Chiral Phosphinophenyloxazolines Bearing Alkoxymethyl Substituents: Synthesis and Application in the Palladium Catalyzed Allylic Substitution Reactions

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The chiral phosphine-oxazoline ligands **3** and **4** bearing 4-alkoxymethyl substituents on the oxazoline ring with (*R*)-configuration were prepared from L-serine methyl ester in 66% and 33% yields, respectively. Along this synthetic pathway, the β-hydroxylamides derived from L-serine methyl ester and 2-halobenzoyl chlorides were expediently converted to the corresponding oxazolines by using diethylaminosulfur trifluoride as the activation agent. Potassium diphenylphosphide was the reagent of choice for replacing the bromine atom on the phenyl ring, giving the desired oxazoline-phosphine ligands **3** and **4**. Together with [Pd(η^3-allyl)Cl]$_2$, ligands **3** and **4** induced an enantioselective allylic substitution reaction of 1,3-diphenyl-2-propenyl acetate by dimethyl malonate. Although ligands **3** and **4** exhibit the (*R*)-configuration, differing from the (*S*)-configuration of Pfaltz-Helmchen-Williams phosphine-oxazoline ligands, all these ligands led to the same enantiotopic preference in the allylic substitution reaction. To facilitate the recovery and reuse of the phosphine-oxazoline ligand, immobilization on Merrifield resin was attempted, albeit in low loading.

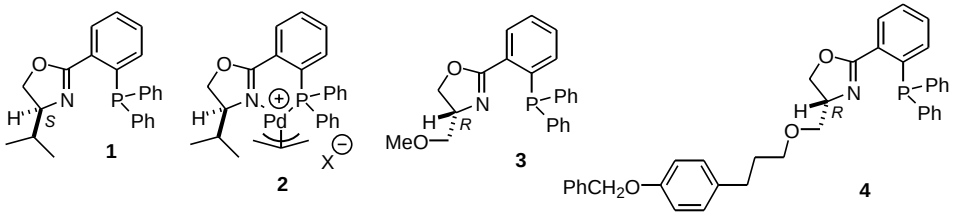
Keywords: Phosphine; Oxazoline; Palladium; Chiral ligands; Allylic substitution.

INTRODUCTION

The chiral ligands prepared by connection of phosphine and oxazoline moieties have been successfully used to promote a variety of metal catalyzed asymmetric organic reactions.[1] For example, Pfaltz,[2] Helmchen,[3] and Williams[4] groups have independently found the highly enantioselective substitution reaction of 1,3-diphenyl-2-propenyl acetate with dimethyl malonate by the catalysis of a palladium complex **2** that is prepared in situ from the phosphine-oxazoline ligand **1** and [Pd(η^3-allyl)Cl]$_2$.[5] The (*S*)-configuration of the chiral ligand **1** originates from (*S*)-valinol. We report herein the synthesis of the P,N-ligands **3** and **4** that bear 4-alkoxymethyl substituents on the oxazoline ring. In addition to the phosphorus and nitrogen atoms, the 4-alkoxymethyl group may also serve as a coordination site for a metal ion to render a stereocontrol in organic transformation, such as the Pd-mediated allylic substitution reactions.[5]

RESULTS AND DISCUSSION

The condensation reaction of L-serine methyl ester (as the hydrochloric salt **5**) with 2-chlorobenzoyl chloride (**6**) in the presence of Et_3N gave an amide **7** in 78% yield (Scheme I). Several attempts to form oxazoline by activation of the hydroxyl group in **7** failed to give the desired cyclization product. For example, treatment of **7** with *p*-TsCl or $SOCl_2$ in the presence of Et_3N gave only the elimination product **8**.[6] In another approach, the hydroxylamide **7** was heated with PPh_3/CCl_4 in the presence of Et_3N to afford a mixture of alkene **8** and the desired oxazoline **9** in 27% and 30% yields,



Dedicated to Professor Ching-Erh Lin on the Occasion of his 66th Birthday and his Retirement from National Taiwan University

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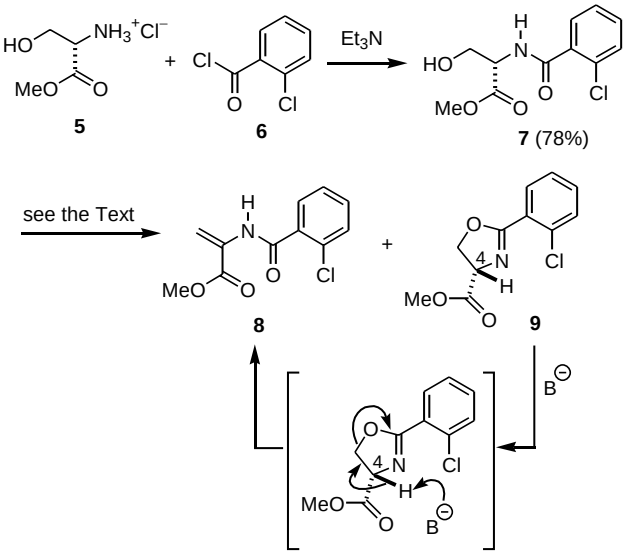
respectively. Finally, diethylaminosulfur trifluoride (DAST) turned out to be the reagent of choice for the transformation of hydroxylamide **7** into oxazoline **9**.[7] Thus, treatment of **7** with DAST at -78 °C in the presence of K_2CO_3 gave **9** exclusively in 99% yield, without complication of the side-product **8**. Unlike the valinol derived oxazolines, e.g., compound **1**, the oxazoline **9** containing an electron-withdrawing ester group renders the proton at C-4 susceptible to alkaline conditions. Indeed, oxazoline **9** was readily changed to alkene **8** upon treatment with a base, e.g., NaOH and NaH, presumably via the H-4 abstraction to cause a rupture of the oxazoline ring (Scheme I).

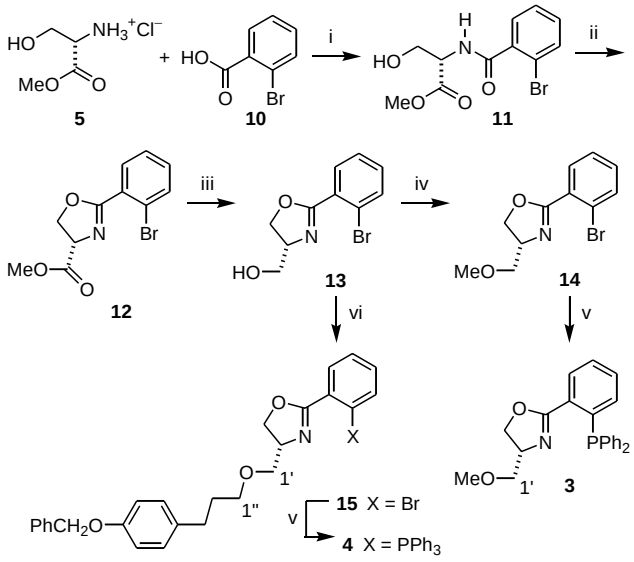
Scheme I



By a procedure similar to that for amide **7**, the acyl chloride derived from 2-bromobenzoic acid (**10**) was reacted in situ with the serine derivative **5** to give the amide **11** in 85% yield (Scheme II). The direct amidation reaction of acid **10** with **5** was also carried out, albeit in modest yields (50-75%), by using dicyclohexylcarbodiimide (DCC) or 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDCI) as the dehydrating agents and Et_3N and 4-dimethylaminopyridine (DMAP) as the reaction promoters. Hydroxylamide **11** was then treated with DAST in the presence of K_2CO_3 to afford the desired oxazoline **12** in a quantitative yield.[7]

The reduction of ester **12** with $LiAlH_4$ at room temperature afforded the alcohol **13**, which was treated with NaH and MeI to give the ether **14** in a 92% overall yield (Scheme II). One should avoid using excessive amounts of $LiAlH_4$; otherwise, the bromophenyl moiety in **12** would also be reduced.

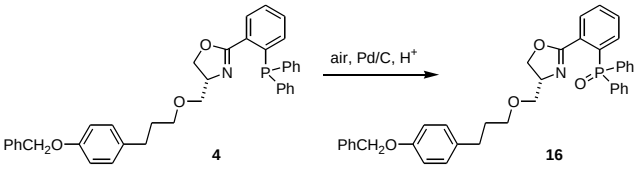
Scheme II



Reagents and conditions: (i) $SOCl_2$, 25 °C, 3 h; Et_3N, CH_2Cl_2, 25 °C, 4 h; 85%. (ii) DAST, CH_2Cl_2, -78 °C, 1 h; K_2CO_3, -78 °C, 3 h; 99%. (iii) $LiAlH_4/Et_2O$, THF, 25 °C, 4 h; 95%. (iv) NaH, MeI, THF, 25 °C, 3 h; 96%. (v) $KPPh_2$, THF, 25 °C, 24 h; 86% for **3** and 75% for **4**. (vi) NaH, $PhCH_2OC_6H_4(CH_2)_3Br$, Ag_2CO_3, THF/DMF (5:1), 0 °C, 5 h; 58%.

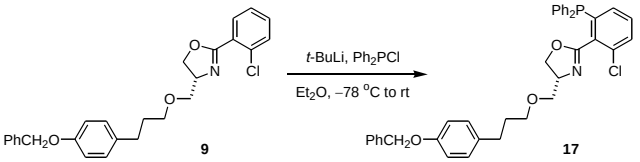
The alkylation reaction of alcohol **13** with 1-benzyloxy-4-(3-bromopropyl)benzene was achieved in THF/DMF (5:1) solution by the assistance of Ag_2CO_3, giving ether 1**5** in 58% yield. Substitution of bromine atom with diphenylphosphine group was not trivial as one would expect. We have tried several methods using different combinations of reagents, e.g., BuLi (or *t*-BuLi)/Ph_2PCl in tetramethylethylenediamine (TMEDA), Li (or Mg)/Ph_2PCl (or PPh_3) in various conditions, and even with catalysts of CuI or $Pd(PPh_3)_2Cl_2$, but failed to procure the desired substitution product.[8] Finally, the bromophenyl compounds **14** and **15** were reacted with $KPPh_2$ to afford the desired oxazoline-phosphine ligands **3** and **4**.[9] The ^{1}H NMR spectra indicated that the aromatic protons ($H_{3''}$) at the *ortho*-position of the PPh_2 group appeared at the relatively high fields of δ 6.49 (for **3**) and 6.86 (for **4**), presumably due to the shielding effect of the phenyl group in a pseudo-equatorial orientation (Fig. 1, see below). The methylene protons ($H_{1'}$) adjacent to the methoxy group in **3** also appeared at the relatively high fields of δ 2.44 and 2.66, presumably due to the shielding effect of the pseudo-axial phenyl group. The optimal yields of **3** (86%) and **4** (75%) were procured by stirring **14** and **15**, respectively, with 5 equiv of $KPPh_2$ in THF at room temperature for 24 h. Use of less

amounts (1-3 equiv) of $KPPh_2$ resulted in lower yields. When **15** was heated with $KPPh_2$ in refluxing THF (68 °C), a complicated product mixture containing the alcohol **13** and 3-(4-benzyloxyphenyl)propanol, in addition to the desired phosphine product **4**, was obtained in considerable amounts. The cleavage of ether linkage in **15** might result from the nucleophilic attack at the carbinyl carbons (C-1′ and C-1″) by diphenylphosphine or bromine anions.

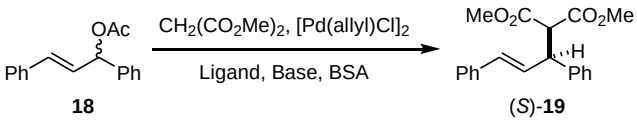


Phosphine **4** were partially oxidized in the air by the catalysis of Pd/C under acidic conditions,[10] e.g., in AcOH/MeOH solution (1:10), to give the corresponding phosphine oxide **16**. The characteristic trivalent phosphorus signal in **4** occurred at δ -22.96 in the ^{31}P NMR spectrum, whereas the pentavalent phosphorus in **16** appeared at a much lower field of δ 32.76.

Interestingly, treatment of the chlorophenyl oxazoline **9** with *t*-BuLi/Ph_2PCl in Et_2O (-78 to 25 °C, 18 h) gave a 32% yield of **17** with retention of the chlorine atom. By the chelation effect of the neighboring oxazoline moiety,[11] compound **9** might undergo the *ortho*-lithiation, and then react with Ph_2PCl to afford the product **17**.



With compounds **3** and **4** in hand, a wide range of asymmetric organic reactions with catalysis of transition metals could be assessed by using these chiral oxazoline-phosphine ligands.[1-5] To demonstrate this possible application of compounds **3** and **4**, we firstly investigated the substitution reaction of 1,3-diphenyl-2-propenyl acetate (**18**) with dimethyl malonate by the catalysis of $[Pd(\eta^3\text{-allyl})Cl]_2$.[5] According to the previously reported reaction protocol,[12] *N*,*O*-bis(trimethylsilyl)acetamide (BSA) and a base (KOAc or CsOAc) were also used as the promoters in addition to the chiral ligands (**3** or **4**). The best result (entry 4, Table 1), in 96% chemical yield and 90% ee, was obtained from the reaction using 3 equiv of dimethyl malonate, 20 mol % of ligand **3**, 5 mol % of $[Pd(\eta^3\text{-allyl})Cl]_2$, 1 mol % of CsOAc and 10 equiv of BSA in CH_2Cl_2 solution. By comparison with the previous reports,[13] the optically active product **19** with levorotation predominated in the (*S*)-enantiomer. The ee value was determined by HPLC analysis on a Chiralcel OD column, where the (*S*)-enantiomer was more polar than the (*R*)-enantiomer. Using ligand **4** for the allylic substitution reaction resulted in the same stereoselectivity, albeit in modest enantioselectivity (≤ 65% ee).



In comparison, the (*R*)-configuration in ligands **3** and **4** (the alkoxymethyl substituents shown on the α-face) differs from the (*S*)-configuration in ligand **1** (the isopropyl substitutent shown on the β-face). However, either the (*S*)-ligand **1** or the (*R*)-ligands **3**/**4** induced the same enantiotopic preference in the allylic substitution reaction, giving (*S*)-**19** as the dominant product. The rationale for the stereoselectivity using ligand **1** has been proposed by Helmchen and coworkers.[3,5] Their proposed transition state (Fig. 1a) includes several important features: (i) the isopropyl substituents on the oxazoline ring forces the triarylphosphine scaffold to tilt toward the π-allyl moiety, (ii) the π-allyl moiety prefers the *exo*-orientation to minimize the steric effect against the pseudo-equatorial phenyl group on the phosphorus center, and (iii) the nucleophilic attack of dimethyl malonate occurs at C-1 that is *trans* to the phosphorus atom. On the other hand, the alkoxy group in ligand **3** (or **4**) can coordinate to the palladium, and thus exposes the less hindered *exo*-face to accommodate the π-allyl moiety (Fig. 1b). These two working models interpret well how the allylic substitution reaction occurs in a highly stereoselective manner to afford the product pre-

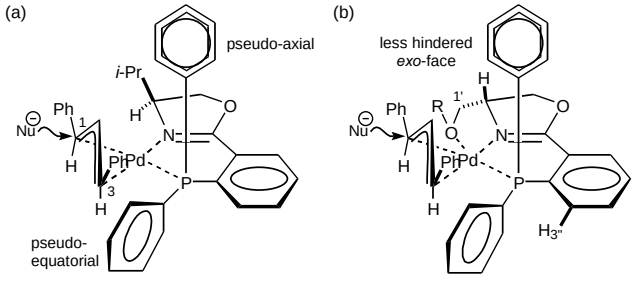


Fig. 1. Working models for the enantioselective allylic substitution reactions: (a) using (*S*)-ligand **1**, and (b) using (*R*)-ligand **3** or **4**.

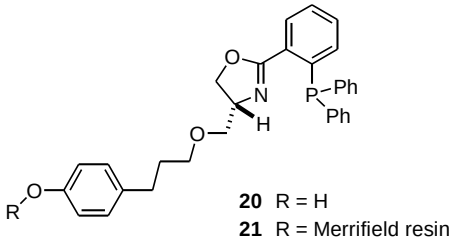
Table 1. Allyllic substitution reactions of 1,3-diphenyl-2-propenyl acetate (**18**) with dimethyl malonate using [Pd(η^3-allyl)Cl]$_2$ and chiral ligand (**3** or **4**), giving product **19**[a]

Entry	Ligand (mol %)	[Pd(allyl)Cl]$_2$ (mol %)	Base (mol %)	BSA (equiv)	Solvent	Reaction time (h)	Yield (%)	Ee (%)	Config.[b]
1	**3** (10)	5	KOAc (150)	0	CH_2Cl_2	72	0	-	-
2	**3** (10)	5	KOAc (5)	3	CH_2Cl_2	48	21	3	ND[c]
3	**3** (10)	5	KOAc (5)	3	CH_2Cl_2/DMF	48	70	49	*S*
4	**3** (20)	5	CsOAc (1)	10	CH_2Cl_2	48	96	90	*S*
5	**3** (20)	5	CsOAc (1)	10	CH_3CN	48	98	79	*S*
6	**4** (20)	10	KOAc (5)	1.5	CH_2Cl_2	40	96	53	*S*
7	**4** (20)	10	KOAc (5)	1.5	THF	54	63	65	*S*
8	**4** (20)	5	CsOAc (1)	10	CH_2Cl_2	6	97	42	*S*
9	**4** (20)	5	CsOAc (1)	2	CH_3CN	2	98	10	*S*

[a] The reaction was conducted with 3 equiv of dimethyl malonate at 25 °C.
[b] Configuration of major enantiomer.
[c] Not determined.

dominating in the (*S*)-isomer. In comparison with the present study, somewhat higher enantioselectivity in the previously reports[3,5] may be accounted for by the slight orientation twist of the pseudo-equatorial phenyl groups in the two transition states.

Immobilization on polymer and other supports is a general method for facilitation of the recovery and reuse of the ligand and metal catalyst.[14] In one approach, the benzyl protecting group in **4** was removed by treatment with $AlCl_3$ and *N*,*N*-dimethylaniline,[15] and the resulting phenol product **20** was reacted with Merrifield resin (chloromethylated polystyrene) in the presence of Cs_2CO_3 in DMF to give the resin-supported oxazoline-phosphine ligand **21**.[16] However, the loading of oxazoline-phosphine ligands was rather low, 0.33 mmol/g as estimated by elemental analysis of the nitrogen content.



20 R = H
21 R = Merrifield resin

CONCLUSION

In summary, we have devised an efficient method for the synthesis of chiral oxazoline-phosphine ligands bearing an alkoxymethyl group as the additional coordination site. The use of these chiral ligands has been demonstrated in a palladium catalyzed asymmetric allylic substitution reaction. We are currently searching for an improved preparation of the immobilized oxazoline-phosphine ligands that may be applied to facilitate catalytic asymmetric reactions.

EXPERIMENTAL

General Procedures

All reactions requiring anhydrous conditions were conducted in flame-dried apparatus under an atmosphere of argon or nitrogen. Syringes and needles for the transfer of reagents were dried at 100 °C and allowed to cool in a desiccator over P_2O_5 before use. Ethers were distilled from sodium benzophenone ketyl; (chlorinated) hydrocarbons, and amines from CaH_2. Reactions were monitored by TLC using precoated with a 0.25 mm layer of silica gel containing a fluorescent indicator. Column chromatography was carried out on Kieselgel 60 (40-63 μm). Melting points are uncorrected. Optical rotations were measured on a digital polarimeter with a cuvette of 10 cm length. $[\alpha]_D$ Values are given in 10^{-1} deg cm^2 g^{-1}. Chemical shifts of ^{1}H, ^{13}C and ^{31}P NMR spectra are reported relative to $CHCl_3$ [δ_H 7.24, δ_C (central line of t) 77.0] and H_3PO_4 (δ_P = 0). Distortionless enhancement polarization transfer (DEPT) spectra were taken to determine the types of carbon signals.

Methyl (*S*)-2-(2-Chlorobenzamido)-3-hydroxypropanoate (7)

A mixture of 2-chlorobenzoic acid (11.6 g, 74 mmol) and $SOCl_2$ (52 g, 224 mmol) was stirred at room temperature for 3 h and then concentrated under reduced pressure to give

the corresponding 2-chlorobenzoyl chloride. A solution of L-serine methyl ester hydrochloride (10 g, 67 mmol) in CH_2Cl_2 (150 mL) and Et_3N (18.9 g, 186 mmol) were added. The reaction mixture was stirred for 4 h at room temperature, and quenched by addition of water (100 mL). The aqueous phase was separated and then extracted with CH_2Cl_2 (100 mL). The combined organic phase was dried ($MgSO_4$), filtered, concentrated, and chromatographed on a silica gel column with elution of EtOAc/hexane (3:7) to give amide **7** (14.8 g, 86%).

TLC (EtOAc/hexane, 1:1) R_f = 0.50; $[\alpha]_D^{23}$ = +26.2 (*c* = 1.0, CH_2Cl_2); IR (KBr, cm^{-1}) 3347, 2962, 1750, 1619, 1546, 1377, 1217, 1060; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.75 (t, *J* = 5.9 Hz, OH), 3.78 (s, 3H), 4.00-4.10 (m, 2H), 4.83 (m, 1H), 7.15-7.40 (m, 4H), 7.62-7.65 (dd, *J* = 1.2, 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 52.9, 55.3, 63.3, 127.1, 130.30, 130.38, 130.9, 131.7, 134.0, 166.5, 170.6; HR-FAB-MS calcd for $C_{11}H_{13}{}^{35}ClNO_4$ (M^+ + H): 258.0455, found: *m/z* 258.0526.

Methyl 2-(2-Chlorobenzamido)-2-propenoate (8) and (*S*)-2-(2-Chlorophenyl)-4-methoxycarbonyl-4,5-dihydro-1,3-oxazole (9)

A mixture of hydroxylamide **7** (200 mg, 0.77 mmol), PPh_3 (300 mg, 1.2 mmol) and Et_3N (120 mg, 1.2 mmol) in CCl_4 (30 mL) was heated under reflux for 24 h. The mixture was concentrated and chromatographed on a silica gel column by elution with EtOAc/hexane (2:8) to give alkene **8** (50 mg, 27%) and oxazoline **9** (56 mg, 30%).

Hydroxylamide **7** was treated with DAST, by a procedure similar to that for **12**, to give oxazoline **9** in a quantitative yield.

Alkene **8**: TLC (EtOAc/hexane, 3:7) R_f = 0.53; IR (KBr, cm^{-1}) 3383, 2968, 1728, 1679, 1532, 1336, 1213, 1050; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.85 (s, 3H), 6.00 (br s, 1H), 6.79 (br s, 1H), 7.33-7.44 (m, 3H), 7.69 (dd, *J* = 7.4, 1.8 Hz, 1H), 8.50 (br s, NH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 53.1, 109.7, 127.2, 130.2, 130.5, 130.7, 130.9, 131.8, 134.5, 164.4, 164.8; HR-FAB-MS calcd for $C_{11}H_{11}ClNO_3$ (M^+ + H): 240.0349, found: *m/z* 240.0428.

Oxazoline **9**: TLC (EtOAc/hexane, 3:7) R_f = 0.22; $[\alpha]_D^{23}$ = +26.9 (*c* = 0.1, CH_2Cl_2); IR (KBr, cm^{-1}) 2958, 1733, 1694, 1594, 1439, 1318, 1267, 1053; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.74 (s, 3H), 4.53 (dd, *J* = 8.8, 10.6 Hz, 1H), 4.63 (dd, *J* = 8.2, 8.6 Hz, 1H), 4.92 (dd, *J* = 8.1, 10.7 Hz, 1H), 7.21-7.39 (m, 3H), 7.72 (dd, *J* = 1.7, 7.7 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 52.6, 68.6, 69.5, 126.4, 126.5, 130.6, 131.5, 131.9, 133.4, 165.1, 171.2; HR-FAB-MS calcd for $C_{11}H_{11}ClNO_3$ (M^+ + H): 240.0349, found: *m/z* 240.0427.

Methyl (*S*)-2-(2-bromobenzamido)-3-hydroxypropanoate (11)

Amidation of 2-bromobenzoic acid with L-serine methyl ester hydrochloride, by a procedure similar to that for **7**, gave **11** in 85% yield. TLC (EtOAc/hexane, 1:1) R_f = 0.50; $[\alpha]_D^{23}$ = +26.9 (*c* = 1.0, CH_2Cl_2); IR (KBr, cm^{-1}) 3401, 3345, 2961, 1750, 1619, 1542, 1376, 1057; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.09 (br s, OH), 3.73 (s, 3H), 3.92-4.07 (m, 2H), 4.76 (m, 1H), 7.06 (d, *J* = 5.6 Hz, NH), 7.18-7.30 (m, 2H), 7.47 (dd, *J* = 1.8, 7.5 Hz, 1H), 7.53 (dd, *J* = 1.2, 7.9 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 52.6, 55.0, 62.7, 119.3, 127.4, 129.4, 131.4, 133.3, 136.7, 167.7, 170.5; HR-FAB-MS calcd for $C_{11}H_{12}{}^{79}BrNO_4$ (M^+ + H): 301.9950, found: *m/z* 302.0028.

(*S*)-2-(2-Bromophenyl)-4-methoxycarbonyl-4,5-dihydro-1,3-oxazole (12)

A solution of hydroxylamide **11** (232 mg, 0.77 mmol) and DAST (0.12 mL, 0.93 mmol) in CH_2Cl_2 (30 mL) was stirred at -78 °C for 1 h and then to which was added K_2CO_3 (0.21 g, 1.6 mmol). The mixture was stirred for 3 h at -78 °C, warmed to room temperature, and quenched by slow addition of an aqueous $NaHCO_3$ solution (5%, 50 mL). The mixture was extracted with CH_2Cl_2 (30 mL × 2). The combined organic phase was dried ($MgSO_4$), filtered, concentrated, and chromatographed on a silica gel column with elution of EtOAc/hexane (3:7) to give oxazoline **12** (216 mg, 99%). TLC (EtOAc/hexane, 1:1) R_f = 0.71; $[\alpha]_D^{23}$ = +90.6 (*c* = 0.1, CH_2Cl_2); IR (KBr, cm^{-1}) 2957, 1745, 1648, 1592, 1437, 1361, 1211, 1027; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.80 (s, 3H), 4.60 (m, 1H), 4.71 (m, 1H), 4.98 (dd, *J* = 8.0, 10.6 Hz, 1H), 7.24-7.34 (m, 2H), 7.61 (dd, *J* = 1.0, 8.0 Hz), 7.72 (dd, *J* = 1.8, 7.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 52.8, 68.7, 69.8, 121.9, 127.1, 128.9, 131.7, 132.1, 133.9, 165.9, 171.3; HR-FAB-MS calcd for $C_{11}H_{11}BrNO_3$ (M^+ + H): 283.9844, found: *m/z* 283.9922.

(*S*)-2-(2-Bromophenyl)-4-hydroxymethyl-4,5-dihydro-1,3-oxazole (13)

A solution of ester **12** (4.41 g, 15.6 mmol) in THF (150 mL) was treated with $LiAlH_4$ (18.7 mL of 1 M solution in Et_2O) at room temperature for 1 h. After sequential addition of water (1 mL), aqueous NaOH (15%, 1 mL) and water (3 mL), the mixture was filtered through a pad of Celite, and washed with CH_2Cl_2 (50 mL) and MeOH/CH_2Cl_2 (5:95, 50 mL). The organic phase was concentrated and then chromatographed on a silica gel column with elution of EtOAc to

give alcohol **13** (3.78 g, 95%). TLC (EtOAc/hexane, 8:2) R_f = 0.26; $[\alpha]_D^{22}$ = +58.3 (*c* = 1.0, CH_2Cl_2); IR (KBr, cm^{-1}) 3351, 2939, 1653, 1591, 1434, 1362, 1250, 1027; ^1H NMR ($CDCl_3$, 400 MHz) δ 3.55 (m, 1H), 3.57 (br s, OH), 3.72 (m, 1H), 4.20 (m, 1H), 4.35 (m, 1H), 7.16-7.24 (m, 2H), 7.52-7.56 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 63.8, 68.3, 69.6, 121.6, 127.0, 128.2, 129.4, 131.1, 131.7, 133.6, 164.8; HR-FAB-MS calcd for $C_{10}H_{11}BrNO_2$ (M^+ + H): 255.9895, found: *m/z* 255.9974.

(*R*)-4-Methoxymethyl-2-(2-bromophenyl)-4,5-dihydro-1,3-oxazole (14)

A solution of alcohol **13** (3.00 g, 11.8 mmol) in THF (30 mL) was stirred with NaH (14.2 mmol, 60% dispersion in mineral oil washed with anhydrous hexane before use) at room temperature for 10 min. A solution of MeI (1.68 g, 11.8 mmol) in THF (30 mL) was added dropwise. The mixture was stirred for 3 h, filtered through a pad of Celite, and washed with EtOAc (50 mL). The organic phase was concentrated and then chromatographed on a silica gel column with elution of EtOAc/hexane (3:7) to give ether **14** (3.04 g, 96%). TLC (EtOAc/hexane, 1:1) R_f = 0.33; $[\alpha]_D^{22}$ = +64.4 (*c* = 1.0, CH_2Cl_2); IR (KBr, cm^{-1}) 2931, 1651, 1593, 1472, 1358, 1245, 1031; ^1H NMR ($CDCl_3$, 400 MHz) δ 3.37 (s, 3H), 3.45 (m, 1H), 3.66 (m, 1H), 4.29 (m, 1H), 4.42-4.53 (m, 2H), 7.22 (m, 1H), 7.29 (m, 1H), 7.59 (dd, *J* = 7.9, 1.3 Hz, 1H), 7.66 (dd, *J* = 7.6, 1.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 58.9, 66.3, 70.3, 74.1, 121.3, 126.6, 129.4, 131.0, 131.3, 133.3, 163.8; HR-FAB-MS calcd for $C_{11}H_{13}BrNO_2$ (M^+ + H): 270.0051, found: *m/z* 270.0129.

(*R*)-4-{[3-(4-benzyloxyphenyl)propoxy]methyl}-2-(2-bromophenyl)-4,5-dihydro-1,3-oxazole (15)

Alcohol **13** treated with NaH, Ag_2CO_3 (1 equiv) and 1-benzyloxy-4-(3-bromopropyl)benzene in THF/DMF (5:1) solution for 5 h at room temperature, by a procedure similar to that for **14**, gave ether **15** in 58% yield. TLC (EtOAc/hexane, 3:7) R_f = 0.45; $[\alpha]_D^{24}$ = +20.0 (*c* = 1.0, CH_2Cl_2); IR (KBr, cm^{-1}) 2928, 1652, 1512, 1456, 1356, 1240, 1025; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.87 (m, 2H), 2.63 (t, *J* = 7.3 Hz, 2H), 3.47-3.52 (m, 3H), 3.74 (dd, *J* = 7.7, 2.5 Hz, 1H), 4.35-4.40 (m, 1H), 4.46-4.55 (m, 2H), 5.02 (s, 2H), 6.89 (d, *J* = 8.6 Hz, 2H), 7.08 (d, *J* = 8.6 Hz, 2H), 7.24-7.45 (m, 7H), 7.62 (dd, *J* = 7.7, 1.0 Hz, 1H), 7.69 (dd, *J* = 7.7, 1.7 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 31.24, 31.28, 66.7, 69.9, 70.5, 70.7, 72.5, 114.6, 121.6, 126.9, 127.3, 127.7, 128.4, 129.2, 129.7, 131.2, 131.5, 133.6, 134.1, 137.1, 156.9, 164.2; HR-FAB-MS calcd for $C_{26}H_{27}BrNO_3$ (M^+ + H): 480.1096, found: *m/z* 480.1165.

(*R*)-4-Methoxymethyl-2-(2-diphenylphosphino)phenyl-4,5-dihydro-1,3-oxazole (3)

Under an atmosphere of argon, $KPPh_2$ (1.05 mmol, 2.1 mL of 0.5 M solution in THF) was added to a solution of the bromophenyl compound **14** (56 mg, 0.21 mmol) in THF (3 mL). The mixture was stirred at room temperature for 24 h, and then to which was added water (20 mL) and CH_2Cl_2 (20 mL). The aqueous phase was separated and then extracted with CH_2Cl_2 (30 mL). The combined organic phase was dried ($MgSO_4$), filtered, concentrated, and chromatographed on a silica gel column with elution of EtOAc/pentane (1:9) to give **3** (68 mg, 86%). TLC (EtOAc/hexane, 3:7) R_f = 0.34; $[\alpha]_D^{22}$ = +33.3 (*c* = 1.0, CH_2Cl_2); IR (KBr, cm^{-1}) 2928, 1643, 1536, 1486, 1299, 1120; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.44 (dd, *J* = 13.9, 7.4 Hz, 1H), 2.60 (dd, *J* = 13.9, 6.7 Hz, 1H), 3.27 (s, 3H), 3.50 (dd, *J* = 9.4, 4.1 Hz, 1H), 3.62 (dd, *J* = 9.4, 3.3 Hz, 1H), 4.42 (m, 1H), 6.49 (d, *J* = 8.0 Hz, 1H), 7.24-7.65 (m, 13H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 48.0, 58.8, 73.6, 73.7, 126.8, 128.33, 128.38, 128.4, 128.51, 128.58, 128.6, 128.7, 131.3, 132.61, 132.66, 132.80, 132.85, 134.3, 137.6, 137.7, 138.3, 138.4, 166.5; ^{31}P NMR ($CDCl_3$, 162 MHz) δ -22.87; HR-FAB-MS calcd for $C_{23}H_{23}NO_2P$ (M^+ + H): 376.1388, found: *m/z* 376.1618.

(*R*)-4-[3-(4-Benzyloxyphenyl)propoxy]methyl-2-(2-diphenylphosphino)phenyl-4,5-dihydro-1,3-oxazole (4)

Treatment of the bromophenyl compound **15** with $KPPh_2$, by a procedure similar to that for **3**, gave compound **4** in 75% yield. TLC (EtOAc/hexane, 3:7) R_f = 0.54; $[\alpha]_D^{23}$ = -12.5 (*c* = 1.0, CH_2Cl_2); IR (KBr, cm^{-1}) 3064, 2926, 1641, 1512, 1485, 1241, 1027; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.83 (m, 2H), 2.47 (dd, *J* = 7.6, 13.8 Hz, 1H), 2.53-2.69 (m, 3H), 3.32-3.45 (m, 2H), 3.54 (m, 1H), 3.72 (m, 1H), 4.42 (m, 1H), 5.01 (s, 2H), 6.86 (d, *J* = 8.4 Hz, 1H), 6.88 (d, *J* = 8.7 Hz, 2H), 7.05 (d, *J* = 8.7 Hz, 2H), 7.27-7.63 (m, 18H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 31.2, 31.3, 48.2, 70.0, 70.3, 71.6, 71.7, 114.7, 126.8, 127.4, 127.8, 128.4, 128.49, 128.55, 128.62, 128.65, 128.7, 129.2, 131.3, 132.6, 132.7, 132.8, 132.9, 137.1, 138.4, 157.0, 166.6; ^{31}P NMR ($CDCl_3$, 162 MHz) δ -22.96; HR-FAB-MS calcd for $C_{38}H_{37}NO_3P$ (M^+ + H): 586.2433, found: *m/z* 586.2503.

(*R*)-4-[3-(4-Benzyloxyphenyl)propoxy]methyl-2-(2-diphenylphosphorino)phenyl-4,5-dihydro-1,3-oxazole (16)

Phosphine **4** in MeOH/AcOH (10:1) solution was stirred in the air for 18 h to give phosphine oxide **16**. TLC (EtOAc/hexane, 8:2) R_f = 0.34; $[\alpha]_D^{23}$ = -13.7 (*c* = 1.0, CH_2Cl_2); IR (KBr, cm^{-1}) 3063, 1658, 1514, 1439, 1322, 1236, 1177, 1117;

^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.79 (m, 2H), 2.53 (t, *J* = 7.6 Hz, 2H), 2.68 (m, 1H), 2.95 (m, 1H), 3.12 (m, 1H), 3.26 (m, 1H), 3.40 (t, *J* = 8.6 Hz, 1H), 3.68 (m, 1H), 4.52 (m, 1H), 5.01 (s, 2H), 6.85 (d, *J* = 8.5 Hz, 2H), 7.03 (d, *J* = 8.4 Hz, 2H), 7.15 (m, 1H), 7.24-7.50 (m, 10H), 7.62-7.89 (m, 7H), 8.02 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 31.3, 31.4, 46.9, 70.0, 70.2, 71.0, 71.1, 114.7, 127.1, 127.4, 127.8, 128.24, 128.36, 128.43, 128.53, 128.67, 128.7, 128.8, 128.9, 129.2, 130.3, 130.4, 130.7, 130.8, 131.1, 131.2, 131.4, 131.9, 133.9, 134.1, 137.1, 156.9, 166.8; ^{31}P NMR ($CDCl_3$, 162 MHz) δ 32.76 ppm; HR-FAB-MS calcd for $C_{38}H_{37}BrNO_4P$ (M^+ + H): 602.2382, found: *m/z* 602.2610; Anal. Calcd for $C_{38}H_{36}NO_4BrP$: C, 75.86; H, 6.03; N, 2.33. Found: C, 75.97; H, 6.12; N, 1.98.

(*R*)-4-[3-(4-Benzyloxyphenyl)propoxy]methyl-2-(2-chloro-6-diphenylphosphino)phenyl-4,5-dihydro-1,3-oxazole (17)

To a solution of **9** (502 mg, 2.1 mmol) in Et_2O (20 mL) was added dropwise *t*-BuLi (1.6 mL of 1.5 M solution in THF) at -78 °C. The mixture was stirred for 3 h; a solution of $ClPPh_2$ (946 mg, 4.3 mmol) in Et_2O (10 mL) was added dropwise at -78 °C. The reaction mixture was stirred at room temperature for 18 h, quenched by addition of water (30 mL), and extracted with CH_2Cl_2 (40 mL × 2). The organic phase was dried ($MgSO_4$), filtered, concentrated, and chromatographed on a silica gel column with elution of EtOAc/hexane (2:8) to give compound **17** (416 mg, 32%). TLC (EtOAc/hexane, 3:7) R_f = 0.54; $[\alpha]_D^{22}$ = +40.1 (*c* = 1.0, CH_2Cl_2); IR (KBr, cm^{-1}) 2965, 1652, 1513, 1460, 1222, 1037; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.85 (m, 2H), 2.62 (t, *J* = 7.3 Hz, 2H), 3.36 (t, *J* = 8.4 Hz, 1H), 3.45 (m, 2H), 3.65 (dd, *J* = 4.6, 9.4 Hz, 1H), 4.17 (m, 2H), 4.38 (m, 1H), 5.03 (s, 2H), 6.89-6.92 (m, 3H), 7.08-7.11 (m, 2H), 7.22-7.24 (m, 2H), 7.31-7.43 (m, 15H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 31.2, 31.3, 66.6, 69.9, 70.4, 70.9, 72.5, 114.6, 127.4, 127.8, 128.42, 128.46, 128.48, 128.49, 128.5, 128.9, 129.2, 129.3, 129.6, 130.5, 131.7, 133.4, 133.71, 133.73, 133.81, 133.88, 133.92, 133.94, 134.1, 136.09, 136.11, 136.21, 136.22, 137.1, 140.5, 140.7, 156.9, 162.4; ^{31}P NMR ($CDCl_3$, 162 MHz) δ -8.33; HR-FAB-MS calcd for $C_{38}H_{36}ClNO_3P$ (M^+ + H): 620.2043, found: *m/z* 620.2120.

Representative Procedure for the Palladium Catalyzed Asymmetric Allylic Substitution Reaction (Table 1)

A mixture of ligand **4** (24 mg, 0.04 mmol) and $[Pd(allyl)Cl]_2$ (7.2 mg, 0.02 mmol) in CH_2Cl_2 (10 mL) was stirred for 10 min. A solution of 1,3-diphenyl-2-propenyl acetate (50 mg, 0.2 mmol) in CH_2Cl_2 (10 mL) was added, followed by dimethyl malonate (78 mg, 0.6 mmol), BSA (122 mg, 0.6 mmol) and KOAc (1 mg, 0.01 mmol). The mixture was stirred at room temperature for 40 h, and taken up with Et_2O (80 mL). The ethereal solution was washed with saturated NH_4Cl (20 mL × 2), dried ($MgSO_4$), filtered, concentrated, and chromatographed on a silica gel column with elution of EtOAc/hexane (1:9) to give dimethyl 2-(1,3-diphenyl-2-propenyl)malonate (**19**). A sample of **19** was analyzed by HPLC on a Chiralcel column (25 cm × 0.46 cm) with elution of 2-propanol/hexane (1:120, flow rate 0.9 mL) using RI and UV (254 nm) detectors. t_R = 13.7 min (*R*-**19**) and 14.6 min (*S*-**19**).

(*R*)-4-[3-(4-Hydroxyphenyl)propoxy]methyl-2-(2-diphenylphosphino)phenyl-4,5-dihydro-1,3-oxazole (20)

To a solution of **4** (500 mg, 0.85 mmol) and $AlCl_3$ (0.34 g, 2.56 mmol) in CH_2Cl_2 (30 mL) was added *N*,*N*-dimethylaniline (1 g, 8.5 mmol). The mixture was stirred at room temperature for 1 h, filtered through a pad of Celite, and washed with CH_2Cl_2 (20 mL) and EtOAc/hexane (1:1, 30 mL). The combined organic phase was concentrated and chromatographed on a silica gel column with elution of EtOAc/hexane (1:9) to give phenol **20** (328 mg, 78%). TLC (EtOAc/hexane, 3:7) R_f = 0.33; $[\alpha]_D^{23}$ = -23.0, (*c* = 1.0, CH_2Cl_2); IR (KBr, cm^{-1}) 3343, 3022, 1653, 1516, 1439, 1352, 1218; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.78-1.85 (m, 2H), 2.48 (dd, *J* = 7.4, 14.0 Hz, 1H), 2.55 (m, 2H), 2.84 (m, 1H), 3.27-3.42 (m, 2H), 3.54 (m, 1H), 3.67 (dd, *J* = 3.3, 9.5 Hz, 1H), 4.40-4.47 (m, 1H), 6.37 (br s, OH), 6.58 (d, *J* = 8.2 Hz, 1H), 6.73 (d, *J* = 8.2 Hz, 2H), 6.90-6.98 (m, 2H), 7.23-7.63 (m, 13H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 30.8, 31.2, 48.0, 70.4, 71.6, 71.7, 115.2, 126.9, 128.4, 128.50, 128.57, 128.62, 128.69, 128.8, 128.9, 129.3, 131.5, 132.6, 132.8, 133.2, 134.2, 154.2, 166.9; ^{31}P NMR ($CDCl_3$, 162 MHz) δ -22.45; HR-FAB-MS calcd for $C_{31}H_{31}NO_3P$ (M^+ + H): 496.1963, found: *m/z* 496.2187.

A Polymer-Supported Ligand 21

Merrifield resins (2% cross-linked, 2-2.5 meq Cl/g, 200-400 mesh) were dried under reduced pressure before use. Under an atmosphere of N_2, a mixture of alcohol **20** (500 mg, 1.0 mmol), Merrifield resins (367 mg, 0.73-0.91 mmol) and Cs_2CO_3 (359 mg, 1.1 mmol) in DMF (10 mL) was agitated at 60 °C for 24 h. The mixture was cooled and the resins were collected by filtration and washed successively with 1:1 H_2O/THF (3 × 25 mL), MeOH (3 × 25 mL), and THF (3 × 25 mL). The product was dried to yield 710 mg of **21**. Elemental analysis showed the average nitrogen content of 0.46 ± 0.09% (three measurements), equivalent to an average loading of 0.33 mmol/g.

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