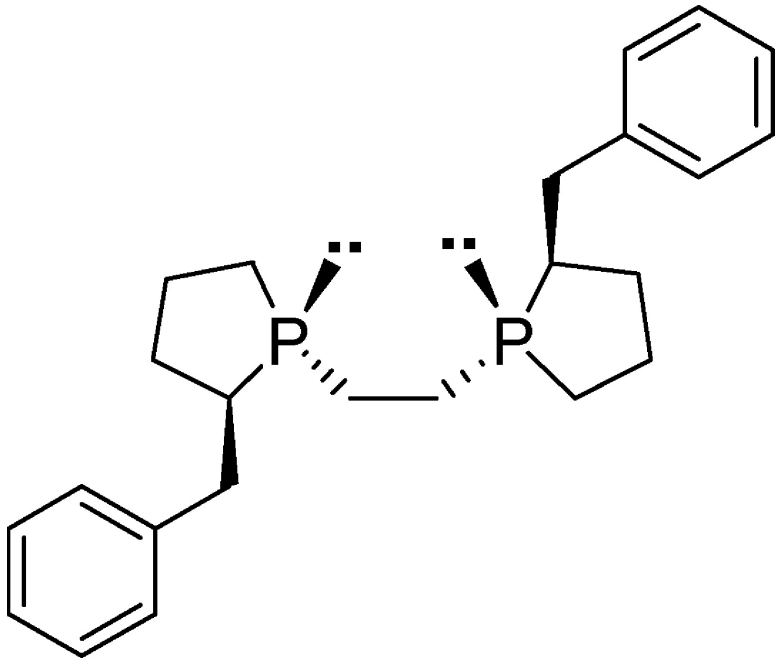
Article

Synthesis of Both Enantiomers of a P-Chirogenic 1,2-Bisphospholanoethane Ligand via Convergent Routes and Application to Rhodium-Catalyzed Asymmetric Hydrogenation of CI-1008 (Pregabalin)

Garrett Hoge

J. Am. Chem. Soc., **2003**, 125 (34), 10219-10227• DOI: 10.1021/ja034715o • Publication Date (Web): 01 August 2003



More About This Article

Additional resources and features associated with this article are available within the HTML version:

- Supporting Information
- Links to the 9 articles that cite this article, as of the time of this article download
- Access to high resolution figures
- Links to articles and content related to this article
- Copyright permission to reproduce figures and/or text from this article

View the Full Text HTML

J|A|C|S
ARTICLES
Published on Web 08/01/2003

Synthesis of Both Enantiomers of a P-Chirogenic 1,2-Bisphospholanoethane Ligand via Convergent Routes and Application to Rhodium-Catalyzed Asymmetric Hydrogenation of CI-1008 (Pregabalin)

Garrett Hoge

Contribution from Pfizer Global Research and Development, 2800 Plymouth Road, Ann Arbor, Michigan 48105

Received February 17, 2003; E-mail: garrett.hoge@pfizer.com

Abstract: Both enantiomers of a P-chirogenic 1,2-bisphospholanoethane ligand are synthesized via two convergent methods. The first method relies on the chiral alkylation of 1-((−)-menthoxy)phospholaneborane using a *s*-BuLi/(−)-sparteine derived chiral base. Only one enantiomer of the catalyst could be synthesized via this method because only one antipode of sparteine is available in nature. The second route relies on the combination of methylphosphine borane and a chiral 1,4-diol. Either enantiomer of the ligand can be synthesized via the second route from the appropriate enantiomer of the 1,4-diol. Asymmetric hydrogenation using catalyst precursor **36** on acetamidoacrylic acid derivatives provided modest to good enantioselectivity (77−95% ee) under low H_2 pressure (30 psi). Asymmetric hydrogenation of CI-1008 (pregabalin) precursors, **39** and **40**, provided good enantioselectivities (92%) at high catalyst loading (1 mol %) and low pressure (30 psi). Enantiomeric excesses dropped sharply with catalyst loading at this pressure. Increasing the pressure of H_2 caused a significant increase in enantiomeric excess for low catalyst loading reactions. Several studies were undertaken to further investigate the enantioselectivity dependence on both pressure and catalyst loading.

Introduction

The development of 1,2-bisphospholane ligands and their application to the highly enantioselective asymmetric hydrogenation of olefin substrates has profoundly influenced the direction of chiral ligand research during the past decade. Some of the highest enantiomeric excesses in asymmetric hydrogenation reported to date have been gleaned from 1,2-bisphospholane catalysts on classes of substrates including *N*-acetamidoacrylic acid derivatives, ene-amines, enol acylates, imines, and itaconates.[1−3] These ligands have also been useful for high asymmetric induction in catalytic [4+2] cycloisomerization reactions,[4] copolymerization between alkenes and carbon monoxide,[5] [4+1] cycloaddition reactions,[6] allylic substitution,[7] and hydroacylation reactions.[8]

In 1987, the first chiral bisphospholanoethane, 3,4-dimethoxy-1,2-bisphospholanoethane, **1**, was reported (Figure 1).[9] This ligand produced low enantiomeric excesses (<20%) in the rhodium-catalyzed asymmetric hydrogenation of *N*-acetamidocinnamic acid. The much-hailed BPE and Duphos ligands, **2** and **3**, respectively, were reported in 1991.[10,11] The overall success and popularity of these ligands is anchored not only in the fact that they gave unprecedented high enantiomeric excesses (for 1991) for a variety of substrate classes in hydrogenations, but also in their commercialization, marketing, and accessibility through chemical supply houses.[12] The success of these ligands has spurred research into an array of novel bisphospholanes and their four-membered analogues, bisphosphetanes, during the past decade.

Groups have focused on the development of C_2-symmetric analogues with a variety of chiral arrays around the five-membered phospholane rings, as well as one report of a bisphospholane with chirality located on the ethane bridge separating the two phosphorus atoms.[13] Some of these ligands, **4**−**6**, demonstrate unique chiral substituents at the 2 and 5 positions of the phospholanes.[14,15] In the case of ligand **4**, the substituents render the ligand's corresponding rhodium catalyst soluble in water. Other groups have prepared phospholanes that

(1) Ohkuma, T.; Kitamura, M.; Noyori, R. In *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; Wiley-VCH: New York, 2000; pp 1−110.
(2) Brown, J. M. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfalz, A., Yamamoto, H., Eds.; Springer-Verlag: Berlin, 1999; Vol. I, pp 121−182.
(3) Burk, M. J. *Acc. Chem. Res.* **2000**, *33*, 363.
(4) Gilbertson, S. R.; Hoge, G. S.; Genov, D. G. *J. Org. Chem.* **1998**, *63*, 10077.
(5) Jiang, Z.; Sen, A. *J. Am. Chem. Soc.* **1995**, *117*, 4455.
(6) Murakami, M.; Itami, K.; Ito, Y. *J. Am. Chem. Soc.* **1999**, *121*, 4130.
(7) Dierkes, P.; Ramdeehul, S.; Barloy, L.; De Cian, A.; Fischer, J.; Kamer, P. C. J.; van Leeuwen, P. W. N. M.; Osborn, *J. A. Angew. Chem., Int. Ed.* **1998**, *37*, 3116.
(8) Barnhart, R. W.; McMorran, D. A.; Bosnich, B. *Chem. Commun*. **1997**, 589.
(9) Brunner, H.; Net, G. *Z. Naturforsch., B: Chem. Sci*. **1996**, *51*, 1210.
(10) Burk, M. J. *J. Am. Chem. Soc.* **1991**, *113*, 8518.
(11) Burk, M. J.; Feaster, J. E.; Harlow, R. L. *Tetrahedron: Asymmetry* **1991**, *2*, 569.
(12) STREM Chemicals currently offers research quantities of the DuPhos and BPE ligands and catalysts.
(13) Burk, M. J.; Pizzano, A.; Martin, J. A. *Organometallics* **2000**, *19*, 250.
(14) Holz, J.; Sturmer, R.; Schmidt, U.; Drexler, H.; Heller, D.; Krimmer, H.; Borner, A. *Eur. J. Org. Chem.* **2001**, *24*, 4615.
(15) RajanBabu, T. V.; Yan, Y.; Shin, S. *J. Am. Chem. Soc.* **2001**, *123*, 10207.

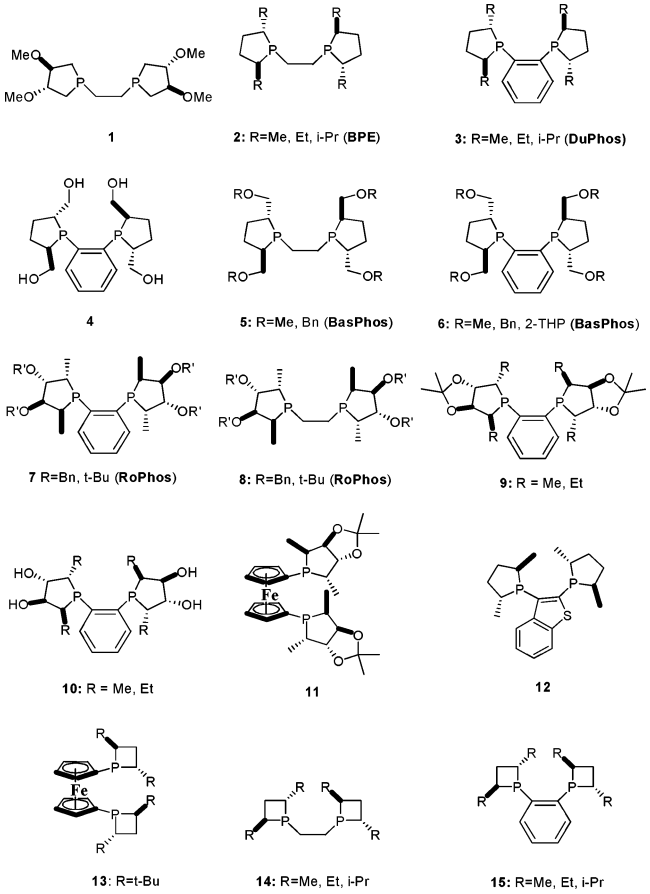
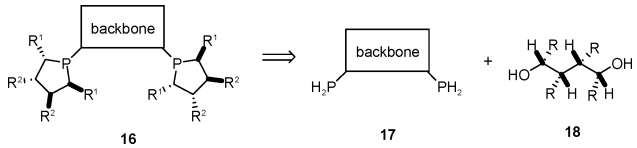


Figure 1. Bisphospholanes and bisphosphetanes.

Scheme 1. Retrosynthetic Analysis of Bisphospholanes **1**−**15**[a]



[a] Backbone = 1,2-ethane, 1,2-benzene, 1,1′-ferrocene, or 2,3-benzothiophene.

contain chirality at every carbon atom on the phospholane ring such as the D-mannitol derived ligands, **7**−**10**.[16] Still others have focused on changing the "backbone" of the bisphospholanes from 1,2-ethane or 1,2-benzene to ferrocene, such as **11**,[17] or even heterocycles, such as **12**.[18] Yet another pathway that groups have taken is the synthesis of four-membered-ring phosphetanes such as the ferrocenyl backbone ligand, **13**,[19] and ligands **14**−**15**.[20,21]

The ligands in Figure 1 have two commonalities: (1) They were all synthesized from a bis-primary phosphine and C_2-symmetric chiral 1,4-diol precursors, and (2) they are all C_2-symmetric (except for **12**). Scheme 1 depicts a retrosynthetic analysis of the bisphospholanes shown in Figure 1. Typically, a chiral 1,4-cyclic sulfate or bismesylate (synthesized from a chiral 1,4-diol) is reacted with the phosphine anions of a 1,2-bis-primary phosphine to form the phospholane ligands. Similarly, phosphetanes are synthesized from chiral 1,3-diols. Seemingly, endless arrays of novel C_2-symmetric bisphospholanes can be synthesized from unique 1,4-chiral diols.[22]

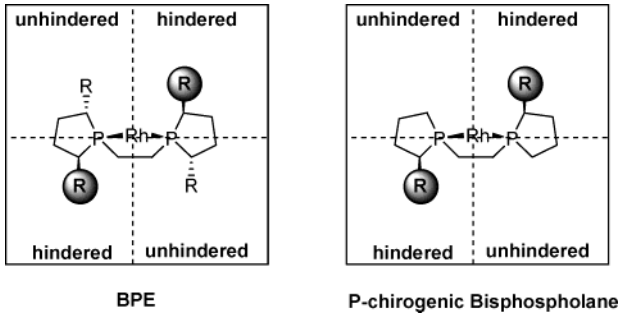


Figure 2. Comparison of P-chirogenic versus non-P-chirogenic bisphospholanes.

Despite the fact that the steric environments around a bound transition metal of C_2-symmetric P-chirogenic bisphospholane ligands would mimic those of their non-P-chirogenic analogues (given the cis orientation of substituents on the phospholane ring with respect to the lone pair on the phosphorus), P-chirogenic 1,2-bisphospholanes have not been reported. The diagrams in Figure 2 depict the similarities between the steric environments around the metal center of the BPE ligand (used here as a generic non-P-chirogenic 1,2-bisphospholane ligand) and a generic P-chirogenic 1,2-bisphospholane. The upper right and lower left quadrants of each complex are similarly hindered. The upper left and lower right quadrants of each complex are unhindered. The corresponding enantiomers, of course, would display the opposite array.

The hindered quadrants of both ligand types exhibit similar steric environments for identical R groups. However, the P-chirogenic ligand's unhindered quadrants are less sterically hindered than the unhindered quadrants of BPE. Although the R substituents of BPE in the upper left and lower right quadrants are trans with respect to the metal, the carbon atom attached to the alkyl substituent is tertiary. In the P-chirogenic complex, secondary carbons occupy the nonsterically hindered quadrants. This might be a structural advantage for higher enantioselectivity in asymmetric catalysis over traditional bisphospholanes. Additionally, P-chirogenic ligands also offer the potential advantage of having chirality attached directly to the metal center instead of chirality that is one atom removed as displayed by all of the ligands shown in Figure 1.[23]

That P-chirogenic bisphospholanes have not been reported is perhaps partially the result of the ease of synthesis of ligands in Figure 1 (Scheme 1) in contrast to the potential synthetic difficulty in preparing a P-chirogenic ligand. Although one of the first chiral bisphosphine ligands was, in fact, P-chirogenic (DiPamp),[24] synthetic methodology to synthesize ligands containing phosphorus chirality has not been extensively developed. Noteworthy exceptions are Imamoto's Bis-P ligand[25] and Zhang's Tangphos (another class of P-chiral bisphospholane!),[26]

(16) Holz, J.; Quirmbach, M.; Schmidt, U.; Heller, D.; Sturmer, R.; Borner, A. *J. Org. Chem.* **1998**, *63*, 8031.
(17) Chiral Quest ligand.
(18) Solvias ligand.
(19) Chirotech Ligand.
(20) Marinetti, A.; Kruger, V.; Buzin, F. *Tetrahedron Lett.* **1997**, *38*, 2947.
(21) Marinetti, A.; Jus, S.; Genet, J. *Tetrahedron Lett.* **1999**, 8365.
(22) This concept has been described in the patent literature. See: Berens, H. International publication number: WO 99/24444, filed 05/11/1998.
(23) It must also be pointed out that the phosphorous atom is rendered chiral because of the existence of stereogenic carbons in the phospholane ring. Therefore, while the described ligands are P-chirogenic, the stereogenic carbon atoms play the major role in defining the steric environment of the ligands and their corresponding rhodium catalysts.
(24) Knowles, W. S. *Angew. Chem., Int. Ed.* **2002,** *41*, 1998.
(25) Imamoto, T.; Watanabe, J.; Wada, Y.; Masuda, H.; Yamada, H.; Tsuruta, H.; Matsukawa, S.; Yamaguchi, K. *J. Am. Chem. Soc.* **1998**, *120*, 1635.

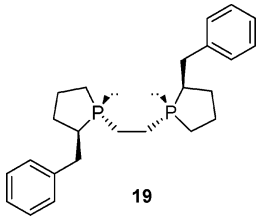
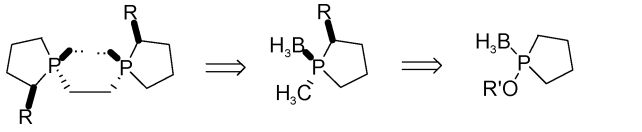


Figure 3. P-Chirogenic 1,2-bisphospholanoethane, **19**.

Scheme 2. Retrosynthetic Analysis of **19**: Chiral Alkylation Route



both of which were synthesized via similar chiral deprotonation/oxidative coupling strategies. Therefore, not only are P-chirogenic 1,2-bisphospholanes interesting from a practical standpoint (i.e., their use in catalysis), but they also represent a worthy synthetic challenge.

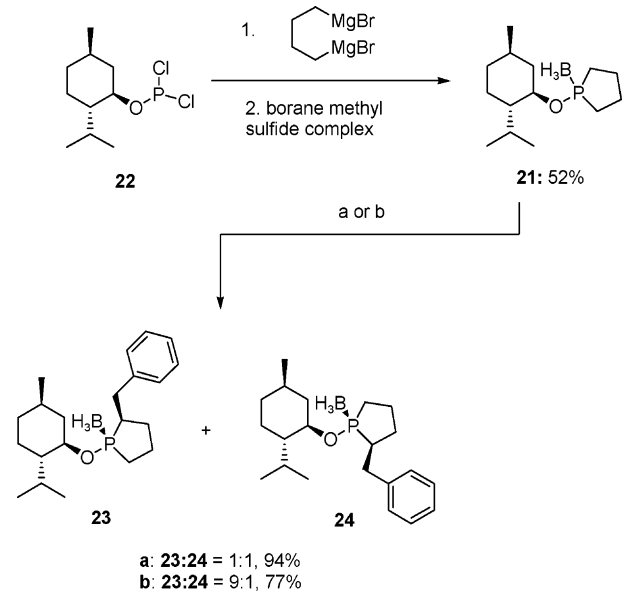
The synthesis of both enantiomers of a P-chirogenic 1,2-bisphospholanoethane ligand, **19** (Figure 3), is reported.[27] Two convergent synthetic strategies were developed to synthesize the 4-chiral center containing ligand. In addition, the rhodium complex of the ligand was prepared, and the results of catalytic asymmetric hydrogenation on both acetamidoacrylic acid derivatives as well as a substrate precursor to an antipsychotic pharmaceutical, CI-1008, are reported. The enantioselectivity dependence on both H_2 pressure and catalyst loading during the asymmetric hydrogenation of a pharmaceutical precursor of CI-1008 is also reported.

Results and Discussion

P-Chirogenic Phospholane Synthesis: Chiral Alkylation Route. Our synthesis revolved around assembly of a chiral 1-methylphospholaneborane, **20**, and then coupling this phospholane with itself to give **19** after borane deprotection (Scheme 2). There is some precedent for coupling methylphosphine oxides, sulfides, and boranes,[28−30] so we felt confident that **20** could be coupled and then deprotected to provide **19**. The real synthetic challenge for this synthesis is the construction of **20**, not **19** itself. However, very few chiral methylphospholanes have been reported, and none of the reports were applicable to our target.[31−34]

Synthesis began with treatment of (−)-menthoxyphosphorus dichloride,[35] **22**, with a bis-Grignard reagent generated from 1,4-dibromobutane followed by complexation of the free phosphine with borane−methyl sulfide complex to form compound **21**

Scheme 3. Formation and Chiral Alkylation of Menthoxyphospholane Borane[a]



[a] Reagents and conditions: (a) (1) *s*-BuLi, THF, −78 °C, (2) benzylbromide; (b) (1) *s*-BuLi, (−)-sparteine, THF, −78 °C, (2) benzylbromide.

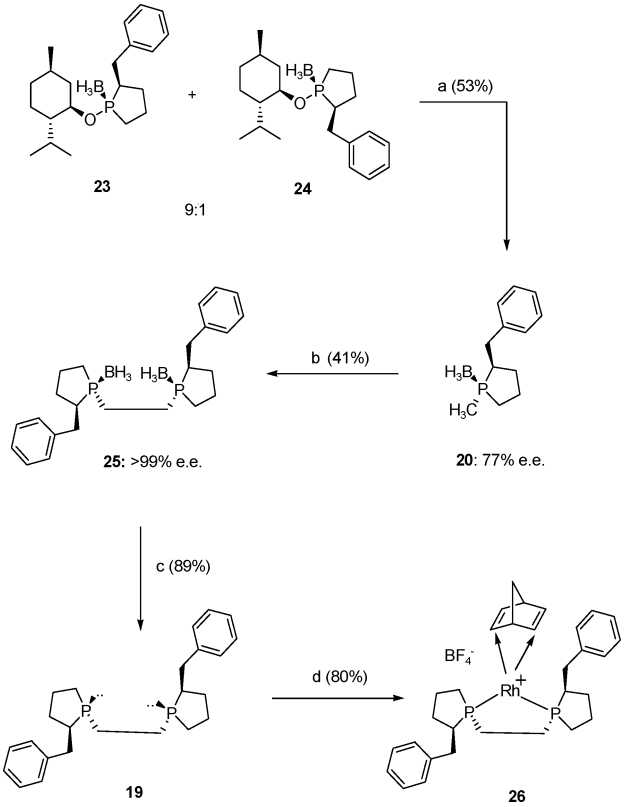
(Scheme 3). Successful selective alkylation at the α-carbons on the five-membered ring of 1-alkoxyphospholane oxides has been documented.[36] Bias was recorded for cis-alkylation with respect to the oxygen atom. Use of *s*-BuLi promoted deprotonation of **21** and, after alkylation with benzylbromide, produced a 1:1 mixture of inseparable diastereomers, **23** and **24**, in 94% yield. The only observed alkylation occurred cis on the phospholane ring with respect to the borane. In efforts to increase the diastereomeric ratio of **23**:**24**, we attempted deprotonation of **21** with a chiral base generated from *s*-BuLi/(−)-sparteine and then alkylation of the resulting anion with benzylbromide. The ratio of **23**:**24** increased to 9:1, and the reaction yielded 77%.[37]

Nucleophilic displacement reactions are capable of inverting or retaining phosphorus stereochemistry.[38,39] The course of reaction often depends on the structure of the molecule, and, in fact, there is some precedent for retention to be observed in nucleophilic displacements of phosphorus atoms in a five-membered ring.[40] Retention of stereochemistry at phosphorus is important for our synthesis because inversion would place the phospholane ring substituents on the opposite side of the ring with respect to the lone pair, an undesirable stereochemical conformation for our ligand synthesis. We treated the 9:1 mixture of **23** and **24** with MeLi to produce **20** in 53% yield with complete retention of stereochemistry (Scheme 4).[41]

The methylphospholane borane, **20**, was then treated with *s*-BuLi to form the methyl anion and then oxidatively coupled with $CuCl_2$ to produce **25**. Although the ee of **20** was only 77%,

(26) Tang, W.; Zhang, X. *Angew. Chem., Int. Ed.* **2002**, *41*, 1612.
(27) A similar P-chirogenic phospholane ligand was reported during the review process of this paper. See: Shimizu, H.; Saito, S.; Kumobayashi, H. *Adv. Synth. Catal.* **2003**, *345*, No. 1+2, 185.
(28) Imamoto, T.; Tsuruta, H.; Wada, Y.; Masuda, H.; Yamaguchi, K. *Tetrahedron Lett.* **1995**, *36*, 8271.
(29) Corey, E. J.; Chen, Z.; Tanoury, G. J. *J. Am. Chem. Soc.* **1993**, *115*, 11000.
(30) Juge, S.; Genet, J. P. *Tetrahedron Lett.* **1989**, *30*, 2783.
(31) Hammond, P. J.; Lloyd, J. R.; Hall, C. D. *Phosphorus Sulfur* **1981**, *10*, 67.
(32) Beer, P. D.; Hammond, P. J.; Hall, C. D. *Phosphorus Sulfur* **1981**, *10*, 185.
(33) Borleske, S. G.; Quin, L. D. *Phosphorus* **1975**, *5*, 173.
(34) Quin, L. D.; Roser, C. E. *J. Org. Chem.* **1974**, *39*, 3423.
(35) Imamoto, T.; Yoshizawa, T.; Hirose, K.; Wada, Y.; Masuda, H.; Yamaguchi, K.; Seki, H. *Heteroat. Chem.* **1995**, *6*, 99.
(36) Polniaszek, R. P.; Foster, A. L. *J. Org. Chem.* **1991**, *56*, 3137.
(37) Muci, A. R.; Campos, K. R.; Evans, D. A. *J. Am. Chem. Soc.* **1995**, *117*, 9075.
(38) Hall, C. R.; Inch, T. D. *Tetrahedron* **1980**, *36*, 2059.
(39) Wadsworth, W. S., Jr.; Larsen, S.; Horten, H. L. *J. Org. Chem.* **1973**, *38*, 256.
(40) Corriu, R.; Lanneau, G.; Leclercq, D. *Tetrahedron* **1986**, *42*, 5591.
(41) It is noteworthy that the 9:1 ratio of diastereomers **28** and **29** translates to 80% de. That compound **20** is produced in 77% ee is consistent with complete retention of configuration during the displacement of the menthoxy group with MeLi.

Scheme 4. Synthesis of P-Chirogenic Bisphospholane, **19**, and Its Rhodium Complex, **26**[a]



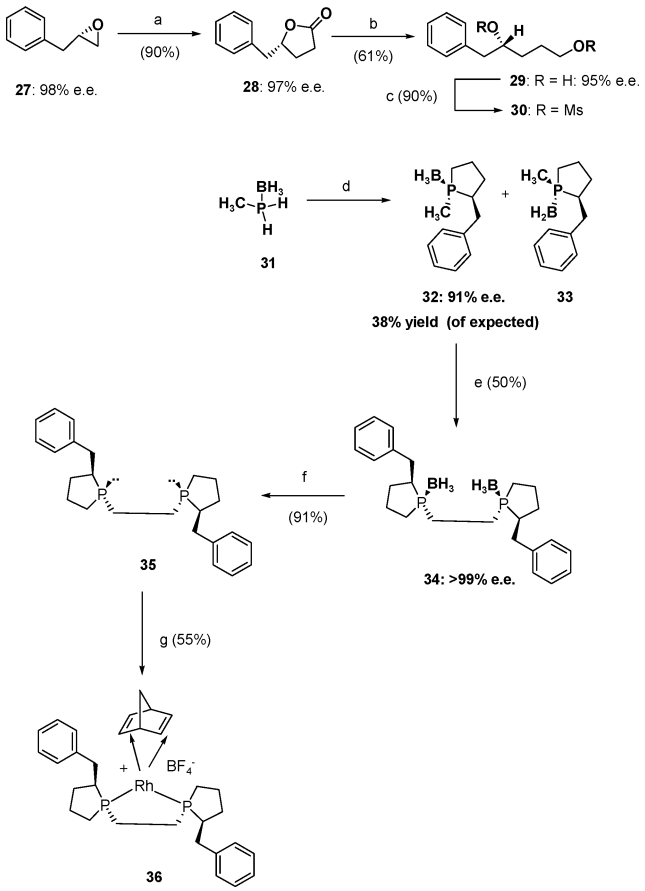
[a] Reagents and conditions: (a) 5 equiv of MeLi, THF, 25 °C; (b) (1) *s*-BuLi, THF, −78 °C, (2) $CuCl_2$, (3) recrystallization from 2-propanol; (c) (1) HBF_4, CH_2Cl_2, 0 → 25 °C, (2) K_2CO_3; (d) $[Rh(NBD)_2]^+BF_4^-$, THF/MeOH, −15 °C.

the coupling of **20** with itself resulted in an enantiomeric amplification from 77% ee to 96% ee (meso ligand was the side product). After one recrystallization from 2-propanol, **25** was isolated in 41% yield with enantiomeric excess >99%. The borane groups were removed via treatment of **25** with HBF_4 followed by hydrolysis with K_2CO_3 to form ligand **19** in 89% yield. Ligand **19** was immediately complexed to rhodium (due to O_2 sensitivity) to produce catalyst precursor **26** in 80% yield.

P-Chirogenic Phospholane Synthesis: Chiral 1,4-Diol Route. The unfortunate reality of all syntheses utilizing (−)-sparteine derived chiral bases is that only one antipode of sparteine is available in nature. Therefore, the (*S*,*S*) enantiomer of catalyst **26** cannot be synthesized via the original route. An alternative synthesis was needed to synthesize the (*S*,*S*) enantiomer. We chose a convergent route to the opposite enantiomer of **20**, the key intermediate in the chiral alkylation route.

Epoxide **27**, generated from the hydrolytic kinetic resolution[42] of its corresponding racemate, was treated with diethylmalonate and K_2CO_3 followed by decarboxylation to form **28** (Scheme 5). The resulting lactone was reduced with LAH to produce **29** which was then converted to bis-mesylate **30**. Methylphosphine is facile to generate, but the malodorous gas is difficult to handle. An alternative is the use of methylphosphine borane, a compound recently reported to be stable, isolatable, and capable of forming phosphorus anions that can be alkylated with alkyl halides.[43] Treatment of methylphosphine borane, **31**, with 2

Scheme 5. Synthesis of Catalyst **36** from a Chiral Epoxide[a]



[a] Reagents and conditions: (a) (1) diethylmalonate, NaOEt, EtOH/THF, 25 °C, (2) 130 °C, DMSO; (b) LAH, THF, 25 °C; (c) MsCl, Et_3N, 0 °C; (d) (1) 2 equiv of *n*-BuLi, THF, −78 °C, (2) **30**, THF, −78 °C → 25 °C; (e) (1) *s*-BuLi, THF, −78 °C, (2) $CuCl_2$, (3) recrystallization from 2-propanol; (f) (1) HBF_4, CH_2Cl_2, 0 → 25 °C, (2) K_2CO_3; (g) $[Rh(NBD)_2]^+BF_4^-$, THF/MeOH, −15 °C.

equiv of *n*-BuLi which produced the phosphorus dianion followed by the addition of **30** to the anion produced a 1:1 diastereomeric mixture of **32** and **33**. These diastereomers were separated via meticulous column chromatography over silica gel to produce the desired phospholane, **32**, in 38% yield (of the expected yield). After separation, **32** was easily converted to **36** via previously described chemistry. Furthermore, either enantiomer of the catalyst can be synthesized via this route depending upon which enantiomer of chiral epoxide is used as starting material.[44]

X-ray Crystal Structure of Rhodium Complex 36. Figure 4 shows the ORTEP diagram generated from the X-ray crystal structure of **36**. Both norbornadiene and BF_4^- counteranion were removed for clarity. The diagram is positioned so that the rhodium atom is in front of the ethane bridge. This view clearly displays the C_2-symmetric binding environment for the substrate around the rhodium atom. The positions of the benzyl groups in the crystalline form give the molecule a propeller-like appearance. Hydrogen atoms are displayed on the stereogenic carbons to demonstrate that the stereochemical configuration

(42) Jacobsen, E. N. *Acc. Chem. Res.* **2000**, *33*, 421.

(43) Bourumeau, K.; Gaumont, A.; Denis, J. *J. Organomet. Chem.* **1997**, *529*, 205.

(44) We have also succeeded in synthesizing the racemic chiral diol on $^1/_2$ kilogram scale via this route and then separating the enantiomers via SMB chromatography.

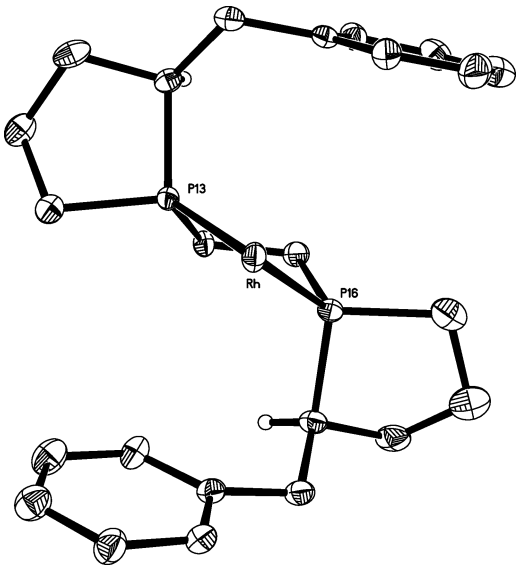
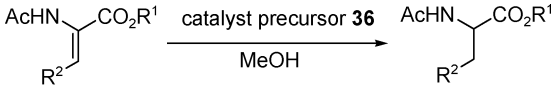


Figure 4. ORTEP diagram of **36** (BF_4^- anion and norbornadiene are removed for clarity).

Table 1. Hydrogenation of Acetamidoacrylic Acid Derivatives Using Catalyst Precursor **36**[a]



37 **38**

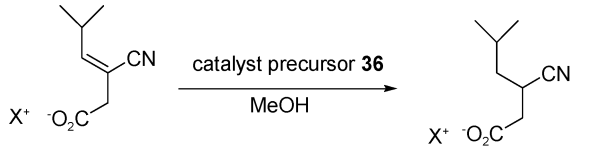
entry	R^1	R^2	mol % catalyst[b]	H_2 pressure (psi)	ee[c] (%)
1	Me	H	1	30	95 (*R*)
2	H	H	1	30	86 (*R*)
3	Me	Ph	1	30	84 (*R*)
4	H	Ph	1	30	77 (*R*)
5	Me	H	0.1	30	93 (*R*)
6	Me	Ph	0.1	30	80 (*R*)
7	H	Ph	0.1	30	77 (*R*)
8	Me	H	0.1	400	68 (*R*)
9	H	H	0.1	400	26 (*R*)
10	H	Ph	0.1	400	37 (*R*)

[a] All reactions were performed at room temperature with a substrate concentration of 0.3 M. All reactions afforded conversion to a single product. [b] All reactions performed with 1 mol % catalyst used 1 mmol of substrate and were complete within 1 h. All reactions performed with 0.1 mol % catalyst used 3 mmol of substrate and were complete within 4 h. [c] Enantiomeric excesses were determined by chiral HPLC or GC as described in the Supporting Information.

of **36** was as expected. The stereochemistry of the phosphorus atoms is also confirmed by observing that the benzyl groups on the phospholane were positioned cis with respect to the coordinated metal.

Rh-Catalyzed Asymmetric Hydrogenation of Acetamidoacrylic Acid Derivatives. Catalyst precursor, **36**, was then screened for the catalytic asymmetric hydrogenation of classic acetamidoacrylic acid substrates, **37** (Table 1). We found selectivity to be modest (77−95% ee) at 1 mol % catalyst loading and 30 psi H_2 (entries 1−4). However, these enantioselectivities were similar to those gleaned from BPE ligands, **2**, on the same substrates.[45] Lowering the catalyst loading to 0.1 mol % at 30 psi H_2 showed a slight decrease in enantioselectivity for these substrates (entries 5−7). Finally, we found that increasing the pressure to 400 psi at 0.1 mol % catalyst loading decreased the enantioselectivities drastically (entries 8−10). This pressure effect is in accord with observations and predictions based on complex equilibria in asymmetric hydrogenations using bisphosphine ligands.[46,47]

Table 2. Pressure Effects versus Enantioselectivity on CI-1008 Precursors, **39** and **40**, Using Catalyst Precursor **36**[a]



39: X^+ = t-$BuNH_3^+$, E/Z (1:5.7) **41**: X^+ = t-$BuNH_3^+$
40: X^+ = K^+, E/Z (1:5.7) **42**: X^+ = K^+

entry	X^+	mol % catalyst[b]	H_2 pressure (psi)	ee[c] (%)
1	*t*-$BuNH_3^+$	1	30	92 (*S*)
2	K^+	1	30	92 (*S*)
3	*t*-$BuNH_3^+$	0.1	30	47 (*S*)
4	*t*-$BuNH_3^+$	0.1	100	69 (*S*)
5	*t*-$BuNH_3^+$	0.1	250	90 (*S*)
6	*t*-$BuNH_3^+$	0.1	400	97 (*S*)
7	*t*-$BuNH_3^+$	0.1	500	97 (*S*)
8	*t*-$BuNH_3^+$	0.1	750	97 (*S*)
9	K^+	0.1	100	71 (*S*)
10	K^+	0.1	250	91 (*S*)
11	K^+	0.1	400	96 (*S*)

[a] All reactions were performed at room temperature with a substrate concentration of 0.3 M. All reactions afforded conversion to a single product. [b] All reactions performed with 1 mol % catalyst used 1 mmol of substrate and were complete within 1 h. All reactions performed with 0.1 mol % catalyst used 3 mmol of substrate and were complete within 4 h. [c] Enantiomeric excesses were determined by chiral GC as described in the Supporting Information.

Rh-Catalyzed Asymmetric Hydrogenation of a Substrate Precursor to CI-1008. Catalyst precursor, **36**, was then used in the asymmetric hydrogenation of two substrate precursors to CI-1008 (pregabalin), **39** and **40**. CI-1008 is a pharmaceutical used to treat psychotic disorders, seizure disorders, and pain.[48] Under mild conditions (30 psi H_2, 25 °C), substrate **39** was converted to product **41** in 92% enantiomeric excess with complete conversion (Table 2, entry 1). Results using substrate **40** under the same conditions provided **42** with similar selectivity (Table 2, entry 2).

Enantioselectivity Dependence on Catalyst Loading. Interestingly, when the catalyst loading was lowered to 0.1 mol % for the hydrogenation of the CI-1008 substrate, **39**, and the pressure of the reaction was kept constant at 30 psi H_2, the enantiomeric excess of the product dropped significantly (Table 2, entry 3). This is in direct contrast to the acetamidoacrylic acid substrate results that were detailed in Table 1 where it was demonstrated that the enantiomeric excesses remained essentially the same at lower catalyst loadings. This inconsistency suggests that during the progression of hydrogenating **39** in entry 3 catalytically active species are being formed that produce low enantiomeric excesses of **41**. One possible explanation for this phenomenon is that the nitrile functionality of the substrate or product might complex with the active catalyst as the hydrogenation progresses.[49] This could alter the highly ordered C_2-symmetric steric environment of the active catalyst, thus preventing the ordered binding of substrate molecules for hydrogenation that is necessary for high enantiomeric excesses.

(45) Murk, M. J.; Feaster, J. E.; Nugent, W. A.; Harlow, R. L. *J. Am. Chem. Soc.* **1993**, *115*, 10125.
(46) Brown, J. M.; Chaloner, P. A. *J. Chem. Soc., Chem. Commun.* **1980**, 344.
(47) Halpern, J. *Science* **1982**, *217*, 401.
(48) Burk, M. J.; Goel, O. P.; Hoekstra, M. S.; Mich, T. F.; Mulhern, T. A.; Ramsden, J. A. PCT Int. Appl., 2001.

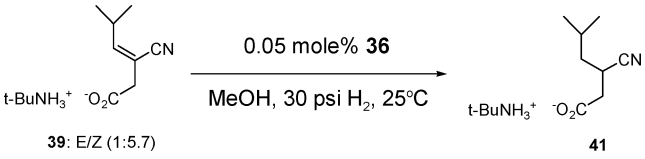
Enantioselectivity Dependence on H_2 Pressure. We next investigated the dependence of enantioselectivity on H_2 pressure during the hydrogenation of **39** and **40** with catalyst precursor **36** (Table 2, entries 4−11). At 0.1 mol % catalyst loading, we observed that the enantiomeric excess of product **41** dramatically increases as the H_2 pressure is increased. When the reaction was performed at 100 psi H_2, the enantiomeric excess of the product at 100% conversion increased to 69% (entry 4). In entry 5, the reaction was performed at 250 psi H_2, and the enantiomeric excess increased to 90%. Further increase in pressure to 400 psi (entry 6) produced 97% enantiomeric excess. Reactions performed at increased pressures of 500 and 750 psi H_2, entries 7 and 8, respectively, showed no further increase in enantiomeric excess of product **41**. The potassium salt substrate, **40**, followed the same trend as that of the *tert*-butylammonium salt substrate, **39** (entries 9−11).[50]

Evidence of enantiomeric excess dependence on pressure has been reported.[51] Our results corroborate the findings that an increase in hydrogen concentration in solution (caused by an increase in hydrogen pressure) can increase the enantiomeric excess of some asymmetric hydrogenation reactions. There are also reports of enantiomeric excess dependence on catalyst loading.[52,53] These reports demonstrate that lower catalyst loadings lead to lower enantiomeric excesses of products for their catalyst systems. Our results also corroborate these reports. However, we have demonstrated that asymmetric hydrogenation enantiomeric excesses can change as a function of both catalyst loading and H_2 pressure.

Enantiomeric Excess Monitoring as a Function of Reaction Completion. We monitored the enantiomeric excess of product **41** as a function of reaction completion during a low catalyst loading hydrogenation of **39** (Table 3). The enantiomeric excess was 88% after 30 min reaction time and then quickly declined to less than 50% ee after 1 h (entry 2). After complete conversion of **39** to **41**, the enantiomeric excess of product **41** was less than 20% (entry 6). Given the data from Tables 2 and 3, it is apparent that increases in pressure (400 psi or greater) are capable of preventing the catalytically active species leading to low enantiomeric excesses from forming, or, if they have formed during the course of the reaction, the increases in pressure prevent them from catalytically converting substrate to product.

Enantioselectivity Dependence on Increasing Pressure during Hydrogenation. We investigated the effect of a significant increase in H_2 pressure on enantioselectivity during a low pressure and low catalyst loading hydrogenation of **39** with catalyst **36** (Scheme 6). In step 1 of the experiment, the reaction was begun at 30 psi H_2 pressure and 0.1 mol % catalyst loading. A sample at the 2 h mark demonstrated, not unexpectedly, that the ee was 67% after 22% conversion to product. The reaction mixture was then pressurized to 400 psi H_2 in step 2 of the experiment and stirred for an additional 4 h. The enantiomeric excess at 100% conversion was 88% (step 1 + step 2). By calculation, the enantiomeric excess of the hydrogenation of 78% of the remaining substrate (step 2 only) was 94%, a result consistent with the high enantiomeric excesses at increased H_2 pressures recorded in Table 2.

Table 3. Enantioselectivity versus Time during Asymmetric Hydrogenation of CI-1008, **39**, Using Catalyst Precursor **36** at Low Catalyst Loading[a]

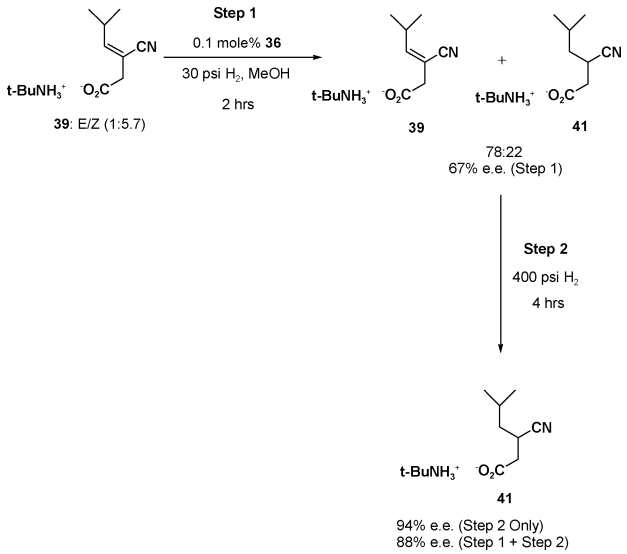


39: E/Z (1:5.7) **41**

entry	time (h)	conversion (%)	ee[b] (%)
1	0.5	3	88 (*S*)
2	1	10	47 (*S*)
3	2	22	42 (*S*)
4	4	43	35 (*S*)
5	8	68	27 (*S*)
6	16	100	18 (*S*)

[a] The reaction was performed at room temperature using 3 mmol of substrate with a concentration of 0.3 M in MeOH. The reaction afforded conversion to a single product. [b] Enantiomeric excesses were determined by chiral GC as described in the Supporting Information.

Scheme 6. Pressure Increase during Hydrogenation of **39** with **36** Increases Selectivity for the Remainder of the Reaction[a]



[a] The reaction was performed at room temperature using 1 mmol of substrate with a concentration of 0.3 M in MeOH. The reaction afforded conversion to a single product with predominantly an *S* configuration. Enantiomeric excesses were determined by chiral GC as described in the Supporting Information.

Summary and Conclusions

Both enantiomers of a new addition to the chiral phospholane family, a P-chirogenic 1,2-bispholanoethane, have been successfully synthesized. Two convergent methods highlight solutions to the synthesis of this P-chirogenic ligand.

While the enantiomeric excesses observed in the hydrogenation of acetamidoacrylic acid derivatives with catalyst **36** were

(49) It has been speculated that substrate **39** can bind with a rhodium complex of Me-DuPhos. See: Burk, M. J.; de Koning, P. D.; Grote, T. M.; Hoekstra, M. S.; Hoge, G.; Jennings, R. A.; Kissel, W. S.; Le, T. V.; Lennon, I. C.; Mulhern, T. A.; Ramsden, J. A.; Wade, R. A. *J. Org. Chem.* **2003**, *68*, 5731.

(50) It should be noted that substrates **39** and **40** are 1:5.7 *E*/*Z* mixtures and that the reaction rates and enantiomeric excesses observed at different reaction pressures might be different for each diastereomer. Pure *E* substrate could not be isolated for these comparisons, but we have observed that pure *Z* substrate follows the same enantioselectivity trends versus pressure as the 1:5.7 *E*/*Z* mixture.

(51) Yongkui, S.; Landau, R. N.; Wang, J.; LeBlond, C.; Blackmond, D. G. *J. Am. Chem. Soc.* **1996**, *118*, 1348.

(52) Bell, D.; Davies, M. R.; Finney, F.; Geen, G. R.; Kincey, P. M.; Mann, I. S. *Tetrahedron Lett.* **1996**, *37*, 3895.

(53) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765.

modest, excellent enantioselectivity was observed for the asymmetric hydrogenation of CI-1008 precursors, **39** and **40**. An interesting combination of pressure and catalyst loading effects on enantioselectivity was also observed during hydrogenation studies on substrates **39** and **40**.

The methodology described in this Article is ideal for the synthesis of a series of P-chirogenic bisphospholanes with varying alkyl substituents. We are currently investigating the synthesis of derivatives of **19** and attempting to synthesize P-chirogenic phospholanes with a variety of "backbones". Furthermore, we are examining the hydrogenation of **39** and **40** with catalyst **36** in more detail to elucidate the mechanism of observed pressure and catalyst loading effects on enantioselectivity.

Experimental Section

General. THF was either distilled from sodium prior to use or obtained from Aldrich Sure-Seal bottles supplied by Aldrich Chemical Co. as 99.9% anhydrous. Dichloromethane (anhydrous, 99.8%) and ether (anhydrous, 99.8%) were used as needed from Aldrich Sure-Seal bottles supplied by Aldrich Chemical Co. (1*R*,2*S*,5*R*)-(−)-Menthol, borane methyl sulfide complex (approximately 10−10.2 M), phosphorus trichloride (98%), *s*-BuLi (1.3 M in cyclohexane), *n*-BuLi (2.5 M in hexanes), MeLi (1.0 M in THF/cumene), (−)-sparteine, benzyl bromide (98%), tetrafluoroboric acid−dimethyl ether complex, trimethylsilyldiazomethane, sodium metal (stick, dry, 99%), diethylmalonate (99%), lithium aluminum hydride (powder, 95%), methanesulfonyl chloride (99.5+%), triethylamine (99.5%), methyl 2-acetamidoacrylate, 2-acetamidoacrylic acid, and α-acetamidocinnamic acid were obtained from Aldrich Chemical Co. $AgBF_4$ (99%) and chloronorbornadiene rhodium(I) dimer (99%) were supplied by Strem Chemicals, Inc. Hydrogen gas (99.995%) was used from a lecture bottle supplied by Specialty Gas. (−)-Menthoxyphosphorus dichloride was synthesized according to literature procedures.[35] (*S*)-(2,3-Epoxypropyl)benzene (99.9% chemical purity, 98.2% enantiomeric excess) was purchased from Rhodia-Chirex on a custom synthesis contract. Methylphosphine borane was synthesized according to literature procedures.[41] Hydrogenations were performed in a Griffin−Worden pressure vessel supplied by Kimble/Kontes.

Preparation of 1-((−)-Menthoxy)phospholaneborane (21). Into a three-neck 250 mL round-bottom flask equipped with a reflux condenser under N_2 was placed 150 mL of freshly distilled THF and magnesium turnings (2.36 g, 0.0973 mol). An iodine crystal was added, and then 1,4-dibromobutane (4.65 mL, 0.0389 mol) was added dropwise over 30 min with a syringe pump while the reaction was stirred with a magnetic stir bar. The reaction became hot during the addition and refluxed near the end of the addition (an ice bath was kept on hand to cool the reaction to prevent it from becoming uncontrollable). After the addition, the reaction was refluxed for 1 h. The Grignard solution (dark gray after reflux) was then cooled to room temperature. Into a separate 500 mL flask were placed **22** (10.0 g, 0.0389 mol) and 250 mL of freshly distilled THF under N_2. The solution of **22** was cooled to 0 °C, and then the Grignard solution was delivered to the flask quickly via cannula. The reaction mixture was warmed to room temperature and then stirred 3 h whereupon $BH_3{\cdot}Me_2S$ (3.9 mL of a 10.0 M solution, 0.0389 mol) was delivered to the reaction via syringe followed by stirring overnight. The reaction was quenched cautiously with 250 mL of H_2O, the organic layer was separated, and the aqueous layer was extracted with 3 × 100 mL of Et_2O. The combined organics were dried over $MgSO_4$, and then the solvent was removed on a rotary evaporator. Flash column chromatography over silica gel (1% ethyl acetate in hexanes) provided the product (5.13 g, 52%). bp 146.9 °C; $[\alpha]^{24}_D = -55.6°$ (*c* 1.0, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.1−1.0 (br m, 3H), 0.78 (d, J = 7.1 Hz, 3H), 0.87 (d, J = 5.4 Hz, 3H), 0.88 (d, J = 4.6 Hz, 3H), 0.91−1.04 (m, 2H), 1.17−1.24 (m, 2H), 1.36−1.48 (m, 1H), 1.57−1.64 (m, 2H), 1.89−1.96 (m, 9H), 2.05−2.08 (m, 1H), 3.90−3.99 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.0, 20.9, 22.1, 23.0, 25.4, 25.80, 25.84, 29.1 (d, J_{C-P} = 42.0 Hz), 30.5 (d, J_{C-P} = 37.4 Hz), 31.3, 34.2, 43.4, 48.6, 79.0 (d, J_{C-P} = 3.8 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 142 (m). Anal. Calcd for $C_{14}H_{30}$-BOP: C, 65.64; H, 11.80. Found: C, 66.24; H, 10.55.

Preparation of (1*S*,2*R*)-1-((−)-Menthoxy)-2-benzylphospholaneborane (23). Into a 500 mL round-bottom flask was dissolved **21** (8.83 g, 0.0345 mol) in 150 mL of Et_2O. The solution was placed under N_2 and then cooled to −78 °C. In a separate 250 mL flask was dissolved (−)-sparteine (9.9 mL, 0.043 mol) in 100 mL of Et_2O. The sparteine solution was placed under N_2 and then cooled to −78 °C. To the sparteine solution was added *s*-BuLi (33.2 mL of 1.3 M in cyclohexane solution reagent, 0.043 mol) via syringe. The *s*-BuLi/sparteine solution was stirred for 30 min at −78 °C and then delivered to the flask containing **21** via cannula over 30 min. After the addition, the reaction was stirred for 2 h at −78 °C. Into a separate 100 mL round-bottom flask was dissolved benzyl bromide (5.3 mL, 0.0449 mol) in 50 mL of Et_2O under N_2. The benzyl bromide solution was delivered quickly to the anion solution via cannula. The cold bath was removed, and the reaction was allowed to warm slowly to room temperature. The reaction was quenched with 500 mL of 1 N HCl, the organic layer was separated, and then the aqueous layer was extracted with 2 × 75 mL of Et_2O. The combined organic layers were dried over $MgSO_4$, and then the solvent was removed on a rotary evaporator. The crude product was flash chromatographed over silica gel (1.5% ethyl acetate in hexanes) providing the product (9.14 g, 77%) as a 9:1 mixture of **23** and **24**, respectively.

23: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.2−1.1 (m, 14H), 1.2−1.4 (m, 3H), 1.3−1.5 (m, 1H), 1.7−2.0 (m, 8H), 2.18−2.30 (m, 1H), 2.20−2.25 (m, 1H), 2.55−2.61 (m, 1H), 3.15−3.21 (m, 1H), 3.96−4.02 (m, 1H), 7.15 (m, 3H), 7.24−7.29 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.2, 20.9, 22.1, 23.1, 23.7, 26.0, 30.3, 31.2, 31.3, 34.2, 34.9, 43.4, 44.3, 48.7, 79.0 (d, J_{C-P} = 4.6 Hz), 126.2, 128.5, 128.7, 140.7 (d, 14.5 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 143.5 (m). HRMS (EI): $(M + Na)^+$ 369.2251 ($(M + Na)^+$, exact mass calcd for $C_{21}H_{36}BNaOP$: 369.2494).

Preparation of (1*S*,2*R*)-1-Methyl-2-benzylphospholaneborane (20). A 9:1 mixture of **23** and **24** (9.14 g, 44.37 mmol), respectively, was placed in a 250 mL round-bottom flask and dissolved in 120 mL of THF under N_2. The solution was warmed to 50 °C. To the solution was added MeLi (1.0 M, 92.4 mL, 92.4 mmol) via syringe. The solution became yellow after addition, and after being stirred for 1 h the solution was light red. The reaction was quenched carefully with 300 mL of 1 N HCl, and then the organic layer was separated. The aqueous layer was extracted with 2 × 100 mL of Et_2O. The combined organic layers were dried over $MgSO_4$, and then the solvent was removed on a rotary evaporator. Flash column chromatography of the crude product over silica gel (2.5% ethyl acetate in hexanes) provided the product (2.83 g, 53%). The product was determined to be 77% ee by HPLC analysis [Chiracel OD-H, 20% 2-propanol in hexanes, 1 mL/min, 214 nm UV detection, enantiomers eluted at 5.29 min (1*R*,2*S*, minor) and 5.59 min (1*S*,2*R*, major)]. The assignment of the relative stereochemistry was accomplished by NOE difference ^{1}H NMR spectra (see Supporting Information). bp 167.6 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.05−0.97 (br m, 3H), 1.25 (d, J = 10.7 Hz), 1.42−1.70 (m, 2H), 1.70−2.20 (m, 5H), 2.64−2.73 (m, 1H), 3.06−3.13 (m, 1H), 7.17−7.29 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.8 (d, J_{C-P} = 31.3 Hz), 24.4, 25.8 (d, J_{C-P} = 37.4 Hz), 25.8, 33.2, 35.4, 41.0 (d, J = 33.6 Hz), 41.0, 126.3, 128.5, 128.8, 140.5 (d, J_{C-P} = 11.5 Hz); ^{31}P (162 MHz, $CDCl_3$) δ 29.4 (m). HRMS (EI): $(MH - BH_3)^+$ 193.0980 ($(MH - BH_3)^+$, exact mass calcd for $C_{21}H_{36}BNaOP$: 193.1146).

Preparation of 1,2-Bis((1*R*,2*R*)-2-(benzylphospholaneborane))-ethane (25). To a 250 mL round-bottom flask was dissolved **20** (2.83 g, 13.74 mmol) in 80 mL of THF. The solution was placed under N_2 and cooled to −78 °C. To this solution was added *s*-BuLi (1.3 M, 11.6

mL, 15.1 mmol) via syringe, and the solution turned red. After the mixture was stirred for 2 h at −78 °C, $CuCl_2$ powder was added to the reaction in one portion with vigorous stirring. The reaction was allowed to warm to room temperature, and then it was stirred overnight. The mixture was quenched with 100 mL of concentrated NH_4OH, and the organic layer was separated. The aqueous layer was then extracted with 3 × 50 mL of ethyl acetate. The combined organic layers were washed successively with 5% NH_4OH, 1 N HCl, and brine. The organic layer was dried over $MgSO_4$, and the solvent was removed on a rotary evaporator. The crude product was from hot 2-propanol to provide the product (1.15 g, 41%). The product was determined to be >99% ee and >98% purity by HPLC analysis [Chiracel OD-H, 20% 2-propanol in hexanes, 0.5 mL/min, 214 nm UV detection, enantiomers eluted at 12.81 min ((1*S*,2*S*), minor) and 16.84 min ((1*R*,2*R*), major), meso complex eluted at 14.51 min]. mp = 128.8 °C; $(\alpha)^{25}_D$ −13.7° (*c* 0.95, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.0−1.0 (m, 6H), 1.15−1.30 (m, 2H), 1.40−1.60 (m, 6H), 1.70−1.80 (m, 4H), 1.90−2.10 (m, 6H), 2.68−2.78 (m, 2H), 2.92−2.99 (m, 2H), 7.16−7.24 (m, 6H), 7.27−7.31 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.9 (d, J_{C-P} = 26.7 Hz), 24.5, 24.6 (d, J_{C-P} = 36.6 Hz), 24.8, 33.9, 35.5, 40.4 (d, J = 32.0 Hz), 126.5, 128.5, 129.1, 140.3; ^{31}P NMR (162 MHz, $CDCl_3$) δ 40 (m). HRMS (EI): $(M + Na)^+$ 433.2293 ($(M + Na)^+$, exact mass calcd for $C_{24}H_{38}B_2NaP_2$: 433.2533).

Preparation of (5*R*)-Benzyldihydrofuran-2-one (28). Sodium metal (6.43 g, 0.28 mol) was dissolved in 200 mL of EtOH. To the solution was added 100 mL of anhydrous THF. Diethylmalonate (51 mL, 0.33 mol) was poured into the reaction, and the reaction was stirred for 5 min and then cooled to 0 °C in an ice bath. To the solution was added (*S*)-(2,3-epoxypropyl)benzene, **27** (15.0 g, 0.11 mol), via syringe, and then the ice bath was removed. The reaction was stirred overnight at room temperature. During the course of the reaction, the reaction mixture turned from a clear solution to a white gel. This gel could be stirred magnetically. After the mixture was stirred overnight, 60 mL of 5 N HCl was added to the reaction making the pH of the reaction 5. The volatiles were then removed under reduced pressure on a rotary evaporator leaving a yellow oil suspended in water. To the suspension was added 65 mL of DMSO, and then the flask was heated to 150 °C in an oil bath. Gas evolved from the solution. After 16 h, no further gas evolution was observed. The reaction was cooled to 0 °C, and then 300 mL of deionized water was added. The resulting solution was extracted with 3 × 150 mL of diethyl ether. The combined organic layers were then washed with 400 mL of deionized water, separated, and then dried over $MgSO_4$. The volatiles were removed on a rotary evaporator, producing the product (17.3 g, 90%). The product was determined to be 97% ee via chiral HPLC analysis [Chiralcel OD-H, 20% 2-propanol in hexane, 1.0 mL/min, 214 nm UV detection, enantiomers eluting at 8.02 min (*S*, minor) and 8.89 min (*R*, major)]. The compound was used in the next step without further purification. bp 199.4 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.90−2.00 (m, 1H), 2.21−2.29 (m, 1H), 2.33−2.51 (m, 2H), 3.07 (dd, J = 14.16 Hz, J = 6.10 Hz, 1H), 3.48 (dd, J = 14.16 Hz, J = 7.08 Hz, 1H), 4.12−4.77 (m, 1H), 7.19−7.34 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.5, 28.3, 41.9, 81.8, 127.5, 128.2, 129.2, 136.1, 177.3. HRMS (EI): $(M + Na)^+$ 199.0679 ($(M + Na)^+$, exact mass calcd for $C_{11}H_{12}O_2$: 199.0735).

Preparation of (*R*)-1-Phenyl-2,5-pentanediol (29). To a 1 L round-bottom flask equipped with a 500 mL pressure equalizing dropping funnel was dissolved LAH (4.6 g, 0.12 mol) in 300 mL of THF under N_2. Into the dropping funnel was placed **28** (17.7 g, 0.1 mol) dissolved in 300 mL of THF. The reaction was cooled to 0 °C in an ice bath, and then the solution of **28** was added dropwise over a period of 30 min. After addition, the reaction was warmed to room temperature and then stirred overnight. The reaction was cooled to 0 °C and then quenched cautiously with 1 N HCl. Deionized water (200 mL) was then added to the reaction mixture, and the contents of the flask were transferred to a separatory funnel. The aqueous solution was extracted with 3 × 200 mL of ethyl acetate. The combined organic layers were then washed successively with 1 N HCl, saturated $NaHCO_3$, brine, and deionized water. The organic layer was dried over $MgSO_4$. The volatiles were removed in vacuo yielding 13.6 g of a yellow oil. The diol was then distilled at 178 °C (8 mmHg) to provide the product (10.1 g, 61%). The product was determined to be 95% ee via chiral HPLC analysis [Chiralcel OD-H, 20% 2-propanol in hexane, 1.0 mL/min, 214 nm UV detection, enantiomers eluting at 4.78 min (*S*, minor) and 5.20 min (*R*, major)]. bp 178 °C (8 mmHg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.51−1.58 (m, 1H), 1.69−1.77 (m, 3H), 2.12 (br s, 2H), 2.70 (dd, J = 13.4 Hz, J = 8.5 Hz, 1H), 2.82 (dd, J = 13.7 Hz, J = 4.4 Hz, 1H), 3.63−3.72 (m, 2H), 3.83−3.89 (m, 1H), 7.20−7.33 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 29.7, 34.0, 44.2, 63.2, 72.8, 126.8, 129.0, 129.7, 138.5. HRMS (EI): $(M + Na)^+$ 203.0855 ($(M + Na)^+$, exact mass calcd for $C_{11}H_{16}NaO_2$: 203.1048).

Preparation of (*R*)-1-Phenyl-2,5-pentane-bis-mesylate (30). The chiral diol, **29** (10.1 g, 0.061 mol), was dissolved in 300 mL of CH_2Cl_2 and placed in a 1 L round-bottom flask equipped with a pressure equalizing dropping funnel. The flask was purged with nitrogen, and then the solution was cooled to 0 °C using an ice bath. To the solution was added triethylamine (21.3 mL, 0.15 mol) via syringe. Into the dropping funnel was placed methanesulfonyl chloride (10.4 mL, 0.135 mol) dissolved in 50 mL of CH_2Cl_2. The methanesulfonyl chloride solution was then delivered to the reaction over a period of 30 min. After the addition, the reaction was stirred 30 min at 0 °C and then warmed to room temperature and stirred for 4 h. The reaction was cooled to 0 °C and then quenched cautiously with 1 N HCl. To this quenched solution was added 100 mL of 1 N HCl, and then the reaction mixture was transferred to a separatory funnel. The CH_2Cl_2 layer was separated. The aqueous layer was extracted with 300 mL of CH_2Cl_2, and then the combined CH_2Cl_2 layers were washed successively with 1 N HCl, saturated $NaHCO_3$, brine, and deionized water. The organic layer was dried over $MgSO_4$, and then the solvent was removed in vacuo, providing the product (18.5 g, 90%). The compound was used in the next step without further purification. mp 151.3 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.82−2.03 (m, 6H), 2.43 (s, 3H), 3.00 (s, 3H), 4.27 (m, 2H), 4.89 (m, 1H), 7.23−7.32 (m, 3H), 7.33−7.35 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.1, 31.2, 37.6, 38.1, 41.4, 69.4, 84.1, 127.5, 129.0, 129.9, 136.7. HRMS (EI): $(M + Na)^+$ 358.9923 ($(M + Na)^+$, exact mass calcd for $C_{13}H_{20}NaO_6S_2$: 359.0599).

Preparation of (1*R*,2*S*)-1-Methyl-2-benzylphospholaneborane (32). Methylphosphineborane was distilled trap-to-trap (2 mmHg) at room temperature prior to the reaction. The receiving trap was kept at −78 °C during distillation. The methylphosphineborane (4.1 g, 0.065 mol) was weighed quickly in air and then dissolved in 600 mL of THF in a 2 L round-bottom flask. The flask was purged with N_2, and then the solution was cooled to −78 °C. To the solution was added *n*-BuLi (52 mL, 2.5 M, 0.13 mol) via syringe over a period of 2−3 min. The reaction was stirred for 1 h at −78 °C. Into a separate 500 mL round-bottom flask was dissolved **30** (18.2 g, 0.054 mol) in 300 mL of THF under N_2. The solution of **30** was then added to the methylphosphineborane anion over a period of 2−3 min via cannula. The reaction was allowed to warm to room temperature over 2 h and then was stirred overnight. The reaction was quenched with 1 N HCl, and then 600 mL of diethyl ether was added to the reaction mixture. The reaction mixture was transferred to a separatory funnel. The organic layer was separated, and then it was washed successively with 1 N HCl, brine, and deionized water. After the layer was dried over $MgSO_4$, the volatiles were removed in vacuo, producing 13 g of a yellow oil. Flash column chromatography over silica gel (1.5% ethyl acetate in hexane) produced product **32** (2.1 g, 38% of expected). The product was determined to be 91% ee via chiral HPLC analysis [Chiralcel OJ-R, 35% water in acetonitrile, 1.0 mL/min, 214 nm UV detection, enantiomers eluting at 3.90 min ((1*S*,2*R*), minor) and 4.29 min ((1*R*,2*S*), major)]. Analytical samples of diastereomer **33** were also isolated (eluted after **32** during flash column chromatography).

32: bp 167.6 °C; $[\alpha]^{24}_D = 0.5$ °C (*c* 0.8, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.05−0.97 (br m, 3H), 1.25 (d, $J = 10.7$ Hz), 1.42−1.70 (m, 2H), 1.70−2.20 (m, 5H), 2.64−2.73 (m, 1H), 3.06−3.13 (m, 1H), 7.17−7.29 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.8 (d, $J_{C-P} = 31.3$ Hz), 24.4, 25.8 (d, $J_{C-P} = 37.4$ Hz), 25.8, 33.2, 35.4, 41.0 (d, $J_{C-P} = 33.6$ Hz), 41.0, 126.3, 128.5, 128.8, 140.5 (d, $J_{C-P} = 11.5$ Hz); ^{31}P (162 MHz, $CDCl_3$) δ 29.4 (m). HRMS (EI): $(MH - BH_3)^+$ 193.0980 ($(MH - BH_3)^+$, exact mass calcd for $C_{12}H_{18}P$: 193.1146).

33: bp 173.3 °C; $[\alpha]^{24}_D = 18.3$ °C (*c* 1.2, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.19−1.00 (br m, 3H), 1.30 (d, $J = 10.3$ Hz, 3H), 1.38−1.44 (m, 1H), 1.61−1.74 (m, 2H), 1.96−2.10 (m, 3H), 2.21−2.26 (m, 1H), 2.43−2.51 (m, 1H), 3.03−3.09 (m, 1H), 7.19−7.33 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 7.9 (d, $J_{C-P} = 29.8$ Hz), 24.7, 25.9 (d, $J_{C-P} = 35.9$ Hz), 32.7, 34.8, 39.8 (d, $J_{C-P} = 34.3$ Hz), 126.8, 128.8, 139.9, 140.0; ^{31}P (162 MHz, $CDCl_3$) δ 27.8 (m). HRMS (EI): $(MH - BH_3)^+$ 193.0981 ($(MH - BH_3)^+$, exact mass calcd for $C_{12}H_{18}P$: 193.1146).

Preparation of 1,2-Bis((1*S*,2*S*)-2-benzylphospholano)ethane (35).[54] The phosphine borane, **34** (100 mg, 0.2439 mmol), was dissolved in 5 mL of degassed CH_2Cl_2 in a Schlenk tube under N_2. The solution was cooled to 0 °C, and then $HBF_4 \cdot Me_2O$ (0.45 mL, 3.66 mmol) was added dropwise via syringe. The reaction was then warmed to room temperature and stirred overnight. The reaction was quenched with a degassed mixture of 6 mL of Et_2O and 6 mL of saturated K_2CO_3. The aqueous layer was removed via pipet while N_2 was blown across the solution. The organic layer was washed with 5 mL of degassed brine. The aqueous layer was removed via pipet, and the organic layer was dried over $MgSO_4$ and then filtered through basic alumina. The solvent was evaporated in vacuo to produce product **35** (85 mg, 91%). The free phosphine ligand was immediately bound to rhodium to prevent oxidation. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.78−0.99 (m, 4H), 1.18−1.32 (m, 6H), 1.53−1.60 (m, 4H), 1.79−1.82 (m, 6H), 2.62−2.69 (m, 4H), 7.11−7.13 (m, 6H), 7.18−7.22 (m, 4H); ^{31}P NMR (162 MHz, $CDCl_3$) δ −7.9.

(54) McKinstry, L.; Livinghouse, T. *Tetrahedron Lett.* **1994**, *35*, 9319.

Preparation of 1,2-Bis((1*R*,2*S*)-2-benzylphospholano)ethanerhodium(I) Tetrafluoroborate (36). In a 25 mL vial was placed $[Rh(norbornadiene)_2]^+BF_4^-$ (232 mg, 0.571 mmol) under nitrogen. To the metal complex was added 2 mL of MeOH via syringe, and the resulting solution was cooled to −15 °C. In a separate vial, **35** (240 mg, 0.6283 mmol) was dissolved in 4 mL of THF under N_2, and then the resulting solution was taken up in a syringe. The solution of **35** was added dropwise to the metal complex solution over a period of 5 min while the temperature of the reaction was maintained at −15 °C. The resulting solution was then allowed to warm to room temperature and was stirred for 2 h. The solvent was removed in vacuo, and then the red powder was recrystallized from hot methanol in a glovebox producing a red crystalline product (213 mg, 55%). X-ray crystallography confirmed the structure and stereochemistry of **36** (see Supporting Information). mp 192.4 °C (decomp.); $[\alpha]^{24}_D = 0.5$ °C (*c* 0.8, MeOH); ^{31}P NMR (162 MHz, $CDCl_3$) δ 66.5 (d, $J_{Rh-P} = 144.6$ Hz). HRMS (EI, direct insert): $(M - BF_4)^+$ 577.0685 ($(M - BF_4)^+$, exact mass calcd for $C_{31}H_{40}P_2Rh$: 577.1660).

Acknowledgment. The author thanks Dainius Macikenas and Ron Rubin for expert assistance in X-ray crystallography and Cassandra Farren for administrative assistance. Om Goel, James Davidson, and Daniel Belmont are acknowledged for stimulating discussion and project support.

Supporting Information Available: Instrumentation descriptions, a general procedure for asymmetric hydrogenation, methods for enantiomeric excess determinations for asymmetric hydrogenation products, proof of relative and absolute stereochemistry for **20** and **23**, X-ray crystal data for **36**, and selected ^{1}H and ^{13}C NMR spectra (PDF and CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA034715O