Synthesis of α-Substituted *β*-Amidophosphines by Diastereoselective Alkylation. A New Access to Chiral Ligands for Asymmetric Catalysis

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Chiral *β*-amidophosphine boranes **7a**−**f** can be diastereoselectively alkylated, using *O*-protected amino-alcohols as chiral inducers, to furnish α-substituted *β*-amidophosphine boranes **8a**−**f** and **9**−**12** with up to 72% diastereoisomeric excess. Selective deprotection afforded optically pure carboxylic derivative **13** which is a key intermediate for the synthesis of various potential chiral ligands for asymmetric catalysis.

Introduction

The increasing practical usefulness of catalytic asymmetric synthesis has received much attention in recent years,[1] especially in the pharmaceutical field for the preparation of biologically active chiral compounds. For this reason, much interest is being focused on the synthesis and the development of new efficient chiral ligands. During the past three decades, numerous potential chiral catalysts have been synthesized and some of them appeared to be excellent ligands (for example DIPAMP[2], DIOP[3], BINAP,[4] PennPHOS,[5] DuPHOS,[6] etc.) and have been developed for a variety of catalytic reactions. However, no structural class is universally suitable for all transformations. Furthermore, it is generally highly desirable to have access to a variety of ligands in order to optimize the reaction when applied to a range of substrates.

All these ligands can be classified into three main families depending on the location of the stereogenic information which can be encountered on a side chain (VALAP,[7] CHIRAPHOS[8]), on the phosphorus atom (DIPAMP), or as an axial chirality (BINAP). Concerning the first series, most of the ligands frequently used are derived from amino acids, limiting the structural diversity of the catalysts. Very few of them are obtained by diastereoselective creation of a stereogenic center. To the best of our knowledge, the ligands developed by Minami[9] and Gilbertson[10] are the only two catalysts of this series possessing such a stereogenic center. However, these syntheses are based on a racemic approach and need either an optical resolution[9] or the separation of a 1/1 mixture of diastereoisomers.[10]

The development of new α-substituted phosphine ligands would therefore be of particular interest. Indeed, the stereogenic α-position next to the phosphine could be of great importance since the phosphorus atom is directly associated with the transition metal in the asymmetric reaction. The presence of a chiral center at the α-position could enhance facial discrimination and thus lead to improved levels of enantioselectivity in catalytic asymmetric reactions.

For these reasons, we became interested in the synthesis and the development of new potential ligands possessing a stereogenic center in the α-position related to the phosphorus atom. A few years ago, Beak[11] reported a new 1,5 diastereoselective alkylation of *β*-aryl secondary amides. The asymmetric induction was explained by the formation of a rigid intermediate in which the benzylic lithium was complexed by the nitrogen of the amide. We then decided to apply this methodology to the alkylation of phosphine-amides **1**, since it is known that phosphine-borane substrates can be easily metalated[12] (Scheme 1). We supposed that the corresponding lithium intermediate could then adopt the same conformation and might lead to high diastereoselectivity during the substitution step.

After deprotection and simple synthetic transformations, chiral derivatives **2** could then furnish a large variety of ligands such as phosphine-amides, phosphine-amines, phosphine-acids, or phosphine-alcohols. Described here is the first application of this methodology to the synthesis of α-substituted phosphines.

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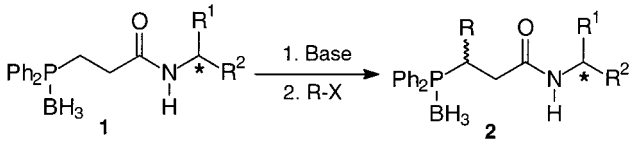
Scheme 1



Results and Discussion

In a first attempt we decided to investigate the direct transposition of Beak's method to substrate **7a**. This amide was synthesized in five steps from chlorodiphenylphosphine using a Michael addition of diphenylphosphine-borane **3** to ethyl acrylate (Scheme 2). A coupling reaction between acyl chloride **6** and (*R*)-α-methylbenzylamine was then performed under standard conditions (NaOH, CH_2Cl_2) leading to the expected phosphines-amides **7a** in 67% yield.

Substrate **7a** was reacted successively with *n*-BuLi and methyl iodide to afford derivative **8a** in 70% yield but only 12% de. This result appeared to be promising as it indicated that alkylation was totally regioselective. We then decided to investigate the influence of the chiral auxiliary on the diastereoselectivity. In connection with our program aiming at the development of new diastereoselective reactions using chiral amino alcohols,[14] we explored the use of these readily available auxiliaries as chiral inducers in this particular reaction. The formation of oxazolines during the alkylation step prevented us from using nonprotected *O*-amino alcohols.[15] Compounds **7b**−**f** were prepared by condensation of acyl chloride **6** with the corresponding *O*-protected amino alcohols synthesized following Hu's procedure.[16]

We then examined several parameters to determine the optimal conditions for this reaction. These parameters were: the nature of lithiated bases (*n*-BuLi, *sec*-BuLi, *tert*-BuLi), the metalation and alkylation temperatures, the reaction time, the concentration of substrate **7**, and the influence of chelating agents. For this preliminary study, we decided to use *O*-benzylated amide **7b** derived from aminobutanol and methyl iodide as an electrophile. Concerning metalation temperature, we observed no reaction at −78 °C, and that the best compromise between the metalation temperature and yield was when the deprotonation process was conducted at −20 °C. For the alkylation step, selectivity fell when methyl iodide was added at a temperature higher than −78 °C. So, to summarize, the standard conditions selected for this process are as follows: metalation conditions (2.1 equiv of lithiated base, temperature: −20 °C, 1 h), alkylation conditions (1.1 equiv of methyl iodide, temperature: −78 °C, 4 h). We then turned our attention toward the influence of the concentration of **7b**. The results are collected in Table 1.

The results depicted in Table 1 clearly indicated the dramatic influence of the concentration of **7b** on diastereoisomeric excesses (from 9 to 60%). These results were probably due to the formation of aggregates during the metalation process. We could not raise the concentration above 2.3×10^{-1} mol L^{-1} for solubility problems at the alkylation temperature (−78 °C). To confirm this hypothesis, we studied the influence of chelating agents. The addition of lithium chloride had small effects on the de (51%) while the addition of HMPA led to a reduced diastereoisomeric excess (19%). Finally, we observed that the nature of the lithiated base had no influence on diastereoselectivity. We next examined the influence of the chiral auxiliary as well as the nature of the protecting groups for amino-alcohols. In addition to (*R*)-aminobutanol, two other chiral auxiliaries were tested, (*R*)-phenylglycinol and valinol. Two protecting groups were investigated: benzyl and methyl ethyl ether (effect of the introduction of one additional oxygen atom). The results obtained for the methylation (Scheme 3) of phosphines-amides **7** are collected in Table 2.

All chiral auxiliaries provided the expected products in good yield (60−70%). The use of different amino-alcohols with an identical O-protecting group (entries 2, 4, and 6; or entries 3 and 5) led to the same level of diastereoselectivity, thus clearly demonstrating that the substituent initially present on the amino-alcohol core had no real influence on the stereochemical control. Variations of the O-protecting group led to enhanced diastereoselectivities (entries 2 and 3) and the methyl ethyl ether group led to the best stereochemical control. These last results support in favor of lithiated intermediate such as **B** (Scheme 4), the lithiated intermediate **A** was the one fully characterized by Beak during the asymmetric substitution of β-phenylcarboxamides.The introduction of oxygen atoms might lead to additional chelation effects between these atoms and the lithium atom (compared with the case when α-methylbenzylamine was used) and therefore could explain the differences observed for the stereochemical control.

A range of electrophiles have been assayed in this reaction using **7c** (chiral vector: O-MEM amino-butanol) as a substrate; the formation of products **9**-**12** is summarized in Table 3. Most of these electrophilic substitutions proceeded in good yields and in moderate to good diastereoselectivities.

For the determination of the absolute configuration of the newly created chiral center, separation of the two diastereoisomers have been carried out by flash chromatography over silica gel but single crystallization was unsuccessful for X-ray analysis. However, deprotection of the major diastereoisomer of **8d** (Scheme 5) provided the known 3-(diphenylphosphino)butanoic acid **13** whose optical rotation has been given by Minami, indicating a (*S*) configuration for the created center. Moreover, its enantiomeric purity has been checked on the borane derivative **14** by chiral HPLC (See Experimental Section).

Mechanism. The diastereo-determining step for these reactions could be an asymmetric deprotonation or an asymmetric substitution. To get information concerning the mechanism involved during this reaction, we studied the results of tin−lithium exchange and the subsequent reaction of the two epimeric stannanes with electrophiles. Scheme 6 outlines the preparation, transmetalation, and electrophilic quench of these compounds. Phosphine-amide **7d** was alkylated to a separable mixture of stannanes (*S*,*R*)-**15** and (*R*,*R*)-**15** in 58% yield and 47% de. After separation of these diastereoisomeric stannanes by flash chromatography over silica gel, both

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Scheme 2

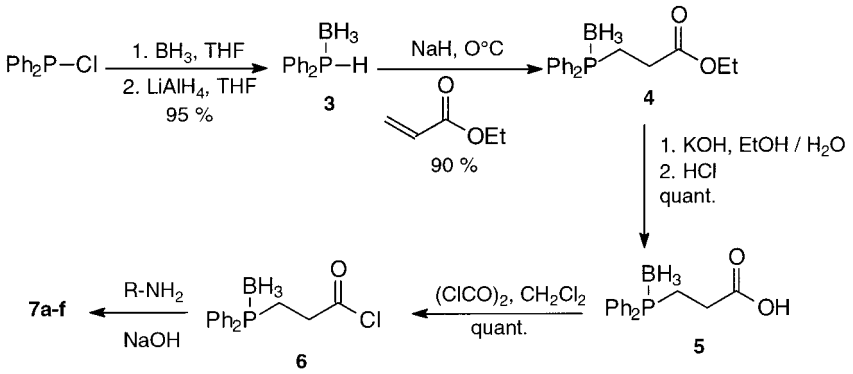
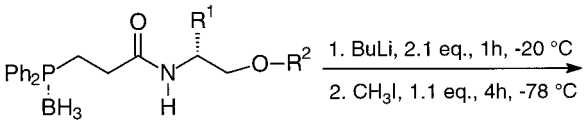


Table 1. Influence of the Concentration during the Methylation of Amide 7b

[**7b**] mol L^{-1}	**8b** de (%)[17]
5.5×10^{-2}	9
8.8×10^{-2}	34
1.66×10^{-1}	51
2.30×10^{-1}	60

Scheme 3



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R^1= C_2H_5, C_6H_5, $(CH_3)_2CH$

R^2= $CH_2C_6H_5$, $CH_2OC_2H_5$

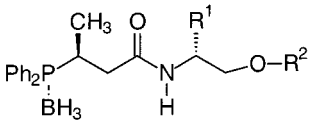

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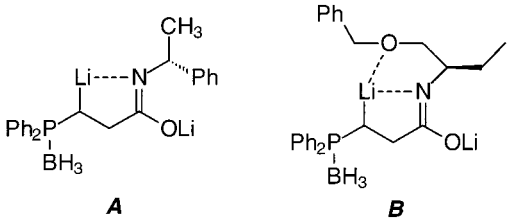
Table 2. Influence of the Chiral Inductor on the Diastereoselective Methylation (electrophile: CH_3I) of 7a–f under Optimum Reaction Conditions

entry	subtrate	R^1	R^2	product	yield[a] (%)	de[b] (%)
1	**7a**	α-methyl-benzylamine		**8a**	70	12
2	**7b**	C_2H_5	$CH_2C_6H_5$	**8b**	70	60
3	**7c**	C_2H_5	$CH_2OC_2H_5$	**8c**	65	66
4	**7d**	C_6H_5	$CH_2C_6H_5$	**8d**	67	60
5	**7e**	C_6H_5	$CH_2OC_2H_5$	**8e**	65	65
6	**7f**	$(CH_3)_2CH$	$CH_2C_6H_5$	**8f**	60	60

[a] Isolated yield. [b] Determined by ^{31}P NMR on the crude mixture of thiophosphines (see Experimental Section).

diastereoisomers were transmetalated with *n*-BuLi. Addition of MeI gave product **8d** in 60% yield with a dr of 80:20 in favor of the same major diastereoisomer. This result is the same as that obtained by the direct lithiation of **7d** (Table 2, entry 4). As far as we know, tin–lithium exchange is known to proceed with retention of configuration,[18] so these results establish that an asymmetric deprotonation is not the stereochemical-controlling step in this sequence and suggested that the substitution proceeded via rapidly equilibrating diastereoisomeric organolithium intermediates (*S*)-**16** and (*R*)-**16**. Consequently, the enantioselectivity is determined during the post-deprotonation step.

Scheme 4



A de: 12 %

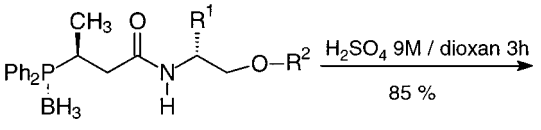
B de: 60 %

Table 3. Electrophilic Substitution of 7b with Electrophiles

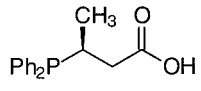
entry	electrophile	product	yield[a] (%)	de[b] (%)
1	Bu_3SnCl	**9**	60	58
2	Me_3SiCl	**10**	60	46
3	$BrCH_2CO_2Et$	**11**	79	72[c]
4	CH_2=$CHCH_2I$	**12**	85	41

[a] Isolated yield. [b] Determined by ^{31}P NMR on the crude mixture of thiophosphines (See Experimental Section). [c] Determined by ^1H NMR on the crude mixture of phosphine-boranes.

Scheme 5



8e



S-(+)**13**

$[\alpha]_D^{20}$= + 28.7 (c 1.02, $CHCl_3$)

ref. 9 $[\alpha]_D^{34}$= + 29.8 (c 0.97, $CHCl_3$)

To conclude, we have investigated a range of chiral auxiliaries for the distereoselective alkylation of phosphine-amides derived from O-protected amino-alcohols. Using this protocol, we prepared new α-substituted phosphines with different substituents and with modest to reasonable levels of diastereoselectivity. The model

(17) The diastereoisomeric excesses have been measured by three differents methods: by ^1H NMR on the methyl protons, by ^{31}P NMR on the corresponding thiophosphines (as phosphines-boranes exibited broad signals), or by mass-coupled HPLC on the diastereoisomeric phosphines-boranes. The maximum difference registered between these three analysis methods was 2%.

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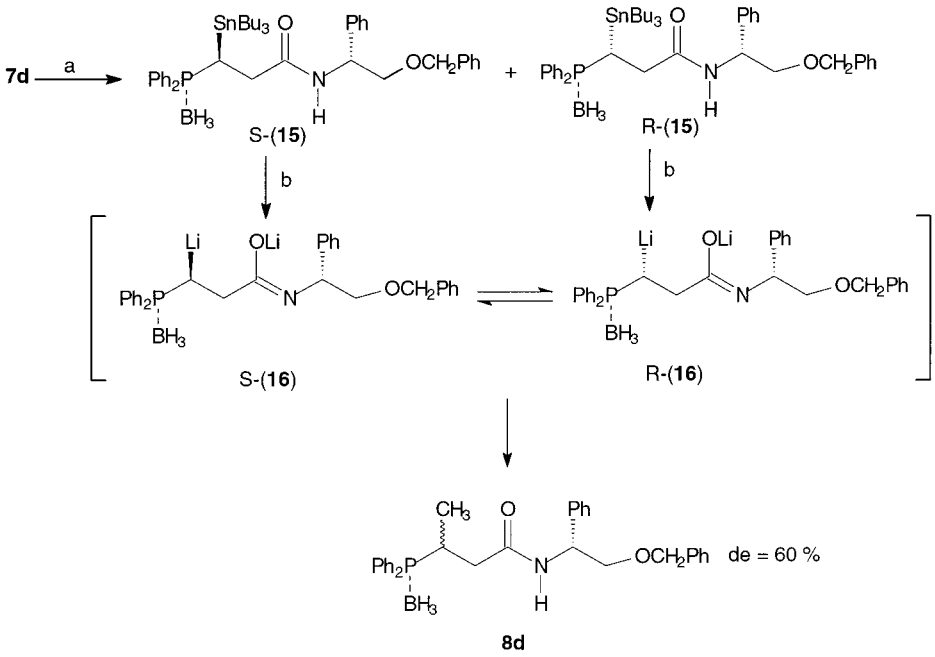
Scheme 6[a]



[a] (a) 1. *n*-BuLi, THF, −20 °C. 2. Bu_3SnCl, −78 °C. (b) 1. *n*-BuLi, THF, −20 °C. 2. CH_3I, −78 °C.

previously described by Beak cannot be used to explain our results. We demonstrated that the chiral auxiliary could be readily removed by treatment with acid to give the corresponding carboxylic acid. The latter one as well as substituted amides **8b**−**f** can be considered as potential chiral ligands and as useful intermediates for the preparation of chiral catalysts. Their synthesis is currently being investigated and will be soon disclosed.

Experimental Section

General. Solvents were purified by conventional methods prior to use. TLC was performed on Merck 60F-250 silica gel plates and column chromatography over silica gel SI 60 (230−240 mesh). Mps were taken on a Kofler apparatus and were uncorrected. Elemental analyses were carried out on a Carlo Erba EA 1100 analyzer. NMR spectra were recorded on a Bruker DXP 300 spectrometer operating at 300 MHz for proton, 75.4 MHz for carbon, and 121.5 MHz for phosphorus. This probe is equipped with pulsed-field (z) gradients. Chemical shifts (δ) are expressed in ppm relative to TMS for ^1H and ^{13}C nuclei and to H_3PO_4 for ^{31}P nuclei; coupling constants (J) are given in Hertz; coupling multiplicities are reported using conventional abbreviations.

3-Boranatodiphenylphosphino Propionic Acid (5). To an ice-cooled solution of 3.51 g (17.5 mmol) of diphenylphosphine-borane **3** in THF (50 mL) was added dropwise ethyl acrylate (1.75 g, 17.5 mmol), then sodium hydride (700 mg, 17.5 mmol) was added portionwise at 0 °C. The mixture was stirred at 0 °C for 2 h, after which water (10 mL) was added and then extracted with diethyl ether (3 × 30 mL). The organic layer was washed with brine (20 mL), dried ($MgSO_4$), and evaporated under reduced pressure. The crude product was purified by chromatography, eluting with 10% diethyl ether in cyclohexane to give the pure product **4** (4.72 g, 15.75 mmol, 90%). To this ester (4.59 g, 15 mmol) was added dropwise at room-temperature potassium hydroxide (0.94 g, 17 mmol) dissolved in a mixture of water (1 mL) and ethanol (2.5 mL). The mixture was stirred for 4 h, and then ethanol was evaporated under reduced pressure. The collected oil was redissolved in water (5 mL) and washed with diethyl ether (3 × 20 mL). The aqueous layer was first acidified until pH = 1 with hydrochloric acid 1 M, saturated with sodium chloride, and extracted with dichloromethane (3 × 20 mL). The organic layer was dried ($MgSO_4$) and evaporated under reduced pressure affording carboxylic acid **5** in quantitative yield as a white powder: mp 147 °C; ^1H NMR δ 0.5−1.2 (b, 3H), 2.5 (m, 4H), 7.4 (m, 6 H), 7.6 (m, 4H); ^{31}P NMR δ 17.4; ^{13}C NMR δ 21.3 (d, J = 39), 27 (d, J = 3), 128.6 (d, J = 57.4), 129.4 (d, J = 11), 131.9 (d, J = 2.3), 132.6 (d, J = 9.1), 174.2 (d, J = 18); IR (neat) 3037, 2924, 2342, 1711, 1437, 1263, 751 cm^{-1}. Anal. Calcd for $C_{15}H_{18}BO_2P$ (272.11): C, 66.22; H, 6.67. Found: C, 66.06; H, 6.56.

3-Boranatodiphenylphosphino Propionyl Chloride (6). To a stirred, cooled (0 °C) solution of 3-diphenylphosphino propionic acid **(5)** (1.5 g, 5.5 mmol) in dichloromethane (30 mL) was added dropwise oxalyl chloride (1.4 g, 11 mmol) under argon. The reactional mixture was stirred at room temperature for 4 h. Removal of solvent and excess of oxalyl chloride under reduced pressure (0.05 mmHg) afforded **6** in quantitative yield as a red oil: ^1H NMR δ 0.5−1.2 (b, 3H), 2.5 (m, 2H), 3 (m, 2H), 7.3 (m, 6H), 7.6 (m, 4H); ^{31}P NMR δ 16.8; ^{13}C NMR δ 21.3 (d, J = 39), 27 (d, J = 3), 128.6 (d, J = 57.4), 129.4 (d, J = 11), 131.9 (d, J = 2.3), 132.6 (d, J = 9.1), 174.2 (d, J = 18).

General Procedure for the Coupling Reaction between O-Protected Amino Alcohols (or α-methylbenzylamine) and 6. To a stirred solution of 3-diphenylphosphino propionic chloride **(6)** (1.16 g, 3.9 mmol) and O-protected amino-alcool or α-methylbenzylamine (3.9 mmol) in dichloromethane (30 mL) was added slowly, at room temperature, sodium hydroxyde (0.176 g, 4.39 mmol) dissolved in water (0.5 mL). The reaction mixture was stirred at room temperature for 4 h and then washed with water (3 × 10 mL). The organic layer was dried ($MgSO_4$) and evaporated under reduced pressure affording phosphine-amide boranes **7a**−**f**. The crude product was purified by chromatography, eluting with 20% ethyl acetate in cyclohexane to give the pure products (**7a**: 67%, **7b**: 72%, **7c**: 50%, **7d**: 67%, **7e**: 57%, **7f**: 47%) as white powders.

***(R)*-3-(Boranatodiphenylphosphino)-*N*-(1-phenylethyl)propionamide (7a):** mp 128 °C; $[\alpha]^{20}_D$ = +62.8 (*c* 1.1, $CHCl_3$); ^1H NMR δ 0.5−1.2 (b, 3H), 1.42 (d, J = 6.9, 3H), 2.4−2.45 (m, 2 H), 2.5−2.6 (m, 2H), 5 (m, 1H), 5.9 (d, J = 7.6, 1H), 7.2−73 (m, 5H), 7.35−7.5 (m, 6H), 7.6−7.8 (m, 4H); ^{31}P NMR δ 17.1; ^{13}C NMR δ 21.4 (d, J = 39.6), 22.1, 30.2 (d, J = 2.1), 49.5, 126.5, 127.8, 128.7 (d, J = 55.4), 129.1, 129.3 (d, J = 10.3), 131.8 (d, J = 2), 132.5 (d, J = 9.2), 170.4 (d, J = 14.9);

IR (neat) 3270, 2968, 2393, 1644, 1541, 1435, 1108, 736 cm^{-1}. Anal. Calcd for $C_{23}H_{27}$ BNOP (375.26): C, 73.62; H, 7.25; N, 3.73. Found: C, 75.53; H, 7.23; N, 3.63.

(*R*)-3-(Boranatodiphenylphosphino)-*N*-(1-benzyloxymethylpropyl)propionamide (7b): ^{1}H NMR δ 0.5−1.2 (b, 3H), 0.77 (t, J = 7.4, 3H), 1.3−1.6 (m, 2H), 2.2−2.35 (m, 2H), 2.45−2.6 (m, 2H), 3.3 (dd, J = 3.8, J = 9.5, 1H), 3.4 (dd, J = 3.8, J = 9.5, 1H), 3.85 (m, 1H), 4.37 (d, J = 12, 1H), 4.42 (d, J = 12, 1H), 5.58 (d, J = 8.7, 1H), 7.14−7.3 (m, 5H), 7.32−7.46 (m, 6H), 7.54−7.68 (m, 4H); ^{31}P NMR δ 16.73; ^{13}C NMR δ 10.2, 21.5 (d, J = 39.6), 25.1, 30.2 (d, J = 2.3), 51, 71.1, 73.6, 128.2, 129.5 (d, J = 56.3), 128.8, 129.3 (d, J = 10.3), 129.5 (d, J = 2.3), 131.8 (d, J = 2.9), 132.5 (d, J = 9.2), 138.4, 170.9 (d, J = 15.5); IR (neat) 3248, 2931, 2374, 1632, 1551, 1435, 1110, 739 cm^{-1}.

(*R*)-3-(Boranatodiphenylphosphino)-*N*-(1-ethoxymethoxymethylpropyl)propionamide (7c): ^{1}H NMR δ 0.5−1.2 (b, 3H), 0.81 (t, J = 7.4, 3H), 1.12 (t, J = 7.2, 3H), 1.35−1.55 (m, 2H), 2.17−2.4 (m, 2H), 2.45−2.6 (m, 2H), 3.35 (dd, J = 3.8, J = 9.7, 1H), 3.45−3.6 (m, 3H), 3.77−3.9 (m, 1H), 4.56 (s, 2H), 5.67 (d, J = 8.7, 1H), 7.3−7.48 (m, 6H), 7.53−7.7 (m, 4H); ^{31}P NMR δ 16.73; ^{13}C NMR δ 8.4, 13.1, 19.1 (d, J = 39.7), 22.6, 30.2, 48.5, 61.4, 66.8, 93.4, 129.2 (d, J = 55.8), 129.4 (d, J = 10.3), 131.8 (d, J = 2.3), 132.55 (d, J = 9.2), 168.4 (d, J = 15.5); IR (neat) 3299, 2968, 2382, 1648, 1542, 1437, 1110, 738 cm^{-1}.

(*R*)-3-(boranatodiphenylphosphino)-*N*-(2-benzyloxy-1phenylethyl)propionamide (7d): mp 100 °C; $[\alpha]^{20}_D$ = −36.3 (*c* 1.0, $CHCl_3$); ^{1}H NMR δ 0.5−1.2 (b, 3H), 2.3−2.45 (m, 2H), 2.5−2.6 (m, 2H), 3.6 (dd, J = 5.2, J = 11.7, 1H), 3.67 (dd, J = 5.2, J = 11.7, 1H), 4.47 (s, 2H), 5−5.2 (m, 1H), 6.2 (d, J = 7.7, 1H), 7.15−7.3 (m, 10H), 7.37−7.52 (m, 6H), 7.60−7.74 (m, 4H); ^{31}P NMR δ 16.7; ^{13}C NMR δ 21.4 (d, J = 39.6), 30.1, 53.5, 72.7, 73.6, 127.3, 127.8, 128.3, 128.6 (d, J = 55.9), 128.9, 129.4 (d, J = 10.2), 129.6, 131.8 (d, J = 2), 132.5 (d, J = 9.4), 138.1, 140.1, 171 (d, J = 15.7); IR (neat) 3294, 2856, 2378, 1647, 1546, 1436, 1127, 736 cm^{-1}. Anal. Calcd for $C_{30}H_{33}$ BNO_2P (481.42): C, 74.85; H, 6.91; N, 2.91. Found: C, 74.98; H, 7.04; N, 2.86.

(*R*)-3-(Boranatodiphenylphosphino)-*N*-(2-ethoxymethoxy-1-phenylethyl)propionamide (7e): mp 62 °C; $[\alpha]^{20}_D$ = −41.1 (*c* 0.97, $CHCl_3$); ^{1}H NMR δ 0.5−1.2 (b, 3H), 1.12 (t, J = 7, 3H), 2.36−2.5 (m, 2H), 2.5−2.67 (m, 2H), 3.34−3.5 (m, 2H), 3.72 (dd, J = 4.7, J = 10.2, 1H), 3.78 (dd, J = 4.7, J = 10.2, 1H), 4.58 (d, J = 6.7, 1H), 4.62 (d, J = 6.7, 1H), 5.0−5.1 (m, 1H), 6.3 (d, J = 7.4, 1H), 7.15−7.3 (m, 6H), 7.37−7.52 (m, 5H), 7.60−7.74 (m, 4H); ^{31}P NMR δ 16.6; ^{13}C NMR δ 15.4, 21.4 (d, J = 39.7), 30.1, 53.4, 64, 70.8, 95.7, 127.1, 127.9, 128.3 (d, J = 56.3), 128.9, 129.3 (d, J = 9.8), 131.8 (d, J = 2.3), 132.5 (d, J = 9.2), 139.9, 170.8 (d, J = 15.5). Anal. Calcd for $C_{26}H_{33}$ BNO_3P (449.37): C, 69.5; H, 7.4; N, 3.12. Found: C, 69.76; H, 7.39; N, 2.99.

3-(Boranatodiphenylphosphino)-*N*-(1-benzyloxy-2-methylpropyl)propionamide (7f): mp 80 °C; ^{1}H NMR δ 0.5−1.2 (b, 3H), 0.78 (d, J = 6.8, 3H), 0.80 (d, J = 6.8, 3H), 1.78 (oct, J = 6.8, 1H), 2.2−2.3 (m, 2H), 2.4−2.6 (m, 2H), 3.27 (dd, J = 3.8, J = 9.8, 1H), 3.45 (dd, J = 3.8, J = 9.8, 1H), 3.6−3.8 (m, 1H), 4.35 (d, J = 12.1, 1H), 4.4 (d, J = 12.1, 1H), 5.65 (d, J = 7.7, 1H), 7.15−7.3 (m, 10H), 7.37−7.52 (m, 6H), 7.60−7.74 (m, 4H); ^{31}P NMR δ 16.9; ^{13}C NMR δ 19.5, 19.9, 21.5 (d, J = 39.8), 29.8, 30.2 (d, J = 2.3), 54.8, 70.2, 73.6, 128.2, 128.3, 128.6 (d, J = 57.4), 129.4 (d, J = 10.2), 129.5, 131.8 (d, J = 2.9), 132.6 (d, J = 9.4), 138.4, 170.5 (d, J = 15.5); IR (neat) 3434, 2961, 2380, 1647, 1542, 1436, 1109, 738 cm^{-1}. Anal. Calcd for $C_{27}H_{35}$ BNO_2P (447.40): C, 72.49; H, 7.89; N, 3.13. Found: C, 72.59; H, 8.07; N, 3.06.

General Procedure for the Alkylation of Phosphine-Amide Boranes 7. To a stirred, cooled (−20 °C) solution of secondary phosphine-amide boranes **7** (201 μmol) in THF (870 μmol, [**7**] = 2.3 10^{-1} mol L^{-1}) was slowly added *n*-BuLi (429 μmol, 330 μL of a 1.3 M hexane solution). The reaction mixture was stirred at this temperature for 1 h and then cooled to − 78 °C. The alkylating agent (221 μmol) was then added, the mixture was stirred at − 78 °C for 4 h, and then water was added (2 mL). The organic layer was separated, and the aqueous phase was extacted with dichloromethane (3 × 3 mL). The combined organic phases were dried ($MgSO_4$) and evaporated under reduced pressure. The crude product was directly analyzed by ^{1}H NMR, ^{31}P NMR, and mass-coupled HPLC. A pure mixture of diastereoisomers was obtained by chromatography on silica gel preparative plates (cyclohexane/ethyl acetate, 6:4).

(*S*,*R*)-3-(Boranatodiphenylphosphino)-*N*-(2-benzyloxy-1-phenylethyl)butanamide (8d): pale yellow powder; mp 70 °C; $[\alpha]^{20}_D$ = −18.9 (*c* 1.1, $CHCl_3$); ^{1}H NMR δ 0.5−1.2 (b, 3H), 1.05 (dd, J = 6.9, J = 16.2, 3H), 2.1−2.2 (m, 1H), 2.25−2.4 (m, 1H), 3.1−3.3 (m, 1H), 3.6 (dd, J = 5.2, J = 11.7, 1H), 3.67 (dd, J = 5.2, J = 11.7, 1H), 4.4 (s, 2H), 5−5.2 (m, 1H), 6.1 (d, J = 7.7, 1H), 7.15−7.3 (m, 10H), 7.37−7.52 (m, 6H), 7.60−7.74 (m, 4H); ^{31}P NMR δ 24.6; ^{13}C NMR δ 14.3 (d, J = 2.6), 25.5 (d, J = 39.6), 38.8 (d, J = 5), 53.5, 72.7, 73.6, 127.3, 127.8, 128.3, 128.6 (d, J = 55.9), 128.9, 129.4 (d, J = 10.2), 129.6, 131.8 (d, J = 2), 132.5 (d, J = 9.4), 138.1, 140.1, 170.5 (d, J = 16.5); IR (neat) 3300, 2858, 2381, 1645, 1546, 1437, 1125, 737 cm^{-1}; Anal. Calcd for $C_{31}H_{35}BNO_2P$ (495.44): C, 75.16; H, 7.12; N, 2.83. Found: C, 75.13; H, 7.26; N, 2.88. Diastereoisomeric excess determination: HPLC, ODS Inertsil 250 mm × 4.6 × 5 μm, 0.8 mL/min, 10% water/methanol, (*R*,*R*) t_1 = 53.9 min; (*S*,*R*) t_1 = 56.7 min.

General Procedure for the Conversion of 8a−f and 9−12 to Their Corresponding Thiophosphines. A solution of **8a−f** or **9−12** (100 mg) in diethylamine (3 mL) was heated under argon at 40 °C for 8 h. Diethylamine was evaporated under reduced pressure providing crude phosphines. THF (5 mL) was added to the crude phosphine. The solution was cooled to 0 °C, and elemental sulfur (40 mg) was added. The reaction mixture was stirred at 0 °C for 2 h. The solvent was removed under reduced pressure, and the crude thiophosphines were directly analyzed by ^{31}P NMR.

Thiophosphine of **8a:** ^{31}P NMR δ 53.87 (major), 53.85 (minor). Thiophosphine of **8b**: ^{31}P NMR δ 53.79 (major), 53.72 (minor). Thiophosphine of **8c**: ^{31}P NMR δ 53.76 (major), 53.71 (minor). Thiophosphine of **8d**: ^{31}P NMR δ 53.76 (major), 53.67 (minor). Thiophosphine of **8e**: ^{31}P NMR δ 53.76 (major), 53.68 (minor). Thiophosphine of **8f**: ^{31}P NMR δ 53.82 (major), 53.73 (minor). Thiophosphine of **9**: ^{31}P NMR δ 51.11 (major), 51.09 (minor). Thiophosphine of **10**: ^{31}P NMR δ 50.33 (major), 50.27 (minor). Thiophosphine of **11**: ^{31}P NMR δ 54.25 (major + minor), de measured by ^{1}H NMR. Thiophosphine of **12**: ^{31}P NMR δ 53.39 (major), 53.45 (minor).

(*S*)-3-Diphenylphosphino Butanoic Acid (13). A suspension of **8d** (1.5 g, 3.02 mmol**)** in a mixture of sulfuric acid 9 M (45 mL) and dioxane (30 mL) (the solvent mixture was degassed by three freeze−thaw cycles prior to use) was heated at 100 °C for 3 h. The reaction mixture was then cooled to room temperature. Degassed sodium hydroxide 15 M (50 mL) was added, and the aqueous phase was extracted with degassed dichloromethane (2 × 25 mL). The organic phases were dried ($MgSO_4$) and evaporated under reduced pressure giving **13** (0.7 g, 2.57 mmol, 80%). $[\alpha]^{20}_D$ = +28.7 (*c* 1, $CHCl_3$); ^{1}H NMR δ 1.1 (dd, J = 14.8, J = 6.9, 3H), 2.2 (ddd, J = 16.4, J = 11, J = 5.6, 1H), 2.5 (ddd, J = 16.4, J = 11, J = 5.6, 1H), 2.8−3.0 (m, 1H), 7.2−7.4 (m, 6 H), 7.45−7.6 (m, 4H); ^{31}P NMR δ −0.275; ^{13}C NMR δ 17.2 (d, J = 16.6), 27.3 (d, J = 10.3), 38.6 (d, J = 19.5), 128.9 (d, J = 6.9), 129 (d, J = 7.5), 129.5, 129.6, 133.9 (d, J = 19.5), 134 (d, J = 18.9), 136.4 (d, J = 14), 136.5 (d, J = 13.8), 179.5 (d, J = 16.1). Phenylglycinol can be recovered by the following procedure: To the previous aqueous phase was added sodium hydroxide 15 M (2 mL), and then it was extracted with dichloromethane (3 × 25 mL). The organic phases were dried ($MgSO_4$) and evaporated under reduced pressure giving phenylglycinol in 80% yield.

(*S*)-3-Boranatodiphenylphosphino Butanoic Acid (14). To 1.5 g of **13** was slowly added, at 0°C, 3.1 mL of 1 M borane−THF complex solution. The solution was stirred at this temperature for 30 min. Water was then added to the solution (3 mL) and extracted with dichloromethane (3 × 5 mL). The combined organic phases were dried ($MgSO_4$) and evaporated under reduced pressure to afford **14**. The crude product was purified by chromatography, eluting with 20% ethyl acetate in cyclohexane to give **14** as a white powder in a quantitative

yield. Mp: 120 °C; $[\alpha]^{20}_D = +34$ (*c* 1, $CHCl_3$); ^{1}H NMR δ 0.5−1.1 (b, 3H), 1.2 (dd, *J* = 16.1, *J* = 6.9, 3H), 2.4−2.65 (m, 2H), 3−3.3 (m, 1H), 7.2−7.4 (m, 6 H), 7.45−7.6 (m, 4H); ^{31}P NMR δ 25.2; ^{13}C NMR δ 14.7 (d, *J* = 17.3), 25.5 (d, *J* = 38.5), 35.9 (d, *J* = 5.2), 127.9 (d, *J* = 54.5), 128 (d, *J* = 53.4), 129.3 (d, *J* = 9.2), 129.6 (d, *J* = 9.8), 131.9 (d, *J* = 3.4), 132 (d, *J* = 2.3), 132.9 (d, *J* = 8.6), 133 (d, *J* = 8.6), 178.2 (d, *J* = 17.8). Anal. Calcd for $C_{16}H_{20}BO_2P$ (286.12): C, 67.17; H, 7.05. Found: C, 67.31; H, 7.16. HPLC Daicel Chiralcel OJ, 1 mL/min, 4% 2-PrOH/hexane + 0.5 mL formic acid, (*S*) $t_2 = 25.5$ min (for a mixture of enantiomers, (*R*) $t_1 = 22.1$ min; (*S*) $t_2 = 25.5$ min).

(*S*,*R*)-3-(Boranatodiphenylphosphino)-3-tributylstannyl-*N*-(2-benzyloxy-1-phenylethyl)propionamide (15): white oil; $R_f = 0.21$ (cyclohexane/ethyl acetate 9:1); $[\alpha]^{20}_D = -15.4$ (*c* 1, $CHCl_3$); ^{1}H NMR δ 0.4−0.8 (m, 6H), 0.5−1.4 (b, 3H), 0.7 (t, *J* = 7.2, 9H), 0.95−1.3 (m, 12H), 2.4−2.65 (m, 2H), 2.7−2.85 (m, 1H), 3.4 (dd, *J* = 4.8, *J* = 9.7, 1H), 3.5 (dd, *J* = 4.8, *J* = 9.7, 1H), 4.4 (s, 2H), 4.9 (m, 1H), 5.9 (d, *J* = 7.7, 1H), 7.1−7.4 (m, 16H), 7.7−7.9 (m, 4H). ^{31}P NMR δ 21.2; ^{13}C NMR δ 11.8, 13.1 (d, *J* = 24.7), 14, 27.7, 29.2, 34.2, 53.3, 72.4, 73.4, 127.3−129.1, 130.9−132.4, 137.9, 140.1, 171 (d, *J* = 14.3); IR (neat) 3366, 2954, 2921, 2869, 2383, 1674, 1495, 1106, 736, 697 cm^{-1}.

(*R*,*R*)-3-(Boranatodiphenylphosphino)-3-tributylstannyl-*N*-(2-benzyloxy-1-phenylethyl)propionamide (15): white oil; $R_f = 0.31$ (cyclohexane/ethyl acetate 9:1); $[\alpha]^{20}_D = -33.1$ (*c* 1, $CHCl_3$); ^{1}H NMR δ 0.4−0.8 (m, 6H), 0.5−1.4 (b, 3H), 0.75 (t, *J* = 7.2, 9H), 0.95−1.3 (m, 12H), 2.35−2.8 (m, 3H), 3.55−3.65 (m, 2H), 4.35 (d, *J* = 15.6, 1H), 4.4 (d, *J* = 15.6, 1H), 4.9 (m, 1H), 9 (d, *J* = 7.7, 1H), 7.1−7.4 (m, 16H), 7.7−7.9 (m, 4H); ^{31}P NMR δ 21.4; ^{13}C NMR δ 10.4, 11.7 (d, *J* = 24.3), 12.6, 26.3, 27.9, 34.1, 53.2, 72.5, 73.4, 127.1−129, 130.8−132.1, 137.8, 139.9, 171 (d, *J* = 15.4).

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