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[60]Fullerene L-Amino Acids and Peptides: Synthesis under Phase-Transfer-Catalysis using a Phosphine-Borane Linker. Electrochemical Behaviour

Pauline Minois,[§] *Jérôme Bayardon*,* *Rita Meunier-Prest and Sylvain Jugé**

Institut de Chimie Moléculaire de l'Université de Bourgogne (ICMUB-UMR 6302), BP 47870,

Université de Bourgogne-Franche-Comté, 9 avenue A. Savary, 21078 Dijon Cedex, France

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CORRESPONDING AUTHOR FOOTNOTE

[*] To whom correspondence should be addressed. E-mail: Jerome.bayardon@u-bourgogne.fr, E-mail: sylvain.juge@u-bourgogne.fr, Tel: +33 (0)3 80 39 61 13.

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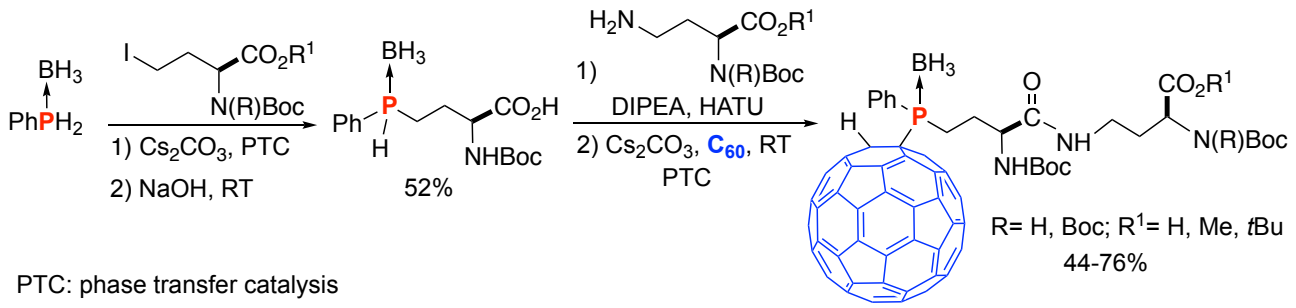


ABSTRACT

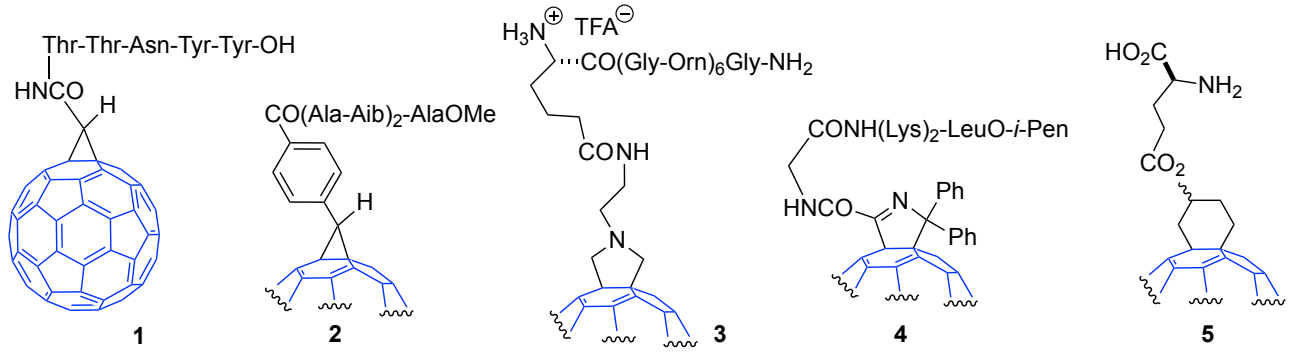
A new method to link amino acid and peptide derivatives to [60]fullerene is described. It uses hydrophosphination with a secondary phosphine borane. Firstly, the stereoselective synthesis of secondary phosphine borane amino acid derivatives was achieved by alkylation of phenylphosphine borane with γ-iodo-α-amino ester reagents under phase transfer catalysis (PTC). Secondly, a *sec*-phosphine borane amino ester was saponified and coupled with α,γ-diamino esters to afford the corresponding dipeptide derivatives in good yields. Finally, the hydrophosphination reaction of [60]fullerene by the *sec*-phosphine borane compounds was performed under phase transfer catalysis (PTC) to obtain C_{60}-amino acid or dipeptide derivatives in yields up to 80% by P-C bond formation. This addition reaction which proceeds in mild and moderate dilute conditions (0.03M) leads to [60]fullerene derivatives as epimeric mixtures (≈ 1:1) due to the P-chirogenic centre but without racemization of the amino acid or peptide moiety. In addition, the electrochemical behavior of a C_{60}-phosphine borane amino ester was investigated by cyclic voltammetry and spectroelectrochemistry after controlled-potential-electrolysis. It showed evidence for the retro-hydrophosphination reaction into free [60]fullerene and *sec*-phosphine borane amino ester compound. Consequently, the synthesis of *sec*-phosphine borane amino acids followed by their use in hydrophosphination reactions of [60]fullerene under phase transfer catalysis, has demonstrated a great utility for the preparation of C_{60}-derivatives. Indeed, the hydrophosphination and the retro-hydrophosphination reactions of [60]fullerene/phosphine borane compounds offer a promising new strategy for the reversible immobilization of amino acid or peptide derivatives on carbon nanomaterials such as [60]fullerene.

KEYWORDS

Fullerene/ phosphines / borane complexes / phase transfer catalysis / amino acid derivatives / peptides / hydrophosphination / retro-hydrophosphination / electrochemistry.

INTRODUCTION

Since the discovery of the fullerenes,[1] an impressive amount of research has resulted,[2,3] which significantly contributed to the development of the molecular chemistry of nanomaterials now expanding to the carbon nanotubes and graphene.[4] The [60]fullerene, which is the smallest stable and most abundant molecule of this carbon allotropic state, is built up from sixty identical Csp^2 atoms disposed according to fused pentagons and hexagons scheme giving a roughly spherical shape with a diameter of 7.14 Å.[1,2,5] The [60]fullerene is a weakly aromatic molecule, which explains the relatively good reactivity of the double bonds located between the hexagons. Today, many methods have been described to functionalize fullerene derivatives by formation of C-C, C-O and C-N bonds using a wide range of reagents, cycloaddition or catalyzed reactions.[2,3] Fullerene derivatives have early arisen an interest towards medical applications due to their size, their hydrophobic character and electronic properties and their weak toxicity and immunogenicity.[6] In addition, these compounds have exhibited major biological activities such as HIV-protease inhibition, antiviral, antibiotic and antioxidant properties and could be used in photodynamic therapy, drug or gene delivery as well as in medical diagnosis.[6-8] Among the many classes of [60]fullerene-based biomolecules that have been described, derivatives supported by amino acids and peptides attracted a particular attention, because the C_{60}-substituent dramatically modify their hydrophilic-hydrophobic balance, their transmembrane transport and their cellular uptake properties.[9] Conceptually, there are two main strategies for the synthesis of such conjugates. These depend on whether the fullerene moiety can be considered as a prosthetic group or as an amino acid residue, as illustrated by the examples **1**-**11** of Figure 1.



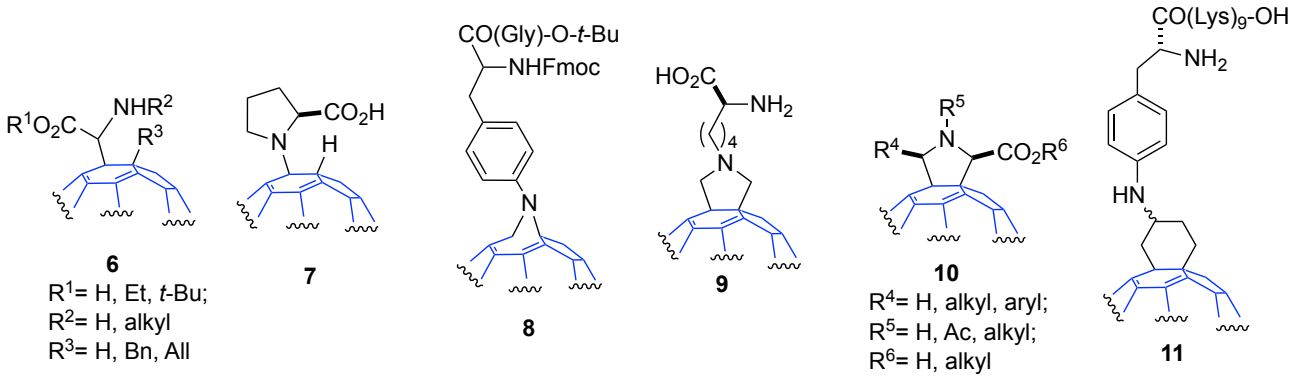


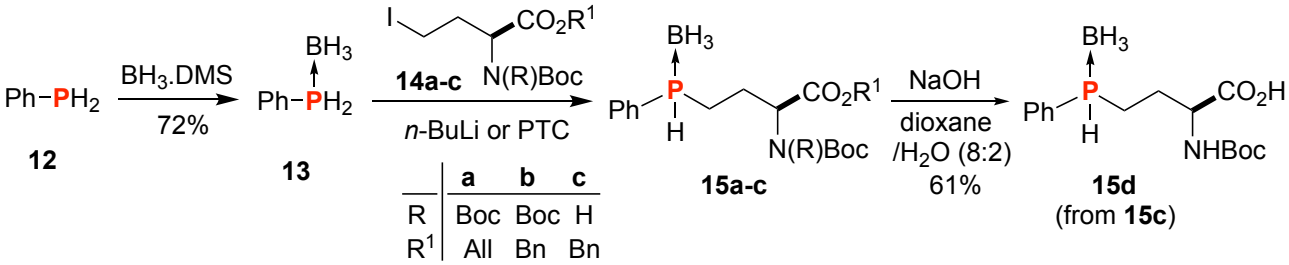
Figure 1. Representative [60]fullerene amino acid and peptide derivatives

In the former case, the [60]fullerene prosthetic groups **1**-**5** were prepared according to procedures deriving from Bingel, Prato or Diels-Alder type reactions which led to the corresponding cyclopropano-,[10] pyrrolidino,[11] pyrrolino-[12] or cyclohexano-[13] functionalized derivatives. In the second case, [60]fullerene derivatives **6**-**11** were synthesized by direct connection of [60]fullerene to the amino acid framework using C-C or C-N bonds formation (Figure 1). Thus, C_{60}-amino acids **6** were synthesized by alkylation of a Schiff base derived from glycine[14] (or a chiral nickel-complex[14c]) with the [60]fullerene used as an electrophilic reagent. On the other hand, the reaction of amino acids with the [60]fullerene could be performed by hydroamination[15] or nitrene addition[16] to afford derivatives **7** or **8**, respectively. Finally, amino acid derivatives **9**-**11** were obtained *via* dipolar or Diels Alder cycloadditions with [60]fullerene.[17-19] It should be highlighted that fulleroproline derivatives **10** are obtained in high e.e. by an efficient asymmetric 1,3-dipolar cycloaddition of Schiff bases with [60]fullerene catalyzed by chiral silver or gold complexes.[18] However and despite these results the stereoselective synthesis of fullerene amino acid and peptide derivatives remains challenging because the solubility of [60]fullerene and the stability of its derivatives are often responsible of low isolated yields. Therefore, it is widely agreed that the fullerene moiety must be introduced at the last step of the peptide synthesis.[9f] However, there is a great interest to prepare fullerene amino acids which could be used in peptide synthesis.

As part of our ongoing research on the chemistry of phosphorus and boron based amino acids which are useful for the synthesis of labeled or customized peptides,[20] we were interested in using phosphine borane precursors for grafting [60]fullerene to an amino acid side chain. So far, the

reaction of *sec*-phosphine borane with fullerene has only been reported for the preparation of tertiary phosphines useful in coordination chemistry.[21] Taking into account the fact that phosphide boranes are powerful nucleophilic reagents for the preparation of functionalized phosphines,[22] we now would like to report: a) the stereoselective synthesis of secondary phosphine borane amino acid derivatives **15** under phase transfer catalysis (PTC) (Scheme 1); b) the efficient use of *sec*-phosphine borane amino acids **15** in peptide coupling (Table 2); c) the reaction of [60]fullerene with *sec*-phosphine borane amino acids **15** and dipeptide derivatives **16** under phase transfer catalysis (PTC) (Table 3); and finally d) the electrochemical behaviour of [60]fullerene phosphino borane amino acid derivatives.

Scheme 1. Synthesis of *sec*-phosphine borane amino acid derivatives 15



RESULTS AND DISCUSSION

Synthesis of *sec*-phosphine borane amino acid derivatives

The synthesis of *sec*-phosphine borane amino acid compounds **15** is achieved by monoalkylation of phenylphosphine borane **13** with the corresponding γ-iodo L-α-amino acid derivatives **14** (Scheme 1). Compounds **13** and **14** were previously prepared from primary phenylphosphine **12**[23] and L-aspartic acid,[20b,c] respectively, according to reported procedures.

Deprotonation of primary phosphine borane complex **13** by *n*-butyllithium in THF at -78°C, followed by reaction with γ-iodo-α-amino ester **14a** led to product **15a** in low yield (20%, Scheme 1). However, as *sec*-phosphine boranes could be alkylated under phase-transfer catalysis using KOH as base,[24] the monoalkylation of primary phosphine borane **13** was considered according to a similar

procedure but using a weak base, in order to avoid side reactions with γ-iodo-α-amino ester reagents **14** (Scheme 1, Table 1).

Table 1. Synthesis of *sec*-phosphine borane amino acid derivatives **15** under phase-transfer catalysis[a]

entry	γ-iodo-α-amino ester R	R[1]		conditions base (equiv.)[b]	*sec*-phosphine borane derivative[c]	yield (%)[d]	e.e.(%)[e]
1	Boc	All	**14a**	Na_2CO_3 (3)	**15a**	0	-
2	”	”	**14a**	K_2CO_3 (3)	**15a**	10	-
3	”	”	**14a**	Cs_2CO_3 (3)	**15a**	60	99
4	”	”	**14a**	Cs_2CO_3 (6)	**15a**	73	99
5	”	”	**14a**	Cs_2CO_3 (3) + ε H_2O[f]	**15a**	98	99
6	Boc	Bn	**14b**	Cs_2CO_3 (3) + ε H_2O[f]	**15b**	58	99
7	H	Bn	**14c**	Cs_2CO_3 (3) + ε H_2O[f]	**15c**	85	99

[a] Reactions were performed at rt during 16 h in 2.5 mL of CH_2Cl_2 and with ratio **13** /**14** /(*n*-Bu)$_4$NBr = 2.5/ 1/ 0.4. [b] Base (equiv.)/ **13**. [c] **15a-c** were obtained as epimeric mixtures in 1:1 ratio. [d] Isolated yield after purification by column chromatography. [e] ee of each P-epimer, determined by HPLC on chiral column. [f] Traces of water (ε) are previously added to the base (see experimental part).

The reaction was investigated in CH_2Cl_2 at room temperature for 16 h using 2.5 equivalents of phosphine borane **13**, 7.5 equivalents of base and 0.4 equivalent of tetrabutylammonium bromide with respect to γ-iodo-α-amino ester **14** (Scheme 1, Table 1). When Na_2CO_3 or K_2CO_3 were used as base, the reaction does not proceed or gives low yield (Table 1, entries 1, 2). By contrast, when the reaction was performed using 3 or 6 equivalents of Cs_2CO_3, the *sec*-phosphine borane amino ester **15a** was obtained in yields up to 73% as a mixture of P-chirogenic epimers in 1:1 ratio, but without racemization at the carbon center (Table 1, entries 3, 4). Finally, the best results were obtained upon adding 10 μL H_2O to the Cs_2CO_3 (3 equivalents): because in these conditions compounds **15a**, **15b** and **15c** were isolated in 98%, 58% and 85% yields, respectively (Table 1, entries 5-7).

In this reaction, which uses CH_2Cl_2 as non-dissociative solvent, the phosphine borane **13** is deprotonated at the surface of Cs_2CO_3. This leads to a phosphide borane **16** which forms a soluble ion pair with tetrabutylammonium as counter-ion, and further reacts with the γ-iodo-α-amino ester **14** to afford **15** (Figure 2a). On the other hand, the role of water could be explained by the activation of the surface of Cs_2CO_3 which deprotonates the phosphine borane **13**.[25]

Under these conditions, the phosphine borane **13** reacts with the γ-iodo amino benzyl ester derivatives **14b** and **14c** to afford the corresponding *sec*-phosphine borane derivatives **15b** and **15c** as 1:1 epimeric mixtures, in 58 and 85% yields, respectively (Table 1, entries 7, 8). Chiral HPLC analysis of (*S*)- and racemic **15c** demonstrates the epimeric nature of the reaction mixtures at the P-stereogenic center. The configurational stability of the sec-phosphine borane epimers is also implied to be substantial, based on the base line-to-base line separation of the peaks in the HPLC analysis with a chiral stationary phase (see Supporting Information).

All attempts to deprotect the ester moiety of *sec*-phosphine borane amino esters **15a-c** by palladium catalyzed deallylation or hydrogenolysis were unsuccessful. By contrast, the debenzylation of compound **15c** was achieved at room temperature by saponification with NaOH 1M in a dioxane-water mixture to afford *sec*-phosphine borane-α-amino acid derivative **15d** in 61% yield (Scheme 1).

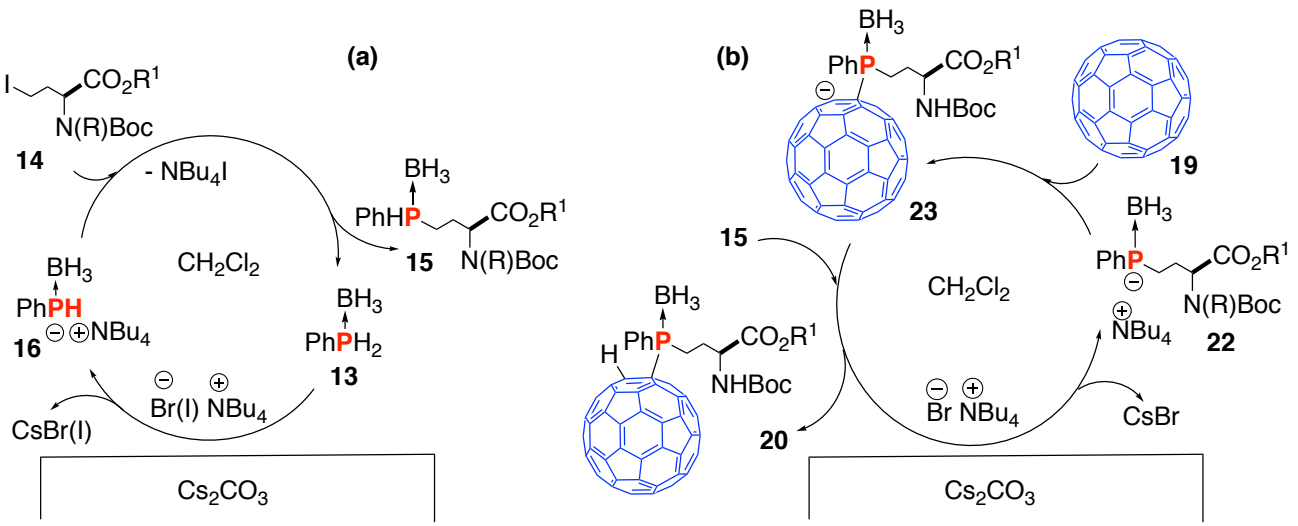


Figure 2. Proposed mechanism for the reaction of *sec*-phosphine borane derivatives under phase-transfer catalysis: (a) with γ-iodo amino esters **14**; (b) with [60]fullerene **19**.

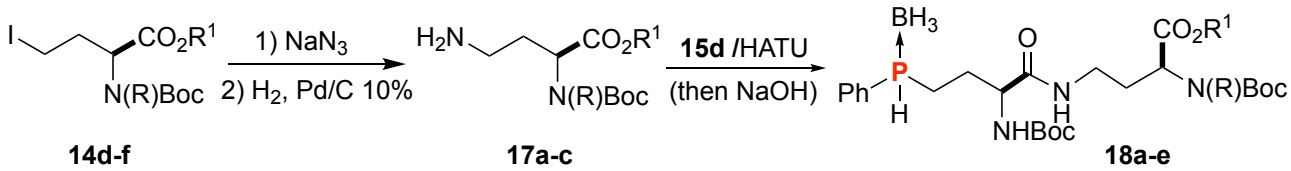
Efficiency of *sec*-phosphine borane amino acid derivatives 15a-c in peptide coupling

The efficiency of the *sec*-phosphine borane amino acid derivatives **15a-c** in coupling with peptides or proteins containing side chain amino groups, was investigated by reaction with α,γ-diamino esters **17a-c**. These compounds were easily prepared in yields up to 71% by reaction of

NaN_3 with the γ-iodo-α-amino esters **14d-f** followed by hydrogenation using Pd/C 10% (Table 2, entries 1-3). It must be pointed out that the use of methyl and *t*-butyl esters in **14d-f** (R^1= Me or *t*-Bu), which are insensitive to hydrogenation, was prefered for the synthesis of the α,γ-diamino esters **17a-c** (Table 2).

The coupling reaction of α,γ-diamino esters **17a-c** with the *sec*-phosphine borane derivative **15d** bearing a free carboxylic acid function was performed using HATU as activating agent. The results are reported in Table 2.

Table 2. Synthesis of the *sec*-phosphine borane dipeptide derivatives **18**



14d-f **17a-c** **18a-e**

entry	R	R^1	γ-iodo-α-amino ester	γ-amino derivative	yield[b] (%)	*sec*-phosphine borane dipeptide[a]	yield[c] (%)
1	Boc	Me	**14d**	**17a**	71	**18a**	46
2	Boc	*t*-Bu	**14e**	**17b**	43	**18b**	46
3	H	Me	**14f**	**17c**	58	**18c**	21
4	Boc	H	-	-	-	**18d**	62
5	H	H	-	-	-	**18e**	86

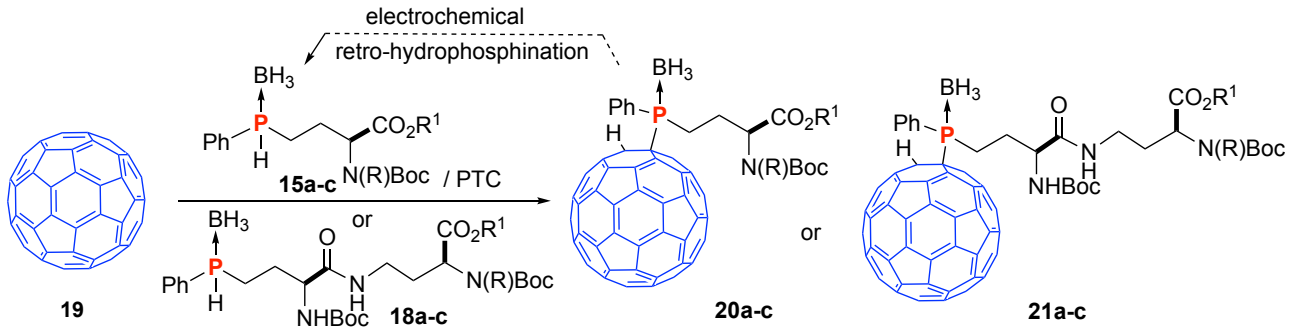
[a] P-epimeric mixtures. [b] Overall yields. [c] Isolated yields.

Coupling the *sec*-phosphine borane α-amino acid **15d** with the γ-amino-α-N,N-diprotected-amino ester **17a** afforded the corresponding dipeptide **18a** in 46% yield (Table 2, entry 1). The ^{1}H NMR spectrum of **18a** exhibits a broad singlet and a doublet at 3.66 and 5.38 ppm (J = 371 Hz), respectively, attesting for the presence of methyl ester and P-H group of the epimeric mixture. Reaction of the γ-amino esters **17b** (R^1= *t*-Bu) and **17c** (R^1= Me) with the *sec*-phosphine-α-amino acid **15d**, produced the corresponding dipeptide derivatives **18b** and **18c** in 46% and 21% yields, respectively (Table 2, entries 2, 3). Saponification of the methyl ester in dipeptide **18a** and **18c** with NaOH 1M at room temperature afforded the corresponding *sec*-phosphine borane derivatives **18d** and **18e** in yields up to 86% (Table 2, entries 4, 5).

Reaction of *sec*-phosphine borane derivatives 15, 18 with the [60]fullerene 19

It was anticipated that *sec*-phosphine borane amino acids and dipeptide derivatives **15** and **18** would react with [60]fullerene **19** *via* nucleophilic attack of their corresponding phosphides (Scheme 2). The results are reported in Table 3. Accordingly, the *sec*-phosphine borane amino acid **15a** was at first deprotonated by *n*-butyllithium in THF at low temperature. The resulting phosphide was next added to a toluene solution of [60]fullerene according to a procedure described for $Ph_2P(BH_3)H$.[21] In these conditions, the compound **20a** was obtained in low yield, and its formation was accompanied with unidentified by-products (Table 3, entry 1). As [60]fullerene derivatives could be prepared by phase-transfer catalysis,[26] we decided to investigate the reaction of *sec*-phosphine borane derivatives **15** and **18** under these conditions. Firstly, the reaction was performed using diphenylphosphine borane in a mixture dichloromethane/toluene (1:1) in order to dissolve the maximum amount of [60]fullerene. After several trials, we found that the fullerenyldiphenylphosphine borane $C_{60}Ph_2P(BH_3)$ was obtained in good yield at room temperature upon stirring the reaction mixture overnight with light exclusion, using one equivalent of Cs_2CO_3, previously hydrated with 10 µL of water, and NBu_4Br.

Scheme 2. Synthesis of [60]fullerene phosphine borane derivatives supported by amino acid or dipeptide side chain



Under conditions (A), *sec*-phosphine borane amino ester **15a** reacted with [60]fullerene **19** to afford compound **20a** which was isolated in 63% yield (Scheme 2; Table 3, entry 2). The ^1H NMR spectrum of this product exhibits two doublets at 7.12 and 7.20 ppm, respectively, which correspond to the fullerene protons resulting from the hydrophosphination. Interestingly, the value of the

coupling constant ($^3J_{HP}$= 23.7 Hz) and the presence of two doublets demonstrate that the 1,2-addition indeed took place and that an epimeric mixture in 1:1 ratio had formed due to the chirality at the phosphorus centre. The NMR analysis did not show the formation of stereoisomers by grafting the P*-chirogenic moitey at the surface of fullerene, due to a possible lack of its symmetry.[3b] The nucleophilic addition of **15** to [60]fullerene **19** under PTC conditions proceeds *via* the deprotonation of the *sec*-phosphine borane amino acid derivative **15** at the surface of Cs_2CO_3 leading to the product **20** after subsequent protonation (Figure 2b). A similar mechanism could be envisaged for the hydrophosphination of [60]fullerene by the *sec*-phosphine borane dipeptide **18** into the addition product **21**.

Table 3. Preparation of [60]fullerene phosphine borane amino acid **20** and dipeptide derivatives **21**

entry	*sec*-phosphine borane substrate R	R[1]		Conditions	C_{60}-phosphine borane derivative	d.r [a]	yield (%)[b]
1	Boc	All	**15a**	*n*-BuLi/ -78°C THF/toluene	**20a**	-	< 10
2	”	”	”	**A**[c]	”	1:1	63
3	Boc	Bn	**15b**	”	**20b**	1:1	60
4	H	Bn	**15c**	”	**20c**	1:0.9	80
5	Boc	Me	**18a**	**B**[d]	**21a**	1.5:1	76
6	Boc	*t*-Bu	**18b**	**A**[c]	**21b**	1:1	76
7	Boc	H	**18d**	”	**21c**	-	44
8	H	H	**18e**	”	**21d**	1:1	39

[a] Diastereomeric ratio determined by NMR and after chromatography. [b] Isolated yields. [c] Conditions **A**: the reactions are performed with protection of light at rt in 4 mL of a mixture CH_2Cl_2/toluene (1:1) and with 1 equiv. of [60]fullerene **19**, dipeptide **18**, $(n\text{-Bu})_4NBr$ and Cs_2CO_3; 10 µL of H_2O are previously added to Cs_2CO_3. [d] Conditions **B**: no addition of H_2O to Cs_2CO_3.

Under the conditions (A), the reaction of *sec*-phosphine borane amino esters **15b** and **15c** with the [60]fullerene **19** led to the corresponding C_{60}-phosphine borane derivatives **20b** and **20c** as epimeric mixtures close to 1:1 and in yields up to 80% (Scheme 2; Table 3, entries 3, 4). In addition, when *sec*-phosphine borane dipeptide compounds **18b**, **18d** and **18e** were reacted with the [60]fullerene under the conditions (**A**), the corresponding C_{60}-derivatives **21b-d** were obtained in yields up to 76% (Table 3, entries 6-8). It should be noted that grafting *sec*-phosphine borane dipeptides **18d** and

18e bearing a free carboxylic acid function to [60]fullerene was also achieved under these conditions (Table 3, entries 7, 8). Finally, when the reaction of *sec*-phosphine borane dipeptide **18a** (bearing a methyl ester group) with [60]fullerene was performed under the PTC-conditions (**A**), the addition product **21a** was not obtained. However, when compound **18a** was reacted with [60]fullerene without previous addition of water to the base (PTC-conditions **B**), the corresponding dipeptide fullerene derivative **21a** was obtained as an epimeric ratio 1.5:1 and in 76% yield (Table 3, entry 5). We explained this result by an easier saponification of the methyl ester group in the presence of traces of water that the corresponding *t*-butyl, allyl or benzyl esters.

Electrochemical behaviour of the C_{60}-phosphine borane amino ester 20c

The electrochemical behaviour of C_{60}-phosphine borane amino ester **20c** was investigated by cyclic voltammetry (CV) at room temperature in dichloromethane containing 0.1M of Bu_4NBF_4. Figure 3a shows the CV of compound **20c** and [60]fullerene **19** recorded at a scan rate of 0.1 Vs^{-1}. They both exhibit three reversible reduction steps at -0.41, -0.81, -1.33 for **20c** and -0.36, -0.75, -1.20 V/ SCE for **19**, respectively, which corresponded each to a single electron transfer, as established by linear voltammetry on ultramicroelectrode. The first reduction step (at -0.41 V/ SCE) corresponds to the reduction of the C_{60} substituent of **20c** into the corresponding radical anion [**20c**]$^{\cdot}$ whereas the two remaining systems are assigned to the formation of di- and tri-anion derivatives, respectively (Figure 3a).[27] It should be noted that the reduction potentials of compounds **20c** are cathodically shifted by -0.05 to -0.13 V, by comparison to the parent [60]fullerene **19** under the same conditions. This shift can be explained by the loss of a double bond on the fullerene core which must raise the LUMO of compound **20c**, as demonstrated in previous substituted fullerene derivatives,[28] and by the weak electron-releasing character of the phosphine borane group.[21b]

Interestingly, careful examination of the third anodic wave of compound **20c** showed a weak additional peak at the same potential as the [60]fullerene parent peak (*i.e.* -1.20 V/ SCE; Figure 3a). The occurrence of this new peak is consistent with partial decomposition of compound **20c**, as similar observation were previously reported by Nakamura *et al*. for C_{60}-phosphine borane

compounds.[21b] We next performed a voltammetry and spectroelectrochemical study of the reduction products obtained after controlled-potential-electrolysis (CPE) of compound **20c** at -0.70 V (first reduction) and at -1.20 V (second reduction). The corresponding cyclic voltammograms before and after CPE at – 1.20 V are shown in Figure 3b.

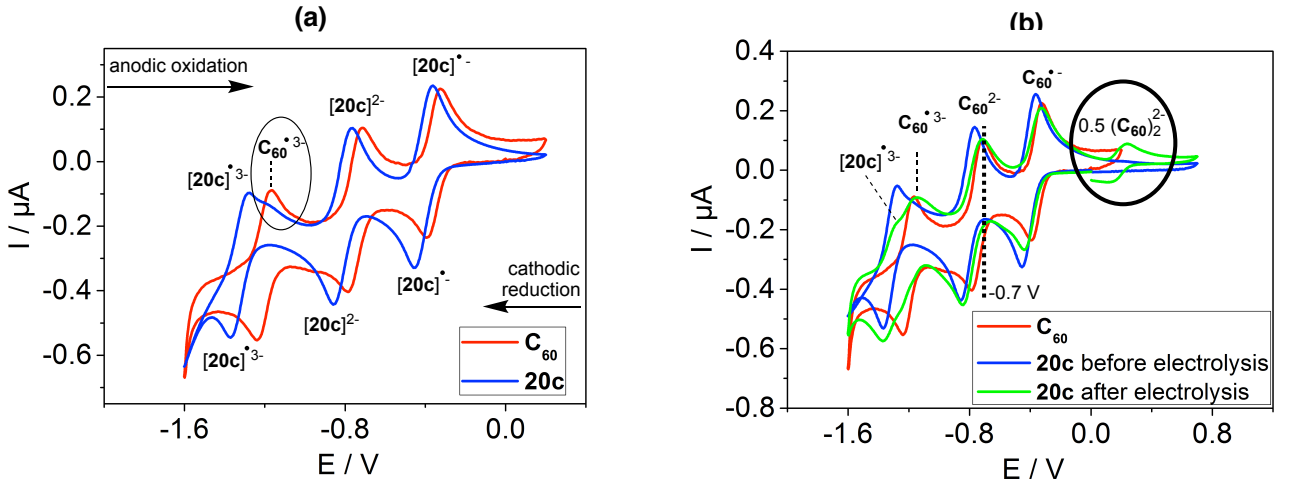


Figure 3. (a) Cyclic voltammograms of compound **20c** and [60]fullerene **19** (c= 2.10^{-4}M) in CH_2Cl_2 with Bu_4NBF_4 (0.1M) at a scan rate of 0.1 $V.s^{-1}$. (b) Cyclic voltammetry of **20c** in the same conditions as (a) (blue curve) and after CPE of **20c** at -1.20 V (green curve).

Interestingly, after electroreduction at -1.20 V the voltammogram exhibits new redox system at +0.19 V whereas the three other reversible processes are anodically shifted as to be superimposable to the CV-pattern of the free [60]fullerene **19** (Figure 3b). The intensity of this new redox system (at +0.19 V) increased with the charge consumed and when the imposed potential moved from -0.70 to -1.20 V). We attribute the new waves to the formation of a species arising from the retro-hydrophosphination of compound **20c** into free [60]fullerene and *sec*-phosphine borane amino ester **15c** (Scheme 2). This is supported by the mass spectroscopy analysis of the electrolyzed mixture of **20c** at -1.20 V, which showed two ions at m/z 721 and 460 assigned to the $[C_{60}+H]^+$ and [**15c**+2Na-H]$^+$ adducts, respectively, corresponding to the presence of free [60]fullerene and *sec*-phosphine borane amino ester moiety in the medium (see Supplementary Information). Single electron reduction of **20c** must lead to the corresponding radical anion [**20c**]$^{\bullet-}$ which dissociates into **15c** and

the radical anion $[C_{60}]^{\bullet-}$, the latter dimerizing to the dianion $(C_{60})_2^{2-}$ responsible of the waves at +0.19 V (Figure 3b). On the other hand, the formation of the dianion $[(C_{60})_2]^{2-}$ could also come from interaction of the dianion formed at the second reduction stage (*i.e.* $(C_{60})_2^{2-}$) with the free [60]fullerene.[29] While the dimeric [60]fullerene species $(C_{60})_2^{2-}$ is not detected by mass spectroscopy, probably because of its instability, its formation has been previously reported in the case of the retro Bingel-Hirsch reaction of methanofullerene by CPE.[30]

Additional informations about the retro-hydrophosphination reaction are obtained by spectroelectrochemistry of compound **20c** at -0.70 V and -1.20 V (Figure 4). Prior to electrolysis, the absorption spectra of [60]fullerene **19** and compound **20c** show two strong bands at 273, 332 nm and 284, 318 nm, as well as a weaker third one at 409, 437 nm, respectively (Figure 4a).

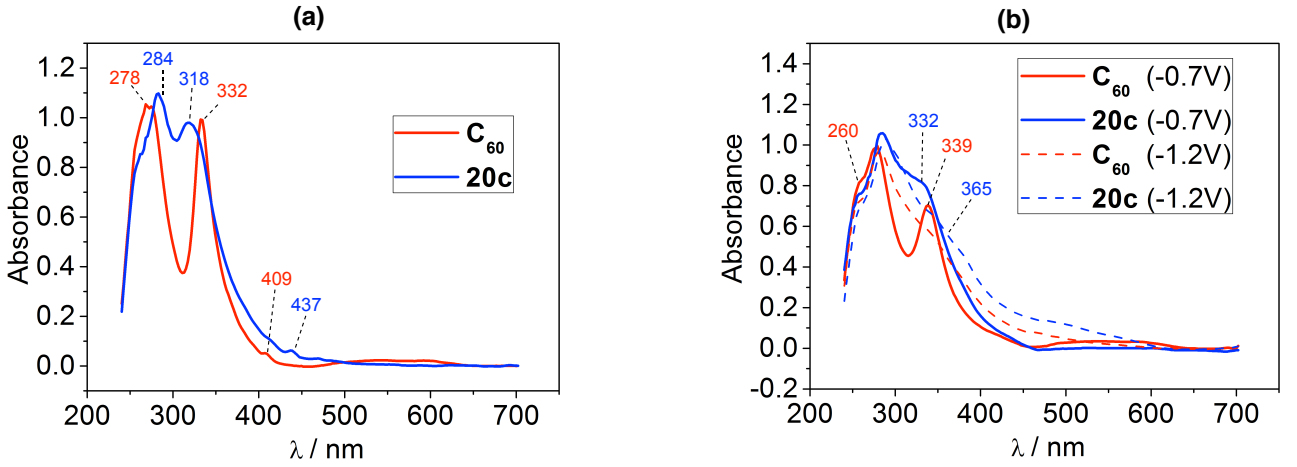


Figure 4. UV-vis spectra of [60]fullerene **19** and compound **20c** (c= 2.10^{-4}M) in CH_2Cl_2 with Bu_4NBF_4 (0.1M): (a) before electrolysis. (b) after electrochemistry at -0.70 V and -1.20 V.

Figure 4b shows the absorption spectra of [60]fullerene **19** and compound **20c** after electrolysis at -0.70 V and -1.20 V. In the former case, spectra became broader and does not change after 15 min, showing a lower intensity for the second band at 339 and 332 nm, respectively, the strengthening and the apparition of shoulders at 260 and 365 nm. When the electrolysis is achieved at -1.20 V, the absorption spectra of [60]fullerene **19** and compound **20c** are striking similar and show a complete loss of resolution in the 250-400 nm region (Figure 4b). These results which are consistent with the

spectroelectrochemistry of free [60]fullerene **19**,[31] confirm its formation by electrolysis of **20c** and the retro-hydrophosphination reaction under these conditions.

CONCLUSION

This article describes a new method for linking amino acid and peptide derivatives to [60]fullerene by hydrophosphination using a secondary phosphine borane as grafting group. Firstly, the stereoselective synthesis of secondary phosphine borane amino acid derivatives bearing suitable protecting groups was achieved in excellent yields, by alkylation under phase transfer catalysis (PTC) of phenylphosphine borane with γ-iodo-α-amino ester reagents. Secondly, saponification of a *sec*-phosphine borane amino ester and coupling with α,γ-diamino esters led to the corresponding dipeptide compounds which could be deprotected to afford derivatives bearing a free carboxylic acid function. Finally, the grafting of the *sec*-phosphine borane amino acid or dipeptide compounds to C_{60} was achieved by hydrophosphination reaction under phase transfer catalysis (PTC), to afford the corresponding [60]fullerene derivatives in yields up to 80%. This synthesis, which proceeds under moderate basic and dilute conditions (0.03 M), affords [60]fullerene amino acid or peptide derivatives as epimeric mixtures (≈ 1:1) due to the P-chirogenic centre, but without racemization of the asymmetric carbon atoms.

The electrochemical behavior of a C_{60}-phosphine borane amino ester has been investigated by cyclic voltammetry and spectroelectrochemistry after controlled-potential-electrolysis, and this has clearly shown that reduction of the adduct led to a retro-hydrophosphination reaction releasing the free [60]fullerene and the starting *sec*-phosphine borane amino ester moiety.

Consequently, the use of *sec*-phosphine borane amino acid and dipeptide derivatives in the hydrophosphination under phase transfer catalysis has demonstrated its efficiency in the functionalization of [60]fullerene derivatives. Finally, the hydrophosphination and retro-hydrophosphination reactions offer a promising new strategy for a reversible immobilization of amino acids or peptides on carbon nanomaterials such as [60]fullerene.

EXPERIMENTAL SECTION

General Information. All reactions were carried out using standard Schlenk techniques under inert atmosphere. Tetrahydrofuran (THF), diethyl ether and toluene were distilled from sodium/benzophenone and stored under argon. Dimethylformamide (DMF) and dichloromethane were distilled from CaH_2 under argon prior to use. The ethyl acetate, petroleum ether (PE), ethanol, were purchased in anhydrous form. For HPLC, hexane and 2-propanol were of chromatographic grade and used without purification. The reagents phenylphosphine **12**, borane dimethylsufide (BH_3.DMS), [60]fullerene, cesium carbonate (Cs_2CO_3), cerium chloride ($CeCl_3$. 7 H_2O), ethyl-di-*i*-propylamine (DIPEA), O-(7-Aza-1H-benzotriazol-1-yl)-*N*,*N*,*N*',*N*'-tetramethyl uronium hexafluorophosphate (HATU), tetrabutylammonium bromide, L-aspartic acid were purchased from commercial sources. Cs_2CO_3 are previously dried by heating at 200°C under vacuum, during 5 min. Reactions were monitored by thin-layer chromatography (TLC) using 0.25 mm E. Merck precoated silica gel plates. Flash chromatographies were performed with the indicated solvents using silica gel 60 (60AAC, 35-70 μm). The ^{1}H-, ^{13}C-, ^{31}P-spectra were recorded on 600, 500 or 300 MHz spectrometers at ambient temperature using TMS as internal reference for ^{1}H, ^{13}C NMR and phosphoric acid (85%) as external references for ^{31}P-NMR. Data are reported as s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br.s = broad signal, coupling constant(s) in Hertz, integration. HPLC analyses were performed on a chromatograph equipped with a UV detector at λ = 210 and 254 nm. Infrared spectra were recorded on FT-IR instrument and the data are given in cm^{-1}. Melting points were measured on a Kofler melting points apparatus and are uncorrected. Optical rotation values were determined at 20 °C on a polarimeter at 589 nm (sodium lamp). The mass spectra and accurate mass measurements (HRMS) were performed under (ESI) conditions with a micro Q-TOF detector or Orbitrap detector, or in the MALDI/TOF reflectron mode using dithranol as a matrix. Elemental analyses were measured with a precision superior to 0.3% on a CHNS-O instrument apparatus. The phenylphosphine borane **13** was prepared by complexation of **12** with the borane dimethylsulfure according to a modified procedure described in literature.[23] The allyl, benzyl,

methyl (*S*)-2-amino-4-iodobutanoate derivatives **14a-d** and **14f** were synthesized as previously described from L-aspartic acid.[20b,c] All PTC reactions with [60]fullerene **19** was performed out of light by wrapping the flask with aluminium foil.

Electrochemistry. An Amel 552 potentiostat (output voltage 200 V at full load) and a Tacusel IGN5-N an integrator were used in preparative electrolysis. All the other electrochemical experiments were performed with a μAUTOLAB III (Metrohm) potentiostat connected to a PC and the data collected were analyzed using the Nova® 1.11 software. Electrochemistry was carried out by means of a three-electrode configuration consisting of a platinum working electrode, a platinum wire as counter-electrode and a saturated calomel electrode (SCE) as reference. The reference electrode was separated from the solution by a glass chamber with a porous tip filled up with a saturated solution of Bu_4NBF_4 in CH_2Cl_2. Potentials were reported *vs* the SCE. The working electrode was a platinum disk (1.6 mm in diameter) in cyclic voltammetry (CV), a homemade ultramicroelectrode (100 μm in diameter, Bioanalytical System) in linear voltammetry (LV) and a large Pt grid electrode in electrolysis. The Pt disk electrodes were soaked for 10 min in KOH (2M), polished with 0.1 μm alumina, etched for 10 min in concentrated sulfuric acid (2M) and sonicated 10 min in water, and then in absolute ethyl alcohol. The solutions were deoxygenated for 10 min with argon and a positive overpressure of argon was maintained above the electrolyte during the entire measurement performed at room temperature. In LV, the scan rate was lowered to 20 $mV.s^{-1}$ to ensure the establishment of a steady-state regime.

Spectroelectrochemistry. The *in situ* spectroelectrochemical experiments were performed with a BioLogic cell having an optical path of 1 mm. The working electrode was a Pt grid, the reference electrode an SCE and the counter electrode a Pt wire. The spectroelectrochemical experiments were carried out with a μAUTOLAB III (Metrohm) potentiostat. The spectra were recorded every 9 seconds by a UV-visible diode array spectrometer (KINSPEC II/MMS-16 VIS, BIOLOGIC) running in the kinetic mode with external trigger. The 150 W Xe lamp and the spectrometer were connected to the cell by optical fibers.

***t*-Butyl (*S*)-2-bis(*t*-butoxycarbonyl)amino-4-iodo-butanoate 14e.** To a solution of triphenylphosphine (1.76 g, 6.7 mmol) and iodine (1.77 g, 7.0 mmol) in THF (10 mL) was added a solution of *t*-butyl (*S*)-2-bis(*t*-butoxycarbonyl)amino-4-hydroxy-butanoate[32] (1.39 g, 3.7 mmol) and imidazole (0.61 g, 8.9 mmol) in THF (100 mL). The mixture was stirred during 2 h at room temperature before hydrolysis with a 20% NaCl solution (100 mL). After extraction with ethyl acetate (3 x 50 mL), the organic phases were dried over $MgSO_4$, filtered and evaporated. The residue was purified by column chromatography on silica gel using a mixture ethyl acetate/petroleum ether (1:9) as eluent to give **14e** as a white amorphous solid (1.53 g, 85%). R_f: 0.43 (ethyl acetate/petroleum ether 1:9); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.44 (s, 9H), 1.51 (s, 18H), 2.35-2.37 (m, 1H), 2.59-2.62 (m, 1H), 3.18-3.25 (m, 2H), 4.83-4.84 (m, 1H); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 2.3, 26.2 (2s), 34.2, 59.4, 81.8, 83.2, 152.4, 169.0; FTIR (neat): 2975, 2934, 1737, 1696, 1365, 1348, 1225, 1133, 993, 962, 852, 806, 780, 770; Analysis calcd. for $C_{18}H_{32}NO_6I$: C 44.54, H 6.65, N 3.64; found: C 44.55, H 6.60, 3.89.

Allyl (*S*)-2-bis(*t*-butoxycarbonyl)amino-4-(phenylphosphino-borane)butanoate 15a. Phenylphosphine borane **13** (62 mg, 0.50 mmol) and tetrabutylammonium bromide (16.1 mg, 0.05 mmol) were dissolved in dichloromethane (1 mL). Allyl (*S*)-2-bis(*t*-butoxycarbonyl)amino-4-iodobutanoate **14a** (94 mg, 0.20 mmol), cesium carbonate (0.49 g, 1.5 mmol) and distilled water (10 μL) were then added. After stirring at room temperature for 16 h, the mixture was filtered and the solvent was removed to afford a residue which was purified by column chromatography on silica gel using a mixture ethyl acetate/petroleum ether (1:8) as eluent. The compound **15a** was obtained as a colorless uncrystallised compound (91 mg, 98% yield). R_f: 0.51 (ethyl acetate/petroleum ether 1:8); $[\alpha]_D^{20°C}$= -15.8 (c 0.4, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.27-1.49 (m, 3H), 1.37 (s, 18H), 1.83-1.86 (m, 2H), 2.03-2.06 (m, 2H), 4.50-4.51 (m, 2H), 4.80-4.81 (m, 1H), 5.17-5.20 (m, 2H), 5.40 (dm, J = 375 Hz, 1H), 5.75-5.85 (m, 1H), 7.32-7.50 (m, 3H), 7.61-7.68 (m, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 20.7 (2d, J = 36.0 Hz), 24.9 (d, J = 22.5 Hz), 28.0, 58.3 (2d, J = 9.6 Hz), 66.0, 83.8, 118.4, 125.2 (2d, J = 30.0 Hz), 129.1 (2d, J = 3.3 Hz), 131.7 (d, J = 2.0 Hz), 131.9, 132.9 (2d, J = 2.7 Hz), 152.0 (2s), 169.6 (2s); ^{31}P {^{1}H} NMR (121.5 MHz, $CDCl_3$): δ -2.7 (br.s); ^{31}P NMR

(121.5 MHz, $CDCl_3$): δ -2.7 (dl, J = 375 Hz); FTIR (neat): 2980, 2384, 1791, 1740, 1700, 1367, 1132, 632; HRMS calcd. for $C_{23}H_{37}BNO_6PNa$ $[M+Na]^+$: 488.2349; found: 488.2363.

The enantiomeric excess (> 99% e.e.) was checked by HPLC analysis using a chiral column (Chiralcel OD-H), flow 0.5 mL.min^{-1}, with a mixture hexane/2-propanol (95:5) as eluent: t_1= 28.5 min, t_2= 33.7 min (D-epimeric mixture: t_3= 14.6 min, t_4= 17.0 min).

Benzyl (*S*)-2-bis(*t*-butoxycarbonyl)amino-4-(phenylphosphino-borane)butanoate 15b. Phenylphosphine borane **13** (180 mg, 1.45 mmol) and tetrabutylammonium bromide (75 mg, 0.23 mmol) were dissolved in dichloromethane (2.5 mL). Benzyl (*S*)-2-[(*t*-butoxycarbonyl)amino]-4-iodobutyrate **14b** (301 mg, 0.58 mmol), cesium carbonate (1.42 g, 4.35 mmol) and distilled water (55 μL) were then added. After stirring at room temperature for 16h, the mixture was filtered, and the solvent was removed to afford a residue which was purified by column chromatography on silica gel using a mixture ethyl acetate/petroleum ether (1:4) as eluent. The compound **15b** was obtained as colorless amorphous solid (0.17 g, 58% yield). R_f: 0.66 (ethyl acetate/petroleum ether 1:4); $[\alpha]_D^{20°C}$= -0.08 (c 0.4, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.3-1.40 (m, 3H), 1.33-1.34 (2s, 18H), 1.81-2.33 (m, 4H), 4.77-4.84 (m, 1H), 4.99-5.10 (m, 2H), 6.00 (d, 1H, J = 384 Hz), 7.24 (m, 5H), 7.35-7.44 (m, 3H), 7.56-7.63 (m, 2H); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 20.6-20.8 (2d, J = 36.0 Hz), 24.7 (d, J = 22.9 Hz), 27.9, 58.3-58.4 (2d, J = 13.5 Hz), 67.0, 83.7, 124.8-125.2 (2d, J = 31.4 Hz), 128.0, 128.3, 128.5, 129.1 (2d, J = 9.9 Hz), 131.8, 132.9 (2d, J = 9.0 Hz), 135.4 (d, J = 1.3 Hz), 152.1 (2s), 169.8 (2s); ^{31}P {^{1}H} NMR (121.5 MHz, $CDCl_3$): δ -2.7 (br.s); ^{31}P NMR (121.5 MHz, $CDCl_3$): δ -2.7 (br.d, J = 384 Hz); FTIR (neat): 2980, 2936, 2386, 2113, 1790, 1744, 1702, 1456, 1367, 1314, 1245, 1221, 1167, 1133, 1066, 1032, 996, 912, 850, 739, 698; HRMS calcd. for $C_{27}H_{39}BNO_6PNa$ $[M+Na]^+$: 538.2500; found: 538.2512.

The enantiomeric excess (> 99% e.e.) was checked by HPLC analysis using a chiral column (lux 5μ cellulose-1); flow: 1 mL.min^{-1} with a mixture hexane/2-propanol (93:7) as eluent: t_1= 36 min, t_2= 43 min (D-epimeric mixture: t_3= 14.2 min, t_4= 17.8 min).

Benzyl *(S)*-2-(*t*-butoxycarbonyl)amino-4-(phenylphosphino-borane)butanoate 15c. Phenylphosphine borane **13** (233 mg, 1.80 mmol) and tetrabutylammonium bromide (93 mg, 0.29

mmol) were dissolved in dichloromethane (2.5 mL). Benzyl (*S*)-2-(*t*-butoxycarbonyl)amino-4-iodobutyrate **14c** (302 mg, 0.72 mmol), cesium carbonate (1.76 g, 5.4 mmol) and distilled water (60 μL) were added. After stirring at room temperature for 16h, the mixture was filtered and the solvent was removed to afford a residue which was purified by column chromatography on silica gel using a mixture ethyl acetate/petroleum ether (1:4) as eluent. The compound **15c** was obtained as a colorless amorphous solid (254 mg, 85% yield). R_f : 0.50 (ethyl acetate/petroleum ether 1:4); $[\alpha]_D^{20°C}$= -22.7 (c 0.2, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.40-1.30 (m, 3H), 1.43 (s, 9H), 1.84-2.14 (m, 4H), 4.38 (s, 1H), 5.09-5.26 (m, 3H), 5.43 (d, 1H, *J* = 369 Hz), 7.28-7.66 (m, 10H); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 19.5 (d, *J* = 35.4 Hz), 19.6 (d, *J* = 35.4 Hz), 27.4 (d, *J* = 32.9 Hz), 28.3, 53.6, 67.4, 80.2, 124.6 (d, *J* = 56.0 Hz), 124.9 (d, *J* = 56.0 Hz), 128.4, 128.6, 128.7, 129.1 (d, *J* = 10.0 Hz), 131.9, 132.8 (d, *J* = 9.0 Hz), 135.2, 155.4, 171.5 (2s); ^{31}P {^{1}H} NMR (121.5 MHz, $CDCl_3$): δ -3.6 (br.s); ^{31}P NMR (121.5 MHz, $CDCl_3$): δ -3.6 (br.d, *J* = 369 Hz); FTIR (neat): 2977, 2665, 2387, 1742, 1712, 1501, 1441, 1366, 1251, 1164, 1063, 909, 699; HRMS calcd. for $C_{22}H_{31}BNO_4PNa$ $[M+Na]^+$: 438.1980, found: 438.1995.

The enantiomeric excess (> 99% e.e.) was checked by HPLC analysis using a Chiralcel OD-H, flow: 0.5 mL.min^{-1} using a mixture hexane/2-propanol (95:5) as eluent: t_1= 50.3 min, t_2= 57.8 min (D-epimeric mixture: t_3= 64.6 min, t_4= 79.6 min).

(*S*)-2-(*t*-Butoxycarbonyl)amino-4-(phenylphosphino-borane)butanoic acid 15d. To a solution of benzyl (*S*)-2-(*t*-butoxycarbonyl)amino-4-(phenylphosphino-borane)butyrate **15c** (0.17 g, 0.40 mmol) in 80% aqueous dioxane (3 mL) was added sodium hydroxide (1M) (0.4 mL, 0.40 mmol). The mixture was stirred at room temperature during 16 hours, acidified with hydrochloric acid (3M) to pH 3 and extracted with ethyl acetate (3 x 5 mL). The combined organic phases were dried over $MgSO_4$ and the solvent removed under vacuum to give the compound **15d** as colorless amorphous compound (79 mg, 61% yield). R_f : 0.27 (ethyl acetate); $[\alpha]_D^{20°C}$= +29.0 (c 0.4, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.40-1.50 (m, 3H), 1.42 (s, 9H), 1.94-2.12 (m, 4H), 4.21 (m, 1H), 5.10 (br.s, 1H), 5.15 (d, 1H, *J* = 357 Hz), 7.36-7.47 (m, 3H), 7.68 (m, 2H); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ

19.1-19.9 (2d, *J* = 36.5 Hz), 27.4-27.7 (2s), 28.4, 53.7-54.6 (2s), 80.8-82.6 (2s), 124.9 (d, *J* = 55.0 Hz), 129.3 (d, *J* = 10.3 Hz), 132.0, 133.0 (d, *J* = 8.9 Hz), 155.8-156.9 (2s), 174.6-175.5 (2s); $^{31}P\{^{1}H\}$ NMR (121.5 MHz, $CDCl_3$): δ -3.6 (br.s); ^{31}P NMR (121.5 MHz, $CDCl_3$): δ -3.6 (dl, *J* = 357 Hz); FTIR (neat): 3332, 2976, 2931, 2384, 1679, 1513, 1439, 1394, 1367, 1339, 1288, 1248, 1158, 1059, 1027, 910, 852, 742, 694; HRMS calcd. for $C_{15}H_{22}NO_4PNa$ $[M\text{-}BH_3+Na]^+$: 334.1178; found: 334.11546.

Methyl (*S*)-4-amino-2-bis(*t*-butoxycarbonyl)aminobutanoate 17a. This compound was prepared from the γ-iodo amino acid derivative **14d**, by subsequent substitution with sodium azide, then hydrogenation in presence of palladium catalyst (see Supporting Information).

Methyl (S)-2-bis(t-butoxycarbonyl)amino-4-azido-butanoate **24a**. A solution of methyl (*S*)-2-bis(*t*-butoxycarbonyl)amino-4-iodo-butanoate **14d** (0.50 g, 1.13 mmol) and NaN_3 (0.36 g, 5.52 mmol) in DMF (25 mL) was stirred at 40°C during 16 hours. The solvent was removed under vacuum and water was added (20 mL). The aqueous phase was extracted with ethyl acetate (3 x 20 mL) and the organic phases were dried over $MgSO_4$, filtered and evaporated. The crude product was purified by column chromatography on silica gel using a mixture ethyl acetate/petroleum ether (1:4) as eluent to give the methyl (*S*)-2-bis(t-butoxycarbonyl)amino-4-azido-butanoate **24a** as a yellow amorphous solid (0.39 g, 96% yield). R_f: 0.46 (ethyl acetate/petroleum ether 1:4): ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.47 (s, 18H), 2.06-2.08 (m, 1H), 2.39 (m, 1H), 3.40 (m, 1H), 3.69 (s, 3H), 4.97 (m, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 27.6, 33.9, 38.6, 52.0, 55.6, 83.0, 152.1, 171.2, 174.4; HRMS calcd. For $C_{15}H_{26}N_4O_6Na$ $[M+Na^+]$: 381.1745; found: 381.1739.

Compound **17a**. To a solution of methyl (*S*)-2-bis(*t*-butoxycarbonyl)amino-4-azido-butanoate **24a** (0.16 g, 0.44 mmol) in ethanol (10 mL) was added Pd/C 10% (16 mg). The solution was stirred at room temperature under H_2 (1 bar) during one hour. After filtration, the solvent was removed under vacuum to afford the compound **17a** as a colorless amorphous solid (0.108 g, 74% yield). R_f: 0.47 (ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.43 (s, 18H), 1.95-2.00 (m, 1H), 2.17-2.18 (m, 1H), 2.70 (m, 2H), 3.65 (s, 3H), 4.94-4.95 (m, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 27.8 (2s), 33.9, 38.6, 52.0, 55.6, 83.0, 152.1, 171.2, 174.4.

***t*-Butyl (*S*)-4-amino-2-bis(*t*-butoxycarbonyl)aminobutanoate 17b.** This compound was prepared from the γ-iodo amino acid derivative **14e**, by subsequent substitution with sodium azide, then hydrogenation in presence of palladium catalyst (see Supporting Information).

t-Butyl (S)-2-bis(t-butoxycarbonyl)amino4-azido-butanoate **24b**. A solution of *t*-butyl (*S*)- 2-bis(*t*-butoxycarbonyl)amino-4-iodo-butanoate **14e** (0.20 g, 0.41 mmol) and NaN_3 (0.13 g, 2.03 mmol) in DMF (10 mL) was stirred at 40°C during 16 hours. The solvent was removed under vacuum and water was added (20 mL). The aqueous phase was extracted with ethyl acetate (3 x 20 mL) and the organic phases were dried over $MgSO_4$, filtered and evaporated. The crude product was purified by column chromatography on silica gel with ethyl acetate/petroleum ether (1:9) as eluent to afford the *t*-Butyl (*S*)-2-bis(*t*-butoxycarbonyl)amino-4-azido-butanoate **24b** as white solid (0.125 g, 76% yield). mp < 40 °C; R_f 0.68 (ethyl acetate/petroleum ether 1:9); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.40 (s, 9H), 1.46 (s, 18H), 2.04-2.07 (m, 1H), 2.31 (m, 1H), 3.36 (m, 2H), 4.80 (m, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 28.0 (2 s), 29.2, 49.0, 56.6, 81.8, 83.2, 152.5, 169.3; FTIR (neat): 2979, 2937, 2362, 2101, 1734, 1690, 1568, 1463, 1435, 1381, 1307, 1270, 1237, 1148, 1121, 1051, 975, 909, 848, 789, 766, 734; HRMS calcd. for $C_{18}H_{32}N_4O_6Na$ $[M+Na]^+$: 423.2214; found: 423.2209.

Compound **17b**. To a solution of *t*-butyl (*S*)-2-bis(*t*-butoxycarbonyl)amino-4-azido-butanoate **24b** (0.13 g, 0.32 mmol) in ethanol (10 mL) was added Pd/C 10% (11 mg). The solution was stirred at room temperature under H_2 (1 bar) during one hour. After filtration, the solvent was removed under vacuum to afford the compound **17b** as colorless amorphous solid (0.07 g, 57% yield). R_f: 0.21 (ethyl acetate). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.40 (s, 9H), 1.46 (s, 18H), 1.85-2.13 (m, 4H), 2.72-2.74 (m, 2H), 4.81-4.82 (m, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 28.1 (2 s), 33.1, 39.0, 56.7, 81.4, 83.0, 152.7, 169.9; FTIR (neat): 3393, 2978, 2935, 2361, 1735, 1700, 1478, 1457, 1364, 1248, 1134, 972, 851.

Methyl (*S*)-4-amino-2-(*t*-butoxycarbonyl)aminobutanoate 17c. This compound was prepared from the γ-iodo amino acid derivative **14f**, by subsequent substitution with sodium azide, then hydrogenation in presence of palladium catalyst (see Supporting Information).

Methyl (S)-2-(t-butoxycarbonyl)amino-4-azido-butanoate **24c**.[33] A solution of methyl (*S*)-2-(*t*-butoxycarbonyl)amino-4-iodo-butanoate **14f** (0.40 g, 1.16 mmol) and NaN_3 (0.37 g, 5.72 mmol) in DMF (8 mL) was stirred at 40 °C during 16 h. The solvent was removed under vacuum and water was added (10 mL). Aqueous phase was extracted with ethyl acetate (3 x 10 mL) and the organic phases were dried over $MgSO_4$, filtered and evaporated. The residue was purified by column chromatography on silica gel using a mixture ethyl acetate/petroleum ether (1:4) as eluent to afford the methyl (*S*)-2-(*t*-butoxycarbonyl)amino-4-azido-butanoate **24c** as a colorless amorphous compound (0.29 g, 97% yield). R_f: 0.30 (ethyl acetate/petroleum ether 1:4); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.43 (s, 9H), 1.87-1.94 (m, 1H), 2.02-2.10 (m, 1H), 3.39 (t, J = 6.5 Hz, 2H), 3.75 (s, 3H), 4.37-4.39 (m, 1H), 5.19-5.21 (m, 1H); ^{13}C NMR (151 MHz, $CDCl_3$): δ 28.4, 32.0, 47.8, 51.4, 52.6, 80.3, 155.4, 172.6.

Compound **17c**.[34] To a solution of methyl (*S*)-2-(*t*-butoxycarbonyl)amino-4-azido-butanoate **24c** (0.21 g, 0.84 mmol) in ethanol (10 mL) was added Pd/C 10% (30 mg). The solution was stirred at room temperature under H_2 (1 bar) during one hour. After filtration, the solvent was removed under vacuum to afford the compound **17c** as colorless amorphous solid (60%, 0.12 g). R_f: 0.17 (ethyl acetate). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.45 (s, 9H), 2.00-2.20 (m, 1H), 2.33-2.50 (m, 1H), 2.75-2.95 (m, 2H), 3.66 (s, 3H), 4.10-4.30 (br.s, 2H), 4.90-5.00 (m, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 28.0, 31.7, 47.5, 52.4, 55.9, 83.7, 152.2, 171.0.

(*sec*-Phenylphosphino-borane)dipeptide 18a. To a mixture of (*S*)-2-[(*t*-Butoxycarbonyl)amino]-4-(phenylphosphino-borane)butyric acid **15d** (101 mg, 0.31 mmol), methyl *(S)*-4-amino-2-bis(*t*-butoxycarbonyl)amino-butyrate **17a** (102.5 mg, 0.31 mmol) and HATU (116.7 mg, 0.31 mmol) in dry DMF (0.5 mL) was added distilled DIPEA (0.28 mL, 1.6 mmol). After stirring 15h at room temperature, the solvent was removed under vacuum, water (3 mL) was added and the mixture was extracted with dichloromethane (4 x 5 mL). The organic phase was then dried over $MgSO_4$ and the solvent was removed to afford a residue which was purified by column chromatography on silica gel using a mixture ethyl acetate/petroleum ether (7:3) as eluent. The (*sec*-phenylphosphino)borane dipeptide **18a** was obtained as a yellow amorphous solid (91 mg, 46% yield). R_f: 0.60 (petroleum

ether/ethyl acetate 7:3); $[\alpha]_D^{20°C}$= -26.7 (c 0.7, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.34 (s, 9H), 1.42 (s, 18H), 1.73-1.79 (m, 1H), 1.93-1.96 (m, 4H), 2.23-2.24 (m, 1H), 2.88-2.98 (m, 1H), 3.47-3.53 (m, 1H), 3.64 (s, 3H), 4.05 (m, 1H), 4.69-4.75 (m, 1H), 5.05 (br.s, 1H), 5.38 (dl, *J* = 389 Hz, 1H), 6.58 (br.s, 1H), 7.37-7.40 (m, 3H), 7.57-7.63 (m, 2H); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 19.7 (d, *J* = 36.6 Hz), 27.6, 28.1, 28.4, 30.1, 36.4-36.5 (2s), 52.5, 56.1, 83.9 (2s), 124.8-125.2 (2d, *J* = 55.4 Hz), 129.2-129.3 (2d, *J* = 10.0 Hz), 132.0, 133.0 (2d, *J* = 8.3 Hz), 152.5 (2s), 170.8, 171.0 (2s); ^{31}P {^{1}H} NMR (121.5 MHz, $CDCl_3$): δ -3.5 (br.s); ^{31}P NMR (121.5 MHz, $CDCl_3$): δ -3.3 (br.d, *J* = 389 Hz); FTIR (neat): 3328, 2978, 2387, 1744, 1696, 1518, 1439, 1365, 1246, 1148, 1118, 1062, 914, 853, 752, 696, 663; HRMS calcd. for $C_{30}H_{51}BN_3O_9PNa$ $[M+Na]^+$: 662.3373; found: 662.3353.

(*sec*-Phenylphosphino-borane)dipeptide 18b. To a solution of (*S*)-2-(*t*-butoxycarbonyl)amino-4-(phenylphosphino-borane)butyric acid **15d** (101 mg, 0.31 mmol), *t*-butyl 4-amino-2-bis(*t*-butoxycarbonyl)amino-butyrate **17b** (124 mg, 0.31 mmol) and HATU (116.7 mg, 0.31 mmol) in dry DMF (0.5 mL) was added distilled DIPEA (0.28 mL, 1.6 mmol). After 24 h under stirring at room temperature, the solvent was removed under vacuum, water is added (3 mL) and the mixture washed with dichloromethane (3 x 5 mL). The organic phase was dried over $MgSO_4$ and the solvent was removed to afford a residue which was purified by column chromatography on silica gel using a mixture ethyl acetate/petroleum ether (3:7) as eluent. The (*sec*-phenylphosphino-borane)dipeptide **18b** was obtained as a white solid (97 mg, 46% yield). mp 56 °C (decomp.); R_f: 0.52 (petroleum ether/ethyl acetate 7:3); ^{1}H NMR (300 MHz, $CDCl_3$): 1.37 (m, 18H), 1.43 (m, 18H), 1.80-2.24 (m, 8H), 3.02-3.05 (m, 1H), 3.54-3.60 (m, 1H), 4.12-4.14 (m, 1H), 4.67-4.70 (m, 1H), 5.10 (br.s, 1H), 5.40 (d, *J* = 372 Hz, 1H), 6.70-6.76 (m, 1H), 7.44-7.50 (m, 3H), 7.65-7.68 (m, 2H); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 19.8 (d, *J* = 36.7 Hz), 27.5-27.6 (2s), 27.9, 28.0, 28.3, 29.2, 36.5, 54.5, 56.9, 81.6, 83.3 (2s), 124.7-125.2 (2d, *J* = 55.6 Hz), 129.1 (d, *J* = 10.2 Hz), 131.8, 132.8-132.9 (m), 152.7, 152.8, 169.3, 170.7 (2s); ^{31}P{^{1}H} NMR (121.5 MHz, $CDCl_3$): δ -3.3 (br.s); ^{31}P NMR (121.5 MHz, $CDCl_3$): δ -3.3 (br.d, *J* = 372 Hz); FTIR (neat): 3329, 2977, 2955, 2931, 2869, 2385, 2343, 1734, 1696, 1513, 1479, 1455, 1439, 1381, 1366, 1311, 1275, 1247, 1235, 1151, 1110, 1062, 1025, 955,

912, 848, 744, 694, 665, 609; HRMS calcd. for $C_{33}H_{57}BN_3O_9PNa$ $[M+Na]^+$: 704.3823; found: 704.3810.

(*sec*-Phenylphosphino-borane)dipeptide 18c. To a solution of (*S*)-2-(*t*-butoxycarbonyl)amino-4-(phenylphosphino-borane)butyric acid **15d** (463 mg, 1.43 mmol), methyl *(S)*-4-amino-2-(*t*-butoxycarbonyl)amino-butyrate **17c** (318 mg, 1.43 mmol) and HATU (540.2 mg, 1.43 mmol) in dry DMF (1.5 mL) was added distilled DIPEA (1.25 mL, 7.1 mmol). After 15 h under stirring at room temperature, the solvent was removed under vacuum, water (10 mL) was added and the mixtre was extracted with dichloromethane (4 x 5 mL). The combined organic phases were dried over $MgSO_4$ and the solvent removed to afford a residue which was purified by column chromatography on silica gel using a mixture ethyl acetate/petroleum ether (3:7) as eluent. The (*sec*-phenylphosphino-borane) dipeptide **18c** was obtained as a yellow amorphous product (162 mg, 21% yield). R_f: 0.55 (petroleum ether/ethyl acetate 7:3). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.38 (m, 18H), 1.61-1.99 (m, 6H), 2.97 (m, 1H), 3.53 (m, 1H), 3.66 (br.s, 3H), 4.13 (m, 1H), 5.35 (m, 2H), 5.38 (dl, J = 365 Hz, 1H), 7.11 (br.s, 1H), 7.38-7.46 (m, 3H), 7.62 (m, 2H); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 19.5-19.8 (2d, J = 33.6 Hz), 27.7, 28.3 (2s), 33.0, 35.7, 38.6, 51.0, 52.5, 54.5, 80.1, 80.3, 124.8-125.3 (2d, J = 32.1 Hz), 129.1 (d, J = 10.3 Hz), 131.8, 132.8-132.9 (2d, J = 9.2 Hz), 155.5, 156.0, 171.0, 172.8; ^{31}P $\{^1$H$\}$ NMR (202.5 MHz, $CDCl_3$): δ -3.3 (br.s); ^{31}P NMR (202.5 MHz, $CDCl_3$): δ -3.3 (br.d, J = 365 Hz); HRMS calcd. for $C_{25}H_{43}BN_3O_7PNa$ $[M+Na]^+$: 562.2824; found: 562.2823.

(*sec*-Phenylphosphino-borane)dipeptide 18d. To a solution of (s*ec*-phosphino-borane)dipeptide **18a** (0.85 g, 0.13 mmol) in 80% aqueous dioxane (1.2 mL) was added NaOH 1M (0.27 mL, 0.27 mmol). The mixture was stirred at room temperature during 5 h, then water (5 mL) were added and the aqueous phase was extracted with diethyl ether (3 x 10 mL). After acidification with HCl 3M to pH 3 and extraction with ethyl acetate (3 x 10 mL), the combined organic phases were dried over $MgSO_4$ and the solvent removed under vacuum to afford the (*sec*-phenylphosphino-borane)dipeptide **18d** as a colorless amorphous compound (50.4 mg, 62% yield). R_f: 0.25 (dichloromethane); ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.41 (s, 9H), 1.48 (s, 18H), 1.82-2.30 (m, 6H), 3.01-3.09 (m, 1H), 3.37-3.55 (m, 1H), 4.18 (m, 1H), 4.83 (m, 1H), 5.27-5.35 (m, 1H), 5.47 (d, J =

373 Hz, 1H), 6.84 (br.s, 1H), 7.43-7.52 (m, 3H), 7.65-7.69 (m, 2H); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 28.1, 28.4, 29.8, 36.6, 54.6, 55.9, 84.0, 129.3, 132.0, 133.0, 152.5. ^{31}P {^{1}H} NMR (202.5 MHz, $CDCl_3$): δ -3.5 (br.s); ^{31}P NMR (202.5 MHz, $CDCl_3$); δ -3.5 (br.d, J = 373 Hz); HRMS calcd. for $C_{29}H_{49}BN_3O_9PNa$ $[M+Na]^+$: 648.3213; found: 648.3192.

(*sec*-Phenylphosphino-borane)dipeptide 18e. To a solution of (s*ec*-phosphino-borane)dipeptide **18c** (0.12 g, 0.22 mmol) in 80% aqueous dioxane (1.7 mL) was added NaOH 1M (0.45 mL, 0.44 mmol). The mixture was stirred at room temperature during 5 h, then water (5 mL) was added and was washed with diethyl ether (3 x 10 mL). After acidification with HCl 3M to pH 3 and extraction with ethyl acetate (3 x 10 mL), the combined organic phases were dried over $MgSO_4$ and the solvent removed under vacuum to afford the (*sec*-phenylphosphino-borane)dipeptide **18e** as a colorless amorphous compound (99.3 mg, 86% yield). R_f: 0.25 (dichloromethane); ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.41 (m, 18H), 1.82-2.04 (m, 6H), 3.11 (m, 1H), 3.53 (m, 1H), 4.07-4.22 (m, 3H), 5.46 (d, J = 373 Hz, 1H), 5.50-5.55 (m, 2H), 7.42-7.48 (m, 3H), 7.63-7.73 (m, 2H); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 19.7-19.9 (2d, J = 33.2 Hz), 27.5, 28.4 (2s), 32.9, 36.0, 51.1, 54.7, 80.5 (2s), 124.8-125.2 (2d, J = 25.5 Hz), 128.6 (d, J = 10.2 Hz), 129.2 (d, J = 10.2 Hz), 130.2-130.3 (2d, J = 11.7 Hz), 131.9, 132.9-133.0 (2d, J = 8.8 Hz), 156.1, 156.4, 171.9, 174.4; ^{31}P {^{1}H} NMR (202.5 MHz, $CDCl_3$): δ -3.7 (br.s); ^{31}P NMR (202.5 MHz, $CDCl_3$): δ -3.7 (br.d, J = 373 Hz); HRMS calcd. for $C_{24}H_{40}BN_3O_7P$ $[M-H]^-$: 524.2702; found: 524.2727.

Allyl (*S*)-2-bis(*t*-butoxycarbonyl)amino-4-(fullerenylphenylphosphino-borane)butanoate 20a. To a mixture of 4 mL dichloromethane/toluene (1:1) was added allyl (*S*)-2-bis(*t*-butoxycarbonyl)amino-4-(phenylphosphino-borane)butanoate **15a** (60.5 mg, 0.13 mmol), cesium carbonate (41mg, 0.13 mmol) hydrated by 10 µL of distilled water, tetrabutylammonium bromide (42 mg, 0.13 mmol) and [60]fullerene **19** (93.6 mg, 0.13 mmol). After stirring at room temperature for 17 h under argon and out of light, the mixture was hydrolyzed at room temperature with 40 µL of concentrated HCl. After 5 min, 4 mL of distilled water were then added and the mixture was again stirred for 25 min. After extraction with dichloromethane (3 x 5 mL), the organic phases were dried, filtered and the solvent was removed under vacuum. The residue was purified by column

chromatography on silica gel using a mixture toluene/ethyl acetate (9:1) as eluent to afford the fullerene compound **20a** as a P-epimeric mixture (1:1) (97 mg, 63% yield). Brown amorphous solid; R_f: 0.54 (toluene/ethyl acetate 9:1); ^{1}H NMR (600 MHz, $CDCl_3$): δ 0.80-1.80 (m, 3H) 1.53-1.57 (2s, 18H), 2.53-2.65 (m, 1H), 2.93-3.36 (m, 2H), 4.72 (s, 2H), 5.19-5.20 (m, 1H), 5.31-5.33 (m, 1H), 5.39-5.43 (m, 1H), 5.98-5.99 (m, 1H), 7.10-7.22 (2d, 1H, J = 23.7 Hz), 7.71-7.80 (m, 3H), 8.29-8.41 (m, 2H); ^{13}C NMR (151 MHz, $CDCl_3$): δ 18.9-19.2 (2d, J = 34.4 Hz), 24.3-24.6 (2s), 28.1, 57.7 (m), 58.7-59.0 (2d, J = 16.3 Hz), 64.4 (d, J = 31.8 Hz), 66.1 (2s), 83.8, 83.9 (2s), 118.6 (2s), 123.0-123.2 (2d, J = 47.0 Hz), 125.4, 128.3, 129.1, 129.4, 131.7, 133.3, 134.6-134.7 (2d, J = 8.5 Hz), 135.6, 136.0, 137.4, 138.0, 139.8 (2s), 139.9, 140.6-140.7 (4s), 141.6 (2s), 141.8 (2s), 142.0 (2s), 142.2 (2s), 142.3, 142.7, 142.9, 143.4, 143.5, 144.5 (2s), 145.0 (2s), 145.5-145.9 (m), 146.3-146.6 (m), 146.9 (2s), 147.0 (2s), 147.4, 147.5, 149.2, 152.0 (2s), 152.4, 169.4, 169.9; ^{31}P{^{1}H} NMR (202.5 MHz, $CDCl_3$): δ +40.6 (br.s); HRMS calcd. for $C_{83}H_{37}BNO_6PNa$ $[M+Na]^+$: 1208.2357; found: 1208.2350.

The enantiomeric excess (> 99% e.e.) was checked by HPLC on chiral column (Chiralcel OD-H), flow: 0.5 mL.min^{-1} and using a mixture hexane/2-propanol (95:5) as eluent: t_1 = 22 min, t_2= 27 min.

Benzyl (*S*)-2-bis(*t*-butoxycarbonyl)amino-4-(fullerenylphenylphosphino-borane)butanoate 20b. To a mixture of 4 mL dichloromethane/toluene (1:1) was added benzyl (*S*)-2-[bis(*t*-butoxycarbonyl)amino]-4-(phenylphosphino-borane) butanoate **15b** (67.0 mg, 0.13 mmol cesium carbonate (41 mg, 0.13 mmol) hydrated by 10 µL of distilled water, tetrabutylammonium bromide (42 mg, 0.13 mmol) and [60]fullerene **19** (93.6 mg, 0.13 mmol). After stirring at room for 17 h under argon and out of light, the mixture was hydrolyzed with 40µL of concentrated HCl. After 5 min, distilled water (4 mL) were then added and the mixture was again stirred for 25 min. after extraction with dichloromethane (3 x 5 mL), the organic phases were dried, filtered and evaporated. The residue was purified by column chromatography on silica gel using a mixture of toluene/ethyl acetate (9:1) as eluent to give **20b** as a P-epimeric mixture (1:1) (96 mg, 60% yield). Brown amorphous solid; R_f: 0.75 (toluene/ethyl acetate 9:1); ^{1}H NMR (600 MHz, $CDCl_3$): δ 0.92-1.60 (m, 3H), 1.40 (s, 9H), 1.44 (s, 9H), 2.22-2.23 (m, 0.5H), 2.48-2.56 (m, 1H), 2.98-3.09 (m, 2H), 3.25-

3.28 (m, 0.5H), 5.11-5.20 (m, 3H), 7.01-7.07 (2d, J = 24.8 Hz, 1H), 7.30-7.34 (m, 5H), 7.64-7.65 (m, 3H), 8.20-8.27 (m, 2H); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 19.0-19.4 (2d, J = 34.0 Hz), 24.4-24.5 (2d, J = 3.1 Hz), 28.1, 57.7-57.8 (2d, J = 3.5 Hz), 58.9-59.1 (2d, J = 16.7 Hz), 64.4 (d, J = 32.0 Hz), 67.2-67.3 (2s), 83.8-83.9 (2s), 123.0-123.2 (2d, J = 23.6 Hz), 125.4, 128.2-128.5 (m), 128.7, 129.4 (2d, J = 3.1 Hz), 133.3, 134.6-134.7 (2d, J = 10.5 Hz), 135.5-135.6 (2d, J = 2.1 Hz), 136.1 (2d, J = 8.4 Hz), 137.5 (m), 139.8-139.9 (3s), 140.6, 140.7, 141.6-142.0 (m), 142.2, 142.3 (2s), 142.7, 142.9, 143.4, 143.5, 144.4, 144.5, 145.0, 145.5, 145.6-146.0 (m), 146.3 (2s), 146.5-146.7 (m), 146.9 (2s), 147.0 (2s), 147.5 (d, J = 12.7 Hz), 149.1-149.2 (m), 152.1, 152.4 (2s), 169.6, 170.1; ^{31}P{^{1}H} NMR (202.5 MHz, $CDCl_3$): δ +40.7 (br.s); HRMS calcd for $C_{87}H_{38}BNO_6P$ $[M\text{-}H]^-$: 1234.2524; found: 1234.2560.

Benzyl (*S*)-2-(*t*-butoxycarbonyl)amino-4-(fullerenylphenylphosphino-borane)butanoate 20c. To a mixture of 4 mL dichloromethane/toluene (1:1) was added benzyl (*S*)-2-(*t*-butoxycarbonyl)amino-4-(phenylphosphino-borane)butanoate **15c** (50 mg, 0.12 mmol), cesium carbonate (39 mg, 0.12 mmol) hydrated by 10 µL of distilled water, tetrabutylammonium bromide (39 mg, 0.12 mmol) and [60]fullerene **19** (86.4 mg, 0.12 mmol). After stirring at room temperature for 17 h under argon and out of light, the mixture was hydrolyzed with 40 µL of concentrated HCl. After 5 minutes, at 4 mL of distilled water were added and the mixture was again stirred 25 min. After extraction with dichloromethane (4 x 5 mL), the organic phases were dried, filtered and evaporated. The residue was purified by column chromatography on silica gel using dichloromethane as eluent to afford the compound **20c** as a P-epimeric mixture (1:0.9) (109 mg, 80% yield). Brown amorphous solid; R_f: 0.54 (dichloromethane); ^{1}H NMR (600 MHz, $CDCl_3$): δ 0.8-1.7 (m, 3H), 1.34-1.36 (2s, 9H), 1.92-1.97 (m, 1H), 2.16 (m, 0.5H), 2.55-2.56 (m, 0.5H), 2.70-2.97 (m, 2H), 4.50 (br.s, 1H), 5.13-5.17 (m, 3H), 6.86-6.97 (2d, J = 24.9 Hz, 1H), 7.28 (m, 5H), 7.54-7.61 (m, 3H), 8.08 (dt, J = 31.9, 8.1 Hz, 2H); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 17.8-18.2 (2d, J = 31.0 Hz), 27.3, 28.4-28.5 (2s), 54.1, 57.7 (d, J = 10.7 Hz), 64.3 (d, J = 32.1 Hz), 67.7-67.8 (2s), 80.5, 122.9-123.2 (2d, J = 8.1 Hz), 128.5-128.8 (m), 128.9 (d, J = 3.8 Hz), 129.3-129.4 (m), 133.3 (3s), 134.6 (d, J = 8.2 Hz), 135.1 (d, J = 10.6 Hz), 135.5-135.6 (m), 136.0, 137.3-137.4 (m), 139.8

(2s), 140.6 (3s), 141.6 (br.s), 141.7, 141.8-141.9 (m), 142.0 (3s), 142.2, 142.3 (3s), 142.7, 142.9, 143.4, 143.5, 144.4 (d, J = 6.0 Hz), 144.9, 145.0, 145.5, 145.6 (2s), 145.7, 145.8 (2s), 145.9, 146.5 (3s), 146.6 (3s), 146.8, 146.9, 147.0, 147.5 (d, J = 12.7 Hz), 149.0 (m), 152.2-152.3 (m), 155.5, 171.5-171.6 (2s); FTIR (neat): 3347, 2971, 2923, 2384, 2191, 2086, 1979, 1815, 1707, 1493, 1363, 1246, 1212, 1156, 1054, 999, 910, 856, 727, 694, 620, 576, 523, 457, 441, 427, 414, 396, 368, 327; $^{31}P\{^{1}H\}$ NMR (202.5 MHz, $CDCl_3$): δ +40.5 (br.s); HRMS calcd. for $C_{82}H_{30}BNO_4P$ $[M-H]^-$: 1134.2000; found: 1134.2053.

The enantiomeric excess (> 99% e.e.) was checked by HPLC analysis on Chiralcel OD-H, flow: 1 $mL.min^{-1}$, using a mixture hexane/2-propanol (85:15) as eluent: t_1= 24 min, t_2= 32 min.

(Fullerenylphenylphosphino-borane)dipeptide 21a. To a mixture of 2 mL dichloromethane/toluene (1:1) were added *sec*-phenylphosphine-borane dipeptide **18a** (32 mg, 0.05 mmol, dry cesium carbonate (16.3 mg, 0.05 mmol), tetrabutylammonium bromide (15.5 mg, 0.05 mmol) and [60]fullerene **19** (36 mg, 0.05 mmol). After stirring at room temperature under argon for 23 h and out of light, the mixture was hydrolyzed by 20 µL of concentrated HCl. After 5 minutes, distilled water (4 mL) was added and the mixture again stirred 25 min. After extraction with dichloromethane (3 x 5 mL), the organic phases were dried, filtered and the solvent removed under vacuum. The residue was purified by column chromatography on silica gel using a mixture dichloromethane/ethyl acetate (4:1) as eluent to afford the compound **21a** as a P-epimeric mixture in 1.5:1 ratio (52 mg, 76% yield). Brown amorphous solid; R_f: 0.54 (dichloromethane/ethyl acetate 4:1); ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.40 (s, 9H), 1.49 (2s, 18H), 1.99 (br.s, 1H), 2.00-2.05 (m, 2H), 2.24-2.34 (m, 2H), 2.53-2.54 (m, 0.5H), 2.89 (m, 0.5H), 3.07 (m, 2H), 3.57 (m, 1H), 3.71 (s, 3H), 4.35-4.40 (m, 1H), 5.27-5.30 (m, 1H), 5.35 (d, J = 8.1 Hz, 1H), 6.77-6.85 (2t, J = 7.3 Hz, 1H), 7.00-7.08 (2d, J = 26.0 Hz, 1H), 7.64-7.68 (m, 3H), 8.21-8.25 (m, 2H); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 18.1 (d, J = 34.0 Hz), 27.2, 28.1, 28.4-28.5 (2s), 29.8, 30.0, 36.5 (d, J = 10.7 Hz), 52.6, 55.0, 56.2 (d, J = 8.7 Hz), 57.7 (d, J = 9.6 Hz), 83.9, 123.1 (d, J = 47.3 Hz), 128.7, 129.3, 129.4 (m), 133.3, 134.7 (m), 135.6, 136.1 (2s), 137.4, 139.9 (m), 140.6, 140.7, 141.7-141.9 (m), 142.0 (d, J = 4.1 Hz), 142.2, 142.3 (2s), 142.7, 142.9, 143.2, 143.4 (d, J = 9.2 Hz), 144.5 (d, J = 6.0 Hz), 144.9, 145.0,

145.5, 145.6 (2s), 145.7, 145.8, 145.9, 146.0, 146.3, 146.5-146.7 (m), 146.9 (2s), 147.0 (2s), 147.5 (2s), 149.1-149.2 (m), 152.4 (2s), 152.5 (2s), 155.9, 170.9, 171.0; $^{31}P\{^{1}H\}$NMR (202.5 MHz, $CDCl_3$): δ +40.4 (br.s); FTIR (neat): 3292, 2973, 2922, 2851, 2387, 2346, 1693, 1436, 1364, 1232, 1148, 1117, 1054, 852, 749, 697, 619, 609, 521, 474, 450, 426, 380, 366, 318; HRMS calcd. for $C_{90}H_{51}BN_3O_9PNa$ $[M+Na]^+$: 1382.3362; found: 1382.3455.

(Fullerenylphenylphosphine-borane)dipeptide 21b. To a mixture of 3 mL dichloromethane/toluene (1:1) were added *sec*-phenylphosphine borane dipeptide **18b** (47.7 mg, 0.07 mmol), cesium carbonate (22.8 mg, 0.07 mmol) hydrated by 10 µL of distilled water, tetrabutylammonium bromide (23.7 mg, 0.07 mmol) and [60]fullerene **19** (50.4 mg, 0.07 mmol). After stirring at room temperature under argon for 16 h and out of light, the mixture was hydrolyzed with 30 µL of concentrated HCl. After 5 min, 4 mL of distilled water were added and the mixture again stirred 25 min. After extraction with dichloromethane (3 x 5 mL), the organic phases were dried, filtered and evaporated to afford a residue which was purified by column chromatography on silica gel using a mixture dichloromethane/acetone (25:1) as eluent to afford the compound **21b** as a P-epimeric mixture in 1:1 ratio (75 mg, 76% yield). Brown amorphous solid; R_f: 0.54 (dichloromethane/acetone 25:1); ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.40-1.51 (m, 36H), 2.01 (m, 2H), 2.24-2.28 (m, 2H), 2.92-2.93 (m, 1H), 3.08-3.15 (m, 2H), 3.56-3.74 (m, 1H), 4.35-4.38 (m, 1H), 4.68-4.70 (m, 1H), 5.34 (m, 1H), 6.72-6.82 (m, 1H), 7.04-7.10 (d, J = 24.5 Hz, 1H), 7.64-7.70 (m, 3H), 8.21-8.26 (m, 2H); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 27.4 (d, J = 32.8 Hz), 28.1 (d, J = 1.8 Hz), 28.2, 28.5 (2d, J = 2.8 Hz), 29.4 (br.s), 36.7 (m), 55.0 (br.s), 57.1-57.2 (2d, J = 6.1 Hz), 57.8 (d, J = 10.5 Hz), 64.3 (d, J = 32.4 Hz), 80.5 (br.s), 81.9, 83.5 (br.s), 83.6, 123.0-123.5 (2m), 129.3, 129.4 (3s), 133.3, 134.6-134.9 (m), 135.6, 136.1 (d, J = 7.5 Hz), 137.3-137.5 (m), 139.9 (2s), 140.6 (2s), 140.7, 141.9-142.0 (m), 142.2-142.3 (m), 142.8, 142.9, 143.4, 143.5, 144.5 (2s), 145.0 (3s), 145.5, 145.6 (2s), 145.7-145.8 (m), 145.9, 146.0, 146.4, 146.5-146.7 (m), 146.9-147.1 (m), 147.5, 147.6, 149.2 (2s), 152.4 (m), 152.9-153.0 (2d, J = 8.9 Hz), 155.9 (br.s), 169.4-169.5 (m), 170.6-170.8 (2s); $^{31}P\{^{1}H\}$ NMR (202.5 MHz, $CDCl_3$): δ +40.7 (br.s); FTIR (neat): 3347, 2975, 2928, 2384, 1732, 1696, 1488, 1454, 1436, 1365, 1246,1153, 1123, 1056, 952, 848, 762, 742, 725, 693,

666, 622, 593, 578, 564, 553, 539, 526, 504, 475, 437, 421, 378, 328, 275, 243, 234, 219, 208; HRMS calcd. for $C_{93}H_{56}BN_3O_9P$ $[M-H]^-$: 1400.3856; found: 1400.3883.

(Fullerenylphenylphosphine-borane)dipeptide 21c. To a mixture of 1 mL dichloromethane/toluene (1:1) were added *sec*-phenylphosphine borane dipeptide **18d** (11 mg, 0.017 mmol), cesium carbonate (11 mg, 0.034 mmol) hydrated by 5 µL of distilled water, tetrabutylammonium bromide (5.7 mg, 0.017 mmol) and [60]fullerene **19** (12 mg, 0.017 mmol. After stirring at room temperature under argon for 16 h and out of light the mixture was hydrolyzed with 40 µL of HCl. After 5 min, 4 mL of distilled water were added and the mixture was extracted with dichloromethane (3 x 5 mL). The organic phases were dried, filtered and the solvent removed under vacuum. The residue was purified by column chromatography on silica gel with dichloromethane/acetone (25:1) as eluent to afford the (fullerenylphenylphosphine-borane)dipeptide **21c** as brown amorphous solid (10.0 mg, 44% yield). R_f: 0.50 (dichloromethane/acetone 25:1); ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.41 (s, 9H), 1.50 (s, 18H), 1.91-2.12 (m, 2H), 2.19-2.40 (m, 2H), 2.46-2.64 (m, 1H), 2.82-3.20 (m, 2H), 3.41-3.70 (m, 1H), 4.31 (br.s, 1H), 4.40-4.58 (m, 1H), 5.35-5.46 (m, 1H), 5.73-5.97 (m, 1H), 7.09 (d, J = 23.9 Hz, 0.5H), 7.10 (d, J = 23.9 Hz, 0.5H), 7.58-7.68 (m, 3H), 7.78 (br.s, 1H), 8.19-8.30 (m, 2H); ^{31}P NMR (202.5 MHz, $CDCl_3$): δ +40.7 (br.s); HRMS calcd. for $C_{89}H_{49}BN_3O_9PNa$ $[M+Na]^+$: 1368.3245; found: 1368.3205.

(Fullerenylphenylphosphine-borane)dipeptide 21d. To a mixture of 10 mL dichloromethane/toluene (1:1) were added *sec*-phenylphosphine borane dipeptide **18e** (100 mg, 0.19 mmol), cesium carbonate (123.8 mg, 0.38 mmol) hydrated by 20 µL of distilled water, tetrabutylammonium bromide (61.4 mg, 0.19 mmol) and [60]fullerene **19** (137 mg, 0.19 mmol). After stirring at room temperature under argon for 16 h and out of light, the mixture was hydrolyzed with 70 µL of concentrated HCl. After 5 min, 4 mL of distilled water were added and the mixture was extracted with dichloromethane (3 x 5 mL). The organic phases were dried, filtered and the solvent removed under vacuum to afford a residue which was purified by column chromatography on silica gel using a mixture dichloromethane/acetone (25:1) as eluent to afford the compound **21d** as a P-epimeric mixture in 1:1 ratio (92 mg, 39% yield). Brown amorphous solid; R_f: 0.35

(dichloromethane/acetone 25:1); ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.67 (br.s, 18H), 2.02-2.15 (m, 2H), 2.25-2.54 (m, 2H), 3.08-3.31 (m, 4H), 4.31 (br.s, 1H), 4.46 (m, 1H), 5.38 (m, 1H), 5.77-5.88 (m, 1H), 7.08-7.13 (d, J = 24.4 Hz, 1H), 7.64 (m, 3H), 8.23-8.25 (m, 2H); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 27.6 (d, J = 21.9 Hz), 28.4 (2s), 29.4, 29.7, 33.0 (2br.s), 36.1 (br.s), 51.6, 55.0, 57.7 (d, J = 10.4 Hz), 64.5 (d, J = 31.3 Hz), 80.0 (2s), 123.1 (d, J = 47.8 Hz), 129.2-129.4 (m), 133.1, 134.7-134.8 (m), 135.7, 136.0, 137.3, 139.8 (2s), 140.5-140.6 (m), 141.7, 141.8, 142.0 (2s), 142.2 (m), 142.6, 142.8, 143.2, 143.3, 143.4 (d, J = 8.0 Hz), 144.5, 144.9 (2s), 145.4, 145.5, 145.7 (2s), 145.9 (d, J = 7.0 Hz), 146.4, 146.5-146.6 (m), 146.7, 147.0 (3s), 147.4 (d, J = 6.0 Hz), 149.2-149.4 (m), 152.6 (d, J = 4.0 Hz), 155.9, 171.6, 174.0; ^{31}P{^{1}H} NMR (202.5 MHz, $CDCl_3$) δ +41.2 (br.s); FTIR (neat): 3315, 2960, 2928, 2872, 2383, 2343, 1701, 1665, 1486, 1456, 1436, 1364, 1246, 1160, 1107, 1054, 1025, 878, 860, 728, 694, 622, 611, 577, 525, 486, 328, 233; HRMS calcd. for $C_{84}H_{40}BN_3O_7P$ $[M-H]^-$: 1244.2704; found: 1244.2722.

ASSOCIATED CONTENT

Supporting Information

^{1}H-, ^{13}C-, ^{31}P-NMR spectra of all compounds. HPLC analysis on chiral column of compound **15c**. Mass spectroscopy analysis of compound **20c** before and after electrolysis.

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AUTHOR INFORMATION

Corresponding Authors

* E-mail: Jerome.Bayardon@u-bourgogne.fr ; Sylvain.Juge@u-bourgogne.fr

Present Address

§ Institut Charles Gerhardt de Montpellier (ICGM-UMR 5253 CNRS-UM-ENSCM), Université de Montpellier, Place E. Bataillon, Bât 17, cc 1702, 34095 Montpellier Cedex 5, France

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