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Synthesis and Application of Phosphinoferrocenylaminophosphine Ligands for Asymmetric Catalysis

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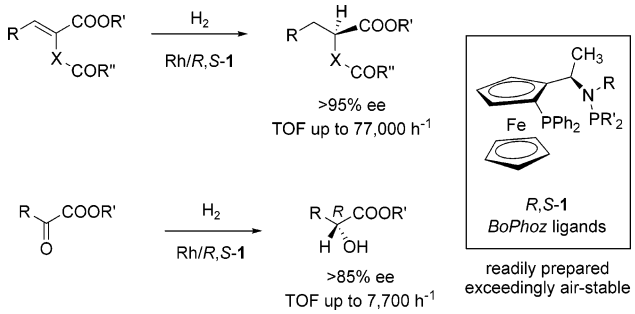

A new class of bidentate ligands utilizing a phosphine−aminophosphine structure has been prepared on a ferrocenylethyl backbone in a straightforward and scalable fashion from acetylferrocene. The unique property of the α-ferrocenyl carbonium ion that allows the replacement of a variety of "leaving groups" with retention of configuration greatly facilitates the synthesis, and a number of ligands have been prepared by varying the nitrogen and phosphorus substituents on the aminophosphine. These readily prepared phosphinoferrocenylaminophosphines, known as *BoPhoz* ligands, show surprising hydrolytic and air stability, with no degradation after 3 years open to the air. The rhodium complexes of these ligands show exceedingly high enantioselectivities (generally >95% ee) and activities often in excess of 50 000 catalyst turnovers per hour for the asymmetric hydrogenation of a wide variety of dehydro-α-amino acid and itaconic acid derivatives. They also show high activity and good to excellent enantioselectivity for the hydrogenation of a number of α-ketoesters.

Introduction

Asymmetric catalysis is at the forefront of organic chemistry research due to the immaturity of the science and its unparalleled potential for the generation of single enantiomer materials. The ever-increasing importance of single enantiomer pharmaceuticals and the lack of general and effective alternative methodology for the preparation of these materials and their building blocks have fueled intense interest in finding useful asymmetric catalysts.

Asymmetric catalysts are usually discrete metal complexes containing one or more chiral ligands. These ligands are usually enantiomerically pure and are the agents inducing the asymmetry, generally through steric interactions, although electronic effects can play a role. The complexes can either be isolated materials or can be prepared in situ using the appropriate amount of ligand and a metal catalyst precursor.

A large number of complexes have been prepared and examined for asymmetric catalysis.[1] The great majority of phosphorus-based ligands are C_2-symmetric carbon-linked phosphines (including triaryl, trialkyl, and aryl-alkyl species). Significantly lesser in number are other arrangements such as bidentate bis-aminophosphines,[2] bis-phosphites,[3] bis-phosphinites,[4] bis-phosphonites,[5] and mixed ligands such as phosphine−phosphite,[6] amino-phosphine−phosphinite,[7] phosphine−phosphonite,[8] phos-

(1) For recent reviews, see: (a) Ohkuma, T.; Kitamura, M.; Noyori, R. In *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; Wiley-VCH: New York, 2000; pp 1−110. (b) Brown, J. M. in *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfalz, A., Yamamoto, H., Eds.; Springer-Verlag: Berlin, 1999; Vol. I, pp 121−182. (c) Tang, W.; Zhang, X. *Chem. Rev.* **2003**, *103*, 3029−3069.

(2) Fiorini, M.; Giongo, G. M. *J. Mol. Catal.* **1980**, *7*, 411 and references therein.

(3) Reetz, M. T.; Neiberger, T.*Angew. Chem., Int. Ed.* **1999**, *38*, 179 and references therein.

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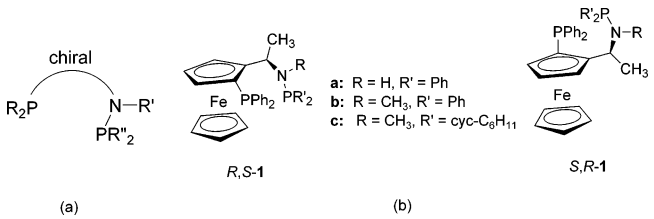


FIGURE 1. Phosphine−aminophosphine ligands.

phine−phosphoramidite,[9] and phosphonite−phosphite[10] systems.

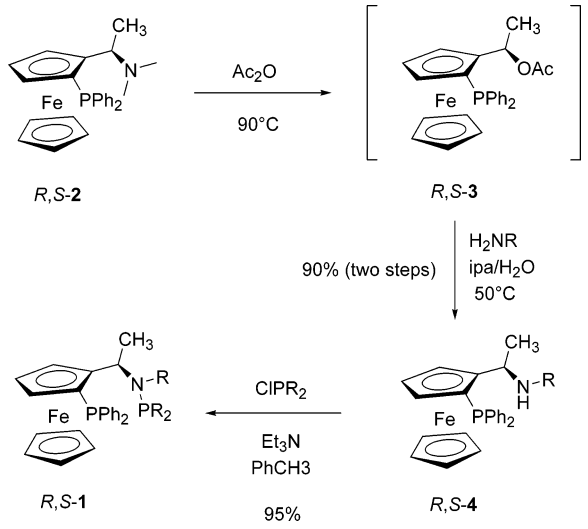
Although many of these ligands afford good asymmetric induction for a narrow set of substrates, there are only a few that consistently afford superior enantioselectivity, even for a single reaction type. Unfortunately, these latter ligands tend to be very dear as they are often structurally complex, challenging to prepare, and not particularly air-stable. Thus, a highly enantioselective readily prepared cost-effective ligand or series of ligands for asymmetric catalysis would be of great interest. This paper deals with the preparation and utility of just such a family of ligands.[11]

Results and Discussion

Ligand Design and Synthesis. Although there are a wide variety of reported ligand substitution patterns, there are no examples of phosphine−aminophosphine species as ligands for asymmetric catalysis. The lone proline-derived example of this type of compound was only examined structurally and not utilized for any reactions.[12]

The simplest approach to the phosphine−aminophosphine ligation motif involves linking the phosphine with the aminophosphine through a chiral backbone (Figure 1a). The ferrocenylethyl moiety was chosen as the chiral backbone as it has a very well-defined three-dimensional structure with a significant steric size, which affords an enhanced possibility for high asymmetric induction (particularly important for ligands without C_2-symmetry). Also, the 1-ferrocenylethyl species is readily generated in high enantiomeric purity, and substitution at the α center is particularly facile and occurs with absolute retention of configuration,[13] greatly simplifying the ligand

SCHEME 1. BoPhoz Ligand Synthesis



syntheses. The preparation of ligands such as BPPFA,[14] JOSIPHOS,[15] and several others[16] are based on this 1-ferrocenylethyl backbone. The phosphine−aminophosphine ligands shown in structures *R*,*S*- and *S*,*R*-**1** (Figure 1b) were designed to take advantage of the synthetic simplicity and strong steric environment of the ferrocenylethyl system while introducing a new phosphine−aminophosphine ligand class for asymmetric catalysis.

The synthesis of **1** is predicated on the preparation of either enantiomer of *N*,*N*-dimethyl 2-diphenylphosphinoferrocenylethylamine (**2**) from acetylferrocene. The initial side-chain chirality can be introduced in high enantiomeric purity (generally >90% ee) via a number of methods including classical resolution,[13a,17] enzymatic resolution,[18] and CBS-catalyzed borane reduction.[19] Diastereoselective lithiation of *R*- or *S*-*N*,*N*-dimethyl ferrocenylethylamine[13a] followed by reaction with chlorodiphenylphosphine as described by Kumada and Hayashi[14a] affords phosphine **2** as a 96:4 ratio of diastereomers (*R*,*S*-**2**:*R*,*R*-**2** or the enantiomeric pair). A single crystallization of this material affords absolute diastereomeric and enantiomeric purity, even when starting with enantiomerically impure precursor (e.g., 90% ee).

Utilizing the unique reactivity of the α-ferrocenylethyl carbonium ion, the dimethylamino compound **2** was converted to acetate **3** by reaction with acetic anhydride at 90 °C for 3.5−6 h (Scheme 1). Although acetate **3** can be precipitated in over 90% yield by addition of the reaction solution to a mixture of 2-propanol and water, the reaction mixture containing **3** was usually added

(4) (a) Cullen, W. R.; Sugi, Y. *Tetrahedron Lett*. **1978**, *19*, 1635. (b) Selke, R.; Pracejus, H. *J. Mol. Catal.* **1986**, *37*, 213. (c) Rajanbabu, T. V.; Ayers, T. A.; Halliday, G. A.; You, K. K.; Calabrese, J. C. *J. Org. Chem.* **1997**, *62*, 6012. (d) Chan, A. S. C.; Hu, W.; Pai, C. C.; Lau, C.-P.; Jiang, Y.; Mi, A.; Yan, M.; Sun, J.; Lou, R.; Deng, J. *J. Am. Chem. Soc.* **1997**, *119*, 9570.

(5) Reetz, M. T.; Gosberg, A.; Goddard, R.; Kyung, S.-H. *Chem. Commun.* **1998**, 2077 and references therein.

(6) Sakai, N.; Mano, S.; Nozaki, K.; Takaya, H. *J. Am. Chem. Soc*. **1993**, *115*, 7033.

(7) (a) Krause, H. W.; Kruezfeld, H.-J.; Schmidt, U.; Dobler, Ch.; Michalik, M.; Taudien, S.; Fischer, C. H. *Chirality* **1996**, *8*, 173. (b) Mi, A.; Lou, R.; Jiang, Y.; Deng, J.; Qin, Y.; Fu, F.; Li, Z.; Hu, W.; Chan, A. S. C. *Synlett* **1988**, 847.

(8) Reetz, M. T.; Gosberg, A. *Tetrahedron: Asymmetry* **1999**, *10*, 2129.

(9) Francio, G.; Faraone, F.; Leitner, W. *Angew. Chem., Int. Ed.* **2000**, *39*, 1428.

(10) Reetz, M. T.; Pasto, M. *Tetrahedron Lett.* **2000**, *41*, 3315.

(11) A preliminary report of this work appeared in: Boaz, N. W.; Debenham, S. D.; Mackenzie, E. B.; Large, S. E. *Org. Lett.* **2002**, *4*, 2421−2424.

(12) Münzenberg, R.; Rademacher, P.; Boese, R. *J. Mol. Struct.* **1998**, *444*, 77−90.

(13) (a) Marquarding, D.; Klusacek, H.; Gokel, G.; Hoffmann, P.; Ugi, I. *J. Am. Chem. Soc*. **1970**, *92*, 5389−5393. (b) Gokel, G. W.; Marquarding, D.; Ugi, I. K. *J. Org. Chem.* **1972**, *37*, 3052−3058.

(14) (a) Hayashi, T.; Mise, T.; Fukushima, M.; Kogatani, M.; Nagashima, N.; Hamada, Y.; Matsumoto, A.; Kawakami, S.; Konishi, M.; Yamamoto, K.; Kumada, M. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 1138−1151. (b) Yamamoto, K.; Wakatsuki, J.; Sugimoto, R. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 1132−1137.

(15) Togni, A.; Bruetel, C.; Schnyder, A.; Spindler, F.; Landert, H.; Tijani, A. *J. Am. Chem. Soc.* **1994**, *116*, 4062−4066.

(16) For reviews, see: (a) Richards, C. J. *Tetrahedron: Asymmetry* **1998**, *9*, 2377−2407. (b) Colcacot, T. J. *Chem. Rev.* **2003**, *103*, 3101−3118.

(17) Gokel, G. W.; Ugi, I. K. *J. Chem. Educ.* **1972**, *49*, 294−296.

(18) Boaz, N. W. *Tetrahedron Lett.* **1989**, *30*, 2061−2064.

(19) (a) Wright, J.; Frambes, L.; Reeves, P. *J. Organomet. Chem.* **1994**, *476*, 215−217. (b) Brieden, W. US Patent No. 5760264, 1998.

directly to the desired amine in aqueous 2-propanol, and the resulting mixture was heated to 50 °C for 12−18 h to afford the secondary amine **4**. The isolation was optimized for the reaction with methylamine, in which case dilution of the reaction mixture with water precipitated the desired amine **4b** in 95% overall yield from **2**.

Derivatization of the amine with chlorodiphenylphosphine in the presence of an acid scavenger proceeded smoothly when the R group of **4** was hydrogen, methyl, ethyl, or *n*-propyl. In addition, the phosphine could be varied by using commercially available chlorophosphines (e.g., chlorodiethylphosphine, chlorodicyclohexylphosphine). Simple removal of the triethylammonium chloride at the end of the reaction by filtration and a solvent strip afforded the desired ligand **1** as a brittle foam. The enantiomeric purity of the final ligand was assumed to be unchanged from **2** due to the retention of configuration observed with nucleophilic substitution at the α-ferrocenylethyl group and was verified by chiral HPLC for the cases where R was hydrogen (**1a**) or methyl (**1b**).

The nature of the ligands **1** as brittle foams posed operational difficulties, particularly for larger scale reactions. It was found that ligand **1b** can be isolated as a melt instead of a foam by concentration from a 2-methyl-2-propanol solution and then crystallized from hot 2-methyl-2-propanol by cooling to ambient temperature. The recovery from 2-methyl-2-propanol was moderate (ca. 50%), but dilution of the cooled crystallization mixture with water prior to filtration afforded improved recovery (>90%) of ligand **1b** with no observable hydrolysis of the N−P bond (presumably due to the insolubility of **1b** in the mixture). This crystallization protocol appears to be specific for 2-methyl-2-propanol, as 2-propanol affords poor recovery, 2-propanol/water affords little solid, and 2-methyl-2-butanol affords **1b** as a gum. In addition, there is limited evidence that the crystallization enhances the enantiomeric purity of ligand **1b** (crystallization has afforded both enantiomers with >99.9% ee). This crystallization procedure has proven effective for most ligands **1**.

Thus ligands **1** are synthetically advantaged over many other species—there are no exotic reagents, no temperature extremes, no air-sensitive intermediates or products, and only one moisture-sensitive (*n*-butyllithium) reaction. Indeed, many of the reactions use water as a solvent! In addition, both enantiomers of ligand **1** are equally available.

Solvolytic Stability. The solvolytic stability of ligands **1** in alcoholic solvents (often used in asymmetric hydrogenations) was a concern, as simple aminophosphines are in general very reactive toward nucleophiles through heterolytic cleavage of the nitrogen−phosphorus bond.[4c] This stability was investigated by stirring **1b** with a large excess of a variety of alcoholic solvents at ambient temperature with periodic examination by ^{1}H NMR. The results (Table 1) indicate moderate stability in methanol with increasing stability upon increasing hindrance around the alcohol. Complexation of **1b** to rhodium had an unexpected stabilizing effect, resulting in an approximate half-life in methanol of 61 h. This is a minimum value and may result from oxidative instability of the complex rather than hydrolytic instability, as no measures were taken to exclude oxygen from the NMR tube. Thus, the ligands and particularly the complexes

TABLE 1. Stability of Ligand 1b and Its Rhodium Complex in Alcohol Solvents at Room Temperature

	half-life (h)	
solvent	ligand **1b**	(COD)Rh-**1b**
methanol	3	61
ethanol	8	nd
2-propanol	48	nd
2-methyl-2-propanol	>1 month	nd

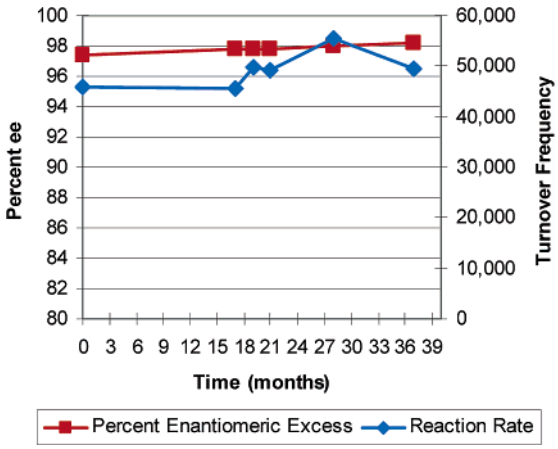


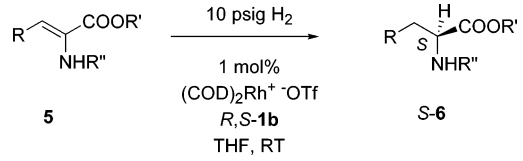
FIGURE 2. Air stability of *R*,*S*-**1b**.

appear to be more stable than anticipated to hydroxylic solvents. Indeed, many of the best reactions under the most demanding conditions of low catalyst loadings have been obtained using methanol as solvent.

Air Stability. Many phosphine ligands are not particularly air-stable, and a large number of ligand intermediates are very air-sensitive. This is due to the very nature of phosphines, which are prone to oxidation, particularly if the phosphines possess hydrogen or alkyl substituents (as opposed to all aryl groups). It was anticipated that the phosphine−aminophosphines **1** might show enhanced air stability due to the combination of a ferrocenyl phosphine (known to be very stable) and an aminophosphine in which the electronegative nature of the nitrogen could decrease the electron density of the phosphorus and reduce its propensity toward oxidation. The air stability of ligand *R*,*S*-**1b** was examined by holding this material at ambient temperature open to the air (in a bottle with the top off) and periodically testing it as the rhodium complex for asymmetric hydrogenation. Over more than a 3 year period, within experimental error no degradation of enantioselectivity or activity for the hydrogenation of 2-acetamidocinnamic acid (substrate-to-catalyst ratio 10 000:1 as described below) was observed (Figure 2).

***N*-Acyl Dehydroamino Acid Asymmetric Hydrogenation Screening.** Asymmetric hydrogenation is one of the most powerful methods for inducing chirality into an achiral substrate, as readily available starting materials (olefins, ketones, imines) can be transformed using an inexpensive reagent (hydrogen) into high-value high-demand products.[1] The area of asymmetric hydrogenation that has received the most attention is the preparation of amino acid derivatives by the asymmetric hydrogenation of *N*-acyl dehydroamino acid species. *N*-Acyl dehydroamino acids are excellent substrates for

TABLE 2. Asymmetric Hydrogenation of Dehydroamino Acid Derivatives[a]



5 **S-6**

entry	substrate	R	R′	R″	ee (%)
1	**a**	phenyl	CH_3	Ac	99.1
2	**b**	phenyl	H	Ac	99.4
3	**c**	phenyl	CH_3	Boc	99.5
4	**d**	phenyl	CH_3	Bz	98.1
5	**e**	*p*-cyanophenyl	CH_3	Ac	99.0
6[b]	**f**	*p*-nitrophenyl	CH_3	Ac	97.7
7[c,d]	**g**	*p*-chlorophenyl	CH_3	Ac	98.1
8	**h**	*p*-fluorophenyl	CH_3	Ac	97.2
9[e,e,f]	**i**	*p*-methoxyphenyl	CH_3	Ac	98.1
10[b,c]	**j**	*m*-methoxyphenyl	CH_3	Ac	98.0
11[c,d]	**k**	*o*-methoxyphenyl	CH_3	Ac	97.7
12	**m**	2-furyl	CH_3	Bz	96.4
13[e]	**n**	2-furyl	CH_3	Boc	97.2
14[e]	**o**	1-naphthyl	CH_3	Ac	99.3
15	**p**	1-naphthyl	CH_3	Boc	98.2
16[e]	**q**	2-naphthyl	CH_3	Ac	98.1
17[e]	**r**	2-naphthyl	CH_3	Boc	97.4
18[g]	**s**	H	CH_3	Ac	98.4
19[h]	**t**	H	H	Ac	96.1
20[i]	**u**	H	CH_3	Cbz	98.8
21[e]	**v**	$PhCH_2$	CH_3	Cbz	98.1
22[j]	**w**	cyclopropyl	CH_2Ph	Boc	98.6

[a] Reactions were run for 1 h at 10 psig hydrogen at ambient temperature, conversion was >95% except where indicated differently. [b] Reaction run for 30 min. [c] Reaction run with 2 mol % catalyst. [d] Reaction run for 2 h. [e] Reaction run for 6 h. [f] Conversion was 92%. [g] Reaction run with 2.5 mol % catalyst. [h] Reaction run for 24 h. [i] Reaction run in ethyl acetate. [j] Reaction run with 0.1 mol % catalyst.

asymmetric hydrogenation using rhodium catalysts due to the bidentate binding of the substrate through the olefin and the *N*-acyl carbonyl oxygen.[1b] Preliminary results indicated that ligand **1b** afforded the highest enantioselectivities for the asymmetric hydrogenation of a limited number of dehydroamino acid derivatives.[11] Thus, the hydrogenations of a wide variety of *N*-acyl dehydroamino acid derivatives were examined with the rhodium complex of this ligand under screening conditions (0.5 mmol of substrate at 0.1 M concentration, 100:1 substrate/catalyst ratio).

The dehydroamino acid hydrogenation substrates were generally prepared by either the classical Erlenmeyer condensation[20] or a Horner−Wadsworth−Emmons condensation of the desired aldehyde with an appropriately substituted amido acid phosphonate reagent.[21]

The results for aromatic amino acids (Table 2, entries 1−17) indicate that these species are hydrogenated with exceedingly high *S* enantioselectivity (using *R*,*S*-**1b**) regardless of the electronic or positional nature of the substitutents on the aromatic ring or whether the carboxyl group was an ester or an acid. Finally, the more synthetically useful carbamate substituents on the amine performed as well as amide groups, a result that is not always the case for other ligands.[22]

There are certain ligands that afford high enantioselectivities for some aromatic amino acids but not for alkyl-substituted analogues.[5c] The results in Table 2, entries 18−22 indicate that the rhodium complex of *R*,*S*-**1b** is a truly general catalyst for amino acid preparation, as in addition to the superior results with the aryl amino acids it affords high enantioselectivity for a large number of alkyl-substituted amino acids with a variety of carboxyl and amino substituents.

One requirement for these reactions is a *Z* configuration of the olefin in substrate **5**. Much lower enantioselectivities (and rates) are observed for *E* olefins, a situation that has been observed with several other ligands.[23] Fortunately, most preparations of dehydroamino acids afford the *Z* isomer selectively, often specifically.

There are a number of factors that can play a role in asymmetric hydrogenation reactions. The optimal ligand-to-metal ratio was determined to be equimolar (bidentate binding), as deviating significantly above or below this ratio resulted in markedly lower substrate conversion over a standard time period (although the enantioselectivity remained the same). It was also noted that prehydrogenation of the rhodium complex prior to substrate introduction afforded a much less active catalyst.

Temperature effects were not highly pronounced, as hydrogenations performed at 0 °C afforded only a slight increase in enantioselectivity (but often within the error of the measurement). Limited results at higher temperature (30−35 °C) indicated little effect on enantioselectivity, although significantly higher temperature would be expected to erode the selectivity.

Solvent can play a crucial role in asymmetric hydrogenations, particularly as the resting state of the catalyst is often depicted as a solvated complex. Standard solvents (THF, toluene, ethyl acetate, acetone, methanol, 2-propanol) afforded nearly identical high enantioselectivity and high conversion in the reduction of substrate **5a** with the rhodium complex of *R*,*S*-**1b**. Strongly ligating solvents such as diethoxymethane (potential bidentate donor), DMF, DMSO, and NMP afforded poor results for this reaction, likely due to stable nonproductive solvent-ligated complexes.

Hydrogen pressure can have a large effect upon the enantioselectivity of rhodium-catalyzed asymmetric hydrogenation reactions. This is perhaps most pronounced with regards to dehydroamino acid hydrogenations. The rationale behind these effects is based on the accepted mechanism of these particular reactions,[1b,24] wherein substrate binding (through both the olefin and amide carbonyl) results in the formation of two diastereomeric complexes in dynamic equilibrium. In many cases the minor diastereomer is sufficiently more reactive toward hydrogen (or perhaps subsequent reductive elimination) and diastereomer interconversion is sufficiently rapid at low hydrogen pressures to overwhelm the diasteromeric ratio and provide the major observed product enantiomer.

(20) See, for example: Herbst, R. M.; Shemin, D. In *Organic Synthesis*; Blatt, A. H., Ed.; John Wiley: New York, 1943; Collect. Vol. 2; pp 1−3.

(21) (a) Schmidt, U.; Lieberknecht, A.; Wild, J. *Synthesis* **1984**, 53−60. (b) Schmidt, U.; Griesser, H.; Leitenberger, V.; Lieberknecht, A.; Mangold, R.; Meyer, R.; Riedl, B. *Synthesis* **1992**, 487−490. (c) Schmidt, U.; Lieberknecht, A.; Wild, J. *Synthesis* **1988**, 159−172.

(22) Kreuzfeld, H.-J.; Döbler, C.; Krause, H. W.; Facklam, C. *Tetrahedron: Asymmetry* **1993**, *4*, 2047−2051.

(23) Reference 1a, pp 11−12.

(24) See ref 1b, pp 124−132 and references therein.

TABLE 3. Pressure Effects on Rhodium−*R*,*S*-1b-Catalyzed Asymmetric Hydrogenation of Dehydroamino Acid Derivatives 5[a]

entry	substrate	R	R″	ee (%) at 10 psig H_2	ee (%) at 300 psig H_2
1	**a**	phenyl	Ac	99.1	96.8
2	**w**	cyclopropyl	Boc	98.6	96.6[b]
3	**s**	H	Ac	98.5	95.2[b]
4	**g**	*p*-chlorophenyl	Ac	98.8	96.2
5	**i**	*p*-methoxyphenyl	Ac	98.1	97.3
6	**k**	*o*-methoxyphenyl	Ac	97.7	96.7
7	**o**	1-naphthyl	Ac	99.3	97.4[b]
8	**q**	2-naphthyl	Ac	98.1	97.6[b]

[a] Reactions were run with 1 mol % catalyst in THF at ambient temperature except where indicated differently. [b] Reaction run in acetone as solvent.

At higher pressures, the enantioselectivity often erodes due to enhancement of the rate of hydrogen addition to both diastereomers such that this rate may begin to compete with their rate of interconversion. In some extreme cases the enantioselectivity can reverse (albeit with low ee) at higher hydrogen pressure.[25]

The hydrogenation of a variety of dehydroamino acid esters **5** using the rhodium complex of ligand **1b** at an elevated pressure of hydrogen (300 psig) showed little pressure dependence, affording the corresponding amino acid derivatives **6** with only slightly lower enantioselectivities (0.5−4.5% ee lower, with the majority only 0.5−3% ee lower) compared to low pressure (10 psig) results (Table 3). Indeed, some of these results (entries 7 and 8) may be due to a solvent rather than a pressure effect. Although the decrease may be due to any number of factors, the limited pressure effect suggests that the diastereomer interconversion rate (and thus the reaction rate) using the rhodium complex of the ligand **1b** might be rapid.

Catalytic Activity in Dehydroamino Acid Asymmetric Hydrogenations. Although high enantioselectivity is a prerequisite for an effective asymmetric catalyst, high catalytic activity is also important, and often overlooked. This activity has a direct effect on the catalyst contribution cost per mole of product, as the cost is a combination of the amount of catalyst used (turnover number) and the reaction time (turnover frequency) of the expensive precious metal complex, unless the catalyst can be reused and/or recycled. The limited pressure effects observed with the rhodium−**1b** complex suggested that this catalyst may possess high inherent reactivity. Thus the kinetics of asymmetric hydrogenation reactions using the rhodium complex of **1b** were investigated and compared to the rhodium complexes of a number of other ligands, as limited literature data is available.[22,26] The catalytic activities (turnover frequencies) were determined in a sealed pressure vessel by correlating pressure drop (initial hydrogen pressure 40 psig) with conversion vs time, utilizing the initial rates wherein the reactions were zero order in substrate (in practice, up to at least 40% conversion) and all afforded excellent linearity ($R^2 > 0.995$).

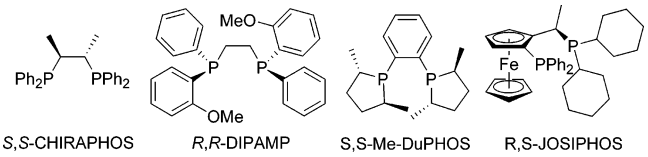
The results for the hydrogenation of substrate **5a** presented in Table 4 indicate that the rhodium complex of **1b** has an exceedingly high turnover frequency. These results validate the literature reports that Rh-methyl DuPHOS (Chart 1) is a highly catalytically active complex;[27] however, Rh−**1b** is nearly an order of magnitude faster for this transformation.

TABLE 4. Catalyst Activity Comparison for the Asymmetric Hydrogenation of 5a[a]

entry	ligand	chelate size	catalyst turnover rate (h^{-1})	ee (%)
1	CHIRAPHOS[b]	5	30	87
2	DIPAMP[b]	5	440	92
3	Methyl DuPHOS	5	4800	97
4	JOSIPHOS[c]	6	960	44
5	*R*,*S*-**1b**	7	30 500	97

[a] Reactions were run at an S/C ratio of 10 000:1 in methanol at ambient temperature under 40 psig hydrogen except where indicated differently. [b] Reaction run at S/C of 1000:1 to afford appreciable rate. [c] Reaction run at S/C of 5000:1 to afford appreciable rate.

CHART 1. Ligand Structures



Part of the reason for this enhanced activity may lie in the size of the metallacycle that is generated from the ligand and the rhodium. Halpern has shown that ligands that afford a seven-membered rhodium chelate (such as **1b**) undergo internal rearrangement (facilitating diastereomer interconversion) much more rapidly than smaller chelate rings,[28] resulting in faster replenishment of the minor diastereomer and thus reaction rate enhancement. Limited data suggests that other seven-membered chelate ligands (e.g., chiral phosphinites) also show rate enhancements over ligands with smaller chelates.[5c] The price exacted for this rate enhancement is often a severe loss of enantioselectivity due to ligand conformational flexibility. Ligand **1b** is an anomaly in this regard, as high enantioselectivity is achieved concurrent with high rates of reaction, perhaps due to conformational restriction enforced by the sp^2-hybridized carbons of the ferrocene cyclopentadiene ring.

The high activity and high enantioselectivity observed for the Rh−*R*,*S*-**1b** asymmetric hydrogenation of **5a** was mirrored in the asymmetric hydrogenations of a variety of dehydroamino acids with this catalyst (Table 5). In particular, even the challenging hydrogenation of the highly hindered *N*-Boc dehydrocyclopropylalanine benzyl ester with the rhodium complex of **1b** exhibited catalytic activity in excess of 9000 turnovers per hour.[29]

These high catalyst turnover frequencies translate directly to high turnover numbers, as these rapid rates allow the use of vanishingly small quantities of catalyst (as low as 0.002 mol %) while maintaining short reaction times, resulting in an advantageously low ligand and

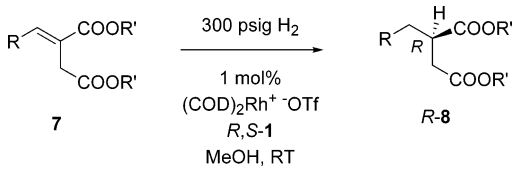
(25) Nogradi, M. In *Stereoselective Synthesis*; VCH: Weinheim, 1995; p 46 and references therein.
(26) Oliver, J. D.; Riley, D. P. *Organometallics* **1983**, *2*, 1032−1038.
(27) Armstrong, S. K.; Brown, J. M. *Tetrahedron Lett.* **1993**, *34*, 879−882.
(28) Landis, C. R.; Halpern, J. *J. Organomet. Chem.* **1983**, *250*, 485−490.
(29) Boaz, N. W.; Debenham, S. D.; Large, S. E.; Moore, M. K. *Tetrahedron: Asymmetry* **2003**, *14*, 3575−3580.

TABLE 5. Catalyst Activity of Rh−1b with Various Dehydroamino Acids 5[a]

entry	substrate	R	R′	R″	catalyst turnover rate (h^{-1})	ee (%)
1[b]	**a**	phenyl	H	Ac	68 100	98.0
2[c]	**g**	4-chlorophenyl	CH_3	Ac	25 300	95.3
3	**h**	4-fluorophenyl	CH_3	Ac	40 100	96.8
4[c]	**r**	2-naphthyl	CH_3	Ac	13 900	98.0
5[d]	**w**	cyclopropyl	$PhCH_2$	Boc	9200	96.4

[a] Reactions were run in methanol with 40 psig hydrogen at an S/C ratio of 2500:1 except where indicated differently. All reactions afforded >98% conversion. [b] Reaction run at S/C of 10 000:1. [c] Reaction run in 9:1 toluene/methanol. [d] Reaction run at S/C of 1000:1.

TABLE 6. Asymmetric Hydrogenation of Itacontate Derivatives



entry	ligand	substrate	R	R′	ee (%)	conv (%)
1	*R*,*S*-**1b**	**a**	H	H	97.6	99.8
2	*R*,*S*-**1b**	**b**	H	CH_3	94.0	99.9
3	*R*,*S*-**1b**	**c**	Ph	H	90	99.5
4[b]	*R*,*S*-**1a**	**a**	H	H	94.0	99.8
5	*R*,*S*-**1a**	**c**	Ph	H	99	>99
6[b]	*R*,*S*-**1a**	**d**	Ph	CH_3	80	>95

[a] Reactions run for 6 h at 300 psig hydrogen at ambient temperature. [b] Reaction run in acetone.

metal contribution cost for the transformation. The only limitation then becomes trace impurities in the substrate or solvent that may act as catalyst poisons.

Thus, the rhodium complex of ligand *R*,*S*-**1b** is a truly general catalyst for the hydrogenation of dehydroamino acid derivatives, affording exceedingly high enantioselectivities independent of the carboxyl, amino, and terminal substituents.

Itaconate Asymmetric Hydrogenations. Itaconic acid derivatives are structurally and electronically similar to *N*-acyl dehydroamino acids, in that the olefin and the distal carbonyl ligating groups of the itaconate are positioned in an identical fashion to the olefin and amide carbonyl of the dehydroamino acids. Thus many catalysts that work well for dehydroamino acid hydrogenation also work well for itaconates. The rhodium complexes of ligands **1** were effective species for the asymmetric hydrogenation of various itaconate derivatives **7** at 300 psig hydrogen to provide the corresponding 2-substituted succinates **8**, with the *R*,*S* enantiomer of the ligands (*R*,*S*-**1**) invariably affording the *R* enantiomer of the succinate **8** (Table 6). For unsubstituted itaconates, the rhodium complex of **1b** afforded the best results (Table 6, compare entries 1 and 4). However, for *β*-substituted itaconates, the rhodium complex of **1a** afforded decidedly superior enantioselectivities (compare entries 3 and 5). In all cases the diacid substrates performed much better than the diesters.

The results shown in Table 7 indicate that, similar to the dehydroamino acid derivatives, the hydrogenation of unsubstituted itaconate derivatives with the rhodium

TABLE 7. Catalyst Activity of Rh−1 with Various Itaconates 7[a]

entry	ligand	R	R′	solvent	TOF (h^{-1})[b]	ee (%)	conv (%)
1	*R*,*S*-**1b**	H	H	MeOH	53 200	96	96.1
2	*R*,*S*-**1b**	H	H	EtOH	46 200	96	95.5
3	*R*,*S*-**1b**	H	CH_3	MeOH	53 800	94	93.8
4	*R*,*S*-**1b**	H	CH_3	EtOH	77 700	94	94.0
5[c]	*R*,*S*-**1a**	Ph	H	MeOH	1200	nd	18.0

[a] Reactions were run at ambient temperature at 40 psig hydrogen at an S/C ratio of 2500:1 except where indicated differently. [b] Turnover frequency. [c] Reaction run at an S/C of 1000:1.

complex of **1b** also affords exceedingly high reaction rates while maintaining high enantioselectivities. In particular, the reaction of dimethyl itaconate with the rhodium complex of *R*,*S*-**1b** in ethanol afforded a turnover frequency in excess of 77 000 per hour, the highest rate observed for a rhodium-**1** catalyzed hydrogenation.

Surprisingly, the hydrogenation of phenylitaconic acid (**7c**) with the rhodium complex of **1a** had a disappointingly low reaction rate of about 1200 turnovers per hour (Table 7, entry 5). The literature suggests that the addition of base affords a rate enhancement in the hydrogenation of itaconic acids.[30] The addition of even a small amount of triethylamine (0.1 equiv) to this reaction with the preferred rhodium−*R*,*S*-**1a** complex afforded a large rate enhancement to 11 000 catalyst turnovers per hour while maintaining exceedingly high enantioselectivity. This effect may be due to the formation of the distal carboxylate anion, which should be a much stronger donor resulting in a stronger bond to the metal, with the improved chelation ability accounting for the increased rate. Surprisingly, there was no enhancement of the rate of itaconic acid (**7a**) hydrogenation with added amine.

α-Ketoester Asymmetric Hydrogenations. The asymmetric hydrogenation of α-ketoesters has received much less attention than the hydrogenation of dehydroamino acid derivatives and itaconates, and there are few ligands that afford high enantioselectivies across this substrate class.[1] This is a different type of reaction relative to dehydroamino acids or itaconates, since similar substrate ligation is not geometrically possible. The asymmetric hydrogenation of α-ketoesters in THF with the rhodium complexes of ligands **1** was ineffective at low pressure (10 psig hydrogen), but at high pressure (300 psig hydrogen) the *R* enantiomer of the hydroxyester **10** was obtained in 80−90+% ee using Rh−*R*,*S*-**1** (Table 8). The dicyclohexylphosphino-substituted ligand **1c** in particular afforded enhanced enantioselectivities (in some cases significantly improved, see entry 5) as compared to the diphenylphosphino species **1b** for these particular transformations. The high enantioselectivity and *R* configuration observed with substrate **9e** suggest that this reaction probably is a direct ketone hydrogenation, and does not proceed through the enol form, as **9e** is prohibited from enolization.

Unlike the hydrogenation of dehydroamino acid derivatives, the hydrogenation of α-ketoesters showed remarkable solvent effects (Table 9). An absolute reversal

(30) Burk, M. J.; Bienewald, F.; Harris, M.; Zanotti-Gerosa, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 1931−1933.

TABLE 8. Asymmetric Hydrogenation of α-Ketoesters 9 Using Rh−1[a]

entry	substrate	R	R′	ee (%) with *R*,*S*-**1b**	ee (%) with *R*,*S*-**1c**
1	**a**	CH_3	CH_3	86.8	88.1
2	**b**	CH_3	CH_2CH_3	83.4	90.8
3	**c**	$PhCH_2$	CH_3	72.8[b]	85.4[c]
4	**d**	$PhCH_2CH_2$	CH_2CH_3	85.2	92.4
5	**e**	-$C(CH_3)_2CH_2$-		71.7	97.2

[a] Reactions were run for 6 h at 300 psig hydrogen and afforded >95% conversion except where noted. [b] Conversion was 50.0%. [c] Conversion was 83.6%.

TABLE 9. Solvent Effects for the Asymmetric Hydrogenation of 9a Using Rh−*R*,*S*-1b[a]

entry	solvent	ee (%)	conv (%)
1	THF	87 *R*	98.3
2[b]	ethyl acetate	87 *R*	99.1
3	2-propanol	15 *S*	96.9
4	acetone	56 *S*	99.0
5	methanol	71 *S*	81.9

[a] Reactions were run with 1 mol % catalyst for 6 h at 300 psig hydrogen. [b] Reaction used 0.1 mol % catalyst.

of stereochemistry from *R* to *S* was observed for the hydrogenation of methyl pyruvate with the rhodium complex of *R*,*S*-**1b** upon changing from THF to methanol. Similar results were obtained with ethyl pyruvate (**9b**), ethyl 4-phenyl-2-oxobutyrate (**9c**), and dihydro-4,4-dimethylfuran-2,3-dione (**9e**) as substrates. Ligand *R*,*S*-**1c** showed similar but less pronounced solvent dependencies.

This type of significant solvent effect is unusual and is not seen with other ligands examined (e.g., **9a** with Rh−*S*-ethyl DuPHOS shows invariant *R* product in 25−44% ee). Potential explanations invoking hydrogen-bonding reactant geometry change (s-trans vs s-cis) or isomeric makeup (keto vs enol) are largely discounted by the analogous solvent effects observed with substrate **9e**, which is constrained both geometrically (s-cis configuration only) and isomerically (no enol form possible). The origin of this startling solvent effect is yet unknown.

The requirement for higher pressure for the effective asymmetric hydrogenation of α-ketoesters using the rhodium complex of **1** suggested that very slow hydrogenations would be observed under the standard reaction conditions (40 psig hydrogen). Although the rates are significantly lower than the dehydroamino acids or the itaconates, these reactions still usually afforded turnover frequencies above 1000 h^{-1}, indicative of a relatively fast reaction (Table 10).

There were several other features of note discovered in this investigation. First, the enantioselectivity dependence on solvent observed during the screening runs was preserved at these pressures and at low catalyst loadings (all reactions were performed at an S/C of 1000:1). Second, the hydrogenation in methanol was significantly

TABLE 10. Catalyst Activity of the Asymmetric Hydrogenation of Various α-Ketoesters 9 with Rh−1 Complex[a]

			R,*S*-**1b** results		*R*,*S*-**1c** results[b]	
entry	substrate	solvent	TOF[e] (h^{-1})	ee[d] (%)	TOF[e] (h^{-1})	ee[d] (%)
1	**a**	9:1 EtOAc/THF	2100	86.6	3360	89.6
2	**a**	MeOH	750	75.4 *S*	2350	11.2[e]
3	**b**	9:1 EtOAc/THF	4440	91.6	6220	91.6
4	**d**	9:1 EtOAc/THF	580	80.2	4370	90.2
5	**e**	9:1 EtOAc/THF	60	74.0	7770	95.8

[a] Reactions were run at ambient temperature at 40 psig hydrogen at an S/C ratio of 1000:1. [b] Reactions afforded >95% conversion except where indicated. [c] Catalyst turnover frequency per hour. [d] *R*-Enantiomer major unless otherwise noted. [e] 94.9% conversion.

slower than in ethyl acetate/THF. Third, although the hydrogenation rates using ligand **1b** exhibited a precipitous decline as the steric congestion of the substrate increased (see entries 4 and 5), this was not the case for the ligand **1c**. Substrate **9e** was particularly intriguing as, despite the large steric demands of a quaternary center next to the reacting ketone, it afforded the fastest overall rate using the rhodium complex of **1c**. The dicyclohexylphosphino ligand **1c** is decidedly faster than the diphenylphosphino ligand **1b** for all substrates, and for substrate **9e** was *over 2 orders of magnitude* faster. This indicates that the asymmetric hydrogenation of α-ketoesters with the rhodium complex of ligand **1c** is of practical value, and is a good addition to the hydrogenations of dehydroamino acid derivatives and itaconates for the rhodium complexes of ligands **1**.

Conclusion

The rhodium complexes of phosphine-aminophosphine ligands **1** are superb species for asymmetric hydrogenation. These species exhibit very high enantioselectivities and activities for the asymmetric hydrogenation of a wide variety of dehydroamino acids and itaconates, and high activities and good to excellent enantioselectivities for the asymmetric hydrogenation of α-ketoesters. Combining these reactivity characteristics with outstanding ligand air-stability and a robust and scalable synthesis affords species that are advantaged ligands for asymmetric catalysis. Additional ligands, complexes, and applications are under development.

Experimental Section

***R*-1-(*S*-2-Diphenylphosphino)ferrocenylethyl Acetate (*R*,*S*-3).**[14a] Dimethylamino compound *R*,*S*-**2** (20.0 g; 45.3 mmol) was combined with acetic anhydride (14.3 mL; 152 mol; 3.35 equiv), and the heterogeneous mixture was heated under nitrogen to 90 °C during which time it became homogeneous. The reaction mixture was held at 90 °C for 6 h, at which point TLC analysis indicated no **2** but much **3** (1:4 EtOAc/heptane, Et_3N deactivated). The mixture was cooled to ambient temperature. A small aliquot was removed, all volatiles were stripped from it, and the resulting material was analyzed directly by chiral HPLC to determine enantiomeric excess. The remainder of the material was poured into 170 mL of a 1:1 (v:v) mixture of 2-propanol and water in a cool water bath and washed in with a minimum volume of 2-propanol. The resulting suspension was stirred vigorously for 1 h, filtered, and

washed with water. The yellow solid was dried in vacuo at ambient temperature under a nitrogen purge to afford 19.08 g (92%) of *R*,*S*-**3**. Mp: 116−118 °C. ^{1}H NMR ($CDCl_3$) δ: 7.54−7.49 (m, 2H); 7.37 (m, 3 H); 7.26−7.15 (m, 5H); 6.210 (q, 1H, J = 3.85 Hz); 4.572 (br s, 1H); 4.356 (m, 1H); 4.048 (s, 5H); 3.80 (m, 1H); 1.631 (d, 3H, J = 6.32 Hz); 1.171 (s, 3H). ^{13}C NMR ($CDCl_3$) δ: 169.9 (s); 139.8 (d, J_{C-P} = 10 Hz); 137.1 (d, J_{C-P} = 9 Hz); 135.2 (d, J_{C-P} = 21 Hz); 132.9 (d, J_{C-P} = 19 Hz); 129.3 (s); 128.3 (d, J_{C-P} = 7 Hz); 128.1 (s); 128.0 (d, J_{C-P} = 5 Hz); 91.8 (d, J_{C-P} = 24 Hz); 72.5 (d, J_{C-P} = 5 Hz); 70.0 (s); 69.7 (s); 69.3 (d, J_{C-P} = 3 Hz); 68.5 (d, J_{C-P} = 10 Hz); 20.2 (s); 18.6 (s). Chiral HPLC (250 × 4.6 mm Chiralpak AD-H, 90:10 hexane/2-propanol, 1 mL/min, λ = 254 nm): t_R (*R*,*S*-**3**) 9.15 min, t_R (*S*,*R*-**3**) 10.18 min. $[\alpha]^{24}_D$ = −307 (*c* 0.92, $CHCl_3$).

***R*-1-(*S*-2-Diphenylphosphino)ferrocenylethylamine (*R*,*S*-4a).**[31] Acetate *R*,*S*-**3** (7.50 g; 16.4 mmol) was combined with 140 mL of 2-propanol. Ammonium hydroxide (17.8 mL; 411 mmol; 25 equiv) was added, and the reaction mixture was heated to 40 °C for 36 h and then to 45 °C for 12 h to completely consume **3**. After cooling to ambient temperature, water (35 mL; 0.25 volume based on 2-propanol) was added, resulting in a yellow precipitate containing various impurities formed during the reaction. After stirring for 30 min, these materials were removed by filtration and the filtrate was concentrated to remove the majority of the 2-propanol. Water (100 mL) was added resulting in a yellow solid. This was stirred for 30 min, and the solid was collected by filtration, washed with water, and dried in vacuo at ambient temperature under a nitrogen purge. This resulted in 5.61 g (83%) of *R*,*S*-**4a**. Mp: 130−131 °C. ^{1}H NMR ($CDCl_3$) δ: 7.56−7.51 (m, 2H); 7.39 (m, 3 H); 7.26 (m, 5H); 4.452 (br s, 1H); 4.284 (m, 1H); 4.248 (m, 1H); 4.022 (s, 5H); 3.772 (br s, 1H); 1.631 (br s, 2H); 1.460 (d, 3H, J = 6.59 Hz). ^{13}C NMR ($CDCl_3$) δ: 140.1 (d, J_{C-P} = 9 Hz); 137.3 (d, J_{C-P} = 9 Hz); 135.0 (d, J_{C-P} = 21 Hz); 132.9 (d, J_{C-P} = 18 Hz); 129.2 (s); 128.5 (s); 128.4 (s); 128.2 (d, J_{C-P} = 7 Hz); 100.6 (d, J_{C-P} = 23 Hz); 71.4 (s); 69.7 (s); 69.2 (s); 68.4 (br s); 45.4 (d, J_{C-P} = 9 Hz); 23.0 (s). HRMS *m*/*z*: calcd for $C_{24}H_{25}FeNP$ (M + H^+) 414.1074, found 414.1074. $[\alpha]^{24}_D$ = −325 (*c* 1.01, $CHCl_3$).

***N*-Diphenylphosphino-*R*-1-(*S*-2-diphenylphosphino)-ferrocenylethylamine (*R*,*S*-1a).** Amine *R*,*S*-**4a** (10.0 g; 24.2 mmol) was dissolved in ethyl acetate (48 mL), and triethylamine (6.75 mL; 48.4 mol; 2.0 equiv) was added. The mixture was cooled in an ice−water bath and purged with argon for 5 min. Chlorodiphenylphosphine (4.56 mL; 25.4 mmol; 1.05 equiv) was added dropwise such that the temperature remained below 15 °C. The reaction mixture was allowed to warm to ambient temperature overnight at which point TLC (1:1 EtOAc/heptane, Et_3N deactivated) indicated no **4a**. The reaction mixture was diluted with heptane (48 mL) to afford a precipitate. The mixture was stirred for 30 min and filtered through Celite and eluted with 1:1 ethyl acetate/heptane. The filtrate was concentrated, resulting in 14.09 g (97%) of *R*,*S*-**1a** as a yellow-orange foam. Mp: 54−55 °C, with 99.6% ee by chiral HPLC. ^{1}H NMR ($CDCl_3$) δ: 7.56−7.51 (m, 2H); 7.36 (m, 4 H); 4.497 (q, 1H, J = 6.32 Hz); 4.462 (m, 1H); 4.293 (m, 1H); 3.912 (s, 5H); 3.83 (m, 1H); 2.26 (m, 1H); 1.515 (d, 3H, J = 6.59 Hz). ^{13}C NMR ($CDCl_3$) δ: 143.6 (d, J_{C-P} = 14 Hz); 142.7 (d, J_{C-P} = 11 Hz); 140.4 (d, J_{C-P} = 10 Hz); 138.1 (d, J_{C-P} = 10 Hz); 135.4 (d, J_{C-P} = 22 Hz); 132.7 (d, J_{C-P} = 18 Hz); 131.4 (d, J_{C-P} = 11 Hz); 131.1 (d, J_{C-P} = 11 Hz); 128.3 (s); 128.2 (s); 128.1 (d, J_{C-P} = 2 Hz); 128.1 (s); 128.0 (s); 100.1 (dd, J_{C-P} = 10, 25 Hz); 74.6 (d, J_{C-P} = 10 Hz); 71.6 (d, J_{C-P} = 4 Hz); 69.9 (s); 69.8 (s); 69.3 (s); 50.9 (dd, J_{C-P} = 7, 25 Hz); 24.1 (d, J_{C-P} = 11 Hz). ^{31}P NMR ($CDCl_3$) δ 33.1 (s); −23.7 (s). HRMS *m*/*z*: calcd for $C_{36}H_{34}FeNP_2$ (M+H^+) 598.1516, found 598.1505. Chiral HPLC (250 × 4.6 mm Chiralpak AD-H, 99:1 hexane/2-propanol, 1 mL/min, λ = 254 nm): t_R (*R*,*S*-**1a**) 10.0 min, t_R (*S*,*R*-**1a**) 10.8 min. FDMS: *m*/*z* 597 (M^+). $[\alpha]^{24}_D$ = −279 (*c* 1.01, $CHCl_3$).

***N*-Methyl *R*-1-(*S*-2-Diphenylphosphino)ferrocenylethylamine (*R*,*S*-4b).** Dimethylamino compound *R*,*S*-**2** (99.9 g; 0.23 mol) was combined with acetic anhydride (72.8 mL; 0.77 mol; 3.35 equiv), and the heterogeneous mixture was heated under nitrogen to 90 °C during which time it became homogeneous. The reaction mixture was held at 90 °C for 3.5 h, at which point TLC analysis indicated no **2** but much **3** (1:4 EtOAc/heptane, Et_3N deactivated). The mixture was cooled to ambient temperature. Aqueous methylamine (359.5 g; 4.63 mol; 20.1 equiv) was dissolved in 2-propanol (463 mL) in a separate flask and cooled to 20 °C. The mixture containing **3** was added over 25 min to the amine mixture with an attendant minor exotherm (maximum temperature was 26.0 °C) and washed in with 116 mL of warm (40−50 °C) 2-propanol. The mixture was heated to 50 °C overnight (17 h) to afford a homogeneous solution which had no remaining **3** according to TLC analysis (1:4 EtOAc/heptane, Et_3N deactivated). The mixture was cooled to 24 °C, and water (1158 mL) was added. This resulted in a moderate exotherm (maximum temperature 32 °C) and an orange precipitate. The mixture was stirred at ambient temperature for 30 min and the solid was filtered, washed with water, and dried in a nitrogen-purged vacuum oven at 40 °C for 2 days to afford 93.8 g (95% overall) of *R*,*S*-**4b** as an orange solid which was pure by ^{1}H NMR analysis. An analytical sample could be obtained by recrystallization from 2-propanol. Mp: 112−113 °C. ^{1}H NMR ($CDCl_3$) δ: 7.55 (m, 2H); 7.37 (m, 3 H); 7.26 (m, 5H); 4.463 (br s, 1H); 4.286 (m, 1H); 4.028 (s, 5H); 3.94 (m, 1H); 3.78 (m, 1H); 1.943 (s, 3H); 1.445 (d, 3H, J = 6.59 Hz). ^{13}C NMR ($CDCl_3$) δ: 140.0 (d, J_{C-P} = 10 Hz); 137.1 (d, J_{C-P} = 9 Hz); 134.9 (d, J_{C-P} = 21 Hz); 132.9 (d, J_{C-P} = 19 Hz); 129.2 (s); 128.6 (s); 128.5 (d, J_{C-P} = 6 Hz); 128.3 (d, J_{C-P} = 7 Hz); 97.5 (d, J_{C-P} = 24 Hz); 75.5 (d, J_{C-P} = 7 Hz); 71.3 (d, J_{C-P} = 4 Hz); 69.8 (s); 69.5 (d, J_{C-P} = 4 Hz); 69.1 (s); 52.5 (d, J_{C-P} = 10 Hz); 32.8 (s); 18.8 (s). ^{31}P NMR (acetone-d_6) δ: −26.0 (s). FDMS: *m*/*z* 427 (M^+). $[\alpha]^{24}_D$ = −309 (*c* 1.55, ethanol). Anal. Calcd for $C_{25}H_{26}FeNP$: C, 70.27; H, 6.13; N, 3.28. Found: C, 70.64; H, 6.37; N, 3.16.

***N*-Diphenylphosphino *N*-Methyl *R*-1-(*S*-2-Diphenylphosphino)-ferrocenylethylamine (*R*,*S*-1b).** Amine *R*,*S*-**4b** (50.0 g; 0.117 mol) was dissolved in ethyl acetate (235 mL), and triethylamine (32.6 mL; 0.234 mol; 2.0 equiv) was added. The mixture was cooled in an ice−water bath and purged with argon for 15 min. Chlorodiphenylphosphine (23.1 mL; 0.129 mol; 1.1 equiv) was added over 15 min such that the temperature remained below 10 °C. The reaction mixture was stirred at 0 °C for 1 h, and the temperature was then raised to 20 °C in 5° hourly increments. The cooling bath was then turned off, and the reaction mixture was stirred at ambient temperature overnight at which point TLC (1:2 EtOAc/heptane, Et_3N deactivated) and ^{1}H NMR analyses indicated very little **4b** (<3%). The reaction mixture was diluted with heptane (235 mL) to afford a precipitate (triethylamine hydrochloride). The mixture was stirred for 30 min and filtered through Celite and eluted with 1:1 ethyl acetate/heptane. The filtrate was concentrated to a small volume. The residue was dissolved in ethyl acetate (75 mL), diluted with heptane (50 mL), and filtered through a fine frit, and the precipitate was washed with 1:1 ethyl acetate/heptane until the wash liquid was colorless. The combined filtrate and wash liquors were concentrated to small volume, diluted with 2-methyl-2-propanol (50 mL), and concentrated once more. The residue was diluted with 2-methyl-2-propanol (900 mL) and heated to reflux to afford a homogeneous solution. The mixture was allowed to cool to ambient temperature overnight to afford a yellow precipitate (precipitation started at around 40 °C). Water (900 mL) was added, resulting in a minor exotherm (from 24 to 28 °C) and the formation of significantly more solid. The mixture was stirred at ambient temperature for 1 h, then filtered and washed with water. The yellow solid was dried under vacuum at ambient temperature with a nitrogen purge to afford 66.25 g of *R*,*S*-**1b** (93%). Mp: 99−101 °C, with 99.96% ee by chiral HPLC. ^{1}H NMR ($CDCl_3$) δ: 7.65 (m, 2H); 7.4−7.0 (m, 14H); 6.82 (m, 4H); 5.006 (m, 1H); 4.502 (br s, 1H); 4.40 (m, 1H); 4.15 (m, 1H); 3.798 (s, 5H); 2.148 (d, 3H, J = 3.30 Hz); 1.471 (d, 3H, J

= 6.87 Hz). ^{13}C NMR ($CDCl_3$) δ: 142.4 (d, J_{C-P} = 9 Hz); 140.3 (d, J_{C-P} = 24 Hz); 140.0 (d, J_{C-P} = 10 Hz); 139.5 (d, J_{C-P} = 7 Hz); 135.9 (d, J_{C-P} = 22 Hz); 134.1 (d, J_{C-P} = 22 Hz); 132.3 (d, J_{C-P} = 17 Hz); 131.7 (d, J_{C-P} = 18 Hz); 129.3 (s); 128.8 (s); 128.1−127.2; 97.9 (dd, J_{C-P} = 14, 28 Hz); 75.7 (d, J_{C-P} = 14 Hz); 72.1 (d, J_{C-P} = 5 Hz); 70.5 (s); 69.9 (s); 69.8 (s); 58.4 (dd, J_{C-P} = 9, 39 Hz); 30.6 (d, J_{C-P} = 11 Hz); 18.5 (d, J_{C-P} = 6 Hz). ^{31}P NMR (CD_2Cl_2) δ: 58.8 (d, J_{P-P} = 7.7 Hz); −25.3 (d, J_{P-P} = 7.7 Hz). Chiral HPLC (250 × 4.6 mm Chiralpak AD-H, 99:1 hexane/2-propanol, 1 mL/min, λ = 254 nm): t_R (*S*,*R*-**1b**) 10.4 min, t_R (*R*,*S*-**1b**) 11.6 min. HRMS *m/z*: calcd for $C_{37}H_{35}FeNP_2$ (M^+) 611.15942, found 611.16429. $[\alpha]^{24}_D$ = −257 (*c* 0.97, toluene).

***N*-Dicyclohexylphosphino *N*-Methyl *R*-1-(*S*-2-Diphenylphosphino)ferrocenylethylamine (*R*,*S*-1c).** Amine *R*,*S*-**4b** (2.0 g; 4.7 mmol) was dissolved in toluene (10 mL), and triethylamine (1.30 mL; 9.4mol; 2.0 equiv) was added. The mixture was cooled in an ice−water bath and purged with argon for 15 min. Chlorodicyclohexylphosphine (1.05 mL; 4.94 mmol; 1.05 equiv) was added, and the reaction mixture was allowed to warm to ambient temperature overnight at which point TLC (1:4 EtOAc/heptane, Et_3N deactivated) indicated partial conversion to **1c**. The reaction mixture was diluted with heptane (10 mL) to afford a precipitate, filtered, and eluted with heptane. The filtrate was were concentrated to a small volume. The crude product was filtered through a pad of neutral alumina and eluted with 5:10:85 triethylamine/ethyl acetate/heptane to afford 1.50 g (52%) of *R*,*S*-**1c**. Mp: 68−69 °C. ^{1}H NMR (DMSO-d_6) δ: 7.61 (m, 2H); 7.42 (m, 3H); 7.19 (m, 3H); 7.04 (m, 2H); 4.532 (br s, 1H); 4.442 (m, 1H); 4.34 (m, 1H); 4.112 (br s, 1H); 3.712 (s, 5H); 2.143 (d, 3H, *J* = 1.92 Hz); 1.549 (d, 3H, *J* = 6.87 Hz); 1.7−0.7 (m, 22 H). ^{13}C NMR (DMSO-d_6) δ: 141.8 (d, J_{C-P} = 9 Hz); 139.4 (d, J_{C-P} = 9 Hz); 135.3 (d, J_{C-P} = 23 Hz); 131.5 (d, J_{C-P} = 17 Hz); 129.2 (s); 128.0 (d, J_{C-P} = 9 Hz); 127.7 (d, J_{C-P} = 5 Hz); 127.1 (s); 98.9 (dd, J_{C-P} = 9, 30 Hz); 73.7 (d, J_{C-P} = 13 Hz); 70.9 (d, J_{C-P} = 5 Hz); 69.7 (s); 69.4 (s); 69.3 (s); 56.9 (dd, J_{C-P} = 9, 36 Hz); 36.1 (d, J_{C-P} = 15 Hz); 34.6 (d, J_{C-P} = 18 Hz); 32.2 (d, J_{C-P} = 9 Hz); 30.0 (d, J_{C-P} = 12 Hz); 29.6−29.2 (m); 26.8−25.8 (m); 20.4 (d, J_{C-P} = 8 Hz). ^{31}P NMR (DMSO-d_6) δ: 67.2 (s); −25.6 (s). FDMS: *m/z* 624 (M^+). HRMS *m/z*: calcd for $C_{37}H_{48}FeNP_2$ ($M + H^+$) 624.2611, found 624.2653. $[\alpha]^{25}_D$ = −320 (*c* 0.54, $CHCl_3$).

Low-Pressure Asymmetric Hydrogenation Screening Example: *N*-Acetyl L-Phenylalanine Methyl Ester (*S*-6a) Using Ligand *R*,*S*-1b. Bis(1,5-cyclooctadiene)rhodium trifluoromethanesulfonate (2.3 mg; 5 μmol; 0.01 equiv) was placed into a reaction vessel and purged with argon for 15 min. A solution of ligand (*R*,*S*)-**1b** (3.7 mg; 6 μmol; 0.012 equiv) in THF (2.0 mL) was degassed with argon for 15 min and then added via cannula to the bis(1,5-cyclooctadiene)rhodium trifluoromethanesulfonate. Methyl 2-acetamidocinnamate (**5a**; 110 mg; 0.50 mmol) in THF (2.0 mL) was degassed with argon for 20 min and then added to the catalyst solution via cannula. The solution was then flushed with hydrogen and pressurized to 10 psig hydrogen for 6 h to afford 100% conversion to *N*-acetyl L-phenylalanine methyl ester (*S*-**6a**) with 99.1% ee as determined by chiral GC analysis. ^{1}H NMR (CD_3OD) δ: 7.28−7.16 (m, 5H); 4.64−4.61 (m, 1H); 3.65 (s, 3H); 3.13−3.08 (dd, 1H *J* = 5.5, 13.9 Hz); 2.94−2.88 (dd, 1H, *J* = 8.9, 13.9 Hz); 1.87 (s, 3H). Chiral GC (Chirasil L-valine [Varian] 25 m × 0.25 mm i.d., film thickness 0.12 μm, 160 °C, 9 min, 160−185 °C 70 °C/min, 185 °C 5 min, 15 psig He): t_R(*R*-**6a**) 7.77 min, t_R(*S*-**6a**) 8.29 min, t_R(**5a**) 13.24 min. $[\alpha]^{24}_D$ = +15.4 (*c* 2.1, methanol) indicates that the *S* enantiomer was obtained from hydrogenation using ligand *R*,*S*-**1**.[32]

High-Pressure Asymmetric Hydrogenation Screening Example: *N*-Acetyl L-Phenylalanine Methyl Ester (*S*-6a). Bis(1,5-cyclooctadiene)rhodium trifluoromethanesulfonate (2.3 mg; 5 μmol; 0.01 equiv) and ligand (*R*,*S*)-**1b** (3.7 mg; 6 μmol; 0.012 equiv) were placed in a high-pressure reaction vessel which was sealed and purged with argon. Anhydrous THF was degassed with argon for 15 min, then 2.0 mL was added to the reaction vessel via syringe. This solution was stirred at 25 °C under argon for 15 min. A solution of methyl 2-acetamidocinnamate (**5a**, 110 mg; 0.50 mmol) in degassed THF (2 mL) was then added to the catalyst solution via syringe. The substrate was washed in with 1 mL of degassed THF. The solution was then purged five times with argon and pressurized with hydrogen to 300 psig for 6 h, then depressurized and purged with argon to afford 100% conversion to *N*-acetyl L-phenylalanine methyl ester (*S*-**6a**) with 97.6% ee as determined by chiral GC analysis.

Turnover Fequency Determination Example: *N*-Acetyl L-Phenylalanine Methyl Ester (*S*-6a). Methyl 2-acetamidocinnamate (**5a**, 2.19 g; 10.0 mmol) was added to a Fisher-Porter bottle. Argon-degassed methanol (12.3 mL) was added to afford a homogeneous solution which was purged with argon for 5 min. The bottle was fitted with a pressure head and evacuated and filled with helium 10 times. Bis(1,5-cyclooctadiene)rhodium trifluoromethanesulfonate (2.3 mg; 0.005 mmol) and the ligand (*R*,*S*)-**1b** (3.7 mg; 0.006 mmol; 1.2 equiv based on rhodium) were added to a 25-mL Schlenk tube and purged with argon for 5 min. Degassed methanol (5.0 mL) was added and the mixture was stirred for 15 min to afford a homogeneous solution. 1.0 mL of this solution (0.001 mmol; 0.0001 equiv; S:C 10,000:1) was added via a gastight syringe to the Fisher-Porter bottle containing the substrate solution. The bottle was evacuated and filled with helium 10 times, and then evacuated and filled with hydrogen 5 times. The bottle was pressurized with 40 psig hydrogen, sealed, and stirred vigorously at ambient temperature and the pressure drop was followed with a pressure sensor. After 1 h, the reaction mixture was evacuated and filled with helium five times and then depressurized. The reaction mixture was sampled and analyzed to indicate 100% conversion to *N*-acetyl L-phenylalanine methyl ester (*S*-**6a**) with 97% ee as determined by chiral GC analysis. Solvent removal afforded 2.23 g (99%) of *S*-**6a**. Graphical analysis of the initial 60% of the reaction and adjusting for the 10 000:1 substrate-to-catalyst ratio indicated a catalyst turnover frequency of 30 500 turnovers per hour.

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Supporting Information Available: General experimental details, additional hydrogenation procedures, analytical data on hydrogenation products, and NMR spectra for compounds **1a**−**c**, **3**, and **4a**,**b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(31) Hayashi, T.; Hayashi, C.; Uozumi, Y. *Tetrahedron: Asymmetry* **1995**, *6*, 2503−2506.

(32) (a) Burk, M. J.; Feaster, J. E.; Nugent, W. A.; Harlow, R. L. *J. Am. Chem. Soc.* **1993**, *115*, 10125. (b) Vineyard, B. D.; Knowles, W. S.; Sabacky, M. J.; Bachman, G. L.; Winkauff, D. J. *J. Am. Chem. Soc.* **1977**, *99*, 5946.