3*, 555. (b) Taudien, S.; Schinkowski, K.; Krause, H.-W. *Tetrahedron: Asymmetry* **1993**, *4*, 73. (c) See, also: Kovacs, J. In *The Peptides: Analysis, Synthesis, and Biology*; Gross, E.; Meienhofer, J., Eds.; Academic Press, New York, 1980; Vol. 2, pp 486.

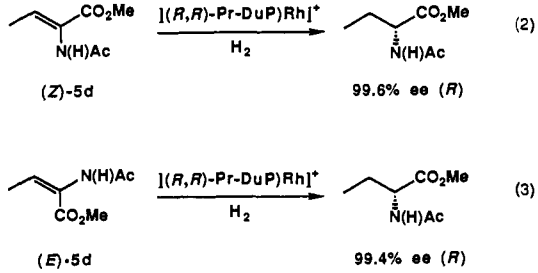
(27) Relatively few examples of asymmetric hydrogenation reactions involving *N*-carbobenzyloxy-, *N*-*tert*-butyloxycarbonyl-, or *N*-carbomethoxy-protected enamides have been reported. See: (a) Schmidt, U.; Weller, D.; Holder, A.; Lieberknecht, A. *Tetrahedron Lett.* **1988**, *29*, 3227. (b) Melillo, D.; Larsen, R. D.; Mathre, D. J.; Shukis, W. F.; Wood, A. W.; Colleluori, J. R. *J. Org. Chem.* **1987**, *52*, 5143. (c) Schmidt, U.; Liebernecht, A.; Kazmaier, U.; Griesser, H.; Jung, G.; Metzger, J. *Synthesis* **1991**, 49. (d) Schmidt, U.; Meyer, R.; Leitenberger, V.; Stabler, F.; Lieberknecht, A. *Synthesis* **1991**, 409.

We have found that (*Z*)-*N*-Cbz-protected (Cbz = carbobenzyloxy; **5**, R′ = OBn) enamide esters[28] could be hydrogenated directly to the *N*-Cbz amino acid esters with similarly high enantiomeric excess. For example, hydrogenation using the (*R*,*R*)-Pr-DuPHOS–Rh catalyst produced the Cbz-protected (*R*)-*p*-fluorophenylalanine, (*R*)-alanine, and (*R*)-2-aminopentanoate derivatives in >99% ee, 99.4% ee, and 99.5% ee, respectively. The advantage of using the *N*-Cbz protecting group is the mild conditions required for removal (Pd/C, H_2).



(*E*)- and (*Z*)-Enamides. The geometry of the enamide substrate **5** has been shown to dramatically influence the rate and the selectivity of hydrogenation with known catalysts.[29] In cases where (*Z*)-enamides are hydrogenated with relatively high enantioselectivity, the corresponding (*E*)-enamides often are reduced with much lower selectivity. In some instances, opposite enantiomers are obtained upon hydrogenation of geometric (*Z*)- and (*E*)-enamides with the same catalyst.[23b] Since many desirable enamides are unavoidably synthesized as a mixture of (*Z*)- and (*E*)-isomers, a separation step generally is required prior to hydrogenation.

Significantly, we have found that with the DuPHOS–Rh catalysts, both (*Z*)- and (*E*)-isomeric enamides may be hydrogenated in high enantiomeric excess to products with the same absolute configuration. For example, hydrogenation of methyl (*Z*)-α-acetamidobutenoate (R = Me, (*Z*)-**5d**) with (*R*,*R*)-Pr-DuPHOS–Rh afforded methyl (*R*)-2-acetamidobutyrate ((*R*)-**6d**) in 99.6% ee (eq 2). Hydrogenation of (*E*)-**5d** with the same catalyst likewise afforded (*R*)-**6d** in 99.4% ee (eq 3). Qualitatively, the rates for the hydrogenation of both (*E*)- and (*Z*)-enamides appear comparable.



In these hydrogenations, no separation of (*E*)- and (*Z*)-isomers is necessary. To demonstrate this, a crude 3:1 mixture of the analogous enamides (*Z*)- and (*E*)-**5f** was reduced with (*R*,*R*)-Pr-DuPHOS–Rh to the 2-aminohexanoic acid derivative (*R*)-**6f** in 99.5% ee. Similarly high enantiomeric excesses were achieved with both (*E*)- and (*Z*)-isomers of most alkyl-substituted enamides examined as well as the ferrocenyl enamide **5i**. These results are particularly important for enamides, such as alkyl-substituted substrates, which are difficult to prepare in isomerically pure form. Eliminating the need to separate isomeric enamides provides a practical route to this class of amino acid derivatives.

We found that in the hydrogenation of *N*-Cbz enamides, slightly lower selectivities were achieved with (*E*)-*N*-Cbz enamides relative to the (*Z*)-isomers. For example, while methyl (*Z*)-α-(carbobenzyloxyamino)-2-pentenoate was hydrogenated in 99.5% ee

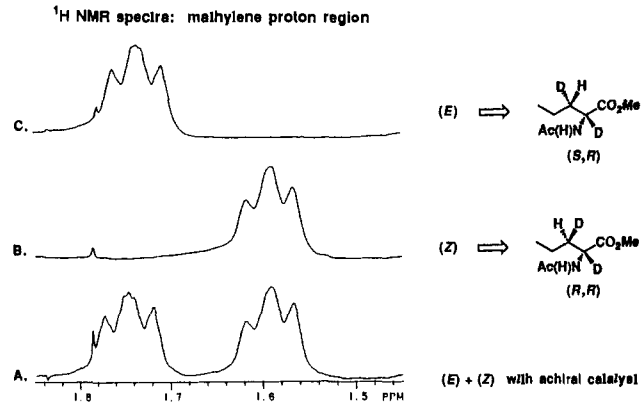
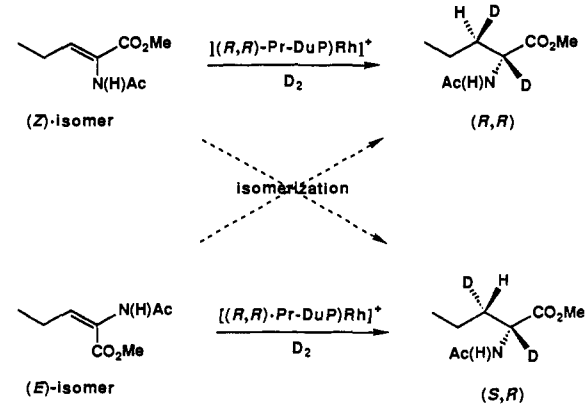


Figure 4. ^1H NMR spectra of the deuteriation products showing diastereotopic β-methylene protons: (A) two signals due to the diastereotopic protons associated with *R*,*R* and *S*,*R* products **6e**-d_2; products formed by deuteriation of a 1:1 mixture of enamides (*E*)-**5e** and (*Z*)-**5e** with achiral catalyst; (B) signal due to deuteriation of (*Z*)-**5e** with (*R*,*R*)-Pr-DuPHOS–Rh catalyst; and (C) signal due to deuteriation of (*E*)-**5e** with (*R*,*R*)-Pr-DuPHOS–Rh catalyst.

Scheme II



using the Pr-DuPHOS–Rh catalyst (*vide supra*), the corresponding (*E*)-enamide was reduced in only 92% ee. Given that *N*-Cbz enamides generally can be prepared enriched in (*Z*)-isomer (*Z*:*E* ≥ 90:10),[28] hydrogenation of crude *Z*/*E* mixtures will still afford products of very high enantiomeric excess (98–99+% ee).

One possible explanation for our ability to hydrogenate both (*E*)- and (*Z*)-enamides with high enantioselectivity could be that isomerization of the (*E*)-isomer to the (*Z*)-enamide is occurring prior to hydrogenation. Isomerization activity can be readily monitored by performing deuteration experiments. Assuming stereospecific *cis* transition-metal-catalyzed addition of D_2 to the enamide carbon–carbon double bond,[30] deuteration of (*E*)- and (*Z*)-enamides will produce diastereomeric products (Scheme II).[31] Any degree of isomerization will lead to a mixture of diastereomers. In the case of complete isomerization from *E* to *Z*, for example, the same diastereomer will be formed from either enamide. Knowledge of the absolute configuration of the products allows us to predict which diastereomers to expect from a particular catalyst. In the absence of isomerization, deuteration of (*Z*)-**5e** with the (*R*,*R*)-Pr-DuPHOS–Rh catalyst should afford the *R*,*R* product, while (*E*)-**5e** should yield the *S*,*R* product **6e**-d_2.

The results of these experiments are shown in Figure 4. The bottom trace shows that the diastereotopic β-methylene protons

(28) (a) Schmidt, U.; Griesser, H.; Leitenberger, V.; Lieberknecht, A.; Mangold, R.; Meyer, R.; Riedl, B. *Synthesis* **1992**, 487. (b) Berti, F.; Ebert, C.; Gardossi, L. *Tetrahedron Lett.* **1992**, *33*, 8145. (c) Bigge, C. F.; Wu, J.-P.; Drummond, J. T. *Bioorg. Med. Chem. Lett.* **1992**, *2*, 207. (d) Schmidt, U.; Lieberknecht, A.; Wild, J. *Synthesis* **1988**, 159.

(29) (a) Scott, J. W.; Kieth, D. D.; Nix, G., Jr.; Parrish, D. R.; Remington, S.; Roth, G. P.; Townsend, J. M.; Valentine, D., Jr.; Yang, R. *J. Org. Chem.* **1981**, *46*, 5086. (b) Vineyard, B. D.; Knowles, W. S.; Sabacky, M. J.; Bachman, G. L.; Weinkauff, D. J. *J. Am. Chem. Soc.* **1977**, *99*, 5946.

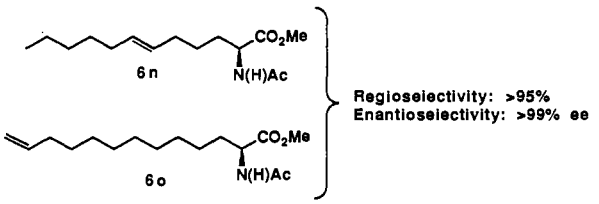
(30) Stereospecific *cis* addition of H_2 (D_2) to olefins by rhodium catalysts is well documented; see, for example: (a) Thompson, H. W.; McPherson, E. *J. Am. Chem. Soc.* **1974**, *96*, 6232. (b) Hussey, A. S.; Takeuchi, Y. *J. Org. Chem.* **1970**, *35*, 643. (c) Kirby, G. W.; Michael, J. *J. Chem. Soc., Chem. Commun.* **1971**, 415. (d) Kirby, G. W.; Michael, J. *J. Chem. Soc., Perkin Trans. 1* **1973**, 115.

(31) (a) Detellier, C.; Gelbard, G.; Kagan, H. B. *J. Am. Chem. Soc.* **1978**, *100*, 7556. (b) Koenig, K. E.; Knowles, W. S. *J. Am. Chem. Soc.* **1978**, *100*, 7561.

are readily distinguished in the ^1H NMR spectrum of the deuterated products **6e**-d_2. Deuteration of (*Z*)-**5e** produced only one diastereomer ((*R*,*R*)-**6e**-d_2). Likewise, deuteration of (*E*)-**5e** afforded only a single diastereomer ((*S*,*R*)-**6e**-d_2). Furthermore, deuterium was only detected in the α- and β-carbons of the reduction product **6**-d_2. The conclusion that can be drawn is that significant isomerization is not occurring and is not responsible for the high enantiomeric exceses we observed with the (*E*)-enamides.

The mechanistic origin of our success with both isomeric enamides is unclear; an explanation requires further kinetic studies with both (*E*)- and (*Z*)-enamides.[32] Likewise, an understanding of the lower selectivity achieved in the hydrogenation of (*E*)-*N*-Cbz enamides relative to that of the (*Z*)-isomers requires more detailed analyses. If only the α-carbon of enamides **5** is considered, the same face of the substrate is preferentially hydrogenated by a particular DuPHOS–Rh catalyst, regardless of the olefin geometry at the β-carbon. These results suggested that disubstitution at the β-carbon (tetrasubstituted enamides) might be tolerated by the DuPHOS–Rh catalysts. Unfortunately, we found that hydrogenation of *N*-acetyldehydrovaline methyl ester with Me- or Pr-DuPHOS–Rh proceeded at relatively low rates (2 d at S/C of 1000) and provided the product *N*-acetylvaline methyl ester with low selectivity (24% ee *R* with (*R*,*R*)-Pr-DuPHOS).

Regioselectivity. The ability of enamides **5** to act as chelating substrates has been shown to be critical for the attainment of high enantioselectivities in rhodium-catalyzed hydrogenation reactions.[1-4,24,25] High selectivities apparently result from the reduced number of degrees of freedom or approach geometries available to the substrate. In addition to higher enantioselectivities, higher hydrogenation rates have been observed for chelating olefins relative to nonchelating olefinic groups due to the larger binding constants associated with the former.[33] Therefore, high regioselectivity in the hydrogenation of polyfunctional enamides should be possible since the chelating enamide group should be hydrogenated at much higher rates. This has been borne out using the (*R*,*R*)-Pr-DuPHOS–Rh catalyst for the preparation of the 12- and 13-carbon α-amino acid derivatives **6n** and **6o**.



In both cases, hydrogenation of the corresponding enamido olefins proceeded quantitatively (10–15-min reaction time at S/C 1000) and with essentially complete regioselectivity in favor of enamide reduction to afford the products in >99% ee. In addition, the Rh–DuPHOS catalysts are tolerant of other reduction-prone functionalities such as ketones, aldehydes, nitro groups, aryl and alkyl halides, and internal alkynes. The high degree of regio- and chemoselectivity exhibited by Rh–DuPHOS suggests that these catalysts may be well-suited for applications in the synthesis of complex organic molecules.

Rhodium Catalysts. The cationic rhodium complexes [(diene)-Rh(DuPHOS)]$^+X^-$ (diene = 1,5-cyclooctadiene or norbornadiene and X = OTf, PF_6, and SbF_6) were found to be the most efficient catalyst precursors for the reduction of α-acetamidoacrylates **5**. The iridium analogs, in contrast, were found to be essentially inactive for these substrates. At S/C ratios of 1000 (i.e., 0.1 mol % Et-DuPHOS–Rh catalyst), the reactions generally were complete in less than 1 h at 20 °C and 30 psi H_2. For larger scale hydrogenations (>10 g), S/C ratios of 10 000 were routinely used with complete reduction often taking place within 20 h and with no loss of enantioselectivity relative to lower S/C ratios.[32] Using deoxygenated methanol (distilled from $Mg(OMe)_2$ under nitrogen) and recrystallized substrate **5a**, S/C ratios of 50 440 were demonstrated with the Et-DuPHOS–Rh catalyst. In this case, complete reduction took place within 12 h. These catalysts are very robust and withstand a variety of solvents and functional groups (*vide infra*). Importantly, the solid catalysts were found to be unaffected by air. For example, no loss of activity or enantioselectivity was observed when the Et-DuPHOS–Rh catalyst was exposed to air for 24 h. This finding has practical significance since the catalyst can be weighed and handled in the atmosphere, although long-term storage under nitrogen or argon is recommended.

Reaction Parameters. We examined the effect of changing various reaction parameters in the hydrogenation of methyl α-acetamidoacrylate (**5a**) to the alanine derivative **6a**. In contrast to many known asymmetric hydrogenation catalysts,[23,24] the selectivities obtained with the DuPHOS–Rh catalysts were relatively unaffected by changes in hydrogen pressure or temperature. At 20 °C and using the Et-DuPHOS–Rh catalyst, virtually no change in the product enantiomeric excess (99.4% ee) was observed over the pressure range of 15–100 psi H_2. At higher pressures, a slight decrease in selectivity was noted; 98.3% ee at 750 psi (50 atm). At constant pressure (30 psi), the selectivities increased only slightly from 98.9% ee to 99.6% ee upon lowering the temperature from 65 to 0 °C. At constant pressure (30 psi) and temperature (20 °C), essentially identical enantiomeric excesses were observed in solvents such as MeOH, EtOH, *i*-PrOH, THF, CH_2Cl_2, and EtOAc. The presence of small amounts (up to 5%) of H_2O in the solvents did not influence the selectivity of the catalyst. Little effect was observed upon changing the complex counterion from OTf^- to SbF_6^-, PF_6^-, or BF_4^-. The triflate (OTf^-) counterion generally was preferred due to enhanced solubility of the complex. Unlike some catalysts which require high dilution for high selectivity,[23b] we have observed no apparent diminution in the selectivity of the DuPHOS–Rh catalysts at concentrations as high as 1.5 M.

***in Situ* Catalysts.** Catalysts generated *in situ* by the addition of DuPHOS (1.05 equiv) to $[(COD)_2Rh]^+OTf^-$ in methanol were found to hydrogenate **5** with high but slightly decreased enantioselectivities relative to those of the isolated catalyst. For example, the *in situ* Et-DuPHOS–Rh catalyst hydrogenated **5a** and **5d** with 99.0% and 99.1% ee, respectively (versus 99.4% ee and 99.5% ee with an isolated catalyst). In general, 0.3–0.6% ee drop was observed for *in situ* generated catalysts. The reason for the slightly decreased values in these reactions is unclear. The presence of a small quantity of achiral catalyst (i.e., derived from $[(COD)_2Rh]^+$) or a different catalytically active species which hydrogenates with lower selectivity are possible explanations.

Absolute Configuration. The absolute configurations of the hydrogenation products **6** were very predictable.[34] In all cases examined to date, (*R*,*R*)-catalysts **2a–c** provided the *R* hydrogenation product, while (*R*,*R*)-**2d** yielded the *S* product. As expected, the catalysts of opposite absolute configuration (i.e., ((*S*,*S*)-**2a**, etc.) afforded products of opposite absolute configuration and with identical enantiomeric excess. The same relationship holds for the ethano-bridged ligands **1**. While the results with **2d** appear inconsistent, amino acid derivatives **6** of *R* absolute configuration actually derive from catalysts having the same sense of chirality. That is, within the homochiral series of ligands **1** and **2**, upon moving from the Me-, Et-, and Pr-

(32) Rates are qualitative and reflect the time allowed for complete reduction; more quantitative mechanistic analyses, including detailed kinetic studies of these reactions, are planned in collaboration with Professor J. M. Brown of Oxford University.

(33) Landis, C. R.; Halpern, J. *J. Organomet. Chem.* **1983**, *250*, 485 and references therein.

(34) Product absolute configurations were determined by comparison with optical rotations for known compounds reported in the literature. A full listing of optical rotations, as well as spectroscopic and analytical data, for all the products 6 are given in the Experimental Section.

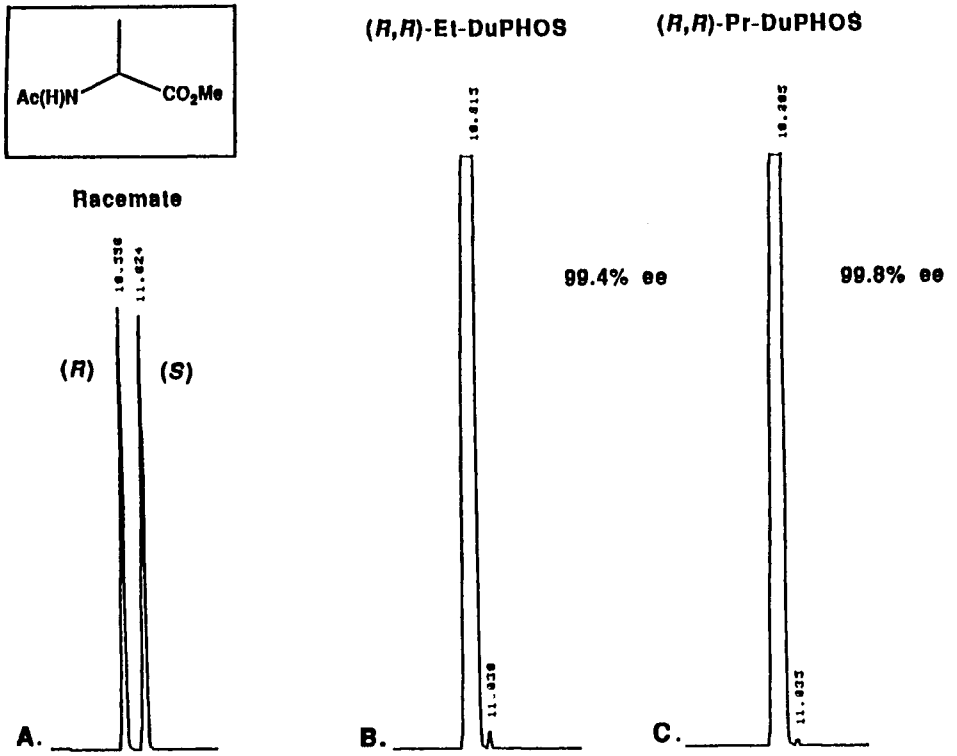


Figure 5. Gas chromatograms showing the separation of *N*-acetylalanine methyl ester (**6a**) using a 50-m chiral capillary column XE-60-S-Val at 140 °C: (A) racemic **6a**; (B) crude product from (*R,R*)-Et-DuPHOS–Rh hydrogenation, 99.4% ee; and (C) crude product from (*R,R*)-Pr-DuPHOS–Rh hydrogenation, 99.8% ee.

substituted ligands (**2a–c**) to the *i*-Pr-substituted analog (**2d**), the Cahn–Ingold–Prelog designation[35] changes from *R* to *S* (or visa versa).

Enantiomeric Excess Determination. The achievement of very high enantiomeric excesses is desirable but carries with it an important and easily overlooked problem: *the accurate and precise determination of enantiomeric excess.* This is an old analytical challenge that simply amounts to detecting and reproducibly integrating a very small quantity of a minor reaction product. In the very high enantiomeric excess range, however, as little as 0.1% of the minor product may be present. We have found that in this range, the current method of choice, when applicable, is chiral capillary GC.[36] The success of this method relies on the large separation factor α and the sharpness of peaks observed for a large number of racemic compounds. These two properties allow one to greatly expand the major enantiomer peak in order to detect and precisely integrate as little as 0.1% of the minor enantiomer (99.8% ee). This stands in contrast to chiral HPLC where the peaks are often relatively broad, making it difficult to observe and integrate the minor enantiomer when present in less than 0.5% (>99% ee). The one disadvantage of GC methods, however, is the requirement of relatively high product volatility; many chiral GC columns have upper temperature limits of 180–200 °C.

The chiral capillary GC column XE-60-S-Val[37] has found extensive application in our studies for the analysis of volatile *N*-acetylamino acid esters **6**. As an example, analysis of *N*-acetylalanine methyl ester (**6a**) is shown in Figure 5. For all products **6**, racemic material was produced by hydrogenation of the enamide substrates with an achiral catalyst. As illustrated in chromatogram A of Figure 5, clean base-line separation of racemic **6a** was achieved at 140 °C. The peak at 10.55 min corresponds to the (*R*)-enantiomer of **6a**, while (*S*)-**6a** eluted in 11.02 min under these conditions. The middle trace (B) corresponds to the crude product formed in the (*R,R*)-Et-DuPHOS–Rh catalyzed hydrogenation, where 0.3% of the minor (*S*)-enantiomer (99.4% ee) is readily visualized and quantified. The crude product from the (*R,R*)-Pr-DuPHOS–Rh hydrogenation (chromatogram C) contained only 0.1% of the minor (*S*)-enantiomer of **6a** (99.8% ee). Although the detection limit is being approached in this case, reproducible integration was achieved. In our experience with chiral capillary GC, we have found the precision of integral values to be very high (error = ±0.1%). All higher molecular weight aryl-containing *N*-acetylamino acid esters **6** were successfully analyzed using Daicel's chiral HPLC columns Chiralcel OJ or Chiralcel OB.[38]

Origin of High Enantioselectivities. The mechanistic details of enantioselective enamide hydrogenation reactions have been delineated for several catalyst systems.[24,25] Thus, far, mechanistic studies have focused on successful rhodium catalysts containing C_2-symmetric chelating diphosphines which possess at least two aryl substituents on each phosphorous atom. The origin of enantioselection in these reactions has been intimately linked to the chiral array of *P*-aryl substituents surrounding the metal. However, our understanding of the precise factors required for the attainment of high enantioselection with predictable absolute stereocontrol remains limited. Furthermore, the critical factors often seem to depend on the reaction at hand.

The new class of asymmetric diphosphine ligands **2** has displayed the highest enantioselectivities yet reported for the hydrogenation of a variety of substrates,[8,9] including the wide range of α-(*N*-acylamino)acrylates described herein. It is assumed that the rhodium-catalyzed hydrogenations described here follow the same mechanistic course outline previously by Halpern, Brown, and others for known asymmetric diphosphine–rhodium catalysts.[24,25] Our preliminary mechanistic work[39] indicates that the DuPHOS–Rh catalysts do indeed behave in an analogous fashion.

(35) See: March, J. *Advanced Organic Chemistry* 4th ed.; John Wiley and Sons, Inc.: New York, 1992; pp 109–111 and references therein.

(36) (a) Konig, W. A. *The Practice of Enantiomer Separation by Capillary Gas Chromatography*; Huthig Press: Heidelberg, 1987. (b) Schurig, V.; Nowotny, H.-P. *Angew Chem., Int. Ed. Engl.* **1990**, *29*, 939 and references therein.

(37) Distributed by Chrompack, Inc., 1130 Route 202 South, Raritan, NJ 08869.

(38) Distributed by Chiral Technologies, Inc., 730 Springdale Drive, Drawer I, Exton, PA 19341.

(39) Armstrong, S. K.; Brown, J. M.; Burk, M. J. *Tetrahedron Lett.* **1993**, 879.

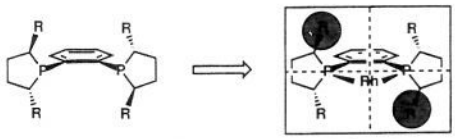


Figure 6. (*R,R*)-DuPHOS blocking the top left and bottom right quadrants.

That is, the minor diastereomeric enamide–Rh(DuPHOS) complex reacts with hydrogen more rapidly than the major diastereomer and leads to the predominant product enantiomer.[32] In terms of further applications of the DuPHOS ligands, as well as future ligand design, an important question that remains to be answered is the following: Which properties of DuPHOS are responsible for the very high levels of enantioselection imparted by these ligands in hydrogenation reactions? Although largely conjecture, valuable insight might be gained by attempting to answer this question.

In searching for an explanation, a good place to begin is the section above entitled Ligand Design. First, the dialkylphosphine moieties of DuPHOS should provide a relative electron-rich Rh center. In olefin hydrogenations, complexation of substrate to the metal is known to be a crucial step in the catalysis.[40] In general, an important component of this bonding is the transfer of electron density from the metal d-orbitals to the π^*-orbital of the olefin (π-back-bonding). Therefore, stronger binding of π-substrates is often associated with electron-rich metals. More tightly bound π-substrates should lead to shorter M–substrate bond distances and thus greater stereochemical communication between the asymmetric ligand and the substrate.

The enantioselectivity achieved with several known asymmetric diphosphine–rhodium catalysts has been explained through the use of a simple heuristic device, quadrant diagrams.[2] Like all other chiral C_2-symmetric diphosphine ligands, DuPHOS effectively blocks two diagonal quadrants (Figure 6). The absolute configuration of the ligand determines which two quadrants are blocked and consequently the absolute configuration of the reaction product.

Unlike most known asymmetric diphosphines, however, DuPHOS does not rely on potentially inefficient secondary transfer of backbone chirality to the metal through a chiral array of *P*-aryl substituents. Rather, the *trans*-2,5-disubstituted phospholane moieties of **2** provide an asymmetric environment which directly interacts with the metal coordination sphere. Only P-chiral diphosphines such as DIPAMP[2] are similar in this aspect. The DuPHOS ligands, therefore, may be expected to more effectively block the same two quadrants relative to other known diphosphines. Furthermore, as outlines below, the extent to which the quadrants are blocked can be varied.

The expected[19] tightly binding nature of the DuPHOS ligands should secure the asymmetric environment around the metal. Such tight binding likely derives from entropic factors associated with the rigid 1,2-phenylene backbone. Dissociation of one arm of a typical alkyl-bridged diphosphine may be accompanied by rotation about the backbone C–C bond(s) and complete loss of that phosphine moiety (entropy can overcome binding energy). The 1,2-phenylene unit precludes this scenario for ligand dissociation. Furthermore, the DuPHOS ligands experience restricted conformational mobility due to the rigid 1,2-phenylene backbone. Consequently, any asymmetric environment presented to a substrate at a given time should closely resemble the time-averaged asymmetric environment.

Another unique and important feature leading to the success of DuPHOS is the ability to readily vary the steric environment imposed by these ligands. Flexibility allows a ligand to adjust its own steric requirements to accommodate various different substrates (substrate generality). Unfortunately, ligand flexibility also is often accompanied by low levels of enantioselectivity. With the DuPHOS ligands, we attempted to replace ligand flexibility with steric variability in order to achieve substrate generality. Such steric variability allows one to match the sterics of the asymmetric environment to the steric requirements of the class of substrates of interest. Furthermore, in asymmetric catalysis, one encounters a fine balancing act. One one hand, a sterically large asymmetric environment around the metal is desired to ensure sufficient interaction with the substrate. On the other hand, a sterically encumbered environment can impede tight binding of a substrate (leading to low enantiomeric excesses) or even shut down catalysis completely. The DuPHOS ligands allow one to fine tune the critical steric environment, thus providing a significant advantage over most known asymmetric ligands.

Summary. We have developed a versatile synthetic protocol for the preparation of a new class of asymmetric diphosphine ligands based on the *trans*-2,5-dialkylphospholane moiety. This procedure utilizes the efficiency of asymmetric catalysis (Ru–BINAP-catalyzed hydrogenation of β-keto esters) to produce new chiral ligands for asymmetric catalytic applications. Initial studies focused on the preparation and use of a series of 1,2-bis(phospholano)ethane ligands **1**. The use of **1** in rhodium-catalyzed enamide hydrogenations afforded high but insufficient enantioselection. X-ray crystallographic analysis of the catalyst precursor $[(COD)Rh((R,R)\text{-Me-BPE})]^+SbF_6^-$, coupled with molecular modeling studies, suggested that flexibility of the ethano bridge of **1** may be a selectivity-limiting feature.

Efforts to reduce conformational mobility of the BPE ligands led us to prepare the series of 1,2-bis(phospholano)benzene ligands **2**. This study culminated in the attainment of very high enantioselectivities in the hydrogenation of enamides **5**. The cationic Et-DuPHOS–Rh and Pr-DuPHOS–Rh catalysts proved to be particularly well-suited for this class of substrates; a wide range of unnatural and nonproteinaceous α-amino acid derivatives were obtained in ≥99% ee. Both (*E*)- and (*Z*)-isomers of alkyl-substituted enamides were reduced with high enantioselectivity. Chelation of the enamide moiety has been utilized in highly regioselective and enantioselective reductions which leave isolated C=C double bonds intact.

Given the substrate generality, catalytic efficiency, functional group and solvent tolerance, and high enantioselectivities achieved in the DuPHOS–Rh–enamide hydrogenations, commerical applications appear imminent. Studies aimed at unveiling the full potential of the DuPHOS ligands continue.

Experimental Section

General Procedures. All reactions and manipulations were performed in a nitrogen-filled continuous purge Vacuum Atmospheres Dri-Lab glovebox or using standard Schlenk-type techniques. Benzene, toluene, diethyl ether (Et_2O), tetrahydrofuran (THF), glyme, hexane, and pentane were distilled from sodium benzophenone ketyl under nitrogen. Acetonitrile (CH_3CN) and methylene chloride (CH_2Cl_2) were distilled from CaH_2. Methanol (MeOH) was distilled from $Mg(OMe)_2$. Hydrogenation reactions were performed with undistilled reagent grade (Baker) methanol which was deoxygenated by sparging with nitrogen for 30 min. The phosphines 1,2-bis(phosphino)ethane and 1,2-bis(phosphino)benzene were purchased from Quantum Design, Inc. (Austin, TX) and used as received. Hydrogen (99.9995%) and deuterium (99.5% minimum) gas were purchased from Matheson and used as received. *n*-Butyllithium (1.6 M in hexanes) was purchased from Foote Chemical Co. All α-(acylamino)acrylate substrates **5** were prepared either by standard Erlenmeyer procedures[28d] or by the method of Schmidt et al.[28a]

Melting points were determined using a Mel-Temp apparatus in capillaries sealed under nitrogen and are uncorrected. GC analyses were performed using a Hewlett-Packard Model HP 5890 GC. HPLC analyses were performed using a Hewlett-Packard Model HP 1090 LC interfaced to a HP 9000 Series 300 computer workstation. Optical rotations were obtained using a Perkin-Elmer Model 241 MC polarimeter. NMR spectra were referenced relative to residual protio-solvent (i.e., $CHCl_3$) peaks and were obtained on Nicolet NT-360 wide-bore (360-MHz ^1H and 146-MHz ^{31}P NMR), Nicolet NMC-300 wide-bore (300-MHz ^1H, 120.5-MHz ^{31}P, and 75.5-MHz ^{13}C NMR), and GE QM-300 narrow-bore

(40) Collman, J. P.; Hegedus, L. S.; Norton, J. R.; Finke, R. G. *Principles and Applications of Organotransition Metal Chemistry*; University Science Books: Mill Valley, 1987; Chapter 10.

(300-MHz ^{1}H NMR) spectrometers. ^{13}C and ^{31}P NMR chemical shifts are positive downfield (and negative upfield) from external Me_4Si and 85% H_3PO_4, respectively. IR spectra were recorded on a Nicolet 5DXB FT-IR spectrometer. Elemental analyses were performed by Schwarzkopf Microanalytical Laboratory, Inc., Woodside, NY, or Pascher Mikroanalytisches Labor, Remagen-Bandorf, FRG.

1,4-Diols 3. The preparation of diols **3a**, **3b**, and **3d** has previously been described.[6] The general three-step procedure is outline below for the new diol **3c**.

Ethyl (3*S*)-3-Hydroxyhexanoate. To a 1-L Hasteloy steel autoclave vessel were added ethyl butyrylacetate (100 g, 0.63 mol), a MeOH/CH_2Cl_2 (100 mL/100 mL) solvent mixture, and the catalyst precursor $[Ru_2((S)\text{-BINAP})_2]Cl_4(NEt_3)$[41] (0.75 g). The reaction was shaken under constant H_2 pressure (1500 psi) for 48 h at 25 °C. Complete conversion to ethyl β-hydroxyhexanoate was indicated by TLC and ^{1}H NMR. Distillation (bp 112–115 °C, ca. 10 Torr) provided the product ethyl (3*S*)-3-hydroxyhexanoate (94.1 g, 94%). Consistent with the results of Noyori, Takaya et al.,[42] the product was determined to be >98% enantiomerically pure (Mosher ester prepared from (*S*)-MPTA-Cl; HPLC: Chiralcel OJ, 40 °C, 0.5 mL/min, 95/5 hexane/EtOAc; (*R*)-alcohol t_1 = 10.48 min, (*S*)-alcohol t_2 = 12.08 min): $[\alpha]^{25}_D$ = +24.4 ± 0.5° (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.95 (t, J_{HH} = 7.2 Hz, 3H, CH_3), 1.25 (t, J_{HH} = 7.3 Hz, 3H, CH_3), 1.20–1.60 (m, 4H, CH_2), 2.45 (m, 2H, diastereotopic CH_2), 2.95 (br, 1H, OH), 4.00 (m, 1H, CH), 4.20 (q, J_{HH} = 7.3 Hz, 2H, CH_2).

(3*S*)-3-Hydroxyhexanoic Acid. Our general protocol[6] for the isolation of large quantities of the chiral 3-hydroxy acids was used. A mixture of ethyl (3*S*)-3-hydroxyhexanoate (94.1 g, 0.59 mol) in water (70 mL) and ethanol (10 mL) was cooled to 0 °C. To this cold solution was added a solution of KOH (49.7 g, 0.89 mol) in water (330 mL). The reaction was then allowed to stir at 25 °C for 48 h. The resulting solution was concentrated to ca. 250 mL and acidified (concentrated HCl) until pH = 1 was reached. The precipitated salts were filtered, and the filtrate was subjected to continuous liquid/liquid extraction with diethyl ether (1 L) for 24 h. The diethyl ether layer was dried over $MgSO_4$, and the solvent was removed on a rotary evaporator to afford a colorless oil. The oil was then subjected to high vacuum (0.01 Torr, 15 h) in order to remove any residual solvent and/or water. The product (3*S*)-3-hydroxyhexanoic acid generally solidified to a low-melting (mp ca. 30–35 °C), crystalline solid during storage at 0 °C (76.6 g, 99%): $[\alpha]^{25}_D$ = +21.0 ± 0.5° (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.98 (t, J_{HH} = 7.2 Hz, 3H, CH_3), 1.25–1.70 (m, 4H, CH_2), 2.50 (m, 2H, diastereotopic CH_2), 4.05 (m, 1H, CH), 6.60 (br, 2H, OH). The crude product thus obtained was sufficiently pure to be used in the next step (Kolbe coupling).

(4*S*,7*S*)-4,7-Decanediol ((*S*,*S*)-3c). A 500-mL jacketed reaction vessel was charged with (3*S*)-3-hydroxyhexanoic acid (66.0 g, 0.5 mol), methanol (368 mL), and sodium methoxide (132 mL of a freshly prepared 0.5 N solution in methanol, 0.055 mol), and the mixture (pH = 5.38) was cooled to 0 °C with a circulating bath. The electrode configuration used consisted of a Pt foil anode (20 cm^2) wrapped around the outside bottom of a small jointed tube which fit inside a larger jointed tube with a Pt foil cathode (30 cm^2) lining the inside (average electrode gap = 2.5 mm). Using an 18-A DC power supply (Sorenson Model DCR 150-18B), a constant current (current density 0.25 A/cm^2) of 5 A was applied until 77 000 C (1.6 F/mol) was passed, at which point complete conversion of the hydroxy acid was indicated by gas chromatography. The reaction and gas evolution (H_2 and CO_2) proceeded normally until ca. 1.0 F/mol current was passed, after which the resistance and solution pH were observed to increase. The colorless reaction mixture was then concentrated on a rotary evaporator, and the resulting solid residue was extracted with EtOAc (500 mL). After filtering, the insoluble material was stirred with EtOAc (100 mL) for 12 h and filtered and the combined EtOAc extracts (600 mL) were concentrated to a semisolid. Column chromatography (500 g of Silica Gel 60; 30/70 EtOAc/hexane) afforded a colorless solid which was recrystallized from cold hexane (0 °C) to afford crystalline (4*S*,7*S*)-4,7-decanediol (17.3 g, 35%): mp 71–72 °C; $[\alpha]^{25}_D$ = +9.2 ± 0.5° (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.92 (t, J_{HH} = 6.3 Hz, 6H, CH_3), 1.20–1.55 (m, 10H, CH_2), 1.62 (m, 2H, CH_2), 3.10 (br 2H, OH), 3.58 (m, 2H, CH); ^{13}C NMR ($CDCl_3$) δ 14.28, 19.13, 34.31, 40.24, 72.18. Anal. Calcd for $C_{10}H_{22}O_2$: C, 68.91; H, 12.73; O, 18.36. Found: C, 68.98; H, 12.97; O, 18.08.

1,4-Diol Cyclic Sulfates. The procedure used was an adaptation of that described by Sharpless and co-workers[11] for the preparation of assorted unsymmetrical 1,2-diol cyclic sulfates. These 1,4-diol cyclic sulfates are best stored at or below 0 °C as thermal decomposition was noted in certain cases.

(2*R*,5*R*)-2,5-Hexanediol Cyclic Sulfate ((*R*,*R*)-4a). To (2*R*,5*R*)-2,5-hexanediol (10.0 g, 0.085 mol) in CCl_4 (60 mL) was added via syring thionyl chloride (7.75 mL, 0.106 mol). The resulting brownish solution was then heated at reflux for 1.5 h. After the solution was cooled to 25 °C, the reaction was concentrated on a rotary evaporator to afford a brown oil. The oil was then dissolved in a mixture of CCl_4 (60 mL), CH_3CN (60 mL), and H_2O (90 mL), and the mixture was cooled to 0 °C. To the cool mixture was added $RuCl_3$ trihydrate (0.12 g, 0.58 mmol) followed by solid $NaIO_4$ (36.2 g, 0.169 mol). The reaction was allowed to stir at 25 °C for 1 h. At this point, H_2O (400 mL) was added, the mixture was extracted with diethyl ether (4 × 200 mL), and the combined ether extracts were washed with brine (2 × 100 mL). After being dried over $MgSO_4$ and filtered through a pad of SiO_2 (important to remove dissolved Ru salts), the colorless solution was concentrated to ca. 20 mL on a rotary evaporator. The addition of hexane (70 mL) and cooling to −10 °C afforded the product as a colorless, crystalline solid which was filtered, washed with cold hexane, and dried. Recrystallization from ether/hexane in a similar manner yielded pure, colorless, crystalline (2*R*,5*R*)-2,5-hexanediol cyclic sulfate ((*R*,*R*)-**4a**) which is best stored below 0 °C (12.4 g, 81%): mp 109.5–110.5 °C dec; $[\alpha]^{25}_D$ = −32.4° (*c*, 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.40 (d, J_{HH} = 6.5 Hz, 6H, CH_3), 1.91 (m, 4H, CH_2), 4.78 (m, 2H, CH); ^{13}C NMR ($CDCl_3$) δ 21.65, 34.60, 81.74; HRMS (EI, direct insert) *m*/*z* 181.0551 (M^+ + H, exact mass calcd for $C_6H_{13}O_4S$ 181.0534), 137.0284 (M − C_2H_3O).

(3*S*,6*S*)-3,6-Octanediol Cyclic Sulfate ((*S*,*S*)-4b). The same procedure as for **4a** except that (3*S*,6*S*)-3,6-octanediol (15.0 g, 0.103 mol) and thionyl chloride (9.4 mL, 0.128 mol) were used. Recrystallization from ether/hexane yielded pure, colorless, crystalline (3*S*,6*S*)-3,6-octanediol cyclic sulfate ((*S*,*S*)-**4b**) (15.1 g, 71%): mp 79.5–80.5 °C; $[\alpha]^{25}_D$ = +28.6° (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.98 (t, J_{HH} = 7.2 Hz, 6H, CH_3), 1.50–1.75 (m, 4H, CH_2), 1.90 (m, 4H, CH_2), 4.54 (m, 2H, CH); ^{13}C NMR ($CDCl_3$) δ 9.75, 28.67, 32.66, 86.76. Anal. Calcd for $C_8H_{16}O_4S$: C, 46.14; H, 7.74; S, 15.39. Found: C, 46.54; H, 7.66; S, 15.29.

(4*S*,7*S*)-4,7-Decanediol Cyclic Sulfate ((*S*,*S*)-4c). The same procedure as for **4a** except that (4*S*,7*S*)-4,7-decanediol (6.5 g, 0.033 mol) and thionyl chloride (3.0 mL, 0.041 mol) were used. Recrystallization from ether/hexane provided pure, colorless, crystalline (4*S*,7*S*)-4,7-decanediol cyclic sulfate ((*S*,*S*)-**4c**) (5.9 g, 76%): mp 85–86 °C; $[\alpha]^{25}_D$ = +15.4° (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.95 (t, J_{HH} = 7.3 Hz, 6H, CH_3), 1.35–1.60 (m, 6H, CH_2), 1.60–1.80 (m, 2H, CH_2), 4.61 (m, 2H, CH); ^{13}C NMR ($CDCl_3$) δ 13.50, 18.37, 33.02, 37.53, 84.78. Anal. Calcd for $C_{10}H_{20}O_4S$: C, 50.82; H, 8.53; S, 13.57. Found: C, 50.81; H, 8.48; S, 13.84.

(3*S*,6*S*)-3,6-Dihydroxy-2,7-Dimethyloctane Cyclic Sulfate ((*S*,*S*)-4d). The same procedure as for **4a** except that (3*S*,6*S*)-3,6-dihydroxy-2,7-dimethyloctane (14.75 g, 0.085 mol) and thionyl chloride (7.75 mL, 0.106 mol) were used. Recrystallization from warm hexane (25 mL) and cooling to −10 °C afforded the product (3*S*,6*S*)-3,6-dihydroxy-2,7-dimethyloctane cyclic sulfate ((*S*,*S*)-**4c**) as a colorless, crystalline solid which was filtered, washed with cold hexane, and dried (18.14 g, 90%): mp 92.5–93.5 °C; $[\alpha]^{25}_D$ = −55.0° (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.97 (d, J_{HH} = 6.72 Hz, 6H, CH_3), 0.98 (d, J_{HH} = 6.66 Hz, 6H, CH_3), 1.85 (m, 2H, CH), 1.90 (m, 4H, CH_2), 4.40 (m, 2H, CH); ^{13}C NMR ($CDCl_3$) δ 17.11, 18.67, 30.01, 32.79, 89.50. Anal. Calcd for $C_{10}H_{22}O_4S$: C, 50.83; H, 8.53; S, 13.57. Found: C, 50.95; H, 8.16; S, 13.28.

Phosphines. All reactions were conducted at room temperature (ca. 25 °C) unless otherwise noted. All new phosphines are somewhat air-sensitive and should be prepared and stored under an inert atmosphere. Bis(phospholane) **1a** was most conveniently prepared by the new procedure involving cyclic sulfate **4a**; the synthesis and spectroscopic and analytical data for **1a** were previously reported.[6]

1,2-Bis((2*R*,5*R*)-2,5-diethylphospholano)ethane ((*R*,*R*)-1b). To 1,2-bis(phosphino)ethane (0.667 g, 7.10 mmol) in THF (100 mL) was added via syringe *n*-BuLi (8.90 mL of a 1.6 M solution in hexane, 2.0 equiv). The pale yellow solution was allowed to stir for 1.5 h. To the resulting mixture was then added a THF solution (10 mL) of (3*S*,6*S*)-3,6-octanediol

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cyclic sulfate (3.0 g, 14.4 mmol), upon which the reaction decolorized. After the solution was stirred for 2 h, *n*-BuLi (10.2 mL of a 1.6 M hexane solution, 2.3 equiv) was again added dropwise via syringe. Initially, a yellow color appeared and then faded, and a gelatinous precipitate formed (additional THF may be added at this point in order to maintain stirring). Toward the end of the addition, the reaction remained pale yellow. The mixture was allowed to stir for 1.5 h, after which MeOH (3 mL) was added to quench any excess *n*-BuLi remaining. The resulting colorless mixture was concentrated to produce a gelatinous residue which was extracted with pentane (150 mL) and filtered. Concentration of the filtrate afforded the product as a colorless oil (1.92 g, 86%). The crude product was essentially pure and may be used without any further purification. If further purification is desired, the product may be distilled *in vacuo*: bp 104–106 °C (0.05 Torr); $[\alpha]^{25}_D = +320 \pm 4°$ (*c* 1, hexane); ^{1}H NMR (C_6D_6) δ 0.93 (t, J_{HH} = 8.2 Hz, 6H, CH_3), 0.95–1.10 (m, 2H, CH_2), 1.03 (t, J_{HH} = 7.8 Hz, 6H, CH_3), 1.15–1.40 (m, 6H, CH_2), 1.45–1.75 (m, 12H, CH_2), 1.80 (m, 2H, CH), 1.95 (m, 2H, CH); ^{31}P NMR (C_6D_6) δ –5.9; ^{13}C NMR (C_6D_6) δ 14.75, 15.00, 20.32, 23.48, 29.46, 34.13, 34.94, 43.08, 45.85; HRMS (EI, direct insert) *m/z* 314.2289 (M^+, exact mass calcd for $C_{18}H_{36}P_2$ 314.2292), 286.1949 ($M - C_2H_4$), 203.1099 ($M - C_8H_{15}$), 172.1372 ($M - C_8H_{15}P$), 144.1037 ($C_8H_{17}P$ fragment).

1,2-Bis((2*S*,5*S*)-2,5-dipropylphospholano)ethane ((*S*,*S*)-1c). Preparation from (4*R*,7*R*)-4,7-decanediol cyclic sulfate (0.5 g, 10.7 mmol) provided the product as a colorless oil (0.325 g, 78%). The crude product thus obtained was spectroscopically pure and used without further purification for the preparation of metal complexes: $[\alpha]^{25}_D = -251 \pm 3°$ (*c* 1, hexane); ^{1}H NMR (C_6D_6) δ 0.83 (t, J_{HH} = 6.8 Hz, 6H, CH_3), 0.87 (t, J_{HH} = 6.8 Hz, 6H, CH_3), 0.95–1.10 (m, 2H, CH_2), 1.15–2.10 (m, 30H, CH, CH_2); ^{31}P NMR (C_6D_6) δ –3.6; ^{13}C NMR (C_6D_6) δ 14.84, 21.11, 21.19, 23.90, 24.09, 33.16, 34.90, 35.54, 39.54 (t, J_{PC} = 13.5 Hz), 41.19 (t, J_{PC} = 6.4 Hz), 44.14 (t, J_{PC} = 6.8 Hz); HRMS (EI, direct insert) *m/z* 370.2909 (M^+, exact mass calcd for $C_{22}H_{44}P_2$ 370.2918), 342.2619 ($M - C_2H_4$), 231.1498 ($C_{12}H_{25}P_2$ fragment), 199.1591 ($C_{12}H_{24}P$ fragment).

1,2-Bis((2*R*,5*R*)-2,5-diisopropylphospholano)ethane ((*R*,*R*)-1d). Preparation from (3*S*,6*S*)-3,6-dihydroxy-2,7-dimethyloctane cyclic sulfate (2.53 g, 10.7 mmol) provided the product as colorless crystals which were filtered and dried *in vacuo* (1.45 g, 74%). If desired, further purification may be accomplished by recrystallization from Et_2O/MeOH at –20 °C to provide **1d** as colorless crystals: mp 68–70 °C; $[\alpha]^{25}_D = -264 \pm 3°$ (*c* 1, hexane); ^{1}H NMR (C_6D_6) δ 0.84 (d, J_{HH} = 6.4 Hz, 6H, CH_3), 0.80–1.10 (m, 2H, CH_2), 0.95 (d, J_{HH} = 6.6 Hz, 6H, CH_3), 1.09 (d, J_{HH} = 6.5 Hz, 6H, CH_3), 1.10 (d, J_{HH} = 6.5 Hz, 6H, CH_3), 1.20–1.45 (m, 8H, CH, CH_2), 1.80–2.05 (m, 4H, CH); ^{31}P NMR (C_6D_6) δ –10.1; ^{13}C NMR (C_6D_6) δ 20.27, 20.36, 22.24, 22.81, 23.21, 24.52, 29.48, 32.84, 33.04, 50.32, 52.19; HRMS (EI, direct insert) *m/z* 370.2894 (M^+, exact mass calcd for $C_{22}H_{44}P_2$ 370.2918), 355.2603 ($M - CH_3$), 342.2634 ($M - C_2H_4$), 327.2336 ($M - C_3H_7$), 231.1241 ($M - C_{10}H_{19}$), 199.166 ($M - C_{10}H_{20}P$ fragment), 172.1387 ($C_{12}H_{23}P$ fragment).

1,2-Bis((2*S*,5*S*)-2,5-dimethylphospholano)benzene ((*S*,*S*)-Me-DuPHOS, (*S*,*S*)-2a). To 1,2-bis(phosphino)benzene (0.79 g, 5.56 mmol) in THF (100 mL) was added dropwise via syring *n*-BuLi (6.95 mL of a 1.6 M solution in hexane, 2.0 equiv). The yellow solution was allowed to stir for 1.5 h, during which time it became slightly cloudy. To the resulting mixture was then added a THF solution (10 mL) of (2*R*,5*R*)-2,5-hexanediol cyclic sulfate (2.03 g, 11.3 mmol), upon which the reaction decolorized. After the solution was stirred for 2 h, *n*-BuLi (7.65 mL of a 1.6 M hexane solution, 2.2 equiv) was again added dropwise via syringe. Initially, a yellow color appeared and then faded, and a gelatinous precipitate formed (additional THF may be added at this point in order to maintain stirring). Toward the end of the addition, the reaction remained yellow. The mixture was allowed to stir for 2 h, after which MeOH (3 mL) was added to quench any excess *n*-BuLi remaining. The resulting colorless mixture was filtered, and the gelatinous precipitate was washed thoroughly with diethyl ether. The filtrate was concentrated to produce a solid residue which was extracted with pentane (2 × 50 mL) and filtered. Concentration of the filtrate to 10 mL and cooling to –20 °C afforded the product as colorless crystals (0.80 g) which were filtered and dried *in vacuo*. Further concentration of the filtrate and recrystallization of the residue from MeOH at –10 °C led to a second crop of crystals (0.83 g) which were filtered and dried *in vacuo*. Combined total yield was 1.53 g (90%): mp 79–81 °C; $[\alpha]^{25}_D = +476 \pm 5°$ (*c* 1, hexane); ^{1}H NMR (C_6D_6) δ 0.95 (ddd, 6H, CH_3), 1.24 (ddd, 6H, CH_3), 1.20–1.35 (m, 2H, CH_2), 1.70 (m, 1H, CH_2), 1.95 (m, 1H, CH_2), 2.45 (m, 2H, CH), 7.05 (m, 2H, Ph), 7.25 (m, 2H, Ph); ^{31}P NMR (C_6D_6) δ 2.9; ^{13}C NMR (C_6D_6) δ 18.65, 20.66 (t, J_{PC} = 18.2 Hz, CH_3), 32.89, 34.38 (t, J_{PC} = 6.8 Hz), 35.91, 36.49, 128.0, 131.49, 144.56; HRMS (EI, direct insert) *m/z* 306.1638 (M^+, exact mass calcd for $C_{18}H_{28}P_2$ 306.1667), 223.0796 ($M - C_6H_1$#1), 192.1064 ($M - C_6H_{11}P$).

1,2-Bis((2*R*,5*R*)-2,5-diethylphospholano)benzene ((*R*,*R*)-Et-DuPHOS (*R*,*R*)-2b). Preparation from (3*S*,6*S*)-3,6-octanediol cyclic sulfate (3.0 g, 14.4 mmol) affo the product as a colorless oil. The crude product may be used without further purification for the preparation of metal complexes. If desired, further purification can be accomplished by distillation. Distillation *in vacuo* (bp 138–145 °C, 0.045 Torr) provided the product 1,2-bis((2*R*,5*R*)-2,5-diethylphospholano)benzene as a colorless oil (2.02 g, 78%): $[\alpha]^{25}_D = -265°$ (*c* 1, hexane); ^{1}H NMR (C_6D_6) δ 0.85 (m, 6H, CH_3), 0.80–0.90 (m, 2H, CH_2), 0.97 (t, J_{HH} = 7.3 Hz, 6H, CH_3), 1.10–1.40 (m, 4H, CH_2), 1.50–1.80 (m, 6H, CH_2), 1.90 (m, 2H, CH), 2.00–2.20 (m, 4H, CH_2), 2.35 (m, 2H, CH), 7.06 (m, 2H, Ph), 7.31 (m, 2H, Ph); ^{31}P NMR (C_6D_6) δ –4.5; ^{13}C NMR (C_6D_6) δ 13.99, 14.11 (d, J_{PC} = 4.15 Hz), 25.37, 28.80 (t, J_{PC} = 16.56 Hz), 33.06, 33.37, 41.92, 42.34 (t, J_{PC} = 6.70 Hz), 127.62, 132.25, 144.33; HRMS (EI, direct insert) *m/z* 362.2245 (M^+, exact mass calcd for $C_{22}H_{36}P_2$ 362.2292), 293.1570 ($M - C_5H_9$), 251.1086 ($M - C_8H_{15}$), 216.1193 ($M - C_{11}H_{14}$), 185.1395 ($M - C_{11}H_{14}P$).

1,2-Bis((2*R*,2*R*)-2,5-dipropylphospholano)benzene ((*R*,*R*)-Pr-DuPHOS, (*R*,*R*)-2c). Preparation from (4*S*,7*S*)-4,7-decanediol cyclic sulfate (7.40 g, 31.3 mmol) afforded a pale yellow oil. The crude product may be used without further purification for the preparation of metal complexes. Distillation *in vacuo* (bp 165–170 °C, 0.07 Torr) afforded the product 1,2-bis((2*R*,5*R*)-2,5-dipropylphospholano)benzene as a colorless oil (4.59 g, 71%). Occasionally, the oil would solidify to a low-melting, colorless solid upon standing in the freezer (–20 °C). This solid may be recrystallized from cold (–20 °C) MeOH: mp 36.5–37.5 °C; $[\alpha]^{25}_D = -268.2°$ (*c* 1, hexane); ^{1}H NMR (C_6D_6) δ 0.60–1.00 (m, 4H, CH_2), 0.72 (t, J_{HH} = 7.3 Hz, 6H, CH_3), 0.89 (t, J_{HH} = 7.3 Hz, 6H, CH_3), 1.05–1.50 (m, 12H, CH_2), 1.50–1.75 (m, 4H, CH_2), 1.91 (m, 2H, CH_2), 2.05 (m, 2H, CH_2), 2.25 (m, 2H, CH), 2.48 (m, 2H, CH), 7.07 (m, 2H, Ph), 7.33 (m, 2H, Ph); ^{31}P NMR (C_6D_6) δ –3.7; ^{13}C NMR (C_6D_6) δ 14.71, 14.92, 23.50 (t, J_{PC} = 3.91 Hz), 23.72 (t, J_{PC} = 6.45 Hz), 34.15, 34.47, 35.72, 39.40 (t, J_{PC} = 16.10 Hz), 40.10, 40.83 (t, J_{PC} = 7.82 Hz), 128.39, 132.75, 145.70; HRMS (EI, direct insert) *m/z* 418.2929 (M^+, exact mass calcd for $C_{26}H_{44}P_2$ 418.2919), 289.2528 ($M - C_2H_5$), 375.2365 ($M - C_3H_7$), 279.1408 ($M - C_{10}H_{19}$).

1,2-Bis((2*R*,5*R*)-2,5-diisopropylphospholano)benzene ((*R*,*R*)-*i*-Pr-DuPHOS, (*R*,*R*)-2d). Preparation from (3*S*,6*S*)-3,6-dihydroxy-2,7-dimethyloctane cyclic sulfate (4.01 g, 17.0 mmol) afforded a viscous, colorless oil. Distillation *in vacuo* (bp 168–173 °C, 0.06 Torr) provided the product 1,2-bis((2*R*,5*R*)-2,5-diisopropylphospholano)benzene as a viscous, colorless oil (2.47 g, 70%); $[\alpha]^{25}_D = +59.6 \pm 1°$ (*c* 1, hexane); ^{1}H NMR (C_6D_6) δ 0.65 (d, J_{HH} = 6.4 Hz, 6H, CH_3), 0.80–1.10 (m, 2H, CH_2), 1.03 (d, J_{HH} = 6.6 Hz, 12H, CH_3), 1.10 (d, J_{HH} = 6.5 Hz, 6H, CH_3), 1.20–1.65 (m, 6H, CH_2), 1.65–2.20 (m, 6H, CH, CH_2), 2.40 (m, 2H, CH), 7.00 (m, 2H, Ph), 7.40 (m, 2H, Ph); ^{31}P NMR (C_6D_6) δ –11.2; HRMS (EI, direct insert) *m/z* 418.2916 (M^+, exact mass calcd for $C_{26}H_{44}P_2$ 418.2918), 403.2633 ($M - CH_3$), 375.2351 ($M - C_3H_7$), 279.1535 ($M - C_{10}H_{19}$), 247.1485 ($M - C_{10}H_{20}P$ fragment).

[(COD)Rh(1,2-Bis((2*R*,5*R*)-2,5diethylphospholano)ethane)]$^+$OTf$^-$. To $[(COD)_2Rh]^+OTf^-$ [21] (0.149 g, 0.32 mmol, COD = 1,5-cyclooctadiene, OTf = CF_3SO_3) in THF (10 mL) at 25 °C was added dropwise a solution of 1,2-bis((2*R*,5*R*)-2,5-diethylphospholano)ethane (0.1 g, 0.32 mol) in THF (3 mL). The solution turned orange from yellow upon phosphine addition. The reaction was allowed to stir for 15 min, and then Et_2O (30 mL) was slowly added to the solution to produce a small amount of brown oil. The orange solution was decanted from the oil. Further slow addition of Et_2O yielded a bright orange precipitate which was filtered and washed with Et_2O. The solids were dissolved in CH_2Cl_2 (5 mL) and filtered, and Et_2O (30 mL) was added slowly to the orange filtrate to provide the product as a bright orange, microcrystalline solid (0.125 g, 58%): ^{1}H NMR (CD_2Cl_2) δ 1.07 (t, J_{HH} = 7.3 Hz, 6H, CH_3), 1.13 (t, J_{HH} = 7.3 Hz, 6H, CH_3), 1.20–1.50 (m, 8H, CH_2), 1.50–2.10 (m, 12H, CH, CH_2), 2.15–2.60 (m, 12H, CH, CH_2), 4.85 (br m, 2H, COD-CH), 5.30 (br m, 2H, COD-CH), 7.70 (m, 4H, Ph); ^{31}P NMR (CD_2Cl_2) δ 71.2 (d, J_{RhP} = 145.3 Hz). Anal. Calcd for $C_{27}H_{48}F_3O_3P_2SRh$: C, 48.07; H, 7.17; P, 9.18. Found: C, 48.19; H, 7.23; P, 9.15.

[(COD)Rh(1,2-bis((2*R*,5*R*)-2,5-diisopropylphospholano)ethane)]$^+$OTf$^-$. This complex was prepared in a manner analogous to that described above with the exception that the diphospholane 1,2-bis(2*R*,5*R*)-2,5-diisopropylphospholano)ethane was used: ^{1}H NMR (CD_2Cl_2) δ 0.97 (d, J_{HH} = 6.6 Hz, 6H, CH_3), 0.90–1.20 (m, 2H, CH_2), 1.10 (d, J_{HH} = 6.6 Hz, 6H, CH_3), 1.15 (d, J_{HH} = 6.5 Hz, 6H, CH_3), 1.40 (d, J_{HH} = 6.5 Hz, 6H, CH_3), 1.30–1.50 (m, 4H, CH_2), 1.50–2.00 (m, 10H, CH, CH_2),

2.00–2.60 (m, 12H, CH), 4.85 (br m, 2H, COD-CH), 5.30 (br m, 2H, COD-CH); ^{31}P NMR (CD_2Cl_2) δ 65.2 (d, J_{RhP} = 145.2 Hz). Anal. Calcd for $C_{31}H_{56}F_3O_3P_2SRh$: C, 50.96; H, 7.72; P, 8.48. Found: C, 51.15; H, 7.71; P, 8.52.

[(COD)Rh(1,2-bis((2*S*,5*S*)-2,5-dimethylphospholano)benzene)]$^+$-OTf$^-$. This complex was prepared in a manner analogous to that described above with the exception that the diphospholane 1,2-bis(2*S*,5*S*)-2,5-dimethylphospholano)benzene was used: ^{1}H NMR (CD_2Cl_2) δ 1.01 (dd, J_{HH} = 6.8 Hz, J_{PH} = 15.0 Hz, 6H, CH_3), 1.45 (dd, J_{HH} = 7.1 Hz, J_{PH} = 18.2 Hz, 6H, CH_3), 1.55 (m, 2H, CH_2), 1.95 (m, 2H, CH, CH_2), 2.20–2.60 (m, 12H, CH_2, CH), 2.65 (m, 2H, CH, CH_2), 2.75 (m, 2H, CH, CH_2), 5.05 (br 2H, COD-CH), 5.62 (br, 2H, COD-CH), 7.75 (m, 4H, Ph); ^{31}P NMR (CD_2Cl_2) δ 76.3 (d, J_{RhP} = 148.7 Hz). Anal. Calcd for $C_{27}H_{40}F_3O_3P_2SRh$: C, 48.66; H, 6.05; P, 9.29. Found: C, 48.43; H, 6.02; P, 9.31.

[(COD)Rh(1,2-bis((2*R*,5*R*)-2,5-diethylphospholano)benzene)]$^+$-OTf$^-$. To $[(COD)_2Rh]^+OTf^-$ [21] (0.13 g, 0.28 mmol) in THF (10 mL) at 25 °C was added dropwise a solution of 1,2-bis((2*R*,5*R*)-2,5-diethylphospholano)benzene (0.10 g, 0.28 mmol) in THF (5 mL). The solution turned orange from a yellow color upon phosphine addition. The reaction was allowed to stir for 15 min, and then Et_2O (30 mL) was slowly added to the solution to produce an orange, microcrystalline precipitate which was filtered, washed with Et_2O, and briefly dried. The solids were dissolved in CH_2Cl_2 (5 mL) and filtered (if necessary), and Et_2O (30 mL) was added slowly to the orange filtrate to provide the product as an orange, microcrystalline solid (0.112 g, 56%): ^{1}H NMR (CD_2Cl_2) δ 0.86 (t, J_{HH} = 7.3 Hz, 6H, CH_3), 1.02 (t, J_{HH} = 7.3 Hz, 6H, CH_3), 1.2–1.6 (m, 6H, CH_2), 1.85 (m, 4H, CH, CH_2), 2.20 (m, 2H, CH, CH_2), 2.20–2.70 (m, 14H, CH_2, CH), 4.90 (br m, 2H, COD-CH), 5.60 br m, 2H, COD-CH), 7.70 (m, 4H, Ph); ^{31}P NMR (CD_2Cl_2) δ 69.5 (d, J_{RhP} = 148.3 Hz). Anal. Calcd for $C_{31}H_{48}F_3O_3P_2SRh$: C, 51.53; H, 6.69; P, 8.57. Found: C, 52.14; H, 6.72; P, 8.64.

[(COD)Rh(1,2-bis((2*R*,5*R*)-2,5-dipropylphospholano)benzene)]$^+$-OTf$^-$. This complex was prepared in a manner analogous to that described above with the exception that the diphospholane 1,2-bis((2*R*,5*R*)-2,5-diisopropylphospholano)benzene was used: ^{1}H NMR (CD_2Cl_2) δ 0.76 (t, J_{HH} = 7.1 Hz, 6H, CH_3), 0.81 (t, J_{HH} = 7.3 Hz, 6H, CH_3), 1.15 (m, 4H, CH_2), 1.20–1.65 (m, 10H, CH_2), 1.85 (m, 4H, CH, CH_2), 2.20 (m, 2H, CH, CH_2), 2.20–2.70 (m, 16H, CH_2, CH), 4.95 (br m, 2H, COD-CH), 5.60 (br m, 2H, COD-CH), 7.70 (m, 4H, Ph); ^{31}P NMR (CD_2Cl_2) δ 70.5 (d, J_{RhP} = 148.3 Hz). Anal. Calcd for $C_{35}H_{56}F_3O_3P_2SRh$: C, 53.98; H, 7.25; P, 7.96. Found: C, 53.74; H, 7.13; P, 7.96.

[(COD)Rh(1,2-bis((2*R*,5*R*)-2,5-diisopropylphospholano)benzene)]$^+$-OTf$^-$. This complex was prepared in a manner analogous to that described above with the exception that the diphospholane 1,2-bis((2*R*,5*R*)-2,5-diisopropylphospholano)benzene was used: ^{1}H NMR (CD_2Cl_2) δ 0.72 (d, J_{HH} = 6.6 Hz, 6H, CH_3), 0.73 (d, J_{HH} = 6.7 Hz, 6H, CH_3), 1.13 (d, J_{HH} = 6.5 Hz, 6H, CH_3), 1.14 (d, J_{HH} = 6.6 Hz, 6H, CH_3), 1.60 (m, 4H, CH_2), 1.95 (m, 4H, CH, CH_2), 2.15 (m, 2H, CH_2), 2.20–2.45 (m, 6H, CH_2, CH), 2.45–2.70 (m, 8H, CH, CH_2), 4.95 (br, 2H, COD-CH), 5.60 (br, 2H, COD-CH), 7.65 (m, 2H, Ph), 7.75 (m, 2H, Ph); ^{31}P NMR (CD_2Cl_2) δ 65.5 (d, J_{RhP} = 148.5 Hz).

X-ray Crystallography: [(COD)Rh((*R*,*R*)-Me-BPE)]$^+$SbF$_6^-$. Crystal data for $C_{22}H_{40}F_6P_2RhSb$: orthorhombic, $P2_12_12_1$ (No. 19), a = 14.186(3) Å, b = 16.137(4) Å, c = 11.825(3) Å, T = –100 °C, V = 2707 Å^3, Mo Kα radiation, μ_{calcd} = 17.72 cm^{-3}, d_{calcd} = 1.732 g cm^{-3}, Z = 4, fw = 705.17.

Suitable crystals of the rhodium complex [(COD)Rh-((*R*,*R*)-Me-BPE)]$^+$SbF$_6^-$ were obtained by slow crystallization from a CH_2Cl_2/hexane (2/1) solution at 25 °C. An orange needle of dimensions 0.10 × 0.12 × 0.71 mm^3 was mounted in a nitrogen-filled thin-walled glass capillary, and data were collected on a Syntex R3 diffractometer at –100 °C. The unit-cell dimensions were determined by least-squares refinement of 49 reflections. The crystal stability was monitored throughout the data collection by measuring the intensity of three standard reflections every 182 data points. A 4% fluctuation in intensity was observed over the course of data acquisition. Lorentzian, polarization, and absorption (azimuthal) corrections were applied, due to the relatively large absorption coefficient μ(Mo) = 17.72 cm^{-1}.

The structure was solved using direct methods (SHELXS). All hydrogen atoms were determined from difference Fourier maps and idealized (C–H = 0.95 Å). Anisotropic refinement was carried out by full-matrix least squares on F. Neutral atom scattering factors and anomalous scattering terms for P, Rh, and Sb were obtained from the *International Tables for X-ray Crystallography*, Vol. IV. Non-hydrogen atoms were refined with anisotropic thermal parameters for a total of 289 parameters. Attempts to refine the hydrogen atoms were only partially successful, and so they were idealized and fixed with isotropic thermal parameters one higher than those of their associated carbon atoms. The refinement converged at R = 0.038, R_w = 0.036, and EOF = 1.07. Fractional coordinates and isotropic thermal parameters for all non-H atoms are provided in the supplementary material, Table 1S, while anisotropic thermal parameters are given in Table 2S. A complete listing of bond lengths and angles is also supplied in Tables 3S and 4S.

X-ray Crystallography: [(COD)Rh((*S*,*S*)-Me-DuPHOS)]$^+$SbF$_6^-$. Crystal Data for $C_{26}H_{40}F_6P_2RhSb$: monoclinic, $P2_1$ (No. 4), a = 10.921(4) Å, b = 9.374(3) Å, c = 14.538(4) Å, β = 98.41(1)°, T = –70 °C, V = 1472.3 Å^3, Mo Kα radiation, μ_{calcd} = 16.33 cm^{-1}, d_{calcd} = 1.699 g cm^{-3}, Z = 2, fw = 753.21.

Suitable crystals of the rhodium complex [(COD)Rh-((*S*,*S*)-Me-DuPHOS)]$^+$SbF$_6^-$ were obtained by slow vapor diffusion of Et_2O into a CH_2Cl_2 solution of the complex at 25 °C. An orange parallelpiped of dimensions 0.20 × 0.08 × 0.45 mm^3 was mounted in a nitrogen-filled thin-walled glass capillary, and data were collected on an Enraf-Nonius CAD4 diffractometer at –70 °C. The unit-cell dimensions were determined by least-squares refinement of 25 reflections. The crystal stability was monitored throughout the data collection by measuring the intensity of two standard reflections every 49 data points. The data were adjusted for a 6% decrease in intensity over the course of data acquisition. Lorentzian, polarization, and absorption (azimuthal) corrections were applied, due to the relatively large absorption coefficient μ(Mo) = 16.33 cm^{-1}.

The structure was solved using direct methods (MULTAN). All hydrogen atoms were determined from difference Fourier maps and idealized (C–H = 0.95 Å). Anisotropic refinement was carried out by full-matrix least squares on F. Neutral atom scattering factors and anomalous scattering terms for P, Rh, and Sb were obtained from the *International Tables for X-ray Crystallography*, Vol. IV. Non-hydrogen atoms were refined with anisotropic thermal parameters for a total of 324 parameters. Attempts to refine the hydrogen atoms were only partially successful, and so they were idealized and fixed with isotropic thermal parameters one higher than those of their associated carbon atoms. The refinement converged at R = 0.043, R_w = 0.035, and EOF = 1.07 for 4232 unique reflections with $I > 3.0\sigma(I)$ and 324 variables. Fractional coordinates and isotropic thermal parameters for all non-H atoms are provided in the supplementary material, Table 5S, while anisotropic thermal parameters are given in Table 6S. A complete listing of bond lengths and angles is also supplied in Tables 7S and 8S.

Asymmetric Hydrogenations. General Procedure. In a drybox, a Fisher-Porter tube or bottle was charged with substrate, deoxygenated MeOH, and catalyst (0.1–0.005 mol %). After four vacuum/H_2 cycles, the tube was pressurized to an initial pressure of 30 psig H_2. The reactions were allowed to continue at 20–25 °C until no further hydrogen uptake was observed. The absolute rates varied with the relative molar ratio of catalyst used. Regioselective hydrogenations were allowed to proceed only until complete reduction of the enamide moiety was indicated (usually 10–15 min at S/C 1000). Complete (100%) conversion to product was confirmed by TLC or GC as well as ^{1}H and ^{13}C NMR analyses, unless otherwise noted. All reactions were quantitative unless otherwise noted. The reactions were concentrated on a Rotovap, and the residue was passed through a short SiO_2 column (EtOAc/hexane 50/50) to remove the catalyst. Without further purification, the enantiomeric excesses were determined directly with the crude products thus obtained. In addition to the standard workup and analysis procedures, all chiral *N*-Cbz-protected products were also hydrogenated (Pd/C, 60 psi H_2, MeOH/Ac_2O 5/1) to afford directly the *N*-acetylamino acid derivatives **6** which were analyzed as described below. Spectroscopic and analytical data for products **6** are given below. Unless otherwise noted, the data provided were obtained on products which analyzed at enantiomeric purity levels of ≥99% ee. Data for ring-substituted *N*-acetylphenylalanine derivatives and *N*-Cbz amino acid esters are provided as supplementary material.

(*R*)-*N*-Acetyl-*p*-fluorophenylalanine Methyl Ester. A 500-mL Fisher-Porter bottle was charged with dehydro-*N*-acetyl-*p*-fluorophenylalanine methyl ester (36.8 g, 0.155 mol), MeOH (200 mL), and [(COD)Rh-((*R*,*R*)-Et-DuPHOS)]$^+$OTf$^-$ (0.01 g, 0.014 mmol, S/C = 11 193). After four vacuum/H_2 cycles, the reaction was pressurized to an initial pressure of 30 psig H_2. The reaction was allowed to stir at 20–25 °C and at constant pressure for 24 h. Complete (100%) conversion to product was confirmed by TLC and ^{1}H NMR analyses. The reaction was concentrated on a rotary evaporator, and an aliquot was passed through a short SiO_2 column (EtOAc/hexane 50/50) to remove the catalyst. Without further purification, the enantiomeric excess was determined to be >99% ee as follows: HPLC, Daicel Chiralcel OJ, 0.5 mL/min, 10% 2-PrOH/hexane; (*R*)-enantiomer t_1 = 18.66 min; (*S*)-enantiomer t_2 = 23.59 min. In this

case, the minor (*S*)-enantiomer was not detected. The bulk product (*R*)-*N*-acetyl-*p*-fluorophenylalanine methyl ester was obtained as a colorless, crystalline solid (35.2 g, 95%): mp 89.5–90.5 °C; $[\alpha]^{25}_D = -87.2°$ (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.98 (s, 3H, CH_3), 3.10 (m, 2H, CH_2), 3.72 (s, 3H, OCH_3), 4.83 (dt, 1H, CH), 6.02 (br q, 1H, NH), 6.90–7.10 (m, 4H, Ph); ^{13}C NMR ($CDCl_3$) δ 23.29, 37.27, 52.54, 53.34, 115.59 (d, $J_{CF} = 21.2$ Hz), 130.89 (d, $J_{CF} = 7.8$ Hz), 131.76, 162.17 (d, $J_{CF} = 245.5$ Hz), 169.77, 172.17. Anal. Calcd for $C_{12}H_{14}FNO_3$: C, 60.24; H, 5.90; N, 5.85; F, 7.94. Found: C, 60.36; H, 5.73; N, 5.56; F, 8.02.

(*R*)-*N*-Acetylalanine methyl ester: oil; $[\alpha]^{25}_D = -9.2°$ (*c* 1, $CHCl_3$); $[\alpha]^{25}_D = +91.2°$ (*c* 1, H_2O); ^1H NMR ($CDCl_3$) δ 1.38 (d, $J_{HH} = 7.12$ Hz, 3H, CH_3), 1.98 (s, 3H, CH_3), 3.66 (s, 3H, OCH_3), 4.57 (dq, $J_{HH} = 7.03$ Hz, 7.12 Hz, 1H, CH), 6.38 (br d, $J_{HH} = 7.03$ Hz, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 18.32, 22.89, 48.03, 52.17, 169.39, 173.46; HRMS (EI, direct insert) *m/z* 145.0722 (M^+, exact mass calcd for $C_6H_{11}NO_3$ 145.0739), 86.0589 ($M - C_2H_3O_2$).

(*R*)-*N*-Acetylleucine methyl ester: oil; $[\alpha]^{25}_D = +41.8°$ (*c* 1, MeOH); ^1H NMR ($CDCl_3$) δ 0.92 (d, $J_{HH} = 7.2$ Hz, 3H, CH_3), 0.94 (d, $J_{HH} = 7.15$ Hz, 3H, CH_3), 1.63 (m, 1H, CH_2), 1.50 (m, 1H, CH_2), 1.62 (m, 2H, CH, CH_2), 2.01 (s, 3H, CH_3), 3.68 (s, 3H, OCH_3), 4.62 (m, 1H, CH), 6.00 (br d, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 22.01, 22.71, 23.00, 24.90, 41.77, 50.79, 52.09, 169.64, 173.58; HRMS (EI, direct insert) *m/z* 188.1272 ($M^+ + H$, exact mass calcd for $C_9H_{18}NO_3$ 188.1287), 128.1050 ($C_7H_{14}NO$ fragment).

(*R*)-Methyl 2-(*N*-acetylamino)butanoate: oil; $[\alpha]^{25} = -25.2°$ (*c* 1, $CHCl_3$); $[\alpha]^{25}_D = +69.8°$ (*c* 1, H_2O); ^1H NMR ($CDCl_3$) δ 0.84 (t, 3H, CH_3), 1.63 (m, 1H, CH_2), 1.80 (m, 1H, CH_2), 1.99 (s, 3H, CH_3), 3.65 (s, 3H, OCH_3), 4.55 (m, 1H, CH), 6.35 (br d, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 9.39, 22.90, 25.61, 51.98, 53.32, 169.56, 172.66; HRMS (EI, direct insert) *m/z* 159.0886 (M^+, exact mass calcd for $C_7H_{13}NO_3$ 159.0895), 100.0767 ($M - C_2H_3O_2$).

(*R*)-Methyl 2-(*N*-acetylamino)pentanoate: mp 48.5–49.5 °C; $[\alpha]^{25}_D = -19.0°$ (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.83 (t, 3H, CH_3), 1.24 (m, 2H, CH_2), 1.60 (m, 1H, CH_2), 1.78 (m, 1H, CH_2), 2.00 (s, 3H, CH_3), 3.67 (s, 3H, OCH_3), 4.60 (m, 1H, CH), 6.12 (br d, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 13.82, 18.80, 23.28, 34.92, 52.26, 52.36, 169.79, 173.40. Anal. Calcd for $C_8H_{15}NO_3$: C, 55.47; H, 8.73; N, 8.09. Found: C, 55.82; H, 9.09; N, 8.06.

(*R*)-Methyl 2-(*N*-acetylamino)hexanoate: mp 49–50 °C; $[\alpha]^{25}_D = -36.4°$ (*c* 1, $CHCl_3$); $[\alpha]^{25}_D = +27.6°$ (*c* 1, CH_3OH); ^1H NMR ($CDCl_3$) δ 0.83 (t, 3H, CH_3), 1.22 (m, 4H, CH_2), 1.60 (m, 1H, CH_2), 1.78 (m, 1H, CH_2), 1.99 (s, 3H, CH_3), 3.66 (s, 3H, OCH_3), 4.58 (m, 1H, CH), 6.19 (br d, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 13.97, 22.48, 23.28, 27.57, 32.46, 52.39, 169.78, 173.39. Anal. Calcd $C_9H_{17}NO_3$: C, 57.73; H, 9.15; N, 7.48. Found: C, 58.05; H, 9.15; N, 7.41.

(*R*)-*N*-Acetylphenylalanine methyl ester: mp 87–88 °C; $[\alpha]^{25}_D = -15.8°$ (*c* 1, MeOH); ^1H NMR ($CDCl_3$) δ 2.00 (s, 3H, CH_3), 3.10 (m, 2H, CH_2), 3.74 (s, 3H, OCH_3), 4.85 (dt, 1H, CH), 5.91 (br d, 1H, NH), 7.10 (d, 2H, Ph), 7.32 (m, 3H, Ph); ^{13}C NMR ($CDCl_3$) δ 23.09, 37.87, 52.25, 53.11, 127.06, 128.51, 129.17, 135.81, 169.47, 172.02. Anal. Calcd for $C_{12}H_{15}NO_3$: C, 65.14; H, 6.83; N, 6.33. Found: C, 65.24; H, 6.81; N, 6.05.

(*S*)-*N*-Acetyl-*m*-fluorophenylalanine methyl ester: mp 81–82 °C; $[\alpha]^{25}_D = +97.8°$ (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.99 (s, 3H, CH_3), 3.06 (m, 2H, CH_2), 3.76 (s, 3H, OCH_3), 4.85 (dt, 1H, CH), 6.07 (br d, 1H, NH), 6.75–7.00 (m, 3H, Ph), 7.25 (m, 1H, Ph); ^{13}C NMR ($CDCl_3$) δ 23.29, 37.76, 52.61, 53.18, 114.26 (d, $J_{CF} = 21.0$ Hz), 116.37 (d, $J_{CF} = 21.2$ Hz), 125.10 (d, $J_{CF} = 2.0$ Hz), 130.21 (d, $J_{CF} = 8.25$ Hz), 138.61 (d, $J_{CF} = 7.1$ Hz), 162.96 (d, $J_{CF} = 246.1$ Hz), 169.82, 172.05. Anal. Calcd for $C_{12}H_{14}FNO_3$: C, 60.24; H, 5.90; N, 5.85; F, 7.94. Found: C, 60.58; H, 5.83; N, 5.58; F, 7.82.

(*R*)-*N*-Acetyl-*m*-bromophenylalanine methyl ester: mp 88–89 °C; $[\alpha]^{25}_D = -91.6°$ (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.98 (s, 3H, CH_3), 3.08 (m, 2H, CH_2), 3.74 (s, 3H, OCH_3), 4.84 (dt, 1H, CH), 6.12 (br d, 1H, NH), 7.00–7.40 (m, 4H, Ph); ^{13}C NMR ($CDCl_3$) δ 22.98, 37.64, 52.26, 53.13, 122.52, 127.78, 129.98, 130.19, 132.38, 138.42, 169.44, 171.73; HRMS (EI direct insert) *m/z* 299.0141 (M^+, exact mass calcd for $C_{12}H_{14}BrNO_3$ 299.0157), 239.9805 ($M - C_2H_5NO$).

(*S*)-*N*-Acetyl-*o*-fluorophenylalanine methyl ester: mp 104.5–106 °C; $[\alpha]^{25}_D = +93.0°$ (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.98 (s, 3H, CH_3), 3.12 (m, 2H, CH_2), 3.74 (s, 3H, OCH_3), 4.82 (dt, 1H, CH), 6.05 (br d, 1H, NH), 6.95–7.25 (m, 4H, Ph); ^{13}C NMR ($CDCl_3$) δ 23.24, 31.64, 52.63, 52.67, 115.53 (d, $J_{CF} = 22.3$ Hz), 123.17 (d, $J_{CF} = 16.1$ Hz), 124.36 (d, $J_{CF} = 3.1$ Hz), 129.19 (d, $J_{CF} = 8.2$ Hz), 131.80 (d, $J_{CF} = 4.6$ Hz), 161.51 (d, $J_{CF} = 245.1$ Hz), 169.79, 172.13; HRMS (EI, direct insert) *m/z* 239.0958 (M^+, exact mass calcd for $C_{12}H_{14}FNO_3$ 239.0958), 180.0628 (M^+, exact mass calcd for $C_{12}H_{14}FNO_3$ 239.0958), 180.0628 ($M - C_2H_5NO$).

(*R*)-*N*-Acetyl-3,5-bis(trifluoromethyl)phenylalanine methyl ester: mp 111–112 °C; $[\alpha]^{25}_D = -75.6°$ (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 2.01 (s, 3H, CH_3), 3.31 (m, 2H, CH_2), 3.76 (s, 3H, OCH_3), 4.88 (dt, 1H, CH), 6.10 (br d, 1H, NH), 7.55 (s, 2H, Ph), 7.78 (s, 1H, Ph); ^{13}C NMR ($CDCl_3$) δ 23.20, 37.78, 52.81, 53.33, 121.30, 121.59, 129.75, 131.96 (q, $J_{CF} = 33.25$ Hz, CF_3), 138.90, 169.88, 171.51; HRMS (EI, direct insert) *m/z* 357.0800 (M^+, exact mass calcd for $C_{14}H_3{}^3F_6NO_3$ 357.0799), 338.0816 ($M - F$), 298.0496 ($M - C_2H_5NO$).

(*R*)-*N*-Acetyl-3-ferrocenylalanine methyl ester: mp 147–149 °C; $[\alpha]^{25}_D = -80.2°$ (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.99 (s, 3H, CH_3), 2.91 (d, 2H, CH_2), 3.67 (s, 3H, OCH_3), 3.95 (br, 1H, Cp-H), 4.02 (br, 1H, Cp-H), 4.08 (br, 2H, Cp-H), 4.10 (s, 5H, Cp-H), 4.72 (m, 1H, CH), 5.98 (br d, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 23.40, 33.03, 52.45, 53.54, 68.37, 68.97, 69.39, 77.44, 77.47, 82.15, 169.54, 172.22. Anal. Calcd for $C_{16}H_{19}NO_3Fe$: C, 58.38; H, 5.82; N, 4.26. Found: C, 58.33; H, 5.67; N, 4.02.

(*R*)-*N*-Acetyl-3-(2-thienyl)alanine methyl ester: mp 114–115 °C; $[\alpha]^{25}_D = -109.8°$ (*c* 1, $CHCl_3$); $[\alpha]^{25}_D = -17.8°$ (*c* 1, EtOH); ^1H NMR ($CDCl_3$) δ 2.01 (s, 3H, CH_3), 3.35 (m, 2H, CH_2), 3.76 (s, 3H, OCH_3), 4.83 (m, 1H, CH), 6.15 (br d, 1H, NH), 6.75 (d, 1H, CH), 6.93 (dd, 1H, CH), 7.19 (d, 1H, CH); ^{13}C NMR ($CDCl_3$) δ 23.38, 32.17, 52.69, 53.26, 125.01, 126.86, 127.18, 137.43, 169.76, 171.62. Anal. Calcd for $C_{10}H_{13}NO_3S$: C, 52.84; H, 5.76; N, 6.16; S, 14.11. Found: C, 52.80; H, 5.76; N, 6.04; S, 14.14.

(*S*)-*N*-Acetyl-3-(2-naphthyl)alanine methyl ester: oil; $[\alpha]^{25}_D = +97.8°$ (*c* 1, $CHCl_3$); $[\alpha]^{25}_D = +38.4°$ (*c* 1, EtOH); ^1H NMR ($CDCl_3$) δ 1.99 (s, 3H, CH_3), 3.28 (m, 2H, CH_2), 3.71 (s, 3H, OCH_3), 4.98 (m, 1H, CH), 5.98 (br d, 1H, NH), 7.25 (dd, 1H, Ar), 7.48 (m, 2H, Ar), 7.59 (s, 1H, Ar), 7.82 (m, 3H, Ar); ^{13}C NMR ($CDCl_3$) δ 23.12, 38.06, 52.32, 53.18, 125.76, 126.18, 127.19, 127.52, 127.63, 127.98, 128.23, 132.48, 133.38, 169.54, 172.08; HRMS (EI direct insert) *m/z* 271.1213 (M^+, exact mass calcd for $C_{16}H_{17}NO_3$ 271.1208), 212.0844 ($M - C_2H_5NO$).

(*S*)-*N*-Acetyl-3-(1-naphthyl)alanine methyl ester: mp 63–64.5 °C; $[\alpha]^{25}_D = +55.8°$ (*c* 1, $CHCl_3$); $[\alpha]^{25} = -18.8°$ (*c* 1, EtOH); ^1H NMR ($CDCl_3$) δ 1.95 (s, 3H, CH_3), 3.59 (m, 2H, CH_2), 3.62 (s, 3H, OCH_3), 5.03 (m, 1H, CH), 6.01 (br d, 1H, NH), 7.23 (dd, 1H, Ar), 7.46 (dd, 1H, Ar), 7.52 (m, 2H, Ar), 7.79 (d, 1H, Ar), 7.85 (d, 1H, Ar), 8.09 (d, 1H, Ar); ^{13}C NMR ($CDCl_3$) δ 23.08, 35.12, 52.18, 53.28, 123.52, 125.19, 125.74, 126.24, 127.32, 127.95, 128.80, 132.31, 132.35, 133.89, 169.57, 172.26; HRMS (EI, direct insert) *m/z* 271.1214 (M^+, exact mass calcd for $C_{16}H_{17}NO_3$ 271.1208), 212.0835 ($M - C_2H_5NO$).

(*R*)-*N*-Acetylhomomethionine methyl ester: oil; 95% ee; $[\alpha]^{25}_D = -41.8°$ (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.65 (m, 3H, CH_2), 1.97 (m, 1H, CH32), 2.03 (s, 3H, CH_3), 2.09 (s, 3H, SCH_3), 2.51 (t, 2H, SCH_2), 3.72 (s, 3H, OCH_3), 4.61 (m, 1H, CH), 6.10 (br d, 1H, NH); ^{13}C NMR ($CDCL_3$) δ 15.40, 23.06, 24.84, 31.56, 33.62, 51.76, 52.30, 169.67, 172.84; HRMS (EI, direct insert) *m/z* 219.0952 (M^+, exact mass calcd for $C_9H_{17}NO_3S$ 219.0930), 176.0735 ($M - C_2H_3O$), 172.0954 ($M - SCH_3$), 160.0781 ($M - C_2H_3O_2$).

(*R*)-Methyl 2-(*N*-acetylamino)-4,4-dimethylpentanoate: mp 52–54 °C; 96% ee; $[\alpha]^{25}_D = +6.8°$ (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.95 (s, 9H, CH_3), 1.47 (dd, 1H, CH_2), 1.73 (dd, 1H, CH_2), 1.99 (s, 3H, CH_3), 3.68 (s, 3H, OCH_3), 4.60 (m, 1H, CH), 5.96 (br d, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 23.17, 29.52, 30.70, 46.23, 49.88, 52.22, 169.44, 174.01. Anal. Calcd for $C_{10}H_{19}NO_3$: C, 59.68; H, 9.51; N, 6.96. Found: C, 60.30; H, 9.69; N, 6.62.

(*R*)-Methyl *trans*-2-(*N*-acetylamino)-6-dodecenoate: mp 50.5–51.5 °C; $[\alpha]^{25}_D = -36.0°$ (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.89 (t, 3H, CH_3), 1.37 (m, 8H, CH_2), 1.67 (m, 1H, diastereotopic CH_2), 1.80 (m, 1H, diastereotopic CH_2), 1.98 (m, 4H, allylic CH_2), 2.03 (s, 3H, CH_3), 3.77 (s, 3H, OCH_3), 4.55 (m, 1H, CH), 5.38 (m, 2H, vinylic CH), 5.98 (br d, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 14.28, 22.75, 23.41, 25.41, 29.45, 31.61, 32.26 (2 carbons), 32.74, 52.29, 52.52, 129.19, 131.63, 169.85, 173.39; HRMS (EI, direct insert) *m/z* 269.2007 (M^+, exact mass calcd for $C_{15}H_{27}NO_3$ 269.1990), 226.1791 ($M - C_2H_3O$), 210.1842 ($M - C_2H_3O_2$).

(*S*)-Methyl 2-(*N*-acetylamino)-12-tridecenoate: mp 54–56 °C; $[\alpha]^{25}_D = +26.6°$ (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.28 (m, 14H, CH_2), 1.68 (m, 1H, diastereotopic CH_2), 1.81 (m, 1H, diastereotopic CH_2), 2.04 (m, 2H, allylic CH_2), 2.02 (s, 3H, CH_3), 3.76 (s, 3H, OCH_3), 4.55 (m, 1H, CH), 4.95 (m, 2H, vinylic CH), 5.79 (m, 2H, vinylic CH), 6.06 (br d, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 23.37, 25.40, 29.00, 29.13, 29.30, 29.38, 29.56, 29.63 (2 carbons), 32.75, 33.99, 52.38, 52.47, 114.28, 139.34, 169.87, 173.44; HRMS (EI, direct insert) *m/z* 283.2141 (M^+, exact

mass calcd for $C_{16}H_{29}NO_3$ 283.2147), 240.1959 (M – C_2H_3O), 224.2004 (M – $C_2H_3O_2$), 182.1900 (M – $C_4H_5O_3$).

Enantiomeric Excess Determinations. Chiral Capillary GC. Column: Chrompack XE-60-(*S*)-valine (*S*-)-α-phenylethylamide on WCOT fused silica. Dimensions: 50 m × 0.25 mm (i.d.) × 0.39 mm (o.d.) × 0.12 μm (film thickness). Carrier gas: He (0.85 mL/min). This column was used for all GC analyses except for two compounds: methyl *trans*-2-(*N*-acetylamino)-6-dodecenoate (**6n**) and methyl 2-(*N*-acetylamino)-12-tridecenoate (**6o**). To facilitate analysis, the isolated double bonds of **6n** and **6o** were reduced prior to ee determination. For the fully reduced compounds, the following column was used Chrompack Chirasil-Val-L on WCOT fused silica, dimensions 25 m × 0.25 mm (i.d.) × 0.39 mm (o.d.) × 0.12 μm (film thickness).

Chiral HPLC. Columns: Daicel Chiralcel OJ (*p*-toloyl cellulose ester coated on silica gel) or Chiralcel OB (benzoyl cellulose ester coated on silica gel). Particle size: 5.0 μm. Column dimensions: 25 cm (length) × 0.46 cm (i.d.). Column temperature: 40 °C.

Enantiomeric excesses listed are the average value obtained from two to three experiments. In all cases, the racemic products **6** were prepared by hydrogenation of substrates **5** with an achiral catalyst. The following list describes conditions used for separation of racemic products **6**: ***N*-acetylphenylalanine methyl ester (6b)** (HPLC, Daicel Chiralcel OJ, 1.0 mL/min, 10% 2-PrOH/hexane) (*R*) t_1 = 8.9 min; (*S*) t_2 = 11.4 min; ***N*-acetylalanine methyl ester (6a)** (capillary GC, 140 °C, isothermal) (*R*) t_1 = 10.55 min, (*S*) t_2 = 11.02 min; ***N*-acetylleucine methyl ester (6c)** (capillary GC, 160 °C, isothermal) (*R*) t_1 = 16.49 min, (*S*) t_2 = 17.48 min; **methyl 2-(*N*-acetylamino)butanoate (6d)** (capillary GC, 140 °C, isothermal) (*R*) t_1 = 16.69 min, (*S*) t_2 = 17.67 min; **methyl 2-(*N*-acetylamino)pentanoate (6e)** (capillary GC, 150 °C, isothermal) (*R*) t_1 = 16.15 min, (*S*) t_2 = 16.97 min; **methyl 2-(*N*-acetylamino)hexanoate (6f)** (capillary GC, 160 °C, isothermal) (*R*) t_1 = 17.72 min, (*S*) t_2 = 18.65 min; ***N*-acetyl-3-(2-thienyl)alanine methyl ester (6h)** (HPLC, Daicel Chiralcel OJ, 1.0 mL/min, 10% 2-PrOH/hexane) (*R*) t_1 = 11.74 min, (*S*) t_2 = 14.20 min; ***N*-acetyl-3-ferrocenylalanine methyl ester (6l)** (HPLC, Daicel Chiralcel 0J, 0.5 mL/min, 10% 2-PrOH/hexane) (*R*) t_1 = 22.51 min, (*S*) t_2 = 26.57 min; ***N*-acetyl-3-(2-naphthyl)alanine (6j)** (HPLC, Daicel Chiralcel OJ, 0.5 mL/min, 10% 2-PrOH/hexane) (*R*) t_1 = 42.02 min, (*S*) t_2 = 46.67 min; ***N*-acetyl-3-(1-naphthyl)alanine (6k)** (HPLC, Daicel Chiralcel OJ, 0.5 mL/min, 10% 2-PrOH/hexane) (*S*) t_1 = 27.45 min, (*R*) t_2 = 31.03 min; **methyl 2-(*N*-acetylamino)-4,4-dimethylpentanoate (6l)** (capillary GC, 160 °C, isothermal) (*R*) t_1 = 17.35 min, (*S*) t_2 = 18.42 min; ***N*-acetylhomomethionine methyl ester (6m)** (capillary GC, 180 °C, isothermal) (*R*) t_1 = 41.87 min, (*S*) t_2 = 43.74 min; **methyl *trans*-2-(*N*-acetylamino)-6-dodecenoate (6n)** (capillary GC, 180 °C, isothermal) (*R*) t_1 = 54.42 min, (*S*) t_2 = 56.81 min (A more accurate and precise analysis of enantiomeric purity of **6n** was achieved by reducing the isolated double bond prior to ee determination (capillary GC Chirasil-Val-L, 170 °C, isothermal) (*R*) t_1 = 11.81 min, (*S*) t_2 = 12.96 min); **methyl 2-(*N*-acetylamino)-12-tridecenoate (6o)** (To facilitate analysis, the terminal double bond of **6o** was reduced prior to ee determination; capillary GC Chirasil-Val-L, 170 °C, isothermal) (*R*) t_1 = 17.43 min, (*S*) t_2 = 19.19 min; ***N*-acetyl-*p*-bromophenylalanine methyl ester** (HPLC, Daicel Chiralcel OJ, 0.5 mL/min, 10% 2-PrOH/hexane) (*R*) t_1 = 22.85 min, (*S*) t_2 = 26.14 min; ***N*-acetyl-*p*-methylphenylalanine methyl ester** (HPLC, Daicel Chiralcel OJ, 1.0 mL/min, 10% 2-PrOH/hexane) (*R*) t_1 = 7.82 min, (*S*) t_2 = 10.97 min; ***N*-acetyl-*p*-methoxyphenylalanine methyl ester** (HPLC, Daicel Chiralcel OJ, 1.0 mL/min, 10% 2-PrOH/hexane) (*R*) t_1 = 16.15 min, (*S*) t_2 = 27.44 min; ***N*-acetyl-*m*-fluorophenylalanine methyl ester** (HPLC, Daicel Chiralcel OJ, 1.0 mL/min, 10% 2-PrOH/hexane) (*R*) t_1 = 9.17 min, (*S*) t_2 = 10.54 min; ***N*-acetyl-*m*-bromophenylalanine methyl ester** (HPLC, Daicel Chiralcel OJ, 0.5 mL/min, 10% 2-PrOH/hexane) (*R*) t_1 = 21.38 min, (*S*) t_2 = 25.81 min; ***N*-acetyl-*m*-methylphenylalanine methyl ester** (HPLC, Daicel Chiralcel OJ, 1.0 mL/min, 10% 2-PrOH/hexane) (*R*) t_1 = 14.75 min, (*S*) t_2 = 18.36 min; ***N*-acetyl-*m*-methoxyphenylalanine methyl ester** (HPLC, Daicel Chiralcel OJ, 0.5 mL/min, 10% 2-PrOH/hexane) (*R*) t_1 = 24.79 min, (*S*) t_2 = 31.12 min; ***N*-acetyl-*m*-(benzyloxy)phenylalanine methyl ester** (HPLC, Daicel Chiralcel OJ, 1.5 mL/min, 10% 2-PrOH/hexane) (*R*) t_1 = 19.59 min, (*S*) t_2 = 24.52 min; ***N*-acetyl-*m*-nitrophenylalanine methyl ester** (HPLC, Daicel Chiralcel OJ, 1.5 mL/min, 10% 2-PrOH/hexane) (*R*) t_1 = 19.99 min, (*S*) t_2 = 22.52 min; ***N*-acetyl-*o*-fluorophenylalanine methyl ester** (HPLC, Daicel Chiralcel OJ, 1.0 mL/min, 10% 2-PrOH/hexane) (*R*) t_1 = 8.98 min, (*S*) t_2 = 12.06 min; ***N*-acetyl-3,5-difluorophenylalanine methyl ester** (HPLC, Daicel Chiralcel OJ, 0.5 mL/min, 10% 2-PrOH/hexane) (*R*) t_1 = 16.24 min, (*S*) t_2 = 18.51 min; ***N*-acetyl-3,5-dimethoxyphenylalanine methyl ester** (HPLC, Daicel Chiralcel OJ, 1.0 mL/min, 10% 2-PrOH/hexane), (*R*) t_1 = 16.07 min, (*S*) t_2 = 19.76 min; ***N*-acetyl-3,5-bis(trifluoromethyl)-phenylalanine methyl ester** (capillary GC, 180 °C, isothermal) (*R*) t_1 = 18.73 min, (*S*) t_2 = 19.63 min; ***N*-acetylvaline methyl ester** (capillary GC, 150 °C, isothermal) (*R*) t_1 = 12.97 min, (*S*) t_2 = 13.55 min; ***N*-benzoylphenylalanine methyl ester** (HPLC, Daicel Chiralcel OJ, 1.0 mL/min, 10% 2-PrOH/hexane) (*R*) t_1 = 10.1 min, (*S*) t_2 = 13.4 min; ***N*-(carbobenzoyloxy)alanine methyl ester** (capillary GC, 170 °C, isothermal) (*R*) t_1 = 43.89 min, (*S*) t_2 = 45.01 min; **methyl 2-(*N*-(carbobenzyloxy)amino)pentanoate** (capillary GC, 150 °C for 20 min, 10 °C/min, 180 °C for 45 min) (*R*) t_1 = 63.21 min, (*S*) t_2 = 64.22 min.

Absolute Configurations. Hydrogenation product absolute configurations were established by comparison of the sign of optical rotation with that of the configurationally assigned compound. The following referenced compounds were used for comparison: **(*S*)-*N*-acetylphenylalanine methyl ester** ($[\alpha]^{20}_D$ = +16.4° (*c* 2, MeOH));[43] **(*S*)-*N*-acetylalanine methyl ester** ($[\alpha]^{23}_D$ = –91.7° (*c* 2, H_2O));[44] **(*S*)-*N*-acetylleucine methyl ester** ($[\alpha]^{17}_D$ = –42.0° (*c* 3.3, MeOH));[45] **(*S*)-*N*-benzoylphenylalanine methyl ester** ($[\alpha]^{25}_D$ = –45.3° (*c* 1, MeOH));[46] **(*S*)-methyl 2-(*N*-acetylamino)butanoate** ($[\alpha]^{25}_D$ = –75.1° (*c* 2.2, H_2O));[47] **(*S*)-*N*-acetyl-3-(2-naphthyl)alanine methyl ester** ($[\alpha]^{25}_D$ = +44.6° (*c* 0.4, EtOH));[48] **(*S*)-*N*-acetyl-3-(1-naphthyl)alanine methyl ester** ($[\alpha]^{20}_D$ = –18.1° (*c* 1.59, EtOH));[49] and **(*R*)-*N*-acetyl-3-(2-thienyl)alanine** ($[\alpha]^{25}_D$ = –43.2° (*c* 1.0, EtOH)).[50] All other analogous products which gave the same sign of optical rotation, and which by chiral chromatography eluted in the same order, were assigned the same absolute configuration. In all cases, for example, (*R*,*R*)-Et-DuPHOS–Rh produced *N*-acetylphenylalanine and substituted *N*-acetylphenylalanine derivatives which had a negative sign of rotation in chloroform and which were the first peaks to elude by chiral HPLC (Chiralcel OJ). All such products were assigned the *R* absolute configuration.

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Supplementary Material Available: Spectroscopic and optical rotation data for substituted *N*-acetylphenylalanine methyl esters and X-ray diffraction data including tables of positional and isotropic thermal parameters, anisotropic thermal parameters, interatomic bond distances, intramolecular bond angles, and fully labeled ORTEP plots for complexes [(COD)Rh((*R*,*R*)-Me-BPE)]$^+SbF_6^-$, [(COD)Rh((*S*,*S*)-Me-DuPHOS)]$^+SbF_6^-$, and [(*R*)-[*N*,*N*-dimethyl(α-methylbenzyl)aminato-*C*,*N*]palladium-((*R*,*R*)-*i*-Pr-BPE)]$^+SbF_6^-$ (26 pages); tables of observed and calculated structure factor amplitudes (34 pages). Ordering information is given on any current masthead page.

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