Synthesis of Phosphino Oxazoline Ligand Libraries from Amino Acid and Phosphino Carboxylate Building Blocks

Scott R. Gilbertson* and Cheng-Wei T. Chang

Department of Chemistry, Washington University, St. Louis, Missouri 63130

Received July 21, 1998

A modular route to new phosphine−oxazoline ligands is reported. The ability of these ligands to asymmetrically catalyze the addition of dimethyl malonate to 1,3-diphenylprop-2-enyl acetate was investigated. The best of these ligands gave a palladium complex which catalyzed the addition of dimethyl malonate to 1,3-diphenylprop-2-enyl acetate in a 99% yield and in 98% enantiomeric excess (Table 3, entry 11).

Introduction

Over the last five years the impact of combinatorial chemistry has been felt principally in the area of drug discovery.[1] Most recently this technology has begun to be applied in other areas where the synthesis of large numbers of compounds can be of value. One area where methods to synthesize large numbers of compounds rapidly has great potential is in the development of new catalysts.[2−6] Over the last seven years we have been involved in the development of chemistry that allows for the rapid parallel synthesis of phosphine ligands. These ligands are coordinated to catalytically active transition metals. The resulting catalysts are then evaluated for their ability to do selective catalysis. A significant amount of our work has been devoted to the development of peptide-based systems where phosphine-containing amino acids are embedded in peptide secondary structures. Additionally, we have looked at simpler ligands that can be easily assembled by a modular approach. This paper reports the synthesis of simple phosphine−oxazoline ligands and their use in the catalysis of palladium-catalyzed π-allyl additions. We report a number of successful ligands with the best giving, at room temperature, the addition of malonate with 98% ee. A study of reaction temperature and counterion effects will also be reported. In the course of this work a novel method for the generation of malonate anion with tetraalkylammonium counterions was found and is detailed.

The use of phosphine-containing acids along with amino acids allows for the assembly of ligands by the formation of amide bonds instead of carbon−phosphorus bonds. This coupled to the ready availability of a number of amino acids provides for the rapid synthesis of different ligands. Through basically a three-step process, phosphine−oxazoline ligands are assembled with the R group next to nitrogen varying from methyl and phenyl to *tert*-butyl and isopropyl.

Phosphine−oxazoline ligands have been studied by a number of workers, particularly Pfaltz, Helmchen, and Williams. This type of ligand has proven useful in asymmetric π-allyl additions [7−12] and asymmetric Heck reactions.[13,14] To date, the most successful ligands of this type have been six-member chelates with the phosphine attached to the dihydrooxazole through a phenyl ring. To our knowledge, only a single system with the phosphine attached to the oxazoline ligand by an alkyl bridge has been reported. That system, which forms a five-member chelate, gave poorer selectivity than the best systems.[9] Our approach makes ligands available that link the phosphine and dihydrooxazole groups with a two-carbon alkyl chain, thus forming a six-member chelate upon metal coordination and allowing a direct comparison to the six-member chelates studied previously by others.[7−11] The use of an alkyl chain to connect the chelating functionality allows the introduction of a second chiral center, which is next to the phosphine. This results in diastereomeric ligands in which the two chiral centers can, potentially, act in concert or dissonance. Results with both diastereomeric possibilities are reported.

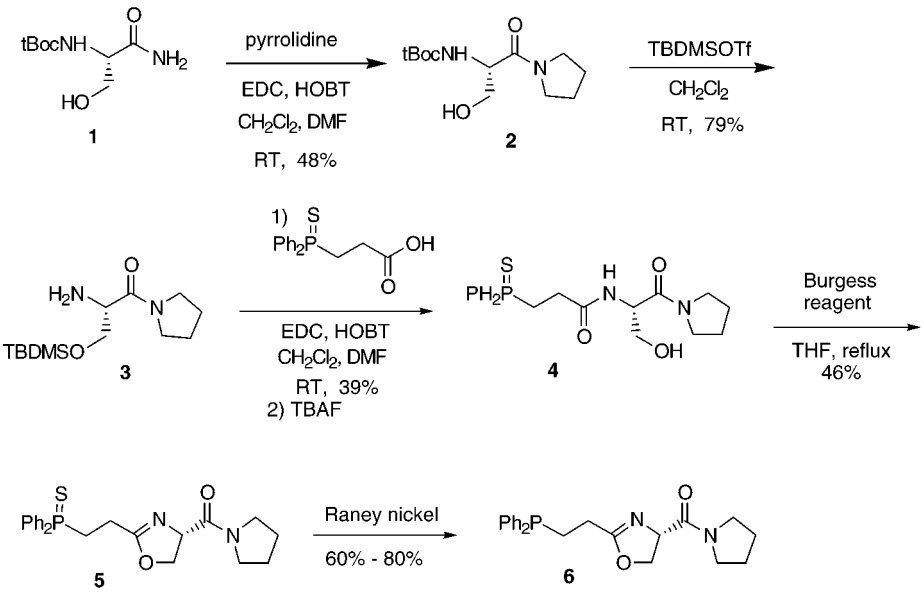
Results and Discussion

Synthesis of Phosphine−Oxazoline Ligands from Serine. In natural products containing oxazoline functionality, this group is usually derived from serine or threonine. The first phosphine−oxazoline ligands we synthesized were based on this biosynthetic pathway. The inital ligand was synthesized by conversion of the primary amide of *N*-BOC-serine amide (**1**) to the pyrrolidine amide **2** (Scheme 1). After removal of the BOC group our phosphine sulfide acid was coupled to the serine. Treatment with Burgess reagent followed by removal of the sulfur gave the desired phosphine−oxazoline **6**.

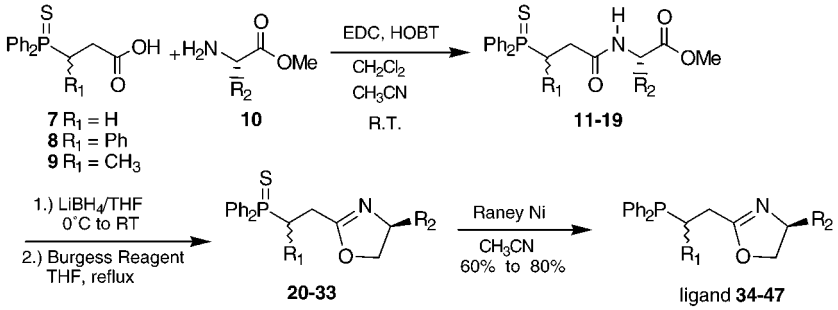
(1) Borman, S. *Chem. Eng. News* **1998**, 47.
(2) Menger, F. M.; Eliseev, A. V.; Migulin, V. A. *J. Org. Chem.* **1995**, *60*, 6666.
(3) Gilbertson, S. R.; Wang, X. *Tetrahedron Lett.* **1996**, *37*, 6475.
(4) Ellman, J. A. *Acc. Chem. Res.* **1996**, *29*, 132.
(5) Cole, B. M.; Shimizu, K. D.; Krueger, C. A.; Harrity, J. P. A.; Snapper, M. L.; Hoveyda, A. H. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1668.
(6) Shimizu, K. D.; Cole, B. M.; Krueger, C. A.; Kuntz, K. W.; Snapper, M. L.; Hoveyda, A. H. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1704−1707.
(7) Lloyd-Jones, G. C.; Pfaltz, A. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 462.
(8) von Matt, P.; Pfaltz, A. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 566−568.
(9) Sprinz, J.; Helmchen, G. *Tetrahedron Lett.* **1993**, *34*, 1769.
(10) Allen, J. V.; Coote, S. J.; Dawson, G. J.; Frost, C. G.; Martin, C. J.; Williams, J. M. J. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2065.
(11) Dawson, G. J.; Frost, C. G.; Williams, J. M. J. *Tetrahedron Lett.* **1993**, *34*, 3149.
(12) Steinhagen, H.; Reggelin, M.; Helmchen, G. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2108−2110.
(13) Loiseleur, O.; Meier, P.; Pfaltz, A. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 200.
(14) Loiseleur, O.; Hayashi, M.; Schmees, N.; Pfaltz, A. *Synthesis* **1997**, 1338−1345.

10.1021/jo981420y CCC: $15.00
Published on Web 10/28/1998

Scheme 1



Scheme 2



Asymmetric catalysis with this ligand proved disappointing. Using conditions that will be discussed later, this ligand catalyzed the addition of dimethyl malonate to 1,3-diphenylprop-2-enyl acetate in 96% yield and 45% ee in CH_3CN and 99% yield and 8% ee in CH_2Cl_2.

Rapid Synthesis of New Phosphine−Oxazoline Ligands. The inital poor result with ligand **6** caused us to develop a second approach to this type of ligand. One of our inital goals was to develop a system that allowed us to synthesize large numbers of ligands quickly. For this to be possible it is necessary to have a number of different structures that can be easily incorporated into the parent template. For this reason we embarked on an approach where we coupled one of our phosphine−amino acids to natural amino acids (Scheme 2). Following amide formation, the carboxyl group of the amino acid was reduced to an alcohol. This molecule was then cyclized with either Burgess reagent or methanesulfonyl chloride and triethylamine to give a phosphine−oxazoline ligand. This method allows for the facile generation of a number of ligands where the important group next to nitrogen (R_2) can be varied by using different amino acids.

The synthesis of the library of ligands began with modular building blocks **7**, **8**, and **9**. Using our approach, new ligands are synthesized by amide bond formation rather than difficult carbon−phosphorus bond formation. For the study reported here, we have used three phosphine-containing acids. One was a diphenylphosphine derivative of acrylate (**7**), another from cinnamic acid (**8**), and one from crotonate (**9**). The acrylate derivative **7** has been reported earlier as an intermediate in the synthesis of (diphenylphosphino)serine.[15,16] The synthesis of the phenyl and methyl derivatives (**8** and **9**) were performed in the same manner.

The synthesis of the ligands began with the coupling of phosphine acids **7**, **8**, or **9** to a given amino acid, yielding the phosphine sulfide amides **11**−**19**. The desired ligands were then obtained by a simple three-step procedure. Reduction of the methyl ester with lithium borohydride followed by cyclization with Burgess reagent[17] $[CH_3O_2CNSO_2N(C_2H_5)_3]$ gave the oxazoline-phosphine sulfides **20**−**33**. Reaction with Raney nickel then removed the sulfur and gave the free phosphines **34**−**47**. Reaction of acids **8** and **9** with an amino acid gave diastereomeric products. These diastereomers were readily separated by chromatography, after the lithium borohydride reduction step, yielding both the *SS* and *RS* pair of diastereomers. The ligands were fully characterized as the phosphine sulfides. After reduction of the phosphine sulfides to the free phosphines, the ligands were treated with palladium and used in catalysis without purification.

Asymmetric Catalysis. The first substrate we decided to study was 1,3-diphenylprop-2-enyl acetate. This molecule has been used as one of the bench mark substrates for palladium-catalyzed allyl additions. The

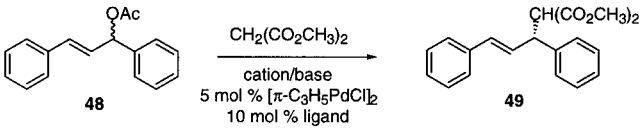
(15) Gilbertson, S. R.; Chen, G.; McLoughlin, M. *J. Am. Chem. Soc.* **1994**, *116*, 4481.
(16) Gilbertson, S. R.; Wang, X. *J. Org. Chem.* **1996**, *61*, 434.
(17) Wipf, P.; Venkatraman, S. *Tetrahedron Lett.* **1996**, *37*, 4659.

Table 1. Synthesis of Phosphine−Dihydrooxazole Ligands

R_1	R_2	compd	% yield	compd	% yield	ligand
H	Me (*S*)	**11**	33	**20**	62	**34**
H	Bn (*S*)	**12**	31	**21**	66	**35**
H	^{i}Pr (*S*)	**13**	64	**22**	72	**36**
H	Ph (*S*)	**14**	56	**23**	84	**37**
CH_3 (*S*)	^{i}Pr (*S*)	**15**	20[a]	**24**	55	**38**
CH_3 (R)	^{i}Pr (*S*)	**15**	20[a]	**25**	65	**39**
Ph (*S*)	Bn (*S*)	**16**	69[a]	**26**	71	**40**
Ph (*R*)	Bn (*S*)	**16**	69[a]	**27**	85	**41**
Ph (*S*)	^{i}Pr (*S*)	**17**	62[a]	**28**	45	**42**
Ph (*R*)	^{i}Pr (*S*)	**17**	62[a]	**29**	91	**43**
Ph (*S*)	Ph (*S*)	**18**	47[a]	**30**	48	**44**
Ph (*R*)	Ph (*S*)	**18**	47[a]	**31**	90	**45**
Ph (*S*)	^{t}Bu (*S*)	**19**	38[b]	**32**	74	**46**
Ph (*R*)	^{t}Bu (*S*)	**19**	39[b]	**33**	69	**47**

[a] The yields reported for compounds **15**−**19** are for the mixture of the two diastereomers. [b] Ligands **46** and **47** were synthesized from the corresponding amino alcohol. Yield is from the corresponding alcohol.

Table 2. Results with Ligands Containing a Single Chiral Center[a]



entry no.	ligand config	cation/base	yield %	ee %[b]	solvent
1	**34** (*S*)	^{n}Bu$_4$N$^+$/BSA	67	82	CH_2Cl_2
2	**35** (*S*)	^{n}Bu$_4$N$^+$/BSA	78	87	CH_2Cl_2
3	**36** (*S*)	^{n}Bu$_4$N$^+$/BSA	94	86	CH_2Cl_2
4	**37** (*S*)	^{n}Bu$_4$N$^+$/BSA	82	37	CH_2Cl_2
5	**36** (*S*)	K$^+$/BSA	87	66	CH_2Cl_2
6	**36** (*S*)	Hex$_4$N$^+$/BSA	62	90	CH_2Cl_2
7	**36** (*S*)	$(CH_3(CH_2)_5)_4$NBr/NaH	22	81	THF
8	**36** (*S*)	^{n}Bu$_4$N$^+$/BSA	93	11	CH_3CN
9	**36** (*S*)	^{n}Bu$_4$N$^+$/BSA	14	64	THF
10	**36** (*S*)	^{n}Bu$_4$N$^+$/BSA	25	78	C_6H_6
11	**36** (*S*)	$(CH_3(CH_2)_3)_4$NBr/NaH	22	81	THF

[a] Unless stated otherwise, reactions were run at 0 °C. [b] The enantiomeric excesses were determined by chiral shift reagent [Eu(hfbc)$_3$].[10]

ligands were investigated in two groups: ligands with one chiral center (Table 2) and ligands with two chiral centers (Table 3). Of the ligands with one chiral center, the ligands derived from phenylalanine (R_2 = benzyl) (**35**) and valine (R_2 = isopropyl) (**36**) gave the highest ees (87% and 86%) (Table 2, entries 2 and 3). The effect of solvent on the reaction was probed using ligand **36** and the ^{n}Bu$_4$N$^+$/BSA cation base combination (Table 2, entries 3, 8, 9, and 10).[18−20] Of the solvents tested, methylene chloride was found to be the best solvent for this ligand (Table 2, entry 3). The counterion and base associated with the malonate anion have been shown to be important in these additions, and so their effect was also investigated (Table 2, entries 3, 5, 6, and 7). The optimal system for this class of ligand was found to be tetrahexylammonium/BSA as the counterion and base and methylene chloride as the solvent (Table 2, entry 6), giving an ee of 90%.

BSA/Ammonium Fluoride Generation of Dimethyl Malonate Anion. The tetrahexylammonium/BSA system mentioned above has been developed during this work. One of the critical factors in controlling the selective addition of nucleophiles to π-allyl palladium intermediates is the counterion.[21,22] The common method, for the addition of malonate with a tetraalkylammonium counterion, is the generation of the malonate ion with a base such as sodium hydride, followed by addition of the appropriate tetraalkylammonium halide. A complication of this approach is the competition between the two cations, alkali metal verses ammonium, in solution. With this method there is the corresponding sodium or potassium halide present, the cation of which can compete with the ammonium ion. To circumvent this problem, crown ethers are sometimes added, but this approach is limited by the expense and availability of the required crown ether.

Another method that has been used successfully is to add potassium acetate and BSA as the bases. Presumably the potassium acetate removes the trimethylsilyl group from the BSA, generating a base to deprotonate the malonate. Tetraalkylammonium salts have been added to these mixtures to give malonate ions with noncoordinating counterions. Despite the success of this method there remains the potential competition between the ammonium counterion and the free potassium in solution.

It was reasoned that if potassium acetate could attack BSA and generate the necessary base for formation of the potassium malonate, then the addition of a tetraalkylammonium fluoride should serve the same purpose, generating a base with an ammonium counterion. Fluoride ion would attack the silicon of BSA forming trimethylsilyl fluoride and acetamide anion. This base could then go on and deprotonate dimethyl malonate and provide the nucleophile for the malonate addition with *only an ammonium counterion present* (Scheme 3). Upon inspection of the literature, we were surprised that, apparently, this approach had not been reported.

This method possesses a number of advantages over the current methods used. Generally, before one is able to use tetraalkylammonium bromides, the salts must be purified by recrystallization. We have found that this is

Table 3. Results with Ligands Containing Two Chiral Centers[a]

entry no.	ligand config	cation/base	yield %	ee %	solvent
1	**38** (*S*,*S*)	^{n}Bu$_4$N$^+$/BSA	86	72	CH_3CN
2	**39** (*R*, *S*)	^{n}Bu$_4$N$^+$/BSA	86	94	CH_3CN
3	**40** (*S*,S)	^{n}Bu$_4$N$^+$/BSA	100	84	CH_3CN
4	**41** (R,*S*)	^{n}Bu$_4$N$^+$/BSA	53	93	CH_3CN
5	**42** (*S*,*S*)	^{n}Bu$_4$N$^+$/BSA	91	90	CH_3CN
6	**43** (*R*,S)	^{n}Bu$_4$N$^+$/BSA	80	95	CH_3CN
7	**44** (S,*S*)	^{n}Bu$_4$N$^+$/BSA	56	22	CH_3CN
8	**45** (*R*,*S*)	^{n}Bu$_4$N$^+$/BSA	37	54	CH_3CN
9	**42** (*S*,*S*)	^{n}Bu$_4$N$^+$/BSA	43	65	CH_2Cl_2
10	**43** (*R*,*S*)	^{n}Bu$_4$N$^+$/BSA	80	93	CH_3CN
11	**43** (*R*,*S*)	^{n}Bu$_4$N$^+$/BSA	33	85	CH_2Cl_2
12	**43** (*R*,*S*)	^{n}Bu$_4$N$^+$/BSA	48	88	THF
13	**43** (*R*,*S*)	^{n}Bu$_4$N$^+$/BSA	49	79	C_6H_6
14	**43** (*R*,*S*)	TBAOAc/BSA	93	82	CH_3CN
15	**43** (*R*,*S*)	^{n}Hex$_4$N$^+$/BSA	99	97	CH_3CN
16	**47** (*R*, *S*)	^{n}Bu$_4$N$^+$/BSA	99	96	CH_3CN
17	**47** (*R*, *S*)	^{n}Hex$_4$N$^+$/BSA	78	98	CH_3CN

[a] The reactions were run at room temperature.

(18) BSA is bis(trimethylsilyl)acetamide.
(19) Trost, B. M.; Murphy, D. J. *Organometallics* **1985**, *4*, 1143.
(20) Brown, J. M.; Hulmes, D. I.; Guiry, P. J. *Tetrahedron* **1994**, *50*, 4493.
(21) Trost, B. M.; Bunt, R. C. *J. Am. Chem. Soc.* **1994**, *116*, 4089.
(22) Sennhenn, P.; Gabler, B.; Helmchen, G. *Tetrahedron Lett.* **1994**, *35*, 8595.

Scheme 3

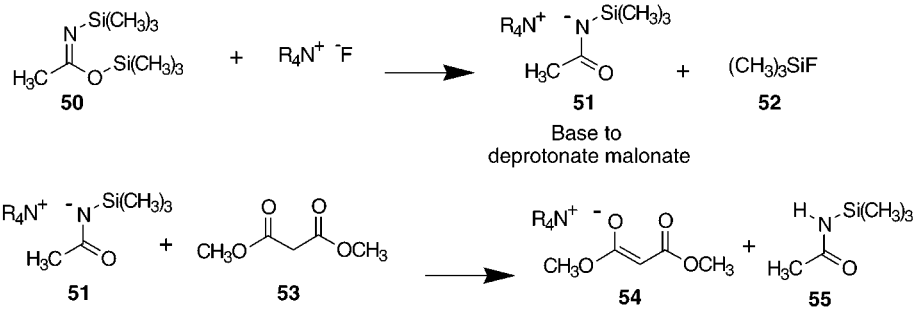
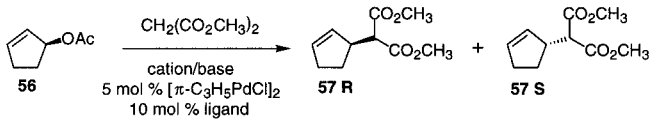


Table 4. Screening of Cyclic Substrate with Phosphine−Oxazoline Ligands



entry no.	ligand config	cation/base	yield %	ee %	solvent
1	**41** (*R*,*S*)	^{n}Bu$_4$N$^+$/BSA	57	35	CH_3CN
2	**43** (*R*,*S*)	^{n}Bu$_4$N$^+$/BSA	56	23	CH_3CN
3	**42** (*S*,*S*)	^{n}Bu$_4$N$^+$/BSA	61	37	CH_3CN
4	**45** (*R*,*S*)	^{n}Bu$_4$N$^+$/BSA	64	0	CH_3CN
5	**44** (*S*,*S*)	^{n}Bu$_4$N$^+$/BSA	69	11	CH_3CN
8	**47** (*R*,*S*)	^{n}Bu$_4$N$^+$/BSA	56	14	CH_3CN
9	**38** (*S*,*S*)	^{n}Bu$_4$N$^+$/BSA	50	42	CH_3CN

not necessary with the available tetraalkylamonium fluoride salts. Commercially available tetrabuylyammonium fluoride was used directly without purification. Also, the use of tetraalkylammonium bromides involves the deprotonation of the malonate followed by addition of the appropriate ammonium bromide. Often strong bases such as sodium hydride are used for the deprotonation. The use of strong base precludes running the reaction in solvents such as acetonitrile, a solvent shown to be valuable in selective π-allyl additions.

The ligand we chose to test this method on was **36**, possessing one chiral center. Four sets of reaction conditions were investigated. The standard BSA method using potassium acetate in methylene chloride gave an enantiomeric excess of 66% (Table 2, entry 5). The conditions using tetrabutylammonium fluoride gave 86% ee (Table 2 entry 3), and the larger counterion, tetrahexylammonium fluoride, gave 90% ee (Table 2, entry 6). Comparison with the system using sodium hydride and added tetrabutylammonium bromide in THF provided the product in 81% enantiomeric excess (Table 2, entry 11).

Not only does the BSA method provide an expedient method for the generation of malonate ion with tetraalkylammonium as the only counterion present, but it actually proves to be the best set of reaction conditions found for phosphine oxazoline type ligands such as **36**.

Ligands with Two Chiral Centers. In the inital screen using standard reaction conditions ligand **43**, with a *RS* configuration, was found to be the most selective ligand (Table 3, entry 6). The optimal reaction conditions were then determined (Table 3, entries 10−15). The best solvent system for this ligand was found to be acetonitrile, and the best counterion system was nHex$_4$N$^+$/BSA (Table 3, entry 15).

Of the ligands with two chiral centers, both combinations of the two chiral centers were examined. It is interesting to note that the chirality at the carbon next to the phosphine has a variable effect. When the group attached to that carbon is methyl, the difference observed between the *S*,*S* and *R*,*S* diastereomers is quite pronounced 72% and 94%, respectively (Table 3, entries 1 and 2). When R_1 is phenyl, the difference between the *S*,*S* and *R*,*S* diastereomers is less, 93% and 90% ee (Table 3, entries 4 and 5). It is also interesting to note that the effect of this group varies as the ability of the oxazoline to direct the reaction changes. In the case of the best directing group, isopropyl, the chirality of the carbon next to the phosphine has a small effect, 90% versus 93% for *S*,*S* and *R*,*S*, respectively (Table 3, entries 5 and 6). In the cases where the group on the oxazoline is phenyl or benzyl the effect of the group next to the phosphine appears to be larger (Table 3, entries 3 versus 4 and 7 versus 8).

In an effort to increase the selectivity of the reaction, the temperature at which the reaction was run was decreased. This change resulted in a decrease in the selectivity of the reaction (93% ee at 0 °C to 61% ee at −30 °C). Increasing the temperature of the reaction to room temperature resulted in an increase in the selectivity to 97% ee. Further increase in the temperature results in an erosion in the selectivity (52% ee at 40 °C). An investigation into the generality of the decrease in selectivity with decreasing temperature indicated that this effect was unique to the ligands with the *R*,*S* configuration (**41** and **43**). In the study of the *S*,*S* diastereomers, ligands **40** and **42**, a normal temperature dependence with lower temperatures giving higher selectivity was observed.

Addition to 2-Cyclopentenyl Acetate. After successfully applying the phosphine−oxazoline ligands to 1,3-diphenylprop-2-enyl acetate, these ligands were tested for their ability to perform asymmetric additions to 2-cyclopentenyl acetate. This is a system that has proven to be significantly more difficult to control than the 1,3-diphenylprop-2-enyl acetate system. Trost has developed a ligand that controls this reaction with good selectivity.[21,23,24] As expected from results with other phosphine−oxazoline ligands, the outcome shown in Table 4 was rather disappointing. A wide variety of conditions and ligands were investigated, with the highest selectivity being 42% ee. It should be noted there is one phosphine−oxazoline system, recently developed by Helm-

(23) Trost, B. M.; Bunt, R. C. *J. Am. Chem. Soc.* **1996**, *118*, 235−236.
(24) Trost, B. M.; Cook, G. R. *Tetrahedron Lett.* **1996**, *37*, 7485−7488.

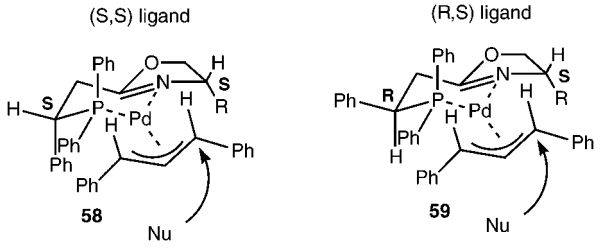


Figure 1.

chen that has proven to be an effective catalyst with these substrates.[25]

Origin of Selectivity. On the basis of the measurement of optical rotation, the major product from the asymmetric π-allylic alkylation of 1,3-diphenylallyl acetate was the *S* isomer when phosphine−oxazoline ligands from L-amino acids were used. Numerous studies on the origin of selectivity for phosphine−oxazoline ligands have been reported.[10,12,20,23,26−31] The belief is that the nucleophile attacks the carbon trans to the phosphine atom in the η^3-allylic cation intermediate (Figure 1). Since the phosphine has an empty d orbital acting as an electron acceptor, the electron density of the metal−carbon bond trans to the metal-phosphine bond will be decreased. Helmchen has shown that the most stable orientation for the allyl group is as shown above, with the phenyl ring toward the R group next to nitrogen. This appears to be the case in the ligands we report as well since we observe the same selectivity as the previous ligands.

The effect of the chiral center next to the phosphine is variable in terms of effecting the selectivity of the reaction. Another difference observed between the ligands with one chiral center and the ligands with two centers is the preferred solvent for reaction. In the cases with one chiral center the best solvent tested was methylene chloride. In the case of the ligands with two chiral centers the best solvent we found was acetonitrile. Currently we do not have a clear explanation for this observation.

Conclusion

As stated in the Introduction there are a number of phosphine−oxazoline ligands that have been developed. To date the most successful systems have been ligands with the phosphine and oxazoline attached through an aromatic ring. The system discussed in this paper has the phosphorus and oxazoline connected by an alkyl chain. In the system covered in this paper, as with many of the systems reported previously, the important group in directing the stereochemical outcome of the reaction is the group next to the nitrogen atom. It was found that a chiral center next to the phosphine can have an effect on the selectivity of reaction but that the effect is generally small and overwhelmed by the chiral center next to nitrogen.

The most striking difference between the systems studied previously and the one reported here is found when the group next to nitrogen is phenyl. Pfaltz has reported that when this group is phenyl high selectivities are found.[8] In our case when this group is phenyl, we observed the lowest selectivity. The ligand with one chiral center synthesized from phenylalanine (**34**) gave a 37% ee (Table 2, entry 4) while ligand **40**, with two chiral centers, gave a 54% ee (Table 3, entry 8). This is compared to ligands **36** and **43** which give 86% (Table 2, entry 3) and 93% (Table 3, entry 6) under the same conditions. Poor selectivity was also observed with ligand **6**, where the group next to the nitrogen is an ester. It appears, with the ligands reported in this paper, that when the group next to nitrogen has an sp^2-hybridized carbon the selectivity is low.

Through the use of modular building blocks we have been able to develop a new ligand for palladium-catalyzed π-allyl additions. We are currently studying the use of these ligands in other metal-catalyzed reactions. Additionally, we report a new method for the facile generation of malonate anions with bulky counterions. Through the use of BSA and the appropriate tetraalkylammonium fluoride, dimethyl malonate is deprotonated in the absence of other potential counterions. We are also using the phosphine acid building blocks discussed in this paper in the synthesis of other collections of ligands for a variety of transition metal-catalyzed reactions.

Experimental Section

General Procedure for Coupling of Phosphinopropionic Acid and Amino Acid. 3-(Diphenylphosphino)thiopropionic acid (1 equiv), amino acid methyl ester (1.2 equiv), EDC (1.5 equiv), and HOBT (1.5 equiv) were dissolved in dry CH_2Cl_2 and CH_3CN (1:1 ratio), and the reaction mixture was stirred under nitrogen at room temperature for 2 days. After rotatory evaporation of the solvent, the crude product was redissolved in ethyl acetate and then transferred to a separatory funnel. The remaining residue was dissolved in small amount of CH_2Cl_2 and combined with the ethyl acetate solution. The combined organic solutions were washed with 1 N HCl, water, saturated $NaHCO_3$, and brine and then dried over anhydrous Na_2SO_4. Evaporation of solvents and purification of the crude product by column chromatography afforded the desired product.

General Procedure for Reduction of Methyl Ester. The methyl ester was dissolved in dried THF and cooled to 0 °C. Two equivalents of lithium borohydride solution (2 M in THF) was slowly added under nitrogen. The ice bath was removed after the addition, and the reaction was monitored by TLC (50% hexane, 50% ethyl acetate). The reaction time varied from 6 h to 2 days. After the reduction was complete, the reaction mixture was cooled to 0 °C, and the reaction was quenched by the slow addition of 2 mL of 10% HCl (caution: foaming). The reaction solution was stirred for another 15 min and then diluted with ethyl acetate. The aqueous layer was discarded. The organic layer was washed with 1 N NaOH, 1 N HCl, water, saturated $NaHCO_3$, and brine then dried over anhydrous Na_2SO_4. For the product with one chiral center: after evaporation of solvent, the crude product was used for the next step directly. For the product with two chiral centers, after evaporation of solvent and purification with column chromatography, two desired diastereomeric products were obtained separately.

(25) Helmchen, G.; Kudis, S.; Sennhenn, P.; Steinhagen, H. *Pure Appl. Chem.* **1997**, *69*, 513−518.
(26) Trost, B. M.; Van Vranken, D. L. *Chem. Rev.* **1996**, *96*, 395.
(27) Sprinz, J.; Kiefer, M.; Helmchen, G.; Reggelin, M.; Huttner, G.; Walter, O.; Zsolnai, L. *Tetrahedron Lett.* **1994**, *35*, 1523.
(28) Pena-Cabrera, E.; Norrby, P.-O.; Sjogren, M.; Vitagliano, A.; DeFelice, V.; Oslob, J.; Ishii, S.; O'Neill, D.; Akermark, B.; Helquist, P. *J. Am. Chem. Soc.* **1996**, *118*, 4299.
(29) Reisei, O. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 547.
(30) Frost, C. G.; Howarth, J.; Williams, J. M. J. *Tetrahedron Asymmetry* **1992**, *3*, 1089.
(31) Mackenzie, P. B.; Whelan, J.; Bosnich, B. *J. Am. Chem. Soc.* **1985**, *107*, 2046.

General Procedure for Oxazoline Formation. (1) Method employing Burgess reagent.[17,32] The β-amido alcohol was dissolved in enough dry THF to make a 0.02 M solution. After addition of Burgess reagent (2 equiv), the reaction mixture was refluxed for 1 h. The reaction was monitored by TLC (65% hexane, 35% ethyl acetate) and was usually complete within 1 h. The reaction mixture was cooled to room temperature and coated on silica gel for loading onto a chromatography column. Purification with flash column chromatography afforded the desired product.

(2) Method Employing Mesyl Chloride. The β-amido alcohol was dissolved in dry CH_2Cl_2 /Et_3N (3/1), and the solution was cooled to 0 °C. To the solution was slowly added MsCl (4 equiv), and the yellow-brownish solution was stirred under nitrogen at room temperature for 1 day. After the reaction was complete (monitored by TLC), the reaction mixture was filtered through Celite to remove most of the ammonium salt, and the residue was rinsed with CH_2Cl_2. Evaporation of solvent and coating the crude product on silica gel, followed by purification with flash column chromatography, afforded the desired product.

Procedure for the Reduction of Phosphine Sulfide to Phosphine. A sample of the phosphine sulfide was dissolved in degassed methanol (3.0 mL) in a Schlenk tube. Raney nickel slush (300 mg) was washed with methanol and was then added to the tube under nitrogen. The reaction mixture was stirred at room temperature for 8.0 h, by which time the ^{31}P NMR spectrum indicated complete conversation of the phosphine sulfide to the phosphine. Raney nickel was then filtered through Celite under nitrogen, and the filtrate was concentrated under vacuum to 0.5 mL.

General Procedure for π-Allyl Addition. The phosphine−oxazoline ligand was mixed with $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ in degassed solvent. After 30 min, 1,3-diphenylprop-2-enyl acetate (10 equiv) in solvent was added. To this solution at the desired reaction temperature was added a solution of dimethyl malonate (30 equiv), TBAF (30 equiv), and BSA (30 equiv) over 1 h. After complete reaction, as judged by TLC, the reaction mixture was worked up extractively.

(*S*)-*N*-(*tert*-Butoxylcarbonyl)-2-hydroxyl-1-(pyrrolidinocarbonyl)ethylamine, (2). A mixture of N-tBoc-L-serine (5.0 g, 24.4 mmol), pyrrolidine (2.03 mL, 24.4 mmol), EDC−HCl (7.0 g, 36.6 mmol), and HOBt (4.9 g, 36.6 mmol) in 100 mL of CH_2Cl_2 and 100 mL of DMF was stirred for 50 h under nitrogen at room temperature. The reaction mixture was poured into a saturated NH_4Cl/CH_2Cl_2 solution, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with 1 N HCl, water, saturated $NaHCO_3$, and brine then dried over anhydrous Na_2SO_4. After removal of the solvent and washing the yellowish solid with anhydrous ether, the desired product was obtained as a white solid (3 g, 11.6 mmol, 48%): ^1H NMR (300 MHz, $CDCl_3$) δ 5.69 (d, J_{HH} = 8.0 Hz, 1H), 4.51 (dt, J_{HH} = 8.0 Hz, J_{HH} = 4.0 Hz, 1H), 3.80 (m, 1H), 3.76 (m, 1H), 3.65 (m, 1H), 3.4−3.6 (m, 4H), 1.8−2.0 (m, 4H), 1.44 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.3 (s), 155.9 (s), 80.1 (s), 64.1 (s), 53.2 (s), 46.7 (s), 46.1 (s), 28.3 (s), 26.0 (s), 24.1 (s); IR (thin film) 1706 (s), 1624 (s), 1538 (s); MS−FAB (EI^+) *m*/*z* (% rel intensity) 259.3 (MH^+, 100). Anal. Calcd for $C_{12}H_{22}N_2O_4$: C, 55.80; H, 8.58; N, 10.84. Found: C, 55.70; H, 8.66; N, 10.82.

(*S*)-3-(Diphenylphosphinothioyl)-*N*-(2′-hydroxyl-1′-(pyrrolidinocarbonyl)ethyl)propanamide (4). To a solution containing **2** (1.0 g, 3.9 mmol) in 30 mL of dry CH_2Cl_2 was slowly added TBDMSOTf (0.9 mL, 4.1 mmol). After stirring the reaction mixture for 6 h, the solvent was evaporated, and the crude product was redissolved in 15 mL dry of CH_2Cl_2 and 15 mL of CH_3CN. To this clear solution were added (diphenylphosphinothioyl)propanoic acid, (1.1 g, 3.9 mmol), EDC−HCl (1.1 g, 5.8 mmol), and HOBt (0.8 g, 5.8 mmol), and the reaction was stirred for 5 days. After pouring the reaction mixture into a saturated NH_4Cl/CH_2Cl_2 solution, the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with 1 N HCl, water, saturated $NaHCO_3$, and brine then dried over anhydrous Na_2SO_4. After removal of solvent, the crude product was dissolved in CH_2Cl_2 , 5 mL of TBAF (1 M in THF) was added, and the reaction mixture was stirred for 2 h. After evaporation of solvent and purification by gradient column chromatography [hexane/ethyl acetate (80/20) to ethyl acetate/methanol (80/20)], the product was obtained as viscous solid (0.647 g, 1.5 mol, 39%): ^1H NMR (300 MHz, $CDCl_3$) δ 7.85 (m, 4H), 7.48 (m, 6H), 6.87 (d, J_{HH} = 9.0 Hz, 1H), 4.70 (dt, J_{HH} = 9.0 Hz, J_{HH} = 3.0 Hz, 1H), 3.4−3.8 (m, 6H), 2.82 (m, 2H), 2.60 (m, 2H), 1.8−2.0 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.5 (d, J_{CP} = 16.8 Hz), 168.5 (s), 132.0 (d, J_{CP} = 8.0 Hz), 131.62 (d, J_{CP} = 1.4 Hz), 131.59 (d, J_{CP} = 3.2 Hz), 131.0 (d, J_{CP} = 10.2 Hz), 130.7 (d, J_{CP} = 9.8 Hz), 128.7 (d, J_{CP} = 12.1 Hz), 63.6 (s), 52.9 (s), 46.7 (s), 46.2 (s), 28.7 (s), 27.8 (d, J_{CP} = 58.6), 25.9 (s), 24.1 (s); ^{31}P NMR (120 MHz, $CDCl_3$) δ 43.1 (s); IR (thin film) 1669 (s), 1603 (s), 1558 (s), 1389 (s), 1374 (s); MS−FAB (EI^+) *m*/*z* (% rel intensity) 431.1 (MH^+, 15); 273.1 (Ph_2PS^+, 100); HRFAB Calcd for $C_{22}H_{28}N_2O_3PS$ (MH^+) *m*/*e* 431.1558; measured *m*/*e* 431.1546.

(*S*)-5-(Pyrrolidonocarbonyl)-4,5-dihydro-2-(2′-(diphenylphosphinothioyl)ethyl-1,3-oxazole (5). ^1H NMR (300 MHz, $CDCl_3$) δ 7.85 (m, 4H), 7.58 (m, 6H), 4.80 (dd, J_{HH} = 8.0 Hz, J_{HH} = 8.0 Hz, 1H), 4.68 (dd, J_{HH} = 8.0 Hz, J_{HH} = 10.0 Hz, 1H), 4.23 (dd, J_{HH} = 8.0 Hz, J_{HH} = 10.0 Hz, 1H), 3.90 (ddd, J_{HH} = 10.0 Hz, J_{HH} = 7.0 Hz, J_{HH} = 7.0 Hz, 1H), 3.48 (m, 3H), 2.80 (m, 2H), 2.62 (m, 2H), 1.8−2.0 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.3 (d, J_{CP} = 18.5 Hz), 167.7 (s), 132.6 (d, J_{CP} = 20.4 Hz), 131.7 (d, J_{CP} = 3.7 Hz), 131.6 (d, J_{CP} = 3.3 Hz), 131.3 (d, J_{CP} = 20.0 Hz), 131.14 (d, J_{CP} = 10.3 Hz), 131.09 (d, J_{CP} = 9.8 Hz), 128.7 (d, J_{CP} = 10.7 Hz), 69.2 (s), 67.7 (s), 46.5 (s), 46.2 (s), 29.0 (d, J_{CP} = 57.8), 26.0 (s), 24.2 (s), 21.4 (s); ^{31}P NMR (120 MHz, $CDCl_3$) δ 42.8 (s); IR (thin film) 1654 (s), 1637 (s), 1624 (s); MS−FAB (EI^+) *m*/*z* (% rel intensity) 413.1 (MH^+, 20); 273.1 (Ph_2PS^+, 70); HRFAB calcd for $C_{22}H_{26}N_2O_2PS$ (MH^+) *m*/*e* 413.1452; measured *m*/*e* 413.1456.

Spectral Data for Phosphine Sulfides 20−33. The spectral data for the intermediates in their synthesis is reported in the Supporting Information.

(*S*)-4,5-Dihydro-2-(2′-(diphenylphosphinothioyl)ethyl)-5-methyl-1,3-oxazole (20): ^1H NMR (300 MHz, $CDCl_3$) δ 7.85 (m, 4H), 7.48 (m, 6H), 4.28 (dd, J_{HH} = 9.0 Hz, J_{HH} = 8.0 Hz, 1H), 4.11 (qdd, J_{HH} = 6.6 Hz, J_{HH} = 8.0 Hz, J_{HH} = 8.0 Hz, 1H), 3.72 (dd, J_{HH} = 8.0 Hz, J_{HH} = 8.0 Hz, 1H), 2.82 (m, 2H), 2.58 (m, 2H), 1.20 (d, J_{HH} = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.3 (d, J_{CP} = 19.1 Hz), 132.1 (d, J_{CP} = 80.0 Hz), 132.0 (d, J_{CP} = 80.9 Hz), 131.6 (d, J_{CP} = 3.2 Hz), 131.1 (d, J_{CP} = 10.4 Hz), 128.7 (d, J_{CP} = 12.2 Hz), 74.1 (s), 61.4 (s), 29.0 (d, J_{CP} = 57.8 Hz), 21.3 (d, J_{CP} = 3.5 Hz); ^{31}P NMR (120 MHz, $CDCl_3$) δ 42.8 (s); IR (thin film), 1734 (w), 1587 (w); MS−FAB (EI^+) *m*/*z* (% rel intensity) 330.1 (MH^+, 50), 112.1 ($[M - Ph_2PS]^+$, 100); HRFAB calcd for $C_{18}H_{21}NOPS$ (MH^+) *m*/*e* 330.1082; measured *m*/*e* 330.1071.

(*S*)-5-Benzyl-4,5-dihydro-2-(2′-(diphenylphosphinothioyl)ethyl)-1,3-oxazole (21): ^1H NMR (300 MHz, $CDCl_3$) δ 7.86 (m, 4H), 7.49 (m, 6H), 7.1−7.3 (m, 5H), 4.31 (dddd, J_{HH} = 8.4 Hz, J_{HH} = 8.4 Hz, J_{HH} = 8.4 Hz, J_{HH} = 5.0 Hz, 1H), 4.11 (dd, J_{HH} = 8.4 Hz, J_{HH} = 8.4 Hz, 1H), 3.92 (dd, J_{HH} = 8.4 Hz, J_{HH} = 8.4 Hz, 1H), 3.05 (dd, J_{HH} = 14.4 Hz, J_{HH} = 5.0 Hz, 1H), 2.80 (m, 2H), 2.60 (dd, J_{HH} = 14.4 Hz, J_{HH} = 8.4 Hz, 1H), 2.58 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.8 (d, J_{CP} = 18.6 Hz), 137.6 (s), 132.0 (d, J_{CP} = 84.2 Hz), 131.6 (d, J_{CP} = 3.1 Hz), 131.0 (d, J_{CP} = 10.3 Hz), 129.1 (s), 128.6 (d, J_{CP} = 12.0 Hz), 128.4 (s), 126.4 (s), 71.8 (s), 67.0 (s), 41.5 (s), 28.9 (d, J_{CP} = 57.9 Hz), 21.3 (s); ^{31}P NMR (120 MHz, $CDCl_3$) δ 42.7 (s); IR (thin film) 1682 (s), 1669 (s), 1654 (s); MS−FAB (EI^+) *m*/*z* (% rel intensity) 406.2 (MH^+, 75), 188.2 ($[M - Ph_2PS]^+$, 100); HRFAB calcd for $C_{24}H_{25}NOPS$ (MH^+) *m*/*e* 406.1394, measured *m*/*e* 406.1399.

(*S*)-4,5-Dihydro-2-(2′-(diphenylphosphinothioyl)ethyl)-5-isopropyl-1,3-oxazole (22): ^1H NMR (300 MHz, $CDCl_3$) δ 7.85 (m, 4H), 7.48 (m, 6H), 4.16 (dd, J_{HH} = 8.0 Hz, J_{HH} = 8.0 Hz, 1H), 3.90 (dd, J_{HH} = 8.0 Hz, J_{HH} = 8.0 Hz, 1H), 3.83 (ddd, J_{HH} = 8.0 Hz, J_{HH} = 8.0 Hz, J_{HH} = 8.0 Hz, 1H), 2.80 (m, 2H), 2.59 (m, 2H), 1.71 (qqd, J_{HH} = 8.0 Hz, J_{HH} = 7.0 Hz, J_{HH} = 7.0

(32) Wipf, P.; Miller, C. P. *Tetrahedron Lett.* **1992**, *33*, 907−910.

Hz, 1H), 0.93 (d, J_{HH} = 7.0 Hz, 3H), 0.83 (d, J_{HH} = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.1 (d, J_{CP} = 19.0 Hz), 132.1 (d, J_{CP} = 86.0 Hz), 132.0 (d, J_{CP} = 86.0 Hz), 131.6 (d, J_{CP} = 3.2 Hz), 131.2 (d, J_{CP} = 2.2 Hz), 131.0 (s), 128.6 (d, J_{CP} = 12.2 Hz), 72.0 (s), 70.1 (s), 32.5 (s), 29.1 (d, J_{CP} = 57.5 Hz), 21.3 (s), 18.8 (s), 17.9 (s); ^{31}P NMR (120 MHz, $CDCl_3$) δ 42.8 (s); IR (thin film) 1725 (s), 1671 (s), 1384 (s), 1366 (s); MS−FAB (EI^+) *m/z* (% rel intensity) 358.1 (MH^+, 50), 140.1 ([M − $Ph_2PS]^+$, 100); HRFAB calcd for $C_{20}H_{25}NOPS$ (MH^+) *m/e* 358.1394, measured *m/e* 358.1405.

(*S*)-4,5-Dihydro-2-(2′-(diphenylphosphinothioyl)ethyl)-5-phenyl-1,3-oxazole (23): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 (m, 4H), 7.48 (m, 6H), 7.34 (m, 3H), 7.21 (m, 2H), 5.11 (dd, J_{HH} = 9.0 Hz, J_{HH} = 9.0 Hz, 1H), 4.58 (dd, J_{HH} = 8.0 Hz, J_{HH} = 9.0 Hz, 1H), 4.05 (dd, J_{HH} = 8.0 Hz, J_{HH} = 8.0 Hz, 1H), 2.91 (m, 2H), 2.72 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.6 (d, J_{CP} = 18.5 Hz), 141.8 (s), 132.0 (d, J_{CP} = 80.4 Hz), 131.9 (d, J_{CP} = 80.4 Hz), 131.5 (d, J_{CP} = 2.6 Hz), 131.03 (d, J_{CP} = 10.1 Hz), 131.0 (d, J_{CP} = 9.9 Hz), 128.61 (s), 128.60 (d, J_{CP} = 11.9 Hz), 127.5 (s), 126.5 (s), 74.8 (s), 69.4 (s), 28.9 (d, J_{CP} = 57.8 Hz), 21.3 (s); ^{31}P NMR (120 MHz, $CDCl_3$) δ 42.8 (s); IR (thin film) 1669 (s), 1495 (s), 1453 (s); MS−FAB (EI^+) *m/z* (% rel intensity) 392.3 (MH^+, 90), 273.2 ($[Ph_2P(S)CH_2CH_2CO]^+$, 60), HRFAB calcd for $C_{23}H_{23}NOPS$ (MH^+) *m/e* 392.1238, measured *m/e* 392.1233.

(5*S*,2′*S*)-4,5-Dihydro-2-(2′-(diphenylphosphinothioyl)-2′-methylethyl)-5-isopropyl-1, 3-oxazole (24): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.99 (m, 4H), 7.48 (m, 6H), 4.13 (dd, J_{HH} = 9.0 Hz, J_{HH} = 8.0 Hz, 1H), 3.93 (dd, J_{HH} = 8.0 Hz, J_{HH} = 8.0 Hz, 1H), 3.87 (ddd, J_{HH} = 9.0 Hz, J_{HH} = 8.0 Hz, J_{HH} = 7.0 Hz, 1H), 3.30 (m, 1H), 2.45 (m, 2H), 1.73 (dqq, J_{HH} = 7.0 Hz, J_{HH} = 7.0 Hz, J_{HH} = 7.0 Hz, 1H), 1.21 (dd, J_{HH} = 7.0 Hz, J_{HP} = 18.7 Hz, 3H), 0.93 (d, J_{HH} = 7.0 Hz, 3H), 0.86 (d, J_{HH} = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.2 (d, J_{CP} = 19.0 Hz), 131.5 (d, J_{CP} = 6.0 Hz), 131.4 (d, J_{CP} = 9.4 Hz), 131.2 (d, J_{CP} = 77.5 Hz), 131.1 (d, J_{CP} = 77.0 Hz), 128.7 (d, J_{CP} = 11.0 Hz), 128.5 (d, J_{CP} = 11.3 Hz), 72.0 (s), 69.8 (s), 32.5 (s), 30.8 (d, J_{CP} = 57.0 Hz), 28.7 (d, J_{CP} = 2.3 Hz), 18.7 (s), 18.0 (s), 12.9 (s); ^{31}P NMR (120 MHz, $CDCl_3$) δ 53.0 (s); IR (thin film) 2960 (s), 1669 (s); MS−FAB (EI^+) *m/z* (% rel intensity) 372.1 (MH^+, 90), 154.1 ([M − $Ph_2PS]^+$, 100); HRFAB calcd for $C_{21}H_{27}NOPS$ (MH^+) *m/e* 372.1551, measured *m/e* 372.1554.

(5*S*,2′*R*)-4,5-Dihydro-2-(2′-(diphenylphosphinothioyl)-2′-methylethyl)-5-isopropyl-1,3-oxazole (25): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.96 (m, 4H), 7.47 (m, 6H), 4.18 (m, 1H), 3.90 (m, 2H), 3.30 (qtd, J_{HH} = 7.0 Hz, J_{HH} = 7.0 Hz, J_{HP} = 7.0 Hz, 1H), 2.45 (dd, J_{HH} = 7.0 Hz, J_{HP} = 7.0 Hz, 2H), 1.75 (dqq, J_{HH} = 7.0 Hz, J_{HH} = 7.0 Hz, J_{HH} = 7.0 Hz, 1H), 1.18 (dd, J_{HH} = 7.0 Hz, J_{HP} = 18.7 Hz, 3H), 0.94 (d, J_{HH} = 7.0 Hz, 3H), 0.85 (d, J_{HH} = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.1 (d, J_{CP} = 18.8 Hz), 131.5 (d, J_{CP} = 9.1 Hz), 131.4 (d, J_{CP} = 9.3 Hz), 131.3 (d, J_{CP} = 77.3 Hz), 131.2 (d, J_{CP} = 77.5 Hz), 128.7 (d, J_{CP} = 11.6 Hz), 128.5 (d, J_{CP} = 11.6 Hz), 72.1 (s), 69.7 (s), 32.3 (s), 30.7 (d, J_{CP} = 57.3 Hz), 28.9 (d, J_{CP} = 2.3 Hz), 18.8 (s), 17.9 (s), 13.0 (s); ^{31}P NMR (120 MHz, $CDCl_3$) δ 53.0 (s); IR (thin film) 2961 (s) 1669 (s); MS−FAB (EI^+) *m/z* (% rel intensity) 372.2 (MH^+, 100), 154.2 ([M − $Ph_2PS]^+$, 65); HRFAB calcd for $C_{21}H_{27}NOPS$ (MH^+) *m/e* 372.1551, measured *m/e* 372.1549.

(5*S*,2′*S*)-5-Benzyl-4,5-dihydro-2-(2′-(diphenylphosphinothioyl)-2′-phenylethyl-1,3-oxazole (26): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.20 (m, 2H), 7.59 (m, 3H), 7.54 (m, 2H), 7.1−7.4 (m, 11H), 7.01 (m, 2H), 4.45 (ddd, J_{HH} = 10.0 Hz, J_{HH} = 3.3 Hz, J_{HP} = 10.0 Hz, 1H), 4.12 (dddd, J_{HH} = 9.0 Hz, J_{HH} = 8.0 Hz, J_{HH} = 7.0 Hz, J_{HH} = 5.0 Hz, 1H), 3.92 (dd, J_{HH} = 8.0 Hz, J_{HH} = 8.0 Hz, 1H), 3.69 (dd, J_{HH} = 8.0 Hz, J_{HH} = 7.0 Hz, 1H), 3.22 (ddd, J_{HH} = 10.0 Hz, J_{HH} = 7.0 Hz, J_{HP} = 16.0 Hz, 1H), 2.81 (dddd, J_{HH} = 7.0 Hz, J_{HH} = 3.3 Hz, J_{HH} = 2.0 Hz, J_{HP} = 16.0 Hz, 1H), 2.72 (dd, J_{HH} = 13.0 Hz, J_{HH} = 5.0 Hz, 1H), 2.13 (dd, J_{HH} = 13.0 Hz, J_{HH} = 9.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.9 (d, J_{CP} = 18.1 Hz), 137.8 (s), 133.9 (d, J_{CP} = 4.2 Hz), 131.9 (d, J_{CP} = 9.2 Hz), 131.7 (d, J_{CP} = 2.9 Hz), 131.49 (d, J_{CP} = 9.5 Hz), 131.44 (d, J_{CP} = 33.8 Hz), 131.1 (d, J_{CP} = 2.9 Hz), 130.4 (d, J_{CP} = 27.9 Hz), 130.0 (d, J_{CP} = 5.3 Hz), 129.0 (s), 128.8 (d, J_{CP} = 11.6 Hz), 128.3 (s), 127.8 (d, J_{CP} = 12.2 Hz), 127.6 (d, J_{CP} = 2.0 Hz), 127.4 (d, J_{CP} = 1.4 Hz), 126.3 (s), 71.5 (s), 67.1 (s), 43.9 (d, J_{CP} = 51.4 Hz), 41.5 (s), 29.2 (d, J_{CP} = 3.5 Hz); ^{31}P NMR (120 MHz, $CDCl_3$) δ 50.8 (s); IR (thin film) 1669 (s), 1491 (s), 1453 (s); MS−FAB (EI^+) *m/z* (% rel intensity) 482.6 (MH^+, 15), 264.4 (M − $[Ph_2PS]^+$, 100); HRFAB calcd for $C_{30}H_{29}NOPS$ (MH^+) *m/e* 482.1707, measured *m/e* 482.1694.

(5*S*,2′*R*)-5-Benzyl-4,5-dihydro-2-(2′-(diphenylphosphinothioyl)-2′-phenylethyl)-1,3-oxazole (27): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.20 (m, 2H), 7.57 (m, 3H), 7.50 (m, 2H), 7.30 (m, 1H), 7.17 (m, 10H), 6.94 (m, 2H), 4.49 (ddd, J_{HH} = 3.5 Hz, J_{HH} = 11.0 Hz, J_{HP} = 11.0 Hz, 1H), 4.15 (dddd, J_{HH} = 9.0 Hz, J_{HH} = 7.5 Hz, J_{HH} = 5.4 Hz, J_{HH} = 8.0 Hz, 1H), 3.92 (dd, J_{HH} = 9.0 Hz, J_{HH} = 9.0 Hz, 1H), 3.73 (dd, J_{HH} = 9.0 Hz, J_{HH} = 7.5 Hz, 1H), 3.21 (ddd, J_{HH} = 11.0 Hz, J_{HH} = 12.0 Hz, J_{HP} = 16.0 Hz, 1H), 2.80 (ddd, J_{HH} = 3.5 Hz, J_{HH} = 12.0 Hz, J_{HP} = 16.0 Hz, 1H), 2.72 (dd, J_{HH} = 5.4 Hz, J_{HH} = 13.5 Hz, 1H), 2.28 (dd, J_{HH} = 8.0 Hz, J_{HH} = 13.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.3 (d, J_{CP} = 18.3 Hz), 137.6 (s), 134.0 (d, J_{CP} = 4.6 Hz), 131.9 (d, J_{CP} = 9.1 Hz), 131.8 (d, J_{CP} = 3.2 Hz), 131.5 (d, J_{CP} = 9.5 Hz), 131.1 (d, J_{CP} = 2.9 Hz), 130.4 (d, J_{CP} = 26.6 Hz), 129.9 (d, J_{CP} = 5.3 Hz), 129.2 (s), 128.8 (d, J_{CP} = 11.3 Hz), 128.3 (s), 127.8 (d, J_{CP} = 12.3 Hz), 127.6 (d, J_{CP} = 1.8 Hz), 127.4 (d, J_{CP} = 3.0 Hz), 126.3 (s), 71.4 (s), 67.1 (s), 43.9 (d, J_{CP} = 51.3 Hz), 41.4 (s), 28.9 (d, J_{CP} = 3.7 Hz); ^{31}P NMR (120 MHz, $CDCl_3$) δ 51.0 (s); IR (thin film) 1669 (s), 1496 (s); MS−FAB (EI^+) *m/z* (% rel intensity) 482.4 (MH^+, 50), 264.3 (M − $[Ph_2PS]^+$, 100); HRFAB Calcd for $C_{30}H_{29}NOPS$ (MH^+) *m/e* 482.1707; Found *m/e* 482.1706.

(5*S*,2′*S*)-4,5-Dihydro-2-(2′-(diphenylphosphinothioyl)-2′-phenylethyl)-5-isopropyl-1,3-oxazole (28): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.18 (m, 2H), 7.57 (m, 3H), 7.48 (m, 2H), 7.30 (m, 1H), 7.21 (m, 4H), 7.12 (m, 3H), 4.42 (ddd, J_{HH} = 11.0 Hz, J_{HH} = 3.0 Hz, J_{HP} = 11.0 Hz, 1H), 4.00 (dd, J_{HH} = 7.0 Hz, J_{HH} = 7.0 Hz, 1H), 3.72 (dddd, J_{HH} = 7.0 Hz, J_{HH} = 7.0 Hz, J_{HH} = 6.0 Hz, J_{HH} = 1.6 Hz, 1H), 3.68 (dd, J_{HH} = 7.0 Hz, J_{HH} = 7.0 Hz, 1H), 3.25 (ddd, J_{HH} = 11.0 Hz, J_{HH} = 8.0 Hz, J_{HP} = 15.0 Hz, 1H), 2.77 (dddd, J_{HH} = 8.0 Hz, J_{HH} = 3.0 Hz, J_{HH} = 1.6 Hz, J_{HP} = 15.0 Hz, 1H), 1.43 (dqq, J_{HH} = 6.0 Hz, J_{HH} = 7.0 Hz, J_{HH} = 7.0 Hz, 1H), 0.60 (d, J_{HH} = 7.0 Hz, 3H), 0.52 (d, J_{HH} = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.0 (d, J_{CP} = 18.6 Hz), 133.7 (d, J_{CP} = 4.6 Hz), 132.0 (d, J_{CP} = 9.3 Hz), 131.7 (d, J_{CP} = 1.2 Hz), 131.51 (d, J_{CP} = 9.3 Hz), 131.48 (d, J_{CP} = 36.0 Hz), 131.1 (d, J_{CP} = 2.9 Hz), 130.5 (d, J_{CP} = 36.1 Hz), 130.0 (d, J_{CP} = 5.4 Hz), 128.8 (d, J_{CP} = 11.6 Hz), 127.8 (d, J_{CP} = 12.2 Hz), 127.6 (d, J_{CP} = 2.9 Hz), 127.4 (d, J_{CP} = 2.9 Hz), 71.7 (s), 69.5 (s), 43.9 (d, J_{CP} = 51.5 Hz), 31.8 (s), 29.3 (d, J_{CP} = 3.5 Hz), 18.1 (s), 17.3 (s); ^{31}P NMR (120 MHz, $CDCl_3$) δ 50.9 (s); IR (thin film) 1670 (s), 1495 (s), 1481 (s), 1453 (s); MS−FAB (EI^+) *m/z* (% rel intensity) 434.2 (MH^+, 30); HRFAB calcd for $C_{26}H_{29}NOPS$ (MH^+) *m/e* 434.1707; measured *m/e* 434.1703.

(5*S*,2′*R*)-4,5-Dihydro-2-(2′-(diphenylphosphinothioyl)-2′-phenylethyl)-4-isopropyl-1,3-oxazole (29): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.19 (m, 2H), 7.56 (m, 3H), 7.48 (m, 2H), 7.30 (m, 1H), 7.20 (m, 4H), 7.10 (m, 3H), 4.49 (ddd, J_{HH} = 11.0 Hz, J_{HH} = 3.0 Hz, J_{HP} = 11.0 Hz, 1H), 3.95 (dd, J_{HH} = 8.0 Hz, J_{HH} = 8.0 Hz, 1H), 3.75 (dd, J_{HH} = 8.0 Hz, J_{HH} = 8.0 Hz, 1H), 3.70 (dddd, J_{HH} = 8.0 Hz, J_{HH} = 8.0 Hz, J_{HH} = 7.0 Hz, J_{HH} = 2.4 Hz, 1H), 3.20 (ddd, J_{HH} = 11.0 Hz, J_{HH} = 8.0 Hz, J_{HP} = 16.0 Hz, 1H), 2.75 (dddd, J_{HH} = 8.0 Hz, J_{HH} = 3.0 Hz, J_{HH} = 2.4 Hz, J_{HP} = 15.0 Hz, 1H), 1.41 (dqq, J_{HH} = 7.0 Hz, J_{HH} = 7.0 Hz, J_{HH} = 7.0 Hz, 1H), 0.60 (d, J_{HH} = 7.0 Hz, 3H), 0.54 (d, J_{HH} = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.5 (d, J_{CP} = 19.1 Hz), 134.0 (d, J_{CP} = 4.0 Hz), 132.0 (d, J_{CP} = 9.0 Hz), 131.7 (d, J_{CP} = 3.0 Hz), 131.5 (d, J_{CP} = 9.0 Hz), 131.4 (d, J_{CP} = 26.0 Hz), 131.1 (d, J_{CP} = 3.0 Hz), 130.4 (d, J_{CP} = 26.0 Hz), 130.0 (d, J_{CP} = 5.0 Hz), 128.8 (d, J_{CP} = 11.0 Hz), 127.8 (d, J_{CP} = 12.0 Hz), 127.5 (d, J_{CP} = 2.0 Hz), 127.2 (d, J_{CP} = 3.0 Hz), 71.7 (s), 69.6 (s), 44.0 (d, J_{CP} = 51.1 Hz), 32.2 (s), 28.7 (d, J_{CP} = 4.1 Hz), 18.0 (s), 17.5 (s); ^{31}P NMR (120 MHz, $CDCl_3$) δ 50.9 (s); IR (thin film) 1674 (s); MS−FAB (EI^+) *m/z* (% rel intensity) 434.4 (MH^+, 100); HRFAB calcd for $C_{26}H_{29}NOPS$ (MH^+) *m/e* 434.1707, measured *m/e* 434.1710.

(5*S*,2′*S*)-4,5-Dihydro-2-(2′-(diphenylphosphinothioyl)-2′-phenylethyl)-5-phenyl-1,3-oxazole (30): ^{1}H NMR (300

MHz, $CDCl_3$) δ 8.20 (m, 2H), 7.60 (m, 3H), 7.50 (m, 2H), 7.33 (m, 1H), 7.1−7.3 (m, 10H), 6.61 (d, J_{HH} = 6.4 Hz, 2H), 4.98 (ddd, J_{HH} = 10.0 Hz, J_{HH} = 8.0 Hz, J_{HH} = 2.4 Hz, 1H), 4.62 (ddd, J_{HH} = 12.0 Hz, J_{HH} = 3.0 Hz, J_{HP} = 10.0 Hz, 1H), 4.38 (dd, J_{HH} = 10.0 Hz, J_{HH} = 8.0 Hz, 1H), 3.35 (ddd, J_{HH} = 12.0 Hz, J_{HH} = 7.5 Hz, J_{HP} = 16.0 Hz, 1H), 2.85 (dddd, J_{HH} = 7.5 Hz, J_{HH} = 3.0 Hz, J_{HH} = 2.4 Hz, J_{HP} = 16.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.6 (d, J_{CP} = 19.2 Hz), 142.1 (s), 134.0 (d, J_{CP} = 4.8 Hz), 132.0 (d, J_{CP} = 9.2 Hz), 131.9 (d, J_{CP} = 5.0 Hz), 131.6 (d, J_{CP} = 9.5 Hz), 131.2 (d, J_{CP} = 3.2 Hz), 130.1 (d, J_{CP} = 5.1 Hz), 128.9 (d, J_{CP} = 11.3 Hz), 128.4 (s), 127.9 (d, J_{CP} = 12.2 Hz), 127.8 (d, J_{CP} = 2.4 Hz), 127.4 (d, J_{CP} = 3.2 Hz), 127.2 (s), 126.3 (s), 74.8 (s), 69.4 (s), 44.1 (d, J_{CP} = 51.1 Hz), 28.6 (d, J_{CP} = 4.0 Hz); ^{31}P NMR (120 MHz, $CDCl_3$) δ 50.8 (s); IR (thin film) 1667 (s); MS−FAB (EI^+) *m/z* (% rel intensity) 468.2 (MH^+, 20), 250.1 ([M − Ph_2PS]$^+$, 100); HRFAB calcd for $C_{29}H_{27}NOPS$ (MH^+) *m/e* 468.1551, measured *m/e* 468.1555.

(5*S*,2′*R*)-4,5-Dihydro-2-(2′-(diphenylphosphinothioyl)-2′-phenylethyl)-5-phenyl-1,3-oxazole (31): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.20 (m, 2H), 7.60 (m, 3H), 7.50 (m, 2H), 7.1−7.4 (m, 11H), 6.59 (d, J_{HH} = 8.0 Hz, 2H), 4.95 (ddd, J_{HH} = 10.0 Hz, J_{HH} = 9.0 Hz, J_{HH} = 2.0 Hz, 1H), 4.50 (ddd, J_{HH} = 12.0 Hz, J_{HH} = 3.0 Hz, J_{HP} = 10.0 Hz, 1H), 4.42 (dd, J_{HH} = 10.0 Hz, J_{HH} = 8.0 Hz, 1H), 3.78 (dd, J_{HH} = 9.0 Hz, J_{HH} = 8.0 Hz, 1H), 3.40 (ddd, J_{HH} = 12.0 Hz, J_{HH} = 7.5 Hz, J_{HP} = 15.0 Hz, 1H), 2.85 (dddd, J_{HH} = 7.5 Hz, J_{HH} = 3.0 Hz, J_{HH} = 2.0 Hz, J_{HP} = 15.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.8 (d, J_{CP} = 19.0 Hz), 142.1 (s), 133.7 (d, J_{CP} = 4.4 Hz), 132.0 (d, J_{CP} = 9.2 Hz), 131.9 (d, J_{CP} = 3.1 Hz), 131.5 (d, J_{CP} = 9.7 Hz), 131.45 (d, J_{CP} = 39.0 Hz), 131.2 (d, J_{CP} = 2.9 Hz), 130.4 (d, J_{CP} = 39.1 Hz), 130.2 (d, J_{CP} = 5.3 Hz), 128.9 (d, J_{CP} = 11.6 Hz), 128.5 (s), 128.0 (d, J_{CP} = 4.3 Hz), 127.9 (d, J_{CP} = 4.4 Hz), 127.6 (d, J_{CP} = 3.2 Hz), 127.3 (s), 126.4 (s), 75.0 (s), 69.6 (s), 44.0 (d, J_{CP} = 51.6 Hz), 29.4 (d, J_{CP} = 3.4 Hz); ^{31}P NMR (120 MHz, $CDCl_3$) δ 50.8 (s); IR (thin film) 3058 (s), 3029 (s), 1669 (s), 1492 (s), 1482 (s); MS−FAB (EI^+) *m/z* (% rel intensity) 468.3 (MH^+, 50), 250.1 ([M − Ph_2PS]$^+$, 100); HRFAB calcd for $C_{29}H_{27}$-NOPS (MH^+) *m/e* 468.1551,s measured *m/e* 468.1454.

(5*S*,2′*S*)-4,5-Dihydro-2-(2′-(diphenylphosphinothioyl)-2′-phenylethyl)-5-*tert*-butyl-1,3-oxazole (32): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.15 (m, 2H), 7.57 (m, 3H), 7.45 (m, 2H), 7.30 (m, 1H), 7.20 (m, 4H), 7.10 (m, 3H), 4.39 (ddd, J_{HH} = 12.1 Hz, J_{HH} = 3.0 Hz, J_{HP} = 10.4 Hz, 1H), 3.99 (dd, J_{HH} = 8.3 Hz, J_{HH} = 9.9 Hz, 1H), 3.75 (dd, J_{HH} = 8.3 Hz, J_{HH} = 8.3 Hz, 1H), 3.64 (ddd, J_{HH} = 2.5 Hz, J_{HH} = 9.9 Hz, J_{HH} = 8.3 Hz, 1H), 3.29 (ddd, J_{HH} = 12.1 Hz, J_{HH} = 15.3 Hz, J_{HP} = 7.0 Hz, 1H), 2.74 (dddd, J_{HH} = 3.0 Hz, J_{HH} = 15.3 Hz, J_{HH} = 2.5 Hz, J_{HP} = 8.5 Hz, 1H), 0.53 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.9 (d, J_{CP} = 19.7 Hz), 133.5 (d, J_{CP} = 4.6 Hz), 132.0 (d, J_{CP} = 9.2 Hz), 131.8 (d, J_{CP} = 2.2 Hz), 131.5 (d, J_{CP} = 9.8 Hz), 131.1 (d, J_{CP} = 2.9 Hz), 131.0 (d, J_{CP} = 33.6 Hz), 130.1 (d, J_{CP} = 5.5 Hz), 128.8 (d, J_{CP} = 11.5 Hz), 127.9 (d, J_{CP} = 12.0 Hz), 127.7 (d, J_{CP} = 2.6 Hz), 127.4 (d, J_{CP} = 3.1 Hz), 75.7 (s), 68.5 (s), 43.9 (d, J_{CP} = 51.5 Hz), 33.1 (s), 29.2 (s), 25.3 (s); ^{31}P NMR (120 MHz, $CDCl_3$) δ 50.9 (s); IR (thin film) 1603 (s); MS−FAB (EI^+) *m/z* (% rel intensity) 470 ([M + Na]$^+$, 100) 448 (MH^+, 50); HRFAB calcd for $C_{27}H_{31}NOPS$ (MH^+) *m/e* 448.1864, measured *m/e* 448.1864.

(5*S*,2′*R*)-4,5-Dihydro-2-(2′-(diphenylphosphinothioyl)-2′-phenylethyl-5-*tert*-butyl-1,3-oxazole (33): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.20 (m, 2H), 7.57 (m, 3H), 7.50 (m, 2H), 7.31 (m, 1H), 7.21 (m, 4H), 7.10 (m, 3H), 4.51 (ddd, J_{HH} = 10.0 Hz, J_{HH} = 3.0 Hz, J_{HP} = 10.0 Hz, 1H), 3.91 (dd, J_{HH} = 8.0 Hz, J_{HH} = 9.0 Hz, 1H), 3.85 (dd, J_{HH} = 8.0 Hz, J_{HH} = 8.0 Hz, 1H), 3.61 (ddd, J_{HH} = 9.0 Hz, J_{HH} = 8.0 Hz, J_{HH} = 2.5 Hz, 1H), 3.21 (ddd, J_{HH} = 12.0 Hz, J_{HH} = 7.0 Hz, J_{HP} = 17.0 Hz, 1H), 2.73 (dddd, J_{HH} = 7.0 Hz, J_{HH} = 3.0 Hz, J_{HH} = 2.5 Hz, J_{HP} = 17.0 Hz, 1H), 0.52 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.4 (d, J_{CP} = 19.3 Hz), 134.1 (d, J_{CP} = 5.0 Hz), 132.0 (d, J_{CP} = 9.1 Hz), 131.7 (d, J_{CP} = 2.2 Hz), 131.5 (d, J_{CP} = 10.0 Hz), 131.4 (d, J_{CP} = 26 Hz), 131.1 (d, J_{CP} = 2.9 Hz), 130.4 (d, J_{CP} = 26.3 Hz), 130.0 (d, J_{CP} = 5.2 Hz), 128.8 (d, J_{CP} = 11.6 Hz), 127.8 (d, J_{CP} = 12.1 Hz), 127.5 (d, J_{CP} = 4.1 Hz), 127.2 (d, J_{CP} = 3.1 Hz), 75.5 (s), 68.4 (s), 43.8 (d, J_{CP} = 51.6 Hz), 33.4 (s), 28.6 (d, J_{CP} = 3.9 Hz), 25.2 (s); ^{31}P NMR (120 MHz, $CDCl_3$) δ 50.9 (s); IR (thin film) 1679 (s); MS−FAB (EI^+) *m/z* (% rel intensity) 448.2 (MH^+, 50), 230.2 ([M − Ph_2PS]$^+$, 100); HRFAB calcd for $C_{27}H_{31}NOPS$ (MH^+) *m/e* 448.1864, measured *m/e* 448.1866. Anal. Calcd for $C_{27}H_{30}NOPS$: C, 72.46; H, 6.76; N, 3.13. Found C, 72.40; H, 6.55; N, 3.47.

Acknowledgment. This work was partially supported by NIH R01 GM56490-01 and Washington University. We also gratefully acknowledge the Washington University High-Resolution NMR Facility, partially supported by NIH 1S10R02004, and the Washington University Mass Spectrometry Resource Center, partially supported by NIHRR00954, for their assistance.

Supporting Information Available: Full spectral data for the compounds **11**−**19** and their corresponding alcohols (19 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO981420Y