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Development of *P*-stereogenic 2-phenyl-1,3,2-oxazaphosphorine ligands and their unexpected sensitivity to oxidation

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ABSTRACT

P-Stereogenic oxazaphosphorine compounds of the form **4** have not previously been reported as asymmetric ligands for metal-catalyzed reactions. In an effort to explore the behavior of such oxazaphosphorine ligands, monomeric oxazaphosphorine borane **9** and dimeric oxazaphosphorine boranes **25** and **26** were synthesized as catalyst precursors. The absolute configuration of the phosphorus center contained in the oxazaphosphorines was determined by X-ray crystallography. Rhodium-catalyzed hydrogenation of methyl 2-acetamidoacrylate using a dimerized spiro oxazaphosphorine ligand was performed with up to 15% ee. The extreme sensitivity of the oxazaphosphorine ligands toward oxidation prevented further optimization of the enantioselectivity.

1. Introduction

Phosphines are a popular ligand choice for transition metal-catalyzed asymmetric organic reactions. These ligands have an affinity to coordinate with a wide variety of metals and their steric bulk and electronic properties can be manipulated thoroughly and systematically.[1] Phosphines have been shown to be useful in many different types of reactions, including rhodium and ruthenium-catalyzed hydrogenations,[2] palladium-catalyzed allylic alkylations,[3] copper-catalyzed conjugate additions,[4] copper-catalyzed hydrosilylations,[5] as well as numerous cross-coupling reactions.[6] Phosphines are also ideal for creating a well-defined chiral environment around the metal center. These phosphine ligands can be synthesized with *C*-stereogenic elements in the backbone and/or with *P*-stereogenic centers. This choice of chirality type greatly increases their versatility as potential ligands. Phosphines with backbone stereogenic elements are readily accessible using appropriate organic fragments available from the chiral pool, and their ease of preparation has led to their prominent use in the literature.[2f,7]

In contrast, phosphorus ligands with *P*-stereogenic centers are much more challenging synthetic targets, as no *P*-stereogenic compounds are found in the chiral pool. The stereogenic phosphorus center must be introduced via asymmetric synthesis. Due to the synthetic challenges posed by *P*-stereogenic centers, less work has been carried out in this area of phosphorus-based ligands. Despite this, *P*-stereogenic ligands are uniquely attractive for asymmetric catalysis because they bring the center of chirality closer to the metal than the chirality from the backbone. Therefore, several approaches have been developed for the synthesis and use of *P*-stereogenic ligands over the last four decades.[8]

There are many reports on the use of heterofunctionalized *P*-stereogenic compounds **1** as ligands for metal-catalyzed asymmetric reactions[9] and 2-alkylated-1,3,2-oxazaphosphorine-2-oxides **2** as substrate-bound chiral auxiliaries for asymmetric synthetic transformations (Fig. 1).[10,11] Surprisingly, no reports could be found in which 2-arylated-1,3,2-oxazaphosphorine-2-oxides **3**[12] or 3-phenyl-1,3,2-oxazaphosphorines **4**[25,13,†] have been used as substrate-bound chiral auxiliaries or as metal-bound ligands in asymmetric transformations. Our interest in the use of spiro 1,3-amino alcohol **5** as an auxiliary in Diels–Alder reactions[14] and in palladium-catalyzed allylation reactions[15] prompted us to investigate whether **5** could be tethered to a phosphorus atom to make 2-phenyl-1,3,2-oxazaphosphorine **6**, or dimerized to make a diphosphine ligand **7**. The advantage of ligands **6** and **7** is that both have *P*-stereogenic atoms and a backbone chirality for enhancing the enantioselectivity in metal-catalyzed reactions. We herein report the preparation of **6** and **7**, and their use in a Rh-catalyzed hydrogenation of methyl 2-acetamidoacrylate and their observed high propensity for oxidation.

2. Results

Spiro 1,3-amino alcohol (−)-**5** was prepared as previously described[14,15] and mono-N-methylated via a modified procedure reported by Paquette and Tae[16] to give **8** (94% over two steps, Scheme 1). The direct treatment of **8** with dichlorophenylphosphine

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† Only one report was found in which a stereogenic center was found in the 1,3,2-oxazaphosphorine ring; however, it was not used in any asymmetric reactions since it readily oxidized to the corresponding oxide. See Ref. 12i.

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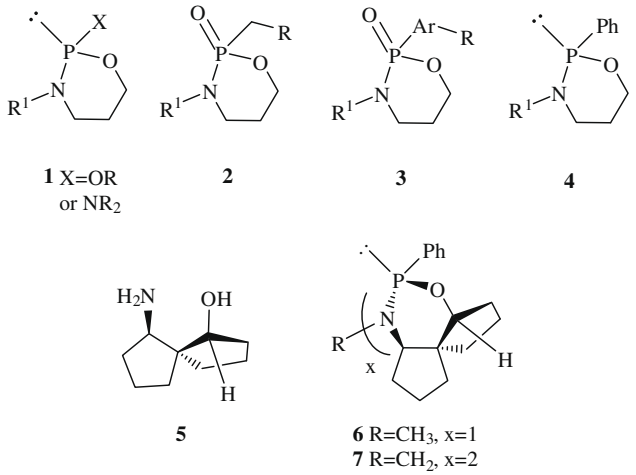
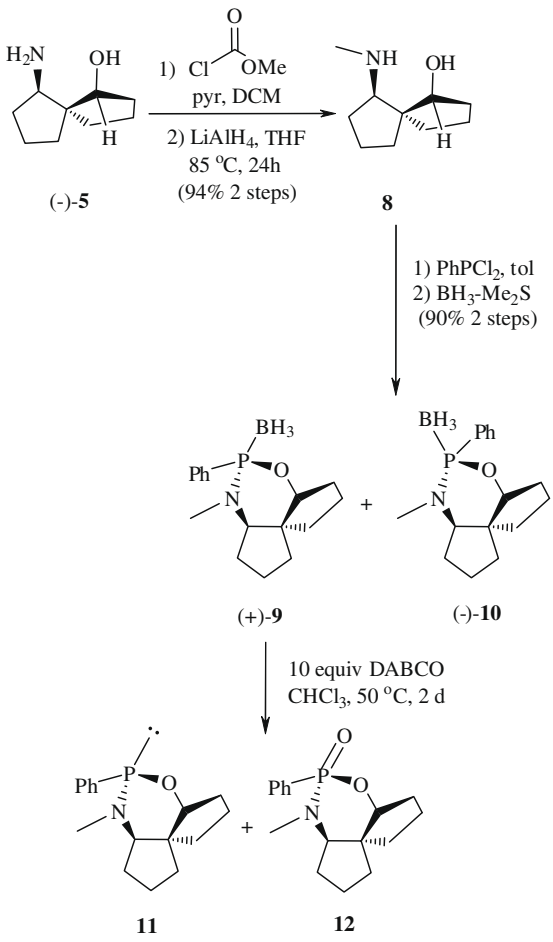


Figure 1.

($PhPCl_2$) gave a complex mixture consisting of two diastereomers of **6** and two diastereomers of the corresponding phosphine oxides, along with unidentified products. In order to minimize the formation of the phosphine oxides, a longer procedure was developed that involved treatment of a precooled solution of dichlorophenylphosphine at −78 °C with triethylamine (Et_3N) and **8**. This mixture was then heated at reflux overnight to allow equilibration through an inversion at the phosphorus atom[17,18] to give an unequal mixture of diastereomers. The solution was not worked up at this stage but further treated with borane–methyl sulfide to give a 2.5:1 mixture of diastereomers **9** and **10** in a 90% yield. The major isomer **9** was crystallized from isopropanol/hexanes and its structure determined by X-ray crystallography (Fig. 2). The crystal structure showed that the thermodynamically favored isomer (+)-**9** had an (*R*)-configuration at the phosphorus atom. The borane was removed by heating **9** at 50 °C in the presence of 10 equiv of DABCO[19] for 2 days in chloroform to afford oxazaphosphorine **11** and a small amount of oxazaphosphorine-2-oxide **12**. The crude product **11** was obtained as a clear, colorless oil. Despite the use of degassed solvents under an inert atmosphere, this sample always contained some of the phosphorine-2-oxide **12**, as noted by ^{31}P NMR analysis.[‡] Any attempt to purify **11** by column chromatography or distillation resulted in the formation of **12**. Therefore, **11** was not isolated but used directly in subsequent hydrogenation reactions.



Scheme 1.

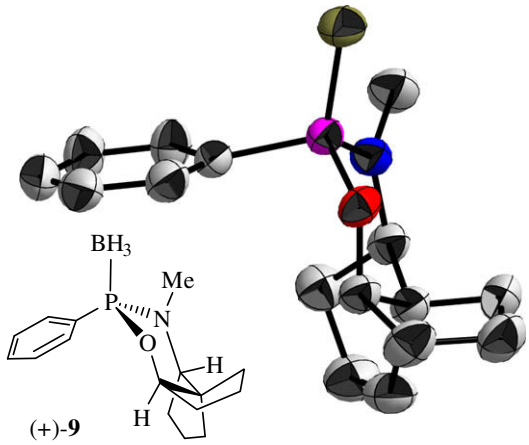
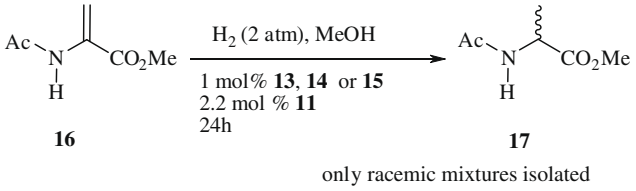


Figure 2. X-ray crystal structure of (+)-9 (hydrogen atoms omitted for clarity).

The crude mixture of **11** and oxide **12** was dissolved in degassed methanol to make a stock solution. A portion was added to each of $Rh(NBD)_2BF_4$ **13**, $Rh(COD)BF_4$ **14**, and $Rh(COD)_2OTf$ **15** (Scheme 2).

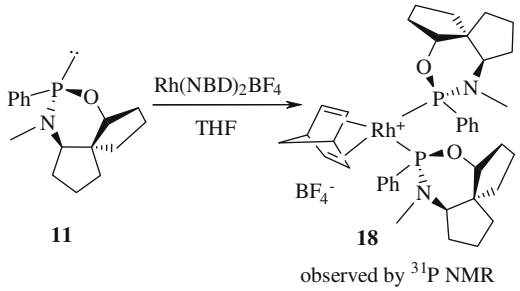


Scheme 2.

Methyl 2-acetamidoacrylate **16** was added to each reaction vial and each was placed under two atmospheres of H_2 (30 psi). These reaction vessels were reacted in a Parr Shaker for 24 h. Each of these hydrogenation attempts resulted in racemic product **17**. These products were analyzed by chiral GC, indicating that the hydrogenations were not taking place in an appropriate chiral environment to induce enantioselectivity. Thus, either the desired chiral rhodium(I) catalyst did not form from the reaction of **13–15** with ligand **11**, or the environments provided by the chiral catalysts were unsuitable for inducing enantioselectivity.

[‡] The reactions with DABCO to remove the borane from **9** were continually monitored by ^{31}P NMR for the formation of a peak at 114 ppm that indicated phosphorine **11** had formed. If the reaction was left for too long, phosphorine-2-oxide **12** was formed, which was identified by a peak at 19 ppm in the ^{31}P NMR spectrum.

To confirm that the oxazaphosphorine ligand was able to form a complex with the rhodium metal, an attempt was made to form and then isolate rhodium(I) complex **18** as shown in Scheme 3. Following a procedure analogous to that reported by Zhang,[20] a sample of mostly oxazaphosphorine **11** (some oxide was unavoidable) was dissolved in degassed THF and added to a solution of $Rh(NBD)_2BF_4$ **13** in THF at 0 °C. After 15 min, degassed diethyl ether was added rapidly in an attempt to precipitate the complex out of solution. A brown sludge resulted, and upon filtration this sludge gave a thick black tar. This black/brown tar was soluble in deuterochloroform, and analysis of the ^{31}P NMR spectrum showed a doublet at δ 119 ppm with a coupling constant of 202 Hz. This coupling constant is characteristic of phosphorus–rhodium one-bond coupling. There was also a singlet at δ 20 ppm. This singlet was due to oxidized oxazaphosphorine **12**. Several other minor by-products were also present, and attempts to crystallize the rhodium complex for further analysis were unsuccessful.

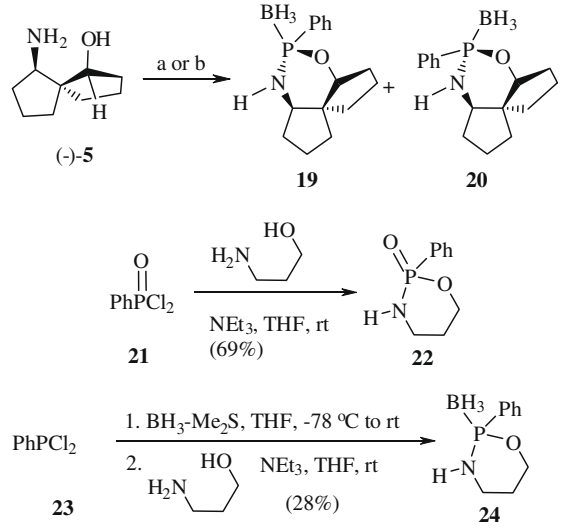


Scheme 3.

The ^{31}P NMR evidence indicated that spiro oxazaphosphorine **11** was able to bind to rhodium metal. Since the hydrogenation reactions all provided **17** as racemic mixtures, the chiral environment created by **11** around the metal center did not induce any enantioselectivity during the reaction. This issue has been raised with many other monomeric ligands in comparison with their bidendate counterparts.[2f,7c,21] Since the bidendate ligands are less labile than their monodendate counterparts,[1e] they can often create a more rigid, controlled chiral environment around a metal center. In an effort to create an optimal environment for asymmetric reactions, it was desirable to access a dimerized form of spiro oxazaphosphorine **11** that could act as a bidendate ligand with a metal center. This dimer **7** (Fig. 1) would then be tested under similar hydrogenation conditions to determine if the enantioselectivity could be achieved.

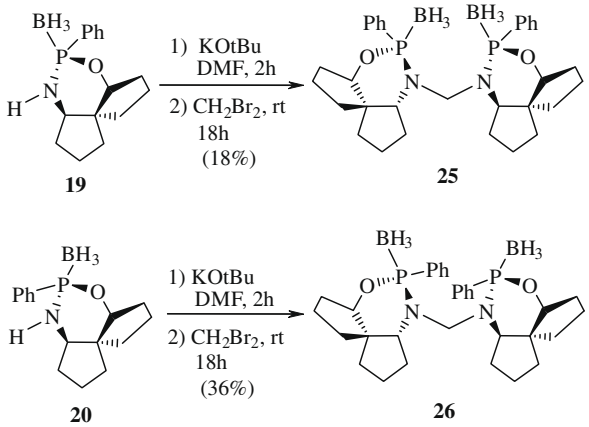
An attempt was made to repeat the successful route to oxazaphosphorine borane **9** (Scheme 1), substituting spiro 1,3-amino alcohol (−)-**5** (Scheme 4) for methylated amino alcohol **8** (Scheme 1), but this led to a complex mixture. Chromatographic purification of the crude product gave a small amount (~4% yield) of **19** and **20** along with their corresponding oxides. Therefore, a more practical synthetic route to **19** and **20** was developed. To facilitate the rapid optimization of the synthesis of **19** and **20**, 3-amino-1-propanol was used in place of spiro 1,3-amino alcohol (−)-**5** (Scheme 4).[22]

The reaction of 3-amino-1-propanol with tricoordinate phosphorus compounds dichlorophenylphosphine or bis(diethylamino)-phosphine (in toluene or THF solution) followed by the addition of borane–methyl sulfide solution resulted in complex mixtures. A literature precedent for the formation of an oxazaphosphorine oxide from phenylphosphonic dichloride and a primary amino alcohol[23] prompted an attempt to synthesize oxide **22** from phenylphosphonic dichloride **21** (69% yield, Scheme 4). This success indicated that a tetracoordinate phosphorus center would be a better substrate for reaction with a primary amino alcohol such as 3-amino-1-propanol or spiro 1,3-amino alcohol **5**. Therefore, the order of addition was modified to form dichlorophenylphosphine borane in situ before reaction with 3-amino-1-propanol. This resulted in the formation of the desired phosphorine-borane complex **24** in 28% yield. Repeating the reaction with spiro 1,3-amino alcohol (−)-**5** afforded a 57% yield of **19** and **20** (1:1 ratio) that were readily separated by column chromatography (Scheme 4).



Scheme 4. Reagents and conditions: (a) (i)$PhPCl_2$, tol, NEt_3, 110 °C, 12 h; (ii) BH_3–Me_2S (~4%over two steps); (b) premix $PhPCl_2$ and BH_3–Me_2S, THF, −78°C to rt; then add NEt_3 and (−)-5 (57%, 1:1 mixture).

Dioxazaphosphorine borane **19** was coupled to itself by treatment with potassium *t*-butoxide (DMF, 2 h) followed by the addition of dibromomethane to afford **25** (18% yield, Scheme 5).[§] The reaction was repeated with **20** to give **26** (36% yield, Scheme 5). Both dimers **25** and **26** were purified by column chromatography or crystallization from ethyl acetate/hexanes.



Scheme 5.

After purification of **25** by flash chromatography (7:1 hexanes/ethyl acetate), a crystal structure was obtained from one of the column fractions (Fig. 3). This allowed the assignment of the absolute configuration at phosphorus to be (S_P) in **25**. This meant that oxazaphosphorine borane **19** also had an (S_P)-configuration, and therefore by default the other diastereomer **26** and its precursor **20** would have to be (R_P).

[§] The reaction conditions for the coupling of **19** (or **20**) to itself with methylene bromide were worked out using model oxazaphosphorine borane **24**. For details, see Ref. 22.

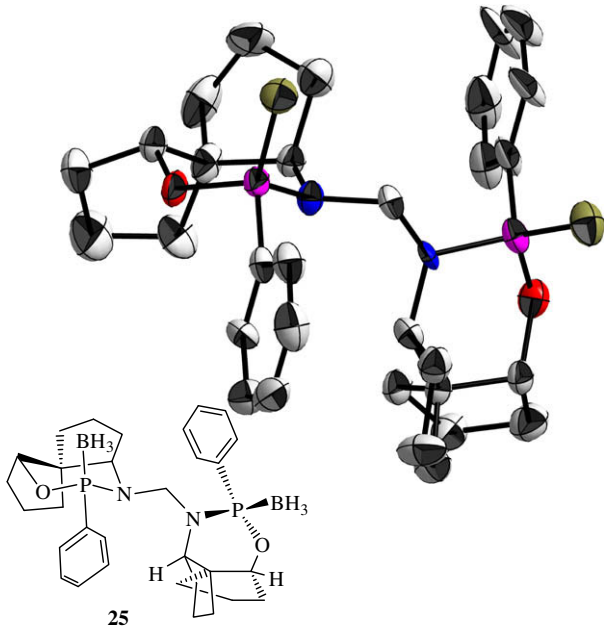


Figure 3. X-ray crystal structure of 25 (hydrogen atoms omitted for clarity).

With compound **25** (and **26**) in hand, steps were then taken to remove the borane protecting groups and to form a rhodium complex that could be tested in asymmetric hydrogenations. The deprotection was carried out with care and precautions to avoid unwanted oxidation of the phosphorus atoms. Borane **25** was treated with 20 equiv of freshly sublimed DABCO[18,19] under an argon atmosphere in an NMR tube containing degassed $CDCl_3$. The NMR tube was placed into an oil bath at 60 °C for 18 h. ^{31}P NMR analysis revealed that the major component was deboronated compound **27** (Spectrum a, Fig. 4) along with a small amount of starting material **25** and bis-phosphine oxide **29**. The solution of dioxazaphosphorine **28** was transferred via syringe to another NMR tube containing $Rh(NBD)_2BF_4$ **13** under nitrogen. Examination of the ^{31}P NMR spectrum at this stage showed the complete disappearance of the deprotected oxazaphosphorine signal at δ 139.2 ppm and the formation of a clean doublet at δ 127.6 ppm with a coupling constant of $^{1}J_{P-Rh}$ = 197.0 Hz, (Spectrum b, Fig. 4). This provided strong evidence for the formation of complex **28**. All attempts to crystalize **28** failed; the ^{31}P NMR spectra showed the obtained crystalline solid and the mother liquor was mainly bis-phosphine oxide **29** and small amount of starting material **25** (Spectra c and d, Fig. 4). This evidence indicated that the rhodium complex **28** was extremely sensitive. Since any attempt to isolate **28** resulted in the rapid formation of bis-phosphine oxide **29**,

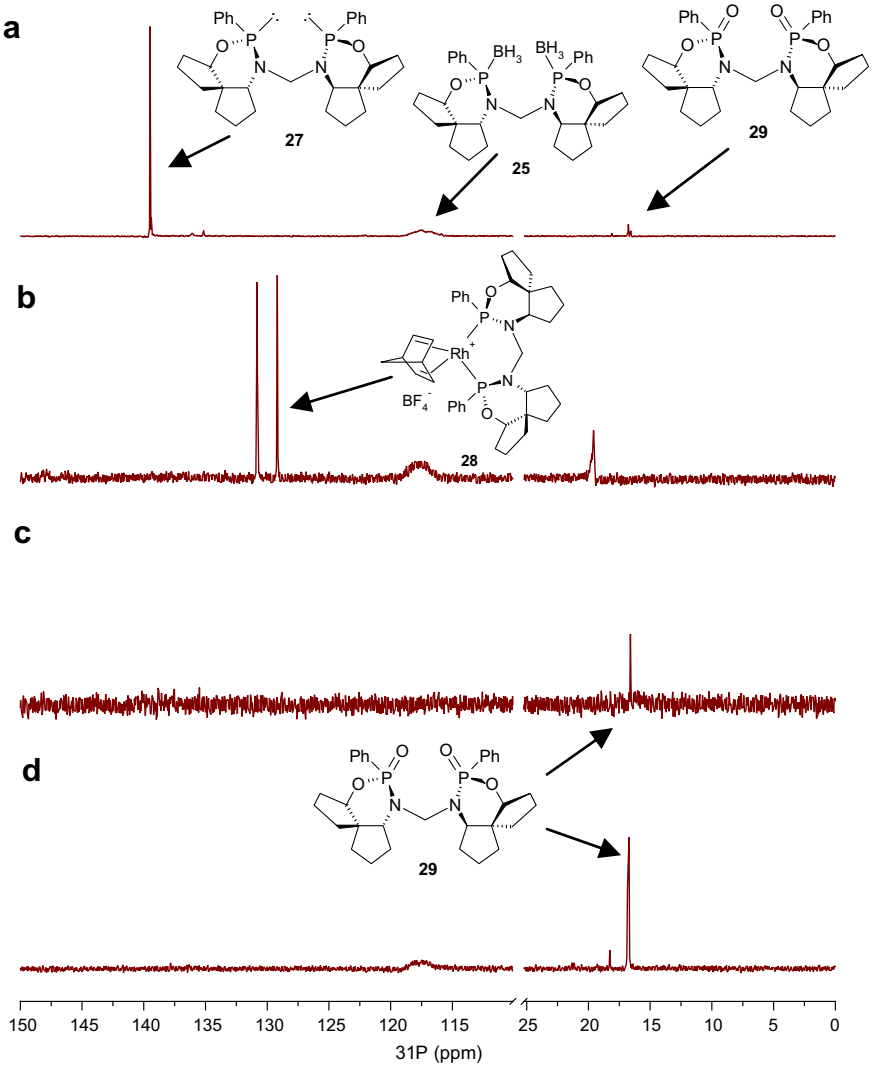
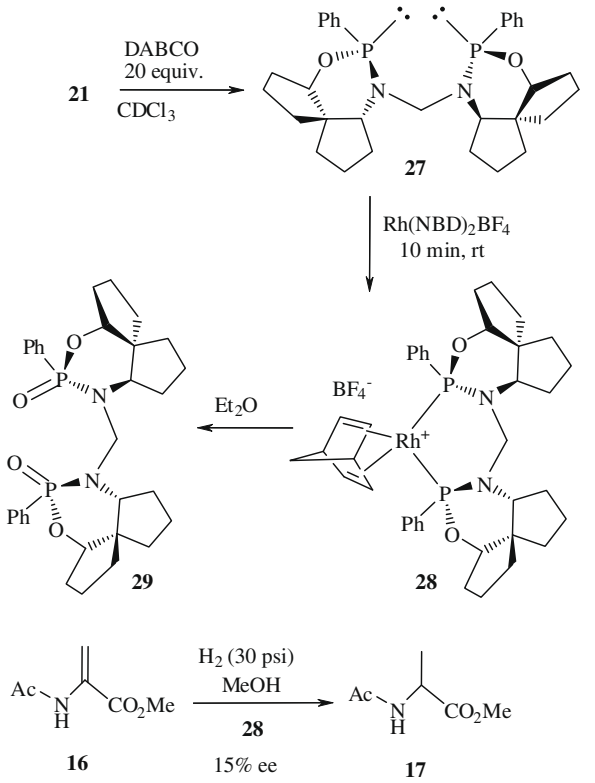


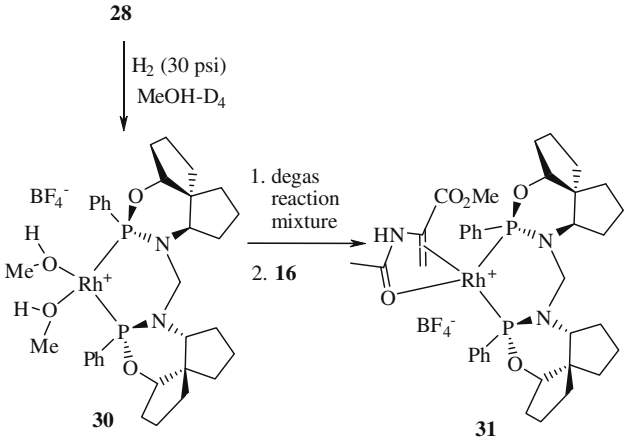
Figure 4. ^{31}P NMR spectra showing the generation of spiro dioxazaphosphorine Rh(I) complex **28**, followed by decomposition to bis-phosphine oxide **29**; (a) Deprotected spiro oxazaphosphorine **27** in $CDCl_3$, (b) rhodium complex **28** in $CDCl_3$, (c) precipitate from crystallization attempt in $CDCl_3$, (d) mother liquor from crystallization attempt in $CDCl_3$.

Rh-complex **28** was generated in situ and used directly in subsequent hydrogenation reactions. Hydrogenation of olefin **16** with **28**, which was generated in situ (2 atm H_2), gave **17** with 15% ee (Scheme 6).



Scheme 6.

The measureable ee obtained using catalyst **28**, although modest (15%), was encouraging. In order to obtain a further understanding of the ligand–catalyst system, the reaction was repeated in a J-Young tube for closer monitoring. The objective was to be able to observe the ^{31}P NMR spectrum of the olefin-bound rhodium complex and determine if any mechanistic insight could be gained by examining the ratio of diastereomeric olefin-bound complexes **31** (Scheme 7).[24] The steps envisioned to achieve this goal are outlined in Scheme 7. To form the desired olefin-bound complexes **31**, complex **28** would be prepared as previously described (Scheme 6), taken up into methanol-d_4 to form **30,** then subsequently treat with olefin **16** to form a mixture of diastereomers **31**. Every attempt to follow the procedure outlined in Scheme 7 did not show any evidence of the formation of olefin-bound complexes **31**. Consequently no further analysis of the enantioselective nature of **31** could be made.



Scheme 7.

3. Discussion

To gain some perspective on this observed sensitivity to oxidation, the literature was searched for comments on the sensitivity and handling of other heterofunctionalized tricoordinate phosphorus ligands, specifically those with O, N, and C atoms attached. However, very few examples of heterobifunctionalized oxazaphosphorines of the general format **32** as shown in Figure 5 have been reported. For quite some time this was attributed to the fact that they are derived from 1,3-amino alcohols, as opposed to the more common 1,2-amino alcohols that can be obtained readily from α-amino acids. On closer examination, however, we found numerous examples of oxazaphosphorines of general structure **33** in the literature. This structural unit is part of many anti-cancer drugs.[25] This observation supported our conclusion that oxazaphosphorines of general structure **32** are especially air sensitive and difficult to handle.

A few oxazaphosphorines of general structure **32** were found in the literature and these structures have the same level of sensitivity as noted with **11** and **27** (Fig. 5). Oxazaphosphorine **34** was formed by Pietrusiewicz and Salamonczyk but was unable to be isolated 'due to its pronounced propensity to oxidation', therefore it was immediately transformed into oxide **35** in situ.[12i] Benzimidazole derivative **36** has been described by Contreras et al. as being 'very reactive to oxygen and moisture, and is easily transformed

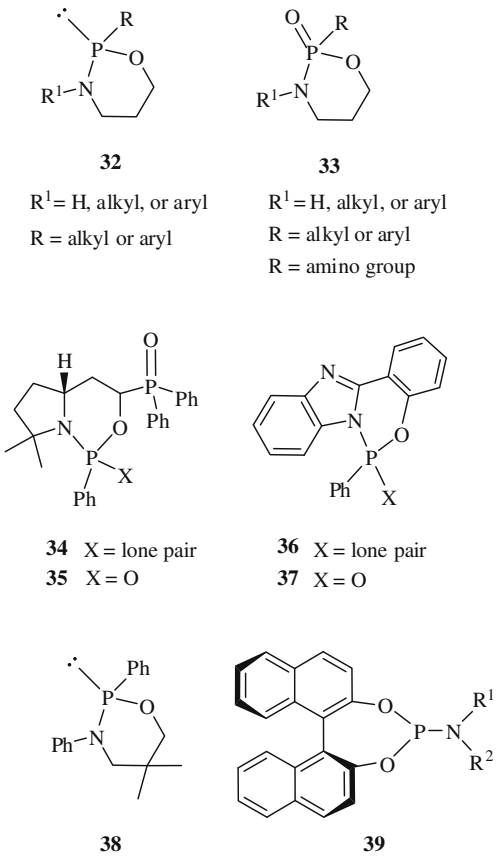


Figure 5.

into its oxide' **37**.[26] Oxazaphosphorine **38** was reported,[27] and although no comments were made about the sensitivity of oxazaphosphorine **38**, it should be noted that crystals were grown at low temperature (−20 °C) and then mounted in a sealed capillary under argon for X-ray crystal analysis at low temperature (−125 °C). Therefore, it is assumed that the sensitivity to oxidation of the oxazaphosphorine unit was taken into account during the X-ray crystal analysis.

The sensitivity to oxidation observed with ligands **11** and **27** and alluded to in reports of compounds **34**, **36**, and **38** contrasts with the behavior of other heterosubstituted phosphorus ligands, such as Feringa's phosphoramidites **39** (Fig. 5), which are known to be 'remarkably stable to air and moisture'.[28] This is in contrast with what might be expected according to trends in basicity, as trialkylphosphines are generally more basic and more susceptible to oxidation than triarylphosphines and heterosubstituted phosphines.[29]

4. Conclusion

1,3,2-Oxazaphosphorine boranes **9**, **25**, and **26** were successfully synthesized in enantiopure form to explore their use as *P*-stereogenic ligand precursors, but the sensitivity to the oxidation of oxazaphosphorines **11** and **27** precluded their effective use in asymmetric reactions. The few examples of general oxazaphosphorine structure **32** in the literature also support the high propensity of systems such as **32** to oxidation. Combined with the success of other heterosubstituted phosphorus ligands and the unexpected opposition to trends in basicity, it was not possible to forsee the extreme challenges phosphorus oxidation would pose for the application of **11** or **27** as chiral ligands in asymmetric catalysis.

A more thorough analysis of the factors that influence the oxidation rates of tricoordinate phosphorus compounds is currently ongoing. There have been no successful examples of *P*-stereogenic ligands with C, N, and O atoms attached to phosphorus reported. Recent investigations have been focused on how this particular combination of heteroatom substituents might be effecting the oxazaphosphorine's reactivity toward oxygen.

5. Experimental

5.1. General considerations

All reactions were carried out under an inert atmosphere of nitrogen or argon gas unless otherwise stated. Glassware was dried in a 120 °C oven overnight or flame dried immediately prior to use, and then cooled to room temperature under a nitrogen or argon atmosphere. When needed, solvents and reagents were purified according to standard methods. Tetrahydrofuran was distilled from sodium benzophenone ketyl immediately prior to use. Toluene and dichloromethane were distilled from calcium hydride immediately prior to use. DABCO was routinely sublimed at 0.02 Torr and stored under an argon or nitrogen atmosphere. Triethylamine was distilled from calcium hydride and stored in Sure/Seal bottles. Recrystallizations were performed with a mixed solvent technique. The crude material was dissolved in the minimum volume of hot solvent (isopropanol or ethyl acetate), and then cold hexane was added until cloudiness was observed. Mixtures were then cooled to room temperature and placed in a freezer to allow more complete crystallization.

NMR spectra were obtained on either a 200 MHz, 300 MHz, or 400 MHz spectrometer. All samples were run in deuterochloroform unless otherwise noted. Proton spectra were referenced to the residual chloroform signal at 7.27 ppm. Carbon spectra were referenced to the deuteriochloroform signal at 77.0 ppm. Phosphorus spectra were referenced to an external standard of 30% phosphoric acid in D_2O set to 0 ppm. Melting points were obtained on a melting point apparatus, and are uncorrected. Optical rotations were measured using a polarimeter at 589 nm using a path cell length of 1 dm. The corresponding concentration (g/100 mL) and solvent for each sample are listed in parentheses. Infrared spectra were obtained using a FT-IR spectrometer. Liquid samples were analyzed neat between KBr plates, and solid samples were analyzed as thin films from $CHCl_3$ or CH_2Cl_2 solutions between KBr plates. Low and high resolution mass spectra and elemental analyses were acquired at the University of Calgary through the Department of Chemistry.

5.2. Synthesis of (5*R*,6*R*)-6-methylamino-spiro[4.4]nonan-1-ol (−)-8

Pyridine (1.02 mL, 12.6 mmol) and methyl chloroformate (0.96 mL, 12.4 mmol) were added to a solution of (−)-spiro 1,3-amino alcohol (−)-**5** (0.370 g, 2.38 mmol) in dichloromethane (12 mL). The reaction mixture was stirred at room temperature overnight. The reaction was quenched with 10% $HCl_{(aq)}$ (20 mL) and then extracted with dichloromethane (3 × 20 mL). The combined organic layers were washed with saturated Na_2CO_3 solution (30 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a yellow-white solid that was identified as the corresponding methyl carbamate of (−)-**5** (0.490 g, 2.30 mmol, 96%): mp 110–112 °C; $[\alpha]_D^{20} = -9.6$ (*c* 0.4, $CHCl_3$); IR (film) 3252, 2958, 2923, 1672, 1553, 1427, 1266, 1090 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.29–5.10 (br s, 1H), 3.99 (br s, 1H), 3.91–3.81 (m, 2H), 3.67 (s, 3H), 2.06–1.84 (m, 2H), 1.82–1.64 (m, 6H), 1.60–1.51 (m, 2H), 1.35–1.20 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.9, 78.0, 58.4, 52.4, 32.7, 32.5, 32.2, 31.4, 20.7, 20.0; MS: *m/z* 214 (M^++1, 100), 120(5), 59(17); HRMS calcd for $C_{11}H_{19}NO_3$ 213.13649, found 213.13562. Anal. Calcd for $C_{11}H_{19}NO_3$: C, 61.95; H, 8.98; N, 6.57. Found: C, 61.89; H, 8.93; N, 6.43.

A solution of the above-mentioned methyl carbamate of (−)-**5** (0.490 g, 2.30 mmol) in THF (20 mL) was added dropwise to a slurry of $LiAlH_4$ (0.456 g, 12.0 mmol) in THF (5 mL) at 0 °C. The solution was gradually warmed to rt, then heated at reflux for 24 h. The reaction mixture was then cooled to 0 °C, quenched with 10% $NaOH_{(aq)}$ (150 mL), and extracted with Et_2O (3 × 50 mL). The combined organic layers were washed with 10% $NaOH_{(aq)}$ (50 mL) and brine (50 mL), then dried over Na_2SO_4, filtered, and concentrated under reduced pressure to yield (−)-**8** as a thick clear colorless oil (0.380 g, 2.24 mmol, 98%): $[\alpha]_D^{19} = -88.5$ (c 0.2, $CHCl_3$); IR (film) 3300, 2853, 2865, 1472, 1384, 1101 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.97–4.17 (br s, 2H), 4.09 (m, 1H), 2.99 (t, *J* = 6.4 Hz, 1H), 2.47 (s, 3H), 1.90–0.91 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 78.5, 68.1, 56.3, 35.6, 35.4, 34.3, 33.4, 29.9, 21.1, 21.0; MS: *m/z* 170 (M^++1, 100); HRMS calcd for $C_{10}H_{19}NO$ 169.14666, found 169.14617.

5.3. Synthesis of (5*R*,6a*R*,9a*R*)-6-methyl-5-phenyl-decahydro-4-oxa-6-aza-5-phosphacyclopenta-[*d*]indene borane (+)-9

Triethylamine (0.85 mL, 6.1 mmol) was added dropwise to a solution of dichlorophenylphosphine (0.367 g, 2.05 mmol) in toluene (4.5 mL) at −78 °C. After 5 min, a solution of methylated spiro 1,3-amino alcohol (−)-**8** (0.380 g, 2.24 mmol) in toluene (5.5 mL) was added and the solution was gradually warmed to room temperature over 2 h. The reaction mixture was then heated at reflux overnight. The mixture was then cooled to room temperature and a solution of $BH_3{\cdot}SMe_2$ in toluene (1.12 mL, 2 M, 2.24 mmol) was added. After 5 h, the mixture was filtered to remove $NEt_3{\cdot}HCl$ salts and the remaining filtrate was concentrated under reduced pressure to give a thick yellow oil (0.5311 g, 1.837 mmol, 90%), which was a mixture of two diastereomers. The crude product was recrys-

tallized from *i*PrOH/hexanes to give pure white crystals of diastereomer (+)-**9** (0.2151 g, 0.7439 mmol, 36%): mp 110–113 °C; $[\alpha]_D^{23} = +27.1$ (*c* 7.0, $CHCl_3$); IR (film) 2952, 2868, 2371, 1589, 1447, 1427, 1369, 1214 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.69–7.62 (m, 2H), 7.51–7.41 (m, 3H), 4.00 (m, 1H), 3.19 (m, 1H), 2.92 (d, J = 11.1 Hz, 3H), 2.16–2.01 (m, 2H), 1.99–1.80 (m, 3H), 1.68–1.36 (m, 7H), 1.32–0.06 (br q, J = 90.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 134.8 (d, J = 57.4 Hz), 131.2 (d, J = 2.0 Hz), 130.6 (d, J = 11.3 Hz), 128.3 (d, J = 9.7 Hz), 80.9 (d, J = 9.0 Hz), 65.1 (d, J = 2.1 Hz), 51.8 (d, J = 3.7 Hz), 37.6 (d J = 12.1 Hz), 35.8, 35.4, 31.9, 31.8, 31.6 (d, J = 1.0 Hz), 21.0, 20.1; ^{31}P NMR (121 MHz, $CDCl_3$) δ 108.0 (q, J = 80.9 Hz); MS: *m/z* 289 (M^+, 1), 275 (M^+-BH_3, 43), 198 (65), 156 (41), 121 (100); HRMS calcd for $C_{16}H_{22}NOP$ (M^+-BH_3) 275.14390, found 275.14574. Anal. Calcd for $C_{16}H_{25}BNOP$: C, 66.46; H, 8.71; N, 4.84. Found: C, 66.13; H, 8.81; N, 4.81.

X-ray crystal data for **(+)-9**: orthorhombic $P2_12_12_1$; a = 8.992(3) Å, b = 11.237(2) Å, c = 16.336(4) Å, a = 90°, b = 90°, g = 90°, V = 1650.6(7) $Å^3$; Z = 4; R = 0.038; R_w = 0.093.

5.4. The in situ deboronation of (+)-9 and rhodium-catalyzed hydrogenation of methyl 2-acetamidoacrylate 16

Freshly sublimed DABCO (0.060 g, 0.53 mmol) was added to a solution of dioxazaphosphorine borane (+)-**9** (0.015 g, 0.027 mmol) in chloroform (0.6 mL). The mixture was heated in a 60 °C oil bath for 18 h. The reaction mixture was then cooled to room temperature and bis(norbornadiene)rhodium(I) tetrafluoroborate (0.011 g, 0.027 mmol) was added. After 15 min, the solution was completely homogeneous and appeared clear orange. The chloroform was removed in vacuo. The orange residue was dissolved in degassed methanol (0.6 mL) and chloroform (2 drops for solubility) and methyl 2-acetamidoacrylate **16** (0.038 g, 0.27 mmol) were added. The reaction vessel was placed under H_2 (30 psi) for 7 h. The mixture was concentrated in vacuo and taken up into 1:1 ethyl acetate/hexanes for filtration through a plug of silica. The enantiomeric excess of the product was determined by chiral GC, (Cyclodex-B column, isothermal 90 °C, t_1 = 31.2 min, t_2 = 32.1 min), which indicated that the product **17** was a racemic mixture.

5.5. Synthesis of 2-phenyl-[1,3,2]oxazaphosphorine 2-oxide 22

Phenylphosphinic dichloride (0.193 g, 0.989 mmol) in THF (9 mL) was added dropwise to a solution of 3-amino-1-propanol (0.08 mL, 1 mmol) and triethylamine (0.28 mL, 2.0 mmol) in THF (16 mL). The mixture was stirred at room temperature for 24 h. The solution was filtered to remove the NEt_3·HCl salts and the resulting filtrate was concentrated under reduced pressure to give a clear colorless oil (0.161 g, 0.82 mmol, 82%). The crude oil was purified by flash chromatography (absolute ethanol) to give **22** as a thick, clear colorless oil (0.135 g, 0.68 mmol, 69%): ^1H NMR (400 MHz, $CDCl_3$) δ 7.85–7.80 (m, 2H), 7.56–7.45 (m, 3H), 4.53–4.44 (m, 1H), 4.19–4.11 (m, 1H), 3.50–3.40 (m, 1H), 3.32–3.19 (m, 2H), 2.13–2.01 (m, 1H), 1.83–1.74 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 131.9 (d, J = 3.1 Hz), 131.6, 131.4 (d, J = 10.4 Hz), 128.6 (d, J = 14.5 Hz), 67.5 (d, J = 6.8 Hz), 40.9 (d, J = 2.7 Hz), 26.4 (d, J = 7.4 Hz); ^{31}P NMR (120 MHz, $CDCl_3$) δ 19.8; MS: *m/z* 198 (M^++H^+); HRMS calcd for $C_9H_{12}NO_2P$ 197.06057, found 197.06233. Anal. Calcd for $C_9H_{12}NO_2P$: C, 54.82; H, 6.13; N, 7.10. Found: C, 54.10; H, 6.08; N, 6.46.

5.6. Synthesis of 2-phenyl-[1,3,2]oxazaphosphorine 2-borane 24

A solution of BH_3·SMe_2 in THF (9.6 mL, 2 M, 19 mmol) was added dropwise to a stirred solution of dichlorophenylphosphine (2.023 g, 11.30 mmol) in THF (120 mL) at −78 °C. The reaction mixture was gradually warmed to room temperature over 2 h. This solution was then cannulated into a room temperature solution of 3-amino-1-propanol (1.5 mL, 19.2 mmol) and triethylamine (4.7 mL, 34 mmol) in THF (200 mL). After stirring at room temperature for 15 min, the solution was filtered to remove NEt_3·HCl salts. The filtrate was concentrated under reduced pressure to give a thick yellow oil (4.41 g, 22.6 mmol, 200%). After flash chromatography (1:1 hexanes/ethyl acetate), oxazaphosphorine borane **24** was obtained as a white solid (0.621 g, 3.18 mmol, 28%): mp 82–84 °C; IR (film) 3347, 2954, 2923, 2239, 1652, 1436, 1383, 1119, 931 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.74–7.67 (m, 2H), 7.50–7.49 (m, 3H), 4.27–4.17 (m, 1H), 4.06–3.97 (m, 1H), 3.39–3.03 (m, 3H), 2.19–2.04 (m, 1H), 1.39 (br d, J = 14.1 Hz, 1H), 0.62 (br q, J = 89.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 131.7, 131.0, 130.9, 130.8, 129.4, 129.3, 66.0, 41.8, 26.3; ^{31}P NMR (120 MHz, $CDCl_3$) δ 104.4 (q, J = 69.6 Hz) ; MS: *m/z* 195 (1, M^+), 194 (6, M^+-H^+), 182 (11), 181 (100, M^+-BH_3); HRMS calcd for $C_9H_{14}BNOP$ (M^+-H^+) 194.09061, found 194.08922. Anal. Calcd for $C_9H_{15}BNOP$: C, 55.39; H, 7.75; N, 7.18. Found: C, 55.36; H, 7.71; N, 7.08.

5.7. Synthesis of (S_p)-(5*R*,6a*R*,9a*R*)-5-phenyl-decahydro-4-oxa-6-aza-5-phosphacyclopenta[*d*]-indene borane 19 and (R_p)-(5*R*,6a*R*,9a*R*)-5-phenyl-decahydro-4-oxa-6-aza-5-phosphacyclopenta-[*d*]indene borane 20

A solution of BH_3·SMe_2 in THF (3.4 mL, 2 M, 6.7 mmol) was added to a solution of dichlorophenylphosphine (0.600 g, 3.35 mmol) in THF (60 mL) at −78 °C. The solution was gradually warmed to room temperature over 1 h and was then cannulated into a solution of (−)-spiro 1,3-amino alcohol (−)-**5** (1.04 g, 6.71 mmol) and triethylamine (1.03 mL, 7.38 mmol) in THF (100 mL) at rt. The mixture was stirred for 15 min and then vacuum filtered to remove the insoluble NEt_3·HCl salts. The filtrate was concentrated under reduced pressure to give a clear colorless thick oil (1.955 g, 212%). After flash chromatography (5:1 hexanes/ethyl acetate), a mixture of diastereomers A and B was isolated as a clear colorless thick oil (0.526 g, 1.91 mmol, 57%). This mixture of diastereomers A and B was then submitted to flash chromatography (30:1 hexanes/ethyl acetate) to isolate each diastereomer. The first diastereomer to elute **19** was a thick clear colorless oil that displayed the following data: $[\alpha]_D^{20} = +11.75$ (*c* 0.4, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.81–7.74 (m, 2H), 7.51–7.46 (m, 3H), 4.44–4.41 (m, 1H), 3.17–3.13 (m, 1H), 2.72–2.53 (m, 1H), 2.13–1.44 (m, 12H), 1.27–0.17 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 131.6 (d, J = 2.2 Hz), 130.8, 130.4 (d, J = 11.8 Hz), 128.4 (d, J = 10.8 Hz), 84.2 (d, J = 4.7 Hz), 58.9 (d, J = 4.6 Hz), 57.9 (d, J = 5.2 Hz), 36.9, 36.6, 34.4 (d, J = 6.5 Hz), 32.6 (d, J = 8.0 Hz), 23.1, 22.7; ^{31}P NMR (121 MHz, $CDCl_3$) δ 106.7 (q, J = 75.4 Hz); MS: *m/z* 276 (100, M^++H^+), 262 (25); HRMS calcd for $C_{15}H_{24}BNOP$ (M^++H^+) 276.1689, found 276.1677.

The second diastereomer to elute **20** was a thick clear colorless oil that displayed the following data: $[\alpha]_D^{20} = -2.6$ (*c* 0.4, $CHCl_3$); IR (film) 3357, 2954, 2870, 1652, 1436, 1346, 1120, 1058 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.79–7.72 (m, 2H), 7.50–7.43 (m, 3H), 4.08 (br s, 1H), 3.50–3.33 (m, 1H), 2.99–2.92 (m, 1H), 2.19–2.10 (m), 2.00–1.87 (m), 1.75–1.15 (m), 1.20–0.04 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 133.8 (d, J = 66.0 Hz), 131.4 (d, J = 2.2 Hz), 130.9 (d, J = 11.2 Hz), 128.5 (d, J = 10.2 Hz), 81.6 (d, J = 9.1 Hz), 57.3 (d, J = 4.8 Hz), 51.2 (d, J = 6.4 Hz), 35.6, 34.6, 33.4 (d, J = 1.7 Hz), 32.4 (d, J = 6.6 Hz), 20.7, 20.6; ^{31}P NMR (121 MHz, $CDCl_3$) δ 98.4 (q, J = 79.8 Hz); MS: *m/z* 276 (95), 261 (100); HRMS calcd for $C_{15}H_{20}NOP$ (M^+-BH_3) 261.12825, found 261.12795.

5.8. Synthesis of (S_p)-bis[(5*R*,6a*R*,9a*R*)-6-methyl-5-phenyl-decahydro-4-oxa-6-aza-5-phospha-cyclopenta[*d*]indene borane] methane (−)-25

Potassium *tert*-butoxide (0.11 g, 0.99 mmol) was added to a solution of **19** (0.136 g, 0.490 mmol) in DMF (1.5 mL). After 1.5 h, dibromomethane (0.03 mL, 0.4 mmol) was added and the reaction mixture was stirred for 16 h. The mixture was then concentrated in vacuo, taken up into ethyl acetate, and filtered through a plug of silica. The ethyl acetate solution was concentrated in vacuo and crystallized from ethyl acetate/hexanes to give a pale yellow solid **(−)-25** (0.025 g, 0.044 mmol, 18%): mp 239–241 °C, $[\alpha]_D^{20} = -54.5$ (*c* 0.5, $CHCl_3$); IR (film) 2930, 2867, 1658, 1455, 1434, 1406, 1120 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.95–7.91 (m, 4H), 7.62–7.58 (m, 2H), 7.54–750 (m, 4H), 4.49 (br d, *J* = 3.6 Hz, 2H), 3.50–3.48 (m, 2H), 3.16–3.08 (m, 2H), 2.32–2.25 (m, 2H), 2.07–1.70 (m, 6H), 1.62–1.26 (m, 10H), 1.05–0.94 (m, 2H), 1.16–0.12 (m, 3H), 0.06–0.04 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 133.0 (d, *J* = 2.0 Hz,), 132.3 (d, *J* = 13.0 Hz), 131.3, 128.6 (d, *J* = 10.9 Hz), 80.9 (d, *J* = 4.4 Hz), 57.9 (d, *J* = 2.3 Hz), 55.7 (t, *J* = 13.8 Hz), 51.6 (d, *J* = 5.1 Hz), 35.4, 34.1, 32.1 (d, *J* = 7.6 Hz), 26.4, 20.6, 20.0; ^{31}P NMR (121 MHz, $CDCl_3$) δ 117.7 (m); MS: *m/z* 563 (M^++1), 274 (17); HRMS calcd for $C_{31}H_{43}BN_2O_2P_2$ (M^+-BH_3) 548.2892, found 548.28540. Anal. calcd for $C_{31}H_{46}B_2N_2O_2P_2$: C, 66.22; H, 8.25; N, 4.98. Found: C, 65.92; H, 8.44; N, 4.80.

X-ray crystal data for (−)-**25**: monoclinic $P2_1$; *a* = 11.660(3) Å, *b* = 22.710(3) Å, *c* = 11.946(4) Å, *a* = 90°, *b* = 93.546(15)°, γ = 90°, *V* = 3157.2(14) $Å^3$; *Z* = 4; *R* = 0.119; R_w = 0.360.

5.9. Synthesis of (R_p)-bis[(5*R*,6a*R*,9a*R*)-6-methyl-5-phenyl-decahydro-4-oxa-6-aza-5-phospha-cyclopenta[*d*]indene borane] methane (−)-26

Potassium *tert*-butoxide (0.087 g, 0.78 mmol) was added to a solution of **20** (0.107 g, 0.39 mmol) in DMF (1.3 mL). After 1.5 h, dibromomethane (0.03 mL, 0.42 mmol) was added and the reaction mixture was stirred for 16 h. The mixture was then concentrated in vacuo, taken up into ethyl acetate, and filtered through a plug of silica. The ethyl acetate solution was concentrated in vacuo and crystallized from ethyl acetate/hexanes to give a pale yellow solid (−)-**26** (0.039 g, 0.069 mmol, 36%): $[\alpha]_D^{20} = -19.1$ (*c* 1.1, $CHCl_3$); IR (film) 2950, 2243, 1652, 1635, 1436, 1099 cm^{-1};^1H NMR (300 MHz, $CDCl_3$) δ 7.56–7.47 (m, 10H), 5.15 (t, *J* = 7.4 Hz, 2H), 4.11–4.05 (m, 2H), 3.87–3.75 (m, 2H), 2.44–2.31 (m, 2H), 2.26–2.13 (m, 2H), 2.09–1.89 (m, 8H), 1.71–1.03 (m, 12H), 1.08–0.15 (br m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.4 (d, *J* = 54.9 Hz), 131.2 (d, *J* = 1.7 Hz), 130.3 (d, *J* = 10..9 Hz), 128.6 (d, *J* = 9.5 Hz), 81.0 (d, *J* = 9.1 Hz), 56.5 (d, *J* = 3.8 Hz), 50.4 (d, *J* = 3.4 Hz), 34.9, 34.8, 31.4 (d, *J* = 7.7 Hz), 29.7 (d, *J* = 5.5 Hz), 20.2, 19.9; ^{31}P NMR (121 MHz, $CDCl_3$) δ 104.0 (m); MS: *m/z* 563 (M^++1), 274 (17); HRMS calcd for $C_{31}H_{43}BN_2O_2P_2$ (M^+-BH_3) MS: *m/z* ; HRMS calcd for $C_{31}H_{43}B_1N_2O_2P_2$ (M^+-BH_3) 548.28623, found 548.28929. Anal. Calcd for $C_{31}H_{46}B_2N_2O_2P_2$: C, 66.22; H, 8.25; N, 4.98. Found: C, 65.91; H, 8.40; N, 4.80.

5.10. Attempts at rhodium-catalyzed hydrogenation of methyl 2-acetamidoacrylate 16 using ligand 25

Freshly sublimed DABCO (0.060 g, 0.53 mmol) was added to a solution of dioxazaphosphorine borane (−)-**25** (0.015 g, 0.027 mmol) in chloroform (0.6 mL). The mixture was heated in a 60 °C oil bath for 18 h. The reaction mixture was then cooled to room temperature and bis(norbornadiene)rhodium(I) tetrafluoroborate (0.011 g, 0.027 mmol) was added. After 15 min, the solution was completely homogeneous and appeared clear orange. The chloroform was removed in vacuo. The orange residue was dissolved in degassed methanol (0.6 mL) and chloroform (2 drops for solubility) and methyl 2-acetamidoacrylate **16** (0.038 g, 0.27 mmol) was added. The reaction vessel was placed under H_2 (30 psi) for 7 h. The mixture was concentrated in vacuo and taken up into 1:1 ethyl acetate/hexanes for filtration through a plug of silica. The enantiomeric excess of the product **17** was determined by chiral GC (Cyclodex-B column, isothermal 90 °C, t_1 = 31.2 min, t_2 = 32.1 min), and was found to be 15% ee.

5.11. Attempt to observe diastereomeric olefin-bound rhodium(I) complexes 31 (see Fig. 4)

All solvents were rigorously degassed before use (three successive freeze–pump–thaw cycles), the reaction was performed using a double manifold line, and all reagents/solvents were added within the inert atmosphere of a dry box. The progress of the reaction was monitored by ^{31}P NMR spectroscopy (162 MHz). Freshly sublimed DABCO (0.044 g, 0.39 mmol) was added to a solution of dioxazaphosphorine borane (−)-**25** (0.011 g, 0.020 mmol) in deuterochloroform (0.6 mL) in a J-Young tube. The mixture was heated in a 60 °C oil bath for 18 h and then cooled to room temperature. The ^{31}P NMR analysis showed the formation of a prominent singlet at δ 139.2 ppm corresponding to **27**. The addition of bis(norbornadiene)rhodium(I) tetrafluoroborate (0.008 g, 0.020 mmol) then resulted in a clear orange solution. The ^{31}P NMR spectrum showed the disappearance of the singlet for **27** at δ 139.2 ppm and the formation of a new doublet at δ 127.6 ppm (*J* = 197.0 Hz) corresponding to complex **28**. The deuterochloroform was then removed in vacuo and the residue was taken up into methanol-d_4. The ^{31}P NMR spectrum at this stage showed the loss of the doublet at δ 139.2 ppm. A new doublet at δ 139.8 ppm (*J* = 161.0 Hz) had formed, along with a roughly equal size signal at δ 17.7 ppm. Introduction of H_2 (30 psi) did not cause any change to the ^{31}P NMR spectrum. The reaction mixture was once again placed under an inert atmosphere (hydrogen was removed through three successive freeze–pump–thaw cycles) and olefin **16** was added to the solution. Again, no change was observed in the ^{31}P NMR spectrum. The reaction mixture was once again placed under H_2 (30 psi). After 7 h, the mixture was concentrated in vacuo and taken up into 1:1 ethyl acetate/hexanes for filtration through a plug of silica. The enantiomeric excess of the product was determined by chiral GC, Cyclodex-B column, isothermal 90 °C, t_1 = 31.2 min, t_2 = 32.1 min. The reaction showed only unreacted olefin 16 (*t* = 19.4 min). This indicated it was unlikely that the species in methanol-d_4 observed by ^{31}P NMR spectroscopy was the same species involved in the hydrogenation of 16 that resulted in a measurable ee.

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