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Tetrahedron: *Asymmetry* 14 (2003) 1637–1644

TETRAHEDRON: *ASYMMETRY*

Diastereoselective synthesis of chiral non-racemic 2-substituted 2-boranatophosphino ethanoic acid: a potential intermediate to chiral ligands for asymmetric catalysis

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Received 20 February 2003; revised 21 March 2003; accepted 1 April 2003

Abstract—Chiral α-amidophosphine boranes **7a**–**b** can be diastereoselectively alkylated, using a phenylglycinol derivative as a chiral inducer, to furnish α-substituted α-amidophosphine boranes **8**–**12** with up to 99% diastereoisomeric excess. Selective reduction of the amidophosphine boranes afforded optically pure β-boranatophosphine-alcohol **13**. The latter one can then be oxidized in boronatophosphine acid **14**. © 2003 Elsevier Science Ltd. All rights reserved.

1. Introduction

During the past three decades, numerous potential chiral ligands[1] have been synthesized and some of them shown to be excellent ligands (for example DIPAMP,[2] DIOP,[3] BINAP,[4] PennPHOS[5] and DuPHOS[6]) and have been developed for a variety of catalytic reactions. However, all the phosphorus containing ligands employed in asymmetric catalysis[1] can be classified into two types depending on the location of the stereogenic information, which may be found on the phosphorus atom (DIPAMP) or on a side chain. For the latter case, the stereogenicity can be carbon centered (VALAP,[7] CHIRAPHOS[8]) or of axial type (BINAP).

When the stereogenicity is carbon centered, most of the ligands in frequent use are derived from amino acids or from the chiral pool,[9] which limits their structural diversity. To the best of our knowledge, very few of them were obtained by creation of a stereogenic center. In those rare examples, their syntheses are based or on racemic starting materials, and need a resolution[10] or are based on an enantioselective synthesis.[11]

The development of new asymmetric phosphine ligands is of great interest. Since the phosphorus atom is directly associated with the transition metal in the catalytic species, the creation of a stereogenic center at the neighboring α-position should enhance facial discrimination and thus lead to an improved level of enantioselectivity. In previous papers, we described diastereoselective alkylation[12] and diastereoselective Michael addition[13] processes to access chiral α-substituted β-amidophosphines **1**, key intermediates for the synthesis of chiral ligands via acid **2** (Scheme 1).

From this acid, a broad range of chiral phosphine–amines **3** were prepared and their application in the field of enantioselective hydrogen-transfer with ruthenium catalysts was assayed.[14] Preliminary experiments gave very encouraging results with more than 82% ee when R = Me in the reduction of aromatic ketones. Following the model of Noyori[15] with our ligands, the phosphorus and the nitrogen atoms would form a six-membered ring with the metal. In order to complete our study and investigate the influence of the ring size, we turned our attention to a general access to chiral β-aminophosphines. In this paper, we wish to report the first general synthesis of the chiral non racemic easily tunable 2-substituted-2-boranatophosphino ethanoic acid, via the diastereoselective alkylation of boronato-α-amidophosphines. Indeed, this key intermediate should give us access to various types of ligands (phosphine–amine, phosphine–amide, phosphine–oxazoline, phosphine–aminophosphine, phosphine–phosphinite…), after simple transformation and removal of borane protection (DABCO, 40°C in toluene).[12]

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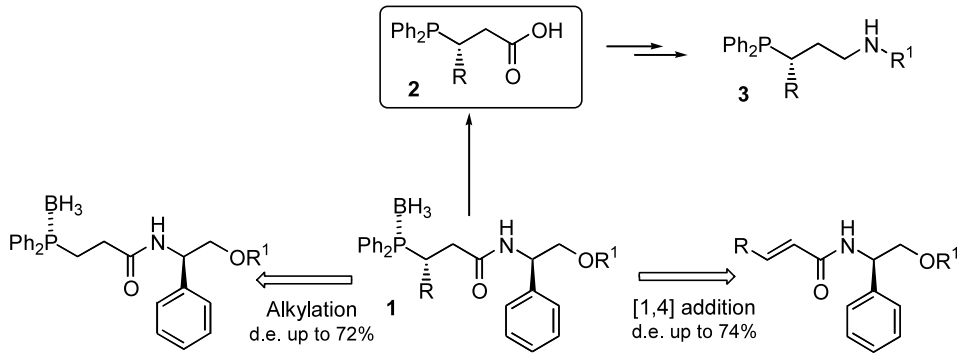
doi:10.1016/S0957-4166(03)00287-8



Scheme 1.

2. Results and discussion

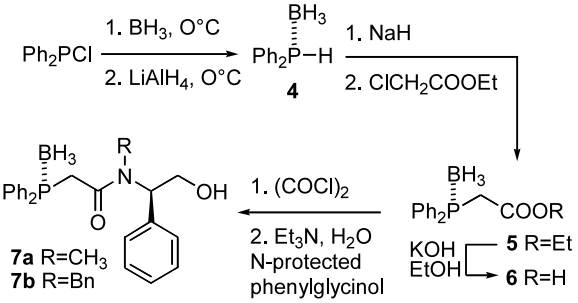
In the course of our study on the diastereoselective functionalization of amides using phenylglycinol as a chiral auxiliary, we described the alkylation of *N*-protected amides with de's higher than 97%.[16] Therefore, to create the asymmetric center α to the phosphorus atom, we decided to apply this methodology to the synthesis of chiral boronato-α-substituted α-amidophosphines.

The starting α-amidophosphines **7** were synthesized in five steps from chlorodiphenylphosphine (Scheme 2): this was protected as its borane derivative and reduced with lithium aluminum hydride to afford hydrogenophosphine borane **4** in 95% yield.[17] Condensation of **4** with ethyl chloroacetate, followed by saponification yielded the acid **6** in 82% yield. Finally the amides **7a**,**b** were obtained by reaction of the acyl chloride of **6** with the corresponding *N*-protected phenylglycinol[18] under standard conditions. For *N*-benzylated phenylglycinol, we observed ester formation as a side reaction, even if intramolecular O→N acyl transfer is predominant and *N*-acyl form is strongly favored under basic conditions.[19]

In a first attempt, compound **7a**[20] was subjected to the conditions already optimized for the diastereoselective alkylation of amide enolates[21] (i.e. formation of the enolate with *s*-BuLi at –20°C and at concentrations above 0.085 mmol mL^{-1}, followed by the addition of the electrophile at –78°C) but using this procedure, no alkylated product was observed. Different temperatures for the addition of the electrophile were then tried. The reaction occurred only at –40°C, yielding compound **8a** in 80% de (Table 1, entry 1).

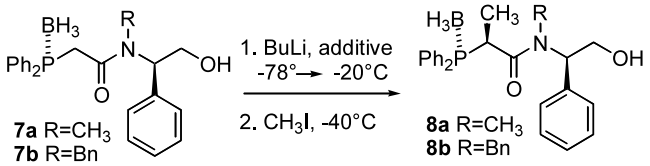
Next, we decided to investigate the influence of the base, the temperature and the presence of additives in the methylation reaction. We only tried lithiated bases, as the lithium ion proved to be the best counter ion for the chemioselectivity (*C*- or *O*-alkylation) and diastereoselectivity (formation of the alcoholate is required).[21] The best results for the alkylation step were obtained at –40°C using *n*-BuLi as base instead of *s*-BuLi. Lower temperatures gave no alkylation product and higher temperatures, lower de's. Addition of chelating agents (HMPA, LiBr, LiCl) surprisingly increased the diastereoisomeric excesses (Table 1, entries 2–4). The conversion rate was always good to excellent after 4 h reaction and the best de (>98%) was obtained using LiCl and LiBr as additive (Table 1, entry 4). Indeed lithium salts are well known to accelerate the alkylation rate which is effectively the case in our study. The role of LiCl on the diastereoselectivity is less well documented but Seebach[22] has proposed that it may modify the aggregation state. For *N*-benzylamide **7b**, LiCl also has a beneficial effect and the de increased to 97% (Table 1, entry 5). The conversion rate was good, but needed more than 6 h to be complete. By increasing the reaction temperature to –20°C, the conversion rate was 99% in less than 2 h, but the de slightly decreased to 93% (Table 1, entry 6). So, to summarize, the standard conditions selected for this process were: metallation conditions, 2.5 equiv. of *n*-butyllithium, 6 equiv. of LiCl, temperature: –20°C, 2 h, and alkylation conditions 3 equiv. of methyl iodide, temperature: –40°C, 4–6 h.

We then turned our attention to the influence of the chiral auxiliary. First, pseudoephedrine, which is known to be an efficient chiral inductor,[19] was tested, but as already observed in our group,[12] introduction of a substituent α to the oxygen atom of the aminoalcohol decreased the diastereoselectivity. When (*S*)-4-benzyl-2-oxazolidinone auxiliary of Evans[23] was used as the chiral auxiliary, no alkylated product could be observed, whatever the conditions.



Scheme 2.

Table 1. Influence of the additive on the diastereoselective alkylation



Entry	R	Additive	Conversion rate[a] (%)	De[a] (%)	Product
1	Me	/	98	80	**8a**
2	Me	HMPA	93	97	**8a**
3	Me	LiBr	87	>98	**8a**
4	Me	LiCl	96	>98	**8a**
5	Bn	LiCl	90	97	**8b**
6	Bn	LiCl[b]	99	93	**8b**

[a] Determined by HPLC.
[b] Addition of MeI at –20°C.

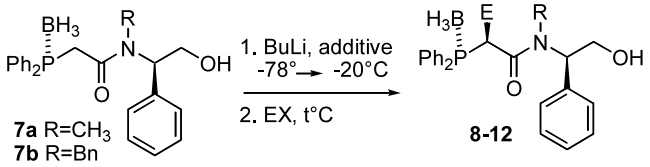
To evaluate the scope of the reaction, a range of electrophiles have been assayed in this reaction using **7a**,**b** (chiral vector: *N*-methyl and *N*-benzylphenylglycinol respectively) as substrates; the formation of products **8**–**12** is summarized in Table 2. The electrophilic substitutions proceeded in good yields and in low to excellent diastereoselectivities depending on the size and of the reactivity of the electrophile.

The results depicted in Table 2 clearly indicate the dramatic influence of the electrophile on diastereoisomeric excesses. Two factors seem to be crucial for the diastereoselectivity: the reactivity and the steric hindrance of the electrophile. Indeed using iodide instead of bromide allowed the reaction to take place at lower temperature and so a better de was observed (Table 2, entries 2, 3, 6 and 7). The same result was obtained with the reactive methyliodide, where the substitution can occur at –40°C and so the de can reach more than 98% (Table 2, entry 1). Steric hindrance also plays an important role as shown in entries 5 and 7 where the de dropped from 91 to 20% with allyl and metallyliodide as electrophiles, respectively. Concerning the nature of the group on the nitrogen atom, *N*-Me afforded slightly better diastereoisomeric excesses than *N*-benzyl confirming the results already obtained in amide alkylation[16] (Table 2, entries 1, 8). It is also to be noted that benzyl protection on nitrogen atom increased the proportion of *O*-alkylation, especially when benzyl bromide was used as electrophile. Indeed in the latter case, only the dialkylated product could be observed. Nevertheless at that stage, whatever the substituents are, the diastereoisomers can be easily separated by simple chromatography on silica gel, affording optically pure α-substituted-α-amidophosphine borane.

X-Ray analysis[24] of the major diastereoisomer of **11** has allowed unambiguous assignment of the (*S*)-configuration to the newly created stereogenic center (Fig. 1).

To explain the diastereoselectivity, a model including a chelating intermediate has been proposed (Scheme 3).[21]

Table 2. Influence of the electrophile



Entry	R	EX	Conversion rate[a] (%)	Yield[a] (%)	t (°C)	Time (h)	De[b] (%)	Product
1	Me	MeI	95	90	–40	4	>98	**8a**
2	Me	BnBr	100	60	rt	24	38	**9**
3	Me	BnI	71	55	0	5	45	**9**
4	Me	$BrCH_2CO_2t$-Bu	77	55	rt	24	77	**10**
5	Me	CH_2=$CHCH_2I$	100	87	0	2	91	**11**
6	Me	CH_2=$C(CH_3)CH_2Br$	55	32	rt	48	15	**12**
7	Me	CH_2=$C(CH_3)CH_2I$	62	51	0	5	20	**12**
8	Bn	MeI	90	80	–40	6	>98	**8b**

[a] Isolated yield.
[b] Determined by HPLC.

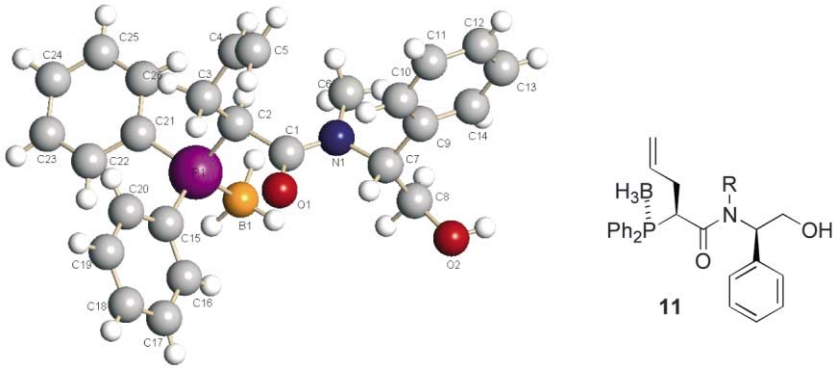
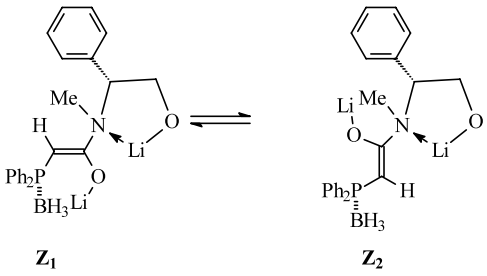


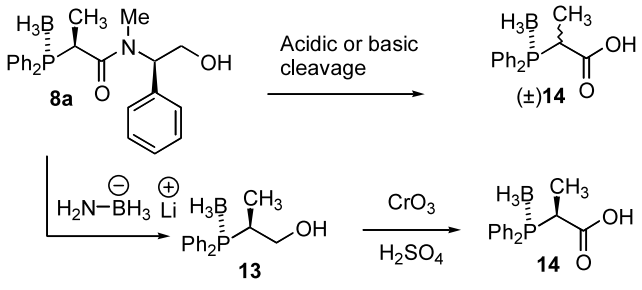
Figure 1. X-Ray structure of the major diastereoisomer of **11**.



Scheme 3.

Indeed Evans has proved that enolates generally adopt a *Z* configuration,[25] and it is also well accepted that $A^{1,3}$ allylic strain favors intermediate *Z*-1 compared to *Z*-2.[26] An approach of the electrophile from the topside of the enolate *Z*-1 (*anti* to the N–Li bond) is in agreement with the observed configuration of the newly created stereogenic center.

As a final step, we studied the removal of the chiral auxiliary as previously depicted.[21] Unfortunately, whatever the conditions were, acid or basic, removal of the chiral auxiliary always led to complete epimerization of the stereogenic center α to the phosphorus atom (Scheme 4). Indeed amide cleavage under acidic or basic conditions needs high temperature, which is not compatible with a stereogenic center α to phosphine and to C=O functional groups.[27,28] To circumvent this epimerization, the enantiomerically pure acid **14** was prepared by a two-step procedure: reduction to the alcohol **13** with lithium amide borane complex,[19] followed by an oxidation at room temperature with chromic acid afforded pure acid **14** ($[\alpha]_D^{20} = +39.0$) without epimerization as confirmed by chiral HPLC studies.



Scheme 4.

To conclude, we have developed a new and general method to introduce, with good to excellent diastereoselectivity, a substituent α to the phosphorus atom of a phosphine. After reduction of the amidophosphine borane, we obtained enantiomerically pure β-boranatophosphine alcohol **13** which can be oxidized in boronatophosphine acid **14**. To the best of our knowledge, this result constitutes the first stereoselective synthesis of such compounds. Phosphine derivatives **13** and **14** can be considered as sources of potential chiral ligands and as useful intermediates for the preparation of chiral catalysts. Their synthesis is currently being investigated.

3. Experimental

3.1. General

Optical rotations were measured using a sodium lamp at ambient temperature and are reported as follows: $[\alpha]_\lambda$ (*c* g/100 mL) with the units of degree g cm^{-3}. IR spectra were recorded using KBr pellets or NaCl plates, and only partial data are reported. NMR spectra were recorded on a Bruker DX 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. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constants (Hz), integration.

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). Mp's were taken on a Kofler apparatus and were uncorrected. Elemental analyses were carried out on a Carlo Erba EA 1100 analyzer.

3.2. 2-Boranatodiphenylphosphino ethyl acetate 5

To an ice-cooled solution of sodium hydride (1.60 g, 65.5 mmol) in THF (30 mL) was added via cannula a solution of diphenylphosphine–borane **4** (5.00 g, 25.0 mmol) and ethyl chloroacetate (3.98 g, 32.5 mmol) in THF (50 mL). The solution was stirred at rt for 2 h, then excess hydride was quenched by the careful addition of 1N aqueous hydrochloric acid solution (20 mL). The mixture was extracted with ethyl acetate (3×30 mL) and the combined organic extracts were dried over magnesium sulfate and concentrated. Purification of the residue by flash column chromatography (cyclohexane/EtOAc, 80:20) afforded ester **5** as a colorless oil (6.17 g, 86%): $R_f = 0.40$ (cyclohexane/EtOAc 70:30). ^{31}P NMR (121.5 MHz, $CDCl_3$): δ 17.79 (d, $J = 57.6$ Hz). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.50–1.42 (br, 3H), 1.04 (t, $J = 7.2$ Hz, 3H), 3.22 (d, $J = 10.7$ Hz, 2H), 3.97 (d, $J = 7.2$ Hz, 2H), 7.43–7.53 (m, 6H), 7.70–7.77 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.8, 33.9 (d, $J = 29.3$ Hz), 61.5, 128.0 (d, $J = 55.7$ Hz), 128.8 (d, $J = 10.3$ Hz), 131.6 (d, $J = 2.9$ Hz), 132.5 (d, $J = 9.8$ Hz), 166.8 (d, $J = 4.0$ Hz). IR (neat): 2983, 2388, 1732, 1266, 1116, 1061, 738, 693 cm^{-1}. Anal. calcd for $C_{16}H_{20}BO_2P$: C, 67.17; H, 7.05. Found: C, 66.87; H, 6.68.

3.3. 2-Boranatodiphenylphosphino ethanoic acid 6

Potassium hydroxide (216.0 mg, 3.80 mmol) dissolved in a mixture of water (250 μL) and ethanol (1 mL) was added dropwise at 0°C to the ester **5** (1.00 g, 3.50 mmol). The mixture was stirred for 2 h at rt, and the ethanol was evaporated under reduced pressure. The collected oil was dissolved in water (3 mL), washed with diethyl ether (3×5 mL). The aqueous layer was first acidified until pH 1, with hydrochloric acid 1 M, saturated with sodium chloride, and extracted with dichloromethane (3×10 mL). The organic layer was dried ($MgSO_4$) and evaporated under reduced pressure affording carboxylic acid **6** (0.9 g) in 99% yield as a white powder: mp 141°C; ^{31}P NMR (121.5 MHz, $CDCl_3$): δ 17.77 (d, $J = 48.2$ Hz). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.20–1.60 (br, 3H), 3.11 (d, $J = 6.6$ Hz, 2H), 7.21–7.32 (m, 6H), 7.44–7.52 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 34.1 (d, $J = 28.2$ Hz), 127.9 (d, $J = 56.3$ Hz), 129.3 (d, $J = 10.9$ Hz), 132.1 (d, $J = 2.3$ Hz), 132.8 (d, $J = 9.8$ Hz), 172.4. IR (neat): 2978, 2663, 2570, 2402, 2361, 1703, 1436, 1303, 1141, 1103, 1060, 739, 692 cm^{-1}. Anal. calcd for $C_{14}H_{16}BO_2P$: C, 65.16; H, 6.25. Found: C, 65.19; H, 6.48.

3.4. General procedure for the coupling reaction between *N*-alkylated amino alcohols and 6

To a stirred ice-cooled solution of 2-boranatodiphenylphosphino ethanoic acid **6** (880.0 mg, 3.40 mmol) in dichloromethane (18 mL) was added dropwise oxalyl chloride (863.0 mg, 6.80 mmol) under argon. The mixture was stirred at rt for 4 h. Removal of solvent and excess of oxalyl chloride under reduced pressure afforded alcoyl chloride in quantitative yield as a red oil. A solution of alcoyl chloride in THF (20 mL) was added via cannula over 10 min to an ice-cooled solution of (*R*)-*N*-alkylated phenylglycinol (4.42 mmol) and triethylamine (447.2 mg, 4.42 mmol) in THF (20 mL). After 2 h at rt, water (5 mL) was added. The product mixture was extracted by ethyl acetate (3×20 mL) and the organic layer was dried over magnesium sulfate. Purification of the product by flash column chromatography eluting with cyclohexane: EtOAc 50:50 afforded the pure amide (**7a**: 63%, **7b**: 31%) as white powders.

3.5. 2-(Boranatodiphenylphosphino)-*N*-(2-hydroxy-1-(*R*)-phenylethyl)-*N*-methylacetamide 7a

$R_f = 0.32$ (cyclohexane/EtOAc, 5:5). mp <50°C. $[\alpha]_D^{20} = -76.7$ (*c* 1.1, $CHCl_3$). ^{31}P NMR (121.5 MHz, $CDCl_3$): δ 17.24 (d, $J = 41.2$ Hz). ^{1}H NMR (83:17 rotamer ratio, asterisk denotes minor rotamer peaks, 300 MHz, $CDCl_3$): δ 0.50–1.30 (br, 3H), 2.20 (s, 1H), 2.57 (s, 3H), 2.59* (s, 3H), 3.32 (dd, $J = 1.8$, 9.5 Hz, 2H), 3.77–3.86 (m, 2H), 4.97* (dd, $J = 4.6$, 8.9 Hz, 1H), 5.55 (dd, $J = 4.5$, 8.2 Hz, 1H), 6.94–6.96 (m, 2H), 7.06–7.13 (m, 3H), 7.24–7.29 (m, 6H), 7.59–7.64 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 32.6 (d, $J = 30.5$ Hz), 32.9, 58.7, 62.7, 126.9, 128.2, 128.2, 129.0, 129.1 (d, $J = 10.3$ Hz), 131.9 (d, $J = 2.3$ Hz), 132.9 (d, $J = 9.9$ Hz), 136.8, 168.1 (d, $J = 2.9$ Hz). IR (neat): 3402, 3059, 2939, 2387, 1628, 1437, 1108, 1062, 752, 698 cm^{-1}. MS (IC, 25 eV) *m/z*: 400.5 [M−BH_3+Na]$^+$. Anal. calcd for $C_{23}H_{27}BNO_2P$: C, 70.61; H, 6.96; N, 3.58. Found: C, 70.34; H, 7.19; N, 3.53. HPLC Kromasil C 18, 1 mL/min, MeOH/H_2O 7/3, $t = 11.30$ min.

3.6. 2-(Boranatodiphenylphosphino)-*N*-benzyl-*N*-(2-hydroxy-1-(*R*)-phenylethyl) acetamide 7b

$R_f = 0.45$ (cyclohexane/EtOAc, 5:5). mp <50°C. $[\alpha]_D^{20} = -44.9$ (*c* 1.0, $CHCl_3$). ^{31}P NMR (121.5 MHz, $CDCl_3$): δ 17.66. ^{1}H NMR (82:18 rotamer ratio, asterisk denotes minor rotamer peaks, 300 MHz, $CDCl_3$): δ 0.20–1.40 (br, 3H), 3.32 (d, $J = 11.3$ Hz, 2H), 3.50–3.98 (m, 4H), 4.42 (s, 2H), 5.21* (dd, $J = 5.1$, 7.4 Hz, 1H), 5.45 (dd, $J = 5.1$, 7.9 Hz, 1H), 7.00–7.19 (m, 10H), 7.37–7.43 (m, 5H), 7.65–7.71 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 33.5 (d, $J = 30.5$ Hz), 49.0, 62.0, 63.3, 126.4, 127.9, 128.1 (d, $J = 54.0$ Hz), 128.4, 128.9, 129.1, 129.2, 129.3, 131.9 (d, $J = 2.3$ Hz), 132.9 (d, $J = 9.8$ Hz), 136.7, 137.3, 168.9 (d, $J = 2.9$ Hz). IR (neat): 3422, 2383, 1637, 1437, 1061, 736, 698 cm^{-1}. MS (IC, 25 eV) *m/z:* 476.4 [M−BH_3+Na]$^+$. Anal. calcd for $C_{29}H_{31}BNO_2P$: C, 74.53; H, 6.69; N, 3.00. Found: C, 74.42; H, 6.76; N, 2.96. HPLC Kromasil C 18, 1 mL/min, MeOH/H_2O 8/2, $t = 8.53$ min.

3.7. General procedure for the alkylation of phosphine–amide boranes 7

All the alkylation reactions were realized under argon with a flame-dried flask. The amide and the lithium chloride (6 equiv.) were weighted and dried under reduced pressure in the presence of silica gel for 12 h. To a stirred, cooled (−78°C) solution of the amide and the lithium chloride in THF ([**7**] = 0.085 mmol mL^{-1}) was slowly added a solution of *n*-butyllithium (1.6 M in

hexanes, 2.5 equiv.). The suspension was warmed to −20°C during 2 h. The electrophile (3 equiv.) was added to the reaction mixture at −40°C. The solution was stirred at temperature from −40 to rt depending on the electrophile during 4 to 24 h and quenched by the addition of saturated aqueous ammonium chloride solution. The mixture was partitioned between saturated aqueous ammonium chloride solution and ethyl acetate, and the aqueous layer was separated and extracted with ethyl acetate. The combined organic extracts were dried over magnesium sulfate and concentrated to afford yellow oil. Purification of the residue by flash chromatography (cyclohexane/ethyl acetate) affords amide.

3.8. 2-(*S*)-(Boranatodiphenylphosphino)-*N*-(2-hydroxy-1-(*R*)-phenylethyl)-*N*-methylpropionamide 8a

Amide **7a** (300.0 mg, 0.767 mmol) was alkylated by iodo methane (326.6 mg, 2.3 mmol) at −40°C. Purification by flash chromatography (40% of ethyl acetate in cyclohexane) gave 240 mg of white powder of the title compound (77%) and 60 mg of diastereoisomers mixture. $R_f = 0.51$ (cyclohexane/EtOAc, 5:5). mp 64°C. $[\alpha]_D^{20} = -63.8$ (*c* 1.34, $CHCl_3$). ^{31}P NMR (121.5 MHz, $CDCl_3$): δ 25.90 (br). ^1H NMR (86:14 rotamer ratio, asterisk denotes minor rotamer peaks, 300 MHz, $CDCl_3$): δ 0.50–1.80 (br, 3H), 1.47 (dd, $J = 6.9$, 14.8 Hz, 3H), 1.93 (s, 1H), 2.62* (s, 3H), 2.76 (s, 3H), 3.85 (m, 1H), 3.96 (m, 2H), 5.06* (dd, $J = 4.6$, 9.2 Hz, 1H), 5.83 (dd, $J = 5.1$, 7.4 Hz, 1H), 7.27 (m, 4H, H_a), 7.50 (m, 6H), 7.78 (m, 3H), 8.06 (m, 2H).). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.7 (d, $J = 2.3$ Hz), 32.3, 36.3 (d, $J = 31.0$ Hz), 58.4, 61.7, 126.6 (d, $J = 56.3$ Hz), 127.3 (d, $J = 40.8$ Hz), 128.1, 128.2, 128.9 (d, $J = 9.8$ Hz), 129.1, 129.2 (d, $J = 8.6$ Hz), 131.8 (d, $J = 2.3$ Hz), 132.0 (d, $J = 2.3$ Hz), 133.7 (d, $J = 9.2$ Hz), 134.3 (d, $J = 9.2$ Hz), 137.2, 172.5 (d, $J = 2.9$ Hz). IR (neat): 3402, 3059, 2928, 2380, 1627, 1437, 1401, 1063, 742, 698 cm^{-1}. MS (IC, 25 eV) *m/z:* 414.0 $[M-BH_3+Na]^+$. Anal. calcd for $C_{24}H_{29}BNO_2P$: C, 71.13; H, 7.21; N, 3.46. Found: C, 70.76; H, 7.58; N, 3.48. HPLC Kromasil C 18, 1 mL/min, MeOH/H_2O 7/3, $t = 12.35$ min (for a mixture of diastereoisomers, (*S*) $t_1 = 12.35$ min; (*R*) $t_2 = 18.15$ min).

3.9. 2-(*S*)-(Boranatodiphenylphosphino)-*N*-benzyl-*N*-(2-hydroxy-1-(*R*)-phenylethyl) propionamide 8b

Amide **7b** (200.0 mg, 0.428 mmol) was alkylated by iodomethane (182.2 mg, 1.28 mmol) at −40°C. Purification by flash chromatography (30% of ethyl acetate in cyclohexane) gave 165 mg of white powder of the title compound (80%).

$R_f = 0.65$ (cyclohexane/EtOAc, 5:5). mp 67°C. $[\alpha]_D^{20} = -62.6$ (*c* 1.07, $CHCl_3$). ^{31}P NMR (121.5 MHz, $CDCl_3$): δ 26.34 (d, $J = 42.3$ Hz). ^1H NMR (77:23 rotamer ratio, asterisk denotes minor rotamer peaks, 300 MHz, $CDCl_3$): δ 0.25–1.75 (br, 3H), 1.17 (dd, $J = 6.9$, 14.3 Hz, 3H), 1.28* (dd, $J = 6.9$, 15.1 Hz, 3H), 2.55 (s, 1H), 3.63 (m, 1H), 3.85* (d, $J = 15.1$ Hz, 1H), 4.06 (m, 2H), 4.40 (d, $J = 17.7$ Hz, 1H), 4.65 (d, $J = 17.7$ Hz, 1H), 5.09* (d, $J = 15.1$ Hz, 1H), 5.56* (dd, $J = 4.9$, 9.0 Hz, 1H), 5.66 (m, 1H), 6.85–7.46 (m, 25H), 7.71–7.77 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.9 (d, $J = 2.9$ Hz), 37.0 (d, $J = 29.9$ Hz), 49.7, 50.7*, 61.4, 62.3*, 63.0, 63.2*, 126.3, 126.7*, 127.1 (d, $J = 56.9$ Hz), 127.8, 128.0 (d, $J = 58.6$ Hz), 128.5, 128.8, 128.9, 129.0*, 129.1, 129.2*, 129.4, 129.4*, 131.8 (d, $J = 2.3$ Hz), 131.9 (d, $J = 2.3$ Hz), 133.8 (d, $J = 9.2$ Hz), 134.2 (d, $J = 9.8$ Hz), 137.3, 137.7, 173.1. IR (neat): 3401, 3060, 2932, 2383, 1640, 1436, 1353, 1064, 740, 698 cm^{-1}. MS (IC, 25 eV) *m/z:* 489.9 $[M-BH_3+Na]^+$. Anal. calcd for $C_{30}H_{33}BNO_2P$: C, 74.85; H, 6.91; N, 2.91. Found: C, 74.62; H, 6.80; N, 3.02. HPLC Kromasil C 18, 1 mL/min, MeOH/H_2O 8/2, $t = 9.42$ min (for a mixture of diastereoisomers, (*S*) $t_1 = 9.42$ min; (*R*) $t_2 = 16.37$ min).

3.10. 2-(Boranatodiphenylphosphino)-*N*-(2-hydroxy-1-(*R*)-phenylethyl)-*N*-methyl-3-phenylpropionamide 9

Amide **7a** (300.0 mg, 0.767 mmol) was alkylated by benzyliodide (501.2 mg, 2.3 mmol) at 0°C. Purification by flash chromatography (30% of ethyl acetate in cyclohexane) gave 203.0 mg (55%) of white powder of the diastereoisomeric mixture (72.5% of 2*S*, 27.5% of 2*R*). $R_f = 0.57$ (cyclohexane/EtOAc, 5:5). ^{31}P NMR (121.5 MHz, $CDCl_3$): δ 23.90 (br). ^1H NMR (75:25 rotamer ratio, asterisk denotes minor rotamer peaks, 300 MHz, $CDCl_3$): δ 0.70–1.60 (br, 3H), 1.85 (s, 1H), 2.19* (s, 3H), 2.30 (s, 3H), 3.16 (m, 2H), 3.78 (m, 2H), 4.02 (m, 1H), 4.44* (m, 1H), 5.68 (m, 1H), 6.71 (m, 3H), 7.20 (m, 8H), 7.56 (m, 4H,), 7.86 (m, 3H), 8.27 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 32.2, 32.8*, 36.0, 36.4*, 44.3 (d, $J = 27.0$ Hz), 45.2* (d, $J = 27.6$ Hz), 58.3, 59.7*, 61.7, 61.9*, 126.6 (d, $J = 51.2$ Hz), 127.2, 127.3 (d, $J = 49.4$ Hz), 127.4*, 127.9, 128.2, 128.7, 129.0, 129.1, 132.0 (d, $J = 2.9$ Hz), 132.1 (d, $J = 2.3$ Hz), 133.5* (d, $J = 9.8$ Hz), 133.9 (d, $J = 9.2$ Hz), 134.3 (d, $J = 9.8$ Hz), 134.9* (d, $J = 9.8$ Hz), 139.0, 139.2, 170.8 (d, $J = 2.3$ Hz), 171.2* (d, $J = 2.3$ Hz). IR (neat): 3430, 3060, 2927, 2383, 1632, 1481, 1438, 1107, 1063, 742, 700 cm^{-1}. MS (IC, 25 eV) *m/z:* 489.9 $[M-BH_3+Na]^+$. Anal. calcd for $C_{30}H_{33}BNO_2P$: C, 74.85; H, 6.91; N, 2.91. Found: C, 74.73; H, 7.25; N, 2.98. HPLC Kromasil C 18, 1 mL/min, MeOH/H_2O 73/27, 72.5% (*S*) $t_1 = 24.46$ min; 27.5% (*R*) $t_2 = 27.32$ min.

3.11. *t*-Butyl 3-(boranatodiphenylphosphino)-3-*N*-(2-hydroxy-1-(*R*)-phenylethyl)-*N*-methyl carboxamide propanoate 10

Amide **7a** (200.0 mg, 0.511 mmol) was alkylated by *t*-butyl bromoacetate (299.1 mg, 1.53 mmol) at rt for 24 h. Purification by flash chromatography (10% of ethyl acetate in cyclohexane) gave 141.0 mg (55%) of white powder of the diastereoisomeric mixture (88.5% of 2*S*, 11.5% of 2*R*). $R_f = 0.42$ (cyclohexane/EtOAc, 7:3). ^{31}P NMR (121.5 MHz, $CDCl_3$): δ 22.68 (br). ^1H NMR (1:1 rotamer ratio, asterisk denotes minor rotamer peaks, 300 MHz, $CDCl_3$): δ 0.60–1.90 (br, 3H), 1.40 (s, 9H), 1.46* (s, 9H), 1.64 (s, 1H), 2.60 (m, 1H), 2.70 (s, 3H), 3.08 (m, 1H), 3.95 (m, 2H), 4.17 (m, 1H), 5.71 (m, 1H), 6.96 (m, 2H), 7.26 (m, 3H), 7.40 (m, 3H), 7.51 (m, 3H), 7.80 (m, 2H), 8.14 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 28.4, 28.5*, 33.5, 36.9 (d, $J = 29.3$ Hz), 56.1,

68.9, 69.9*, 81.1, 81.2*, 126.2 (d, $J=54.6$ Hz), 127.3 (d, $J=52.3$ Hz), 127.6, 128.4, 128.7 (d, $J=12.1$ Hz), 129.0, 129.2 (d, $J=10.3$ Hz), 131.9 (d, $J=1.7$ Hz), 133.1 (d, $J=2.3$ Hz), 133.7 (d, $J=9.2$ Hz), 134.7 (d, $J=9.2$ Hz), 137.2, 170.6 (d, $J=4.6$ Hz), 170.4. IR (neat): 3443, 3278, 2929, 2388, 1726, 1634, 1140, 1063, 742, 699 cm^{-1}. MS (IC, 25 eV) *m/z:* 514.1 $[M-BH_3+Na]^+$. Anal. calcd for $C_{29}H_{37}BNO_4P$: C, 68.92; H, 7.38; N, 2.77. Found: C, 68.82; H, 7.09; N, 2.61. HPLC Kromasil C 18, 1 mL/min, MeOH/H_2O 8/2, 88.5% (*S*) $t_1=34.17$ min; 11.5% (*R*) $t_2=36.95$ min.

3.12. 2-(*S*)-(Boranatodiphenylphosphino)-*N*-(2-hydroxy-1-(*R*)-phenylethyl)-*N*-methylpent-4-enamide 11

Amide **7a** (200.0 mg, 0.511 mmol) was alkylated by 3-iodopropene (257.5 mg, 1.53 mmol) at 0°C for 2 h. Purification by flash chromatography (40% of ethyl acetate in cyclohexane) furnished amide **11** as a mixture of diastereomers (95.5% of 2*S*, 5.5% of 2*R*) (193 mg, 87%). A single recrystallization from mixture of 30% of ethyl acetate in cyclohexane yielded enantiomerically pure (2*S*)-**11**. $R_f=0.57$ (cyclohexane/ethyl acetate, 5:5). Mp 146°C. $[\alpha]_D^{20}=-58.5$ (*c* 1.3, $CHCl_3$). ^{31}P NMR (121.5 MHz, $CDCl_3$): δ 23.85 (d, $J=16.5$ Hz). ^1H NMR (300 MHz, $CDCl_3$): δ 0.50–1.70 (br, 3H), 2.54 (m, 1H), 2.73 (s, 3H), 2.74 (m, 1H), 3.84 (m, 1H), 3.94 (m, 2H), 5.09 (m, 2H), 5.71 (m, 1H), 5.86 (m, 1H), 7.29 (m, 4H), 7.56 (m, 6H), 7.81 (m, 3H), 8.07 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 32.5, 34.4, 41.4 (d, $J=27.6$ Hz), 58.6, 61.7, 118.4, 126.6 (d, $J=55.7$ Hz), 127.4 (d, $J=54.0$ Hz), 128.1, 128.2, 128.9 (d, $J=10.3$ Hz), 129.0, 129.4 (d, $J=10.3$ Hz), 132.0 (d, $J=2.3$ Hz), 132.1 (d, $J=2.3$ Hz), 133.6 (d, $J=9.2$ Hz), 134.0 (d, $J=9.8$ Hz), 134.2 (d, $J=9.2$ Hz), 135.0 (d, $J=12.0$ Hz), 137.2, 171.1 (d, $J=2.9$ Hz). IR (neat): 3500, 3062, 2981, 2921, 2380, 1625, 1478, 1440, 1402, 1108, 1059, 742, 697 cm^{-1}. MS (IC, 25 eV) *m/z:* 439.9 $[M-BH_3+Na]^+$. Anal. calcd for $C_{26}H_{31}BNO_2P$: C, 72.40; H, 7.24; N, 3.25. Found: C, 72.52; H, 7.54; N, 3.22. HPLC Kromasil C 18, 1 mL/min, MeOH/H_2O 8/2, $t=6.99$ min(for a mixture of diastereoisomers, (*S*) $t_1=6.99$ min; (*R*) $t_2=9.09$ min).

3.13. 2-(Boranatodiphenylphosphino)-*N*-(2-hydroxy-1-(*R*)-phenylethyl)-*N*-methyl-4-metylpent-4-enamide 12

Amide **7a** (300.0 mg, 0.767 mmol) was alkylated by 3-iodo-2-methylpropene (418.4 mg, 2.3 mmol) at rt for 48 h. Purification by flash chromatography (40% of ethyl acetate in cyclohexane) furnished amide **12** as a mixture of diastereomers (60% of 2*S*, 40% of 2*R*): white crystalline solid (189 mg, 55%). $R_f=0.41$ (cyclohexane/EtOAc, 5:5). ^{31}P NMR (121.5 MHz, $CDCl_3$): δ 24.55 (br). ^1H NMR (66:34 rotamer ratio, asterisk denotes minor rotamer peaks, 300 MHz, $CDCl_3$): δ 0.50–1.70 (br, 3H), 2.02 (s, 3H), 2.04*(s, 3H), 2.40 (m, 1H), 2.67 (s, 3H), 2.78 (m, 1H), 3.96 (br, 3H), 4.77 (m, 2H), 5.63*(m, 1H), 5.81 (m, 1H), 6.81 (m, 1H), 7.18–7.54 (br, 12H), 7.75–7.83 (br, 2H), 8.04–8.21 (br, 2H). ^{13}C NMR (66:34 rotamer ratio, asterisk denotes minor rotamer peaks, 75 MHz, $CDCl_3$): δ 22.6*, 22.7 32.4, 32.8*, 37.8, 38.3*, 40.2 (d, $J=27.6$ Hz), 41.0* (d, $J=28.2$ Hz), 58.6, 59.8*, 61.6, 61.9*, 113.3, 113.6*, 126.4* (d, $J=55.2$ Hz), 126.7 (d, $J=55.2$ Hz), 126.9* (d, $J=53.4$ Hz), 127.5 (d, $J=53.4$ Hz), 128.0*, 128.0, 128.3*, 128.3, 128.8, 128.9*, 129.1* (d, $J=10.9$ Hz), 129.2 (d, $J=10.3$ Hz), 131.8* (d, $J=2.3$ Hz), 132.0, 133.6* (d, $J=9.2$ Hz), 133.9 (d, $J=9.2$ Hz), 134.1 (d, $J=9.2$ Hz), 134.6* (d, $J=9.2$ Hz), 136.4*, 137.1, 142.6 (d, $J=10.2$ Hz), 143.0* (d, $J=12.1$ Hz), 171.0 (d, $J=2.3$ Hz), 171.7* (d, $J=3.4$ Hz). MS (IC, 25 eV) *m/z:* 453.8 $[M-BH_3+Na]^+$. Anal. calcd for $C_{27}H_{33}BNO_2P$: C, 72.82; H, 7.47; N, 3.15. Found: C, 72.49; H, 7.54; N, 3.11. HPLC Kromasil C 18, 1 mL/min, MeOH/H_2O 75/25, 60% (*S*) $t_1=11.75$ min; 40% (*R*) $t_2=13.12$ min).

3.14. 2-(*S*)-Boranatodiphenylphosphino propan-1-ol 13

To a solution of borane–ammonia complex (90%, 84 mg, 2.45 mmol, 5 equiv.) in THF (2 mL) at 0°C was added a solution of *n*-butyllithium in hexanes (1.6 M, 1.25 mL, 2.0 mmol, 4 equiv.). The resulting solution was stirred at 0°C for 15 min and then warmed to rt. After 15 min, the suspension was cooled to 0°C. A solution of amide **8a** (200.0 mg, 0.49 mmol) in THF (2 mL) was added dropwise and the reaction mixture was held at that temperature for 4 h. The excess hydride was quenched by the careful addition of 2N aqueous hydrochloric acid solution (2 mL). The mixture was stirred for 1 h at 0°C and then extracted with ethyl acetate (3×5 mL). The combined organic extracts were washed sequentially with 2N aqueous sodium hydroxide solution (3 mL) and brine (3 mL). The extracts were dried over magnesium sulfate and concentrated. Purification by preparative TLC on silica gel (40% of ethyl acetate in cyclohexane) afforded the alcohol as white crystals, mp=66°C (112.6 mg, 89%). $R_f=0.47$ (cyclohexane/EtOAc, 5:5). $[\alpha]_D^{20}=-32.5$ (*c* 0.75, $CHCl_3$). ^{31}P NMR (121.5 MHz, $CDCl_3$): δ 20.35 (d, $J=39.2$ Hz). ^1H NMR (300 MHz, $CDCl_3$): δ 0.40–1.80 (br, 3H), 1.18 (dd, $J=7.2$, 15.6 Hz, 3H), 2.83 (m, 1H), 3.78 (m, 2H), 7.46 (m, 6H), 7.70–7.82 (br, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): 12.3, 32.1 (d, $J=35.1$ Hz), 63.7 (d, $J=6.3$ Hz), 128.1 (d, $J=55.2$ Hz), 129.1 (d, $J=9.7$ Hz), 129.2 (d, $J=9.2$ Hz), 131.7, 132.7 (d, $J=8.6$ Hz), 133.0 (d, $J=8.6$ Hz). IR (neat): 4053, 3390, 3058, 2636, 2361, 1436, 1106, 1065, 1028, 738, 694. MS (IC, 25 eV) *m/z:* 245.1 $[M-BH_3+H]^+$. Anal. calcd for $C_{15}H_{20}BOP$: C, 69.80; H, 7.81. Found: C, 69.76; H, 7.83. HPLC Daicel Chiracel OJ, 1 mL/min, 10% 2-PrOH/heptane, $t=17.6$ min (for a mixture of enantiomers, (*S*) $t_1=17.6$ min; (*R*) $t_2=21.0$ min).

3.15. 2-(*S*)-Boranatodiphenylphosphino propanoic acid 14

Jones' reagent (3.60 M, 0.330 mL, 1.16 mmol) was added dropwise to a stirred solution of the alcohol **14** (150 mg, 0.58 mmol) in acetone (15 mL) at 0–5°C. After 1 h, 2-propanol was added to destroy excess oxidant. Water (5 mL) was added, and acetone was removed under reduced pressure. The product was extracted with EtOAc (3×15 mL). The organic layer was washed with brine, dried, and evaporated to a residue, which was purified by flash column chromatography (cyclohexane–ethyl acetate–acetic acid, 70:30:0.5;

v/v) to give acid **13** as a white powder (123.3 mg, 78%). $R_f = 0.24$ (cyclohexane–ethyl acetate–acetic acid, 70:30:0.5; v/v). mp 116°C. $[\alpha]_D^{20} = +39.0$ (c 1, $CHCl_3$). ^{31}P NMR (121.5 MHz, $CDCl_3$): δ 26.41 (br). ^1H NMR (300 MHz, $CDCl_3$): δ 0.60–1.60 (br, 3H), 1.36 (dd, $J = 7.2$, 15.9 Hz, 3H), 3.60 (m, 1H), 7.47 (m, 6H), 7.77 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 12.7, 37.7 (d, $J = 27.0$ Hz), 126.6 (d, $J = 53.5$ Hz), 127.8 (d, $J = 56.9$ Hz), 129.0 (d, $J = 9.8$ Hz), 129.1 (d, $J = 9.8$ Hz), 131.8, 132.1, 133.0 (d, $J = 9.2$ Hz), 133.6 (d, $J = 9.8$ Hz), 175.9. IR (neat): 3059, 2939, 2363, 1707, 1438, 1108, 1069, 737, 688. MS (negative FAB) m/z: 271 $[M-H-BH_3]^-$. Anal. calcd for $C_{15}H_{18}BO_2P$: C, 66.72; H, 6.67. Found: C, 67.06; H, 6.76. HPLC Daicel Chiracel OJ, 1 mL/min, 10% 2-PrOH/heptane+0.5% formic acid, $t = 14.93$ min (for a mixture of enantiomers, (S) $t_1 = 14.93$ min; (R) $t_2 = 21.57$ min).

Acknowledgements

This work is part of the RINCOF/PUNCHORGA program, and we thank the Conseil Régional de Haute-Normandie for their financial support as well The Ministère de la Recherche (Grant to J.-P.E.).

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