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o-Boronato- and o-Trifluoroborato−Phosphonium Salts Supported by L-α-Amino Acid Side Chain

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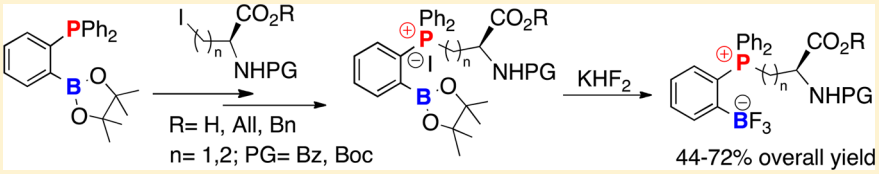
Supporting Information



ABSTRACT: The synthesis of *o*-boronato- and *o*-trifluoroborato−phosphonium salts supported by the L-amino acid side chain is described. The synthesis of these new class of amino acid derivatives was achieved by stereoselective quaternization of *o*-(pinacolato)boronatophenylphosphine with *β*- or *γ*-iodo amino acid derivatives which are prepared from L-serine or L-aspartic acid, respectively. The quaternization of the phosphine was performed using either iodo amino ester or carboxylic acid derivatives. In addition, free carboxylic acid and amine derivatives were obtained by saponification or HCl acidolysis of *o*-boronato−phosphonium amino esters, respectively. The usefulness of these compounds in peptide coupling was demonstrated by coupling an *o*-boronato−phosphonium amino ester with an aspartic acid moiety. When the *o*-boronato−phosphonium amino acid or dipeptide derivatives were mixed with fluoride, the corresponding *o*-trifluoroborated products were cleanly and rapidly obtained in high isolated yields. The hydrolysis of these compounds at room temperature using a phosphate buffer pH 7/CD_3CN mixture has shown only traces of free fluoride F^- after several days. Finally, a preliminary radiolabeling essay has proven the facile [^{18}F]-fluoride incorporation and high stability of the radiolabeled product in aqueous conditions. Indeed, this new class of boron−phosphonium amino acid derivatives shows promising properties for their applications in synthesis and labeling of peptides.

INTRODUCTION

The development of new technologies to improve the diagnosis of certain diseases, to follow their progression or to validate new drugs is a constant challenge. In this context, the use of modified *α*-amino acids to mark all kinds of peptides and proteins while preserving their recognition properties is of considerable interest.[1,2] Among the many classes of unnatural *α*-amino acids, the boron derivatives are increasingly attractive as they can be used as enzyme inhibitors,[3] pharmaceutical agents,[4] in boron neutron capture therapy (BNCT) for cancer treatment,[5] in synthesis of modified peptides or natural products,[6] or in medical imaging.[5,7] For the latter application, radiolabeled amino acids are currently used to explore metabolic pathways, monitoring the tumor response after treatment or for planning surgery, using positron emission tomography (PET) or single photon emission computed tomography (SPECT) technologies, because these compounds have small sizes and hydrophilic−lipophilic balance which modestly alters the peptides and proteins.[8,9] During the past decade, straightforward boron-based methods for incorporation of short-lived isotopes in biomolecules or by the means of prosthetic groups with B-[^{18}F] bond forming have also been intensively developed.[10,11] However, their applications for the direct skeleton labeling of amino acid is still rarely described.[10b,12]

Following up from with their pioneering work on anion capture using cationic borane derivatives,[13] Gabbaï and collaborators have recently reported the [^{18}F]-labeling of *o*-trifluoro boratophenylphosphonium salts **1** (Figure 1) by isotopic exchange reaction.[14] Interestingly, compounds **1a−c** are effectively stabilized *in vivo* against fluoride ion dissociation. Moreover, derivative **1c** can potentially be used for the [^{18}F]-labeling of biomolecules through bioconjugation by the carboxylic acid group.[14]

In connection with our ongoing investigations into organo-phosphorus and amino acid chemistry,[15] we recently reported the phosphonium salt **2** as new amino acid Wittig reagent.[16] Thus, an efficient synthesis of boronato-aryl-L-amino acid derivatives such as **3**, potentially useful for further synthesis or

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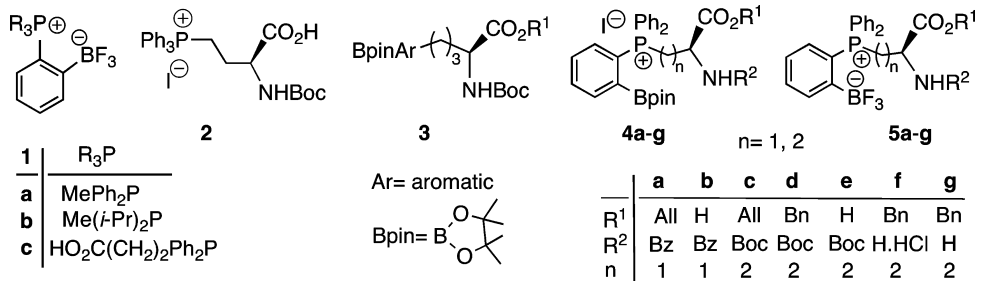


Figure 1. Selection of phosphonium and boronated amino acid derivatives.

Scheme 1. Synthesis of the Boronato–Phosphonium L-Amino Acid Derivatives 4

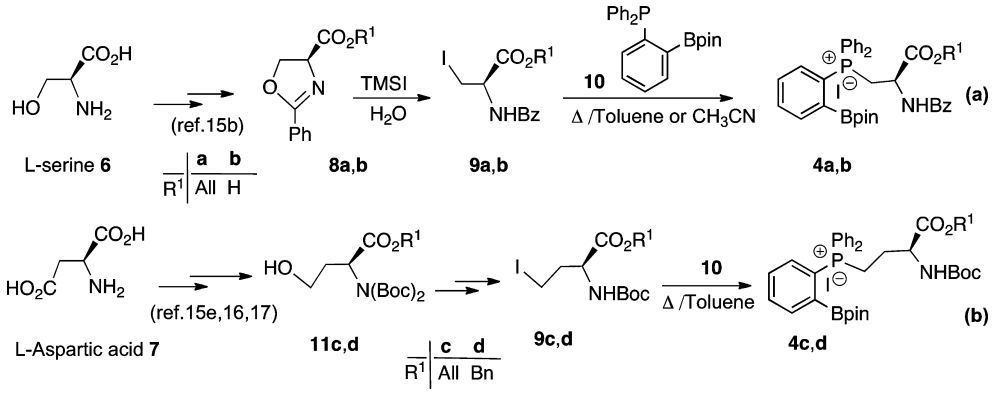
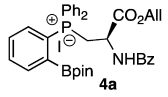
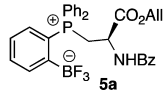
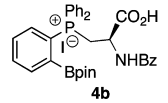
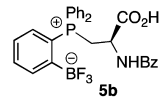
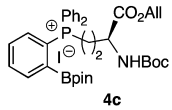
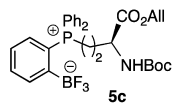
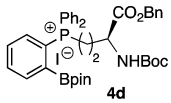
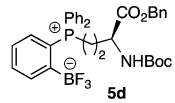
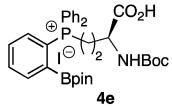
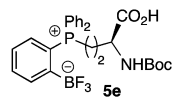
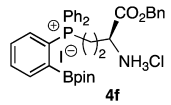
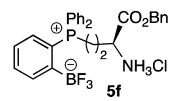


Table 1. *o*-Boronato- and Trifluoroboratophenyl Phosphonium L-Amino Acid Derivatives 4

entry	conditions	*o*-boronato phosphonium salts **4**[a] % yield[b]		*o*-BF_3 derivative **5**[c] % yield[b]	
1	**10** + **9a**, Toluene 60°C, overnight	 **4a**	55	 **5a**	-[e]
2	**10** + **9b**, ACN 60°C, overnight	 **4b**	70	 **5b**	71
3	**10** + **9c**, Toluene 76°C, 6 h	 **4c**	88	 **5c**	84
4	**10** + **9d**, Toluene 76°C, 6 h	 **4d**	80	 **5d**	90
5	**4d** (or **4c**), dioxane/ NaOH 1M, overnight	 **4e**	88[d]	 **5e**	50
6	**4d**, acetone/ HCl 6M, 2 h	 **4f**	78	 **5f**	67

[a]The enantiomeric excesses (e.e.) of the boronates **4** were checked using either BINPHAT or *N*-methyl ephedrine (except **4f**). [b]Isolated yield. [c]The (pinacolato)boronato **4** reacts with KHF_2 (4 equiv) in a methanol/water (5:4) mixture for 1 h at room temperature for **4b**,**4e** or 50 °C for **4a**,**4c–d**,**4f**. [d]Mixture of boronate and boronic acid derivatives. [e]Mixture with byproducts.

labeling reactions, was achieved using Wittig and catalyzed borylation reactions as key steps.[12] As a part of our program on the chemistry of phosphonium salts supported by amino acid chain, we now report the stereoselective synthesis of *o*-

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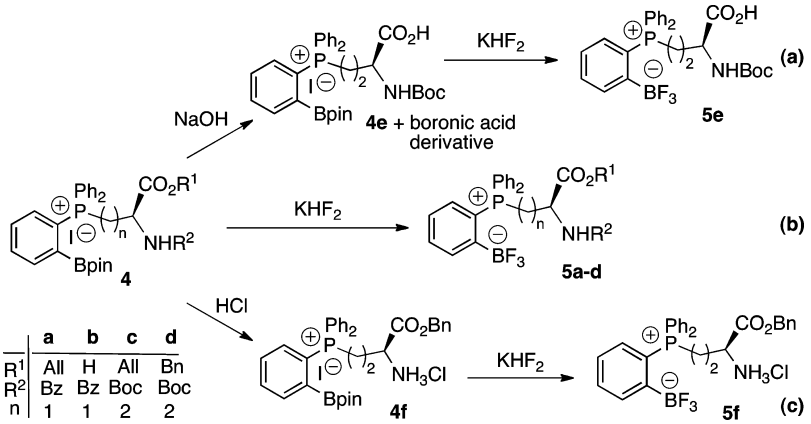
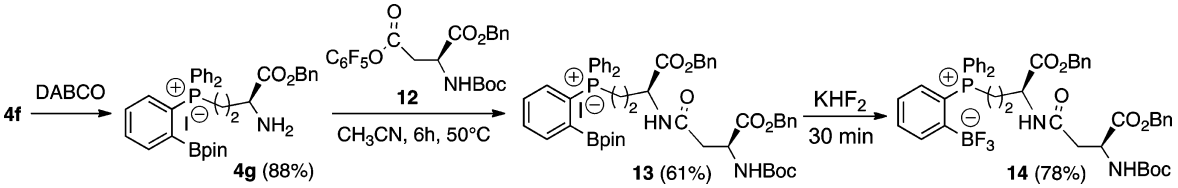
Scheme 2. Deprotection and Fluorination of the Boronato−Phosphonium Amino Acid Derivatives 4



Scheme 3. Synthesis of Boronato- and Trifluoroborato−Phosphonium Dipeptides 13 and 14



boronato- and *o*-trifluoroborato phenylphosphonium amino acid derivatives **4**, **5** starting from L-serine **6** or L-aspartic acid **7** (Scheme 1). In addition, the deprotection of the functional groups and the stability in aqueous media of the boronato- and trifluoroborato amino acid derivatives **4** and **5**, as well as a preliminary [^{18}F]-radiolabeling essay, are reported.

RESULTS AND DISCUSSION

The *o*-(pinacolato)boronatophenylphosphonium salts **4a−d** were stereoselectively obtained by quaternization of phosphine **10**, which was previously prepared from 1,2-dibromobenzene,[18] with the corresponding iodo L-*α*-amino acid derivatives **9** (Scheme 1, Table 1). The *β*-iodo-*α*-amino acid derivatives **9a** and **9b** were easily prepared from L-serine **6** by ring-opening of the corresponding oxazoline derivatives **8a** (or **8b**) with trimethylsilyl iodide.[15b] Alternatively, the synthesis of the allyl and benzyl *γ*-iodo-*α*-amino esters **9c,d** was achieved by starting from the L-aspartic acid **7** via the formation of the *N*,*N*-diBoc-homoserine intermediates **11c,d** (Scheme 1).[15e,16,17] Each step has a 75−98% chemical yield.

Thus, the phosphonium salt allyl ester **4a** was obtained in 55% isolated yield by heating the *o*-(pinacolato)boronatophenyl phosphine **10** with the *β*-iodo-*α*-amino ester **9a** in toluene at 60 °C overnight (Scheme 1a; Table 1, entry 1). The *o*-boronatophenylphosphine **10** also reacts with the *β*-iodo-*α*-amino acid **9b** by heating in acetonitrile to directly afford the corresponding phosphonium salt **4b** bearing a free carboxylic acid function in 70% yield (entry 2). Under alternate conditions, when heated in toluene at 76 °C for 6 h, the *γ*-iodo-*α*-amino esters **9c** and **9d** react with **10** to afford the phosphonium amino esters **4c** and **4d** in 88 and 80% chemical yields, respectively (Scheme 1b; Table 1, entries 3 and 4).

All attempts to deprotect the ester moiety in the boronato−phosphonium salts **4a,c−d** from palladium catalyzed deallylation or debenzylation via hydrogenolysis were unsuccessful.[19] In contrast, the deallylation or the debenzylation of compound **4c** and **4d** was achieved by saponification with NaOH 1 M at room temperature overnight to afford the phosphonium salts **4e** as a mixture with its boronic acid derivative and an isolated yield up to 88% (Scheme 2a; Table 1, entry 5). The formation of the boronic acid derivative has been confirmed by LC−MS and is explained by the partial hydrolysis of the pinacolatoboronato moiety under the aqueous basic conditions. On the other hand, acidolysis with HCl of the pinacolatoboronatophosphonium iodide **4d** led to the corresponding ammonium chloride salt **4f** in 78% chemical yield, which proceeds by the deprotection of the Boc group (Scheme 2c; Table 1, entry 6). Alternatively, the formation of trifluoroborate derivatives **5a−f** was performed by reaction of boronates **4a−f** with 4 equiv KHF_2 in methanol/water (5:4) mixture according to a literature procedure (Scheme 2, Table 1).[20] The presence of the trifluoroborato moiety was characterized by ^{19}F and ^{11}B NMR showing signals in the −133 and +2.5 ppm region, respectively. The boronato−phosphonium amino acid **4b** gave the corresponding trifluoroborato derivative **5b** in 1 h at room temperature in 71% isolated yield (Scheme 2b; Table 1, entry 2). Under the same conditions, the boronate and boronic acid mixture **4e** lead to the trifluoroborato compound **5e** in 50% yield (Scheme 2a; entry 5).

In the case of the boronato−phosphonium amino ester derivatives **5c**, **5d**, or **5f**, the formation of the trifluoroborato derivatives as colorless solids was achieved in 1 h by heating at 50 °C, in isolated yields up to 90% (Scheme 2b,c; entries 3,4,6). However, under these conditions, the boronato−phosphonium amino ester **4a** led to a mixture of phosphonium salt **5a** along with byproducts (entry 1). Their presence is explained by undesired side reactions affording free BF_4, which is characterized by a signal at −152 ppm in the ^{19}F NMR spectra. Noteworthy, the presence of the amino acid on the salts **4a−f** (whether the functional groups is an ester, an acid, a Boc group, an amine or its hydrochloride salt) does not disrupt the recognition of the fluoride ions by the boronato−phosphonium moiety.

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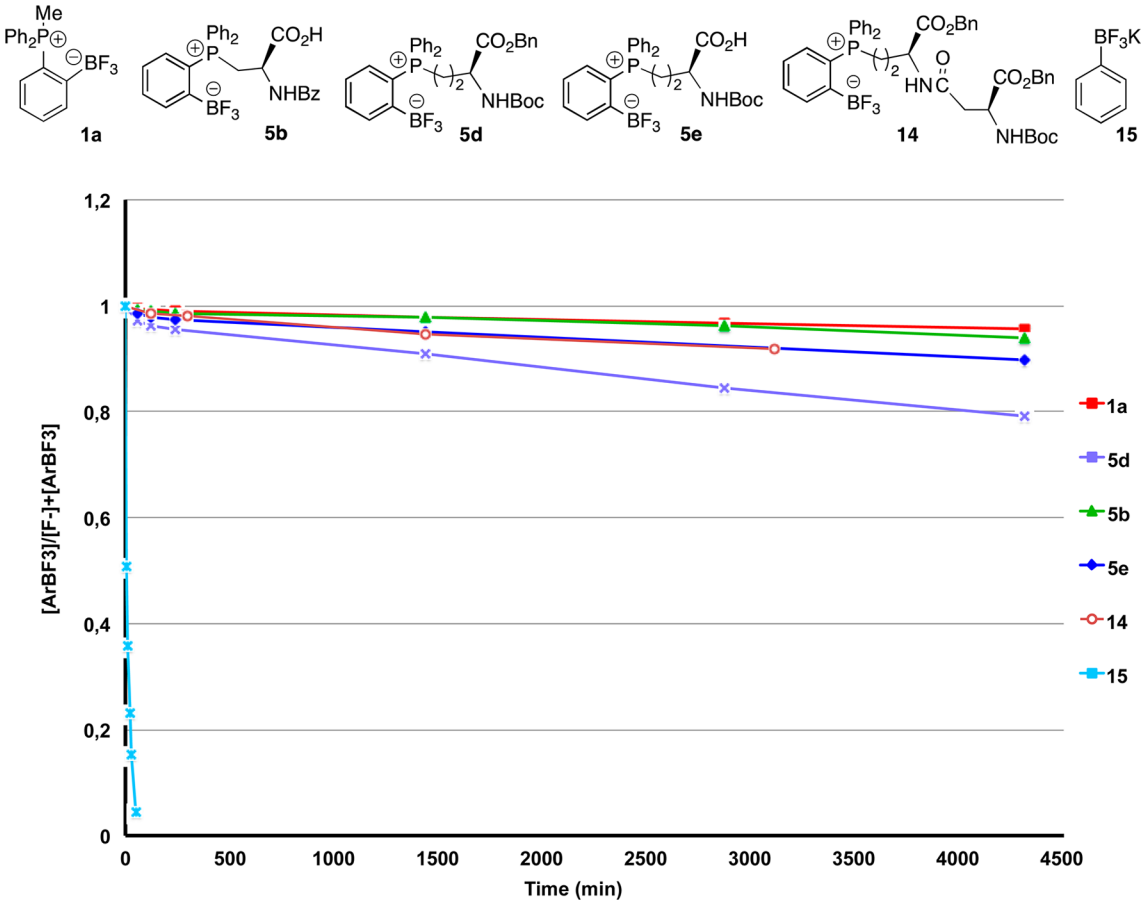

Figure 2. Comparative hydrolysis of trifluoroborato−phosphonium derivatives.

The feasibility and the effectiveness of the boronato−phosphonium derivatives **4** in peptide coupling was investigated by reaction of the amino derivative **4g**, previously obtained by treatment of **4f** with DABCO, with the benzyl-*β*-pentafluorophenate L-aspartate **12**[21] (Scheme 3). After 6 h in acetonitrile at 50 °C, the corresponding dipeptide **13** was obtained in 61% yield. The fluorination reaction of the compound **13** was then achieved in 30 min by reaction KHF_2 to afford the trifluoroborato−phosphonium dipeptide **14** in 78% yield (Scheme 3).

With the short lifetime of the [$^{18}F^-$] radioisotope (half-life = 110 min),[22] the kinetics of the fluorination and the stability of the products under physiological conditions are crucial for appropriate design of radiolabeled agents useful for PET medical imaging.[23] Thus, we investigated the hydrolysis rate of the trifluoroborato−phosphonium amino acid derivatives prepared with those of the known compounds **1a** and **15** used as reference (Figure 2).

First, the hydrolysis of the trifluoroborato-phosphonium amino acid derivatives **5b,d,e** was investigated in a phosphate buffer (pH 7)/acetonitrile-D_3 (8:2) mixture at room temperature and the monitoring was performed using ^{19}F-NMR analysis of their B−F signals by comparison to the trifluoroborates **1a** and **15** as reference compounds (Figure 2).[24] Under these aqueous conditions, compounds **5b,d,e** exhibit only traces of the free fluoride F^- ion after 72 h (Supporting Information).

The kinetic curves of the trifluoroborate hydrolysis into boronic acid derivatives result from nonlinear regression analyses of the cumulative plot (Figure 2). These results are consistent with a kinetic model where the total hydrolysis of the trifluoroborato group is governed by the dissociation of the first fluoride which is the limiting step, thus resulting in a pseudo first order rate (Figure 2).[24a] Treatment of the kinetic data indicates that k_{obs} = 1.28 × 10^{-5} min^{-1} for **5b**, 2.22 × 10^{-5} min^{-1} for **5e** and 4.93 × 10^{-5} min^{-1} for **5d** (Figure 2). The comparison of these rate constants with those obtained for **1a** (0.97 × 10^{-5} min^{-1}) and **15** (5.7 × 10^{-2} min^{-1}) under the same conditions as previously described by Perrin[24a] and Gabbaï[24c] reinforce the significant advantage of having a phosphonium group at the *ortho* position stabilizing the trifluoroborate moiety against hydrolysis and the fluoride loss. The stability of the trifluoroborato-phosphonium derivatives varies as **5b** > **5e** > **5d** and appear somewhat less stable that the reference compound **1a**. This observation may be explained by the hydrophilic character of the amino acid moiety which appears to facilitate a slow hydrolysis (Figure 2). On the other hand, the hydrolysis of the trifluoroborato-phosphonium dipeptide **14** in these conditions shows a similar behavior in regard to the compounds **5**, because only small traces of free fluoride are observed after 48 h (k_{obs} = 2.55 × 10^{-5} min^{-1}) (Figure 2).

The formation of [^{18}F]-containing radiotracers from boron compounds is based either on the [^{18}F]-fluorination of boronates in the presence of KHF_2,[11b,e,i] or on the isotopic exchange of trifluoroborates.[11d,f,h,14] Since some studies showed that the first method can give from satisfactory to high specific activity in the range 7.7 to 70.3 GBq μmol^{-1},[11j] we first applied it to estimate the potential of the boronato−phosphonium

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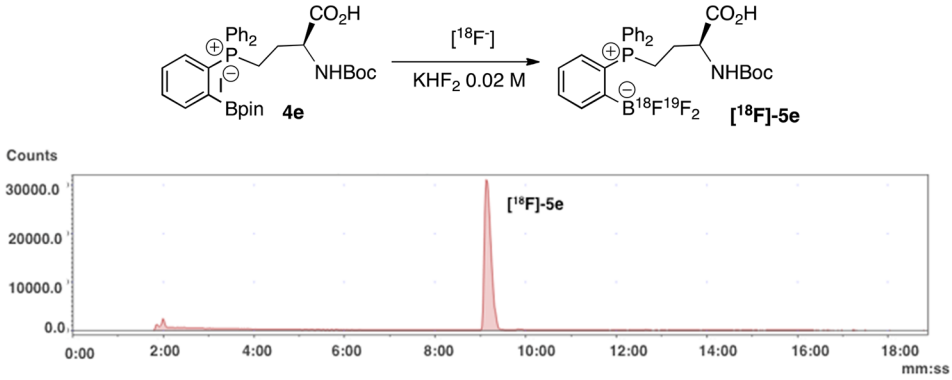

Figure 3. Radiochromatogram of [^{18}F]-**5e** after HPLC purification (radiochemical purity >97%).

amino acid derivatives such as **4e** in radiolabeling. The labeling was demonstrated in the case of trifluoroborate [^{18}F]-**5e**, which was obtained by reaction of the mixture **4e** at room temperature with an aqueous solution of KHF_2 0.02 M mixed to [^{18}F]-fluoride (Figure 3).

Under these conditions, the radiolabeled trifluoroborato derivative [^{18}F]-**5e** was obtained in ∼50 min with 97% radiochemical purity (including azeotropic drying of [^{18}F$^-$], synthesis and purification), 10% radiochemical yield (EOS, decay corrected) and a specific activity of 130 MBq μmol^{-1} (Figure 3). Interestingly, the labeled compound [^{18}F]-**5e** did not show significant degradation after 4 h in aqueous solution, confirming the high stability of this class of compounds.

CONCLUSION

The synthesis of the first examples of boronato−phosphonium salts **4a**−**g** supported by an amino acid side chain is described. The syntheses proceed by stereoselective quaternization of *o*-(pinacolato)boronatophenylphosphine **10** with β- or γ-iodo amino acid derivatives **9** prepared from L-serine or L-aspartic acid, respectively, in isolated yields up to 88%. The saponification of the boronato−phosphonium amino esters **4c** or **4d** leads to the compound **4e** with a free carboxylic acid in 88% yield, while HCl acidolysis then treatment with DABCO affords the amino derivative **4g** in 69% overall yield. Both reactions take place stereoselectively without significant decomposition of the boronato−phosphonium moiety. The effectiveness of the boronato−phosphonium derivatives **4** in peptide coupling was demonstrated by reaction of the amino derivative **4g** with the benzyl-β-pentafluorophenate L-aspartate **12**, leading to the corresponding dipeptide **13** in 61% yield. In addition, the reaction of the boronato−phosphonium amino acid and peptide derivatives **4a**−**f** and **13** with fluoride cleanly affords the corresponding trifluoroborates **5a**−**f** and **14** in approximately 1 h in isolated yields up to 90%, without significant degradation by hydrolysis in a phosphate buffer pH 7. Preliminary radiolabeling essay with the boronato−phosphonium amino acid derivative **4e** demonstrates its labeling into [^{18}F]-**5e** in 10% radiochemical yield and with a specific activity of 130 Mbq μmol^{-1}. Indeed, this new class of *o*-boronato- and trifluoroborato−phenylphosphonium amino acid derivatives **4** and **5** shows promising properties for their applications in synthesis and labeling of peptides.

EXPERIMENTAL SECTION

General Information. The reactions were carried out under argon and solvents were dried and purified by conventional methods prior to use. All commercial reagents, 1-benzyl *N*-(*t*-butoxycarbonyl)-L-aspartate and (Λ,*R*)-BINPHAT-tetrabutyl ammonium salt were purchased from commercial sources and used without purification. The flash chromatography was performed with the indicated solvents using silica gel 60 (35−70 μm mesh). The ^{1}H, ^{13}C, ^{19}F and ^{11}B NMR spectra were recorded on 600, 500, or 300 MHz spectrometers at ambient temperature using TMS as internal reference for ^{1}H, ^{13}C NMR, phosphoric acid (85%), $CFCl_3$ and $BF_3{\cdot}Et_2O$ as external references for ^{31}P-, ^{19}F- and ^{11}B-NMR, respectively. 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 nm and λ = 254 nm. The infrared spectra were recorded on a FT-IR instrument. Melting points were measured on a Kofler melting point apparatus and are uncorrected. Optical rotation values were determined at 20 °C on polarimeter at 589 nm (sodium lamp). High Resolution Mass Spectra (HRMS) were performed under ESI conditions with a micro Q-TOF detector. Elemental analyses were measured with a precision superior to 0.3% on a CHNS-O instrument apparatus. The allyl (*R*)-β-iodo-α-benzamidopropanoate **9a**,[15b] allyl and benzyl (*S*)-2-(*tert*-butyloxycarbonyl)amino-4-iodobutanoates **9c**[16] and **9d**[17] were synthesized as described from L-serine **6** or L-aspartic acid **7**, respectively. The *o*-(pinacolato)boronatophenyl-diphenylphosphine **10**[18] and trifluoroborato compounds **1a**[24c] or **15**,[25] were prepared according to the published procedure. The (−)-*N*-methyl ephedrine (mp = 88 °C) was prepared by heating (−)-ephedrine with a mixture of formic acid and formaldehyde according to a similar described procedure.[26]

For radiolabeling, fluorine-18 (^{18}F) was produced by the ^{18}O-(p,n)^{18}F nuclear reaction using a 7.5 MeV cyclotron and 300 μL of [^{18}O]-H_2O ≥ 98%. HPLC was performed through an Agilent 1200 series with a 254 nm UV detector and radioactivity was detected by a NaI crystal coupled to a photomultiplier tube. An analytical 5 μm C18 150 × 4.60 mm reverse phase column was used with a solvent system of CH_3CN + 0.1% TFA (A) and H_2O + 0.1% TFA (B) (0−2 min 40% A; 2−10 min 40 to 70% A; 10−20 min 70% A; 20−25 min 70 to 40% A; flow rate: 1 mL/min). The purification was realized on a semipreparative HPLC column (C18 10 μm 125A, 7.8 × 300 mm) with a solvent system of CH_3CN + 0.1% TFA (A) and H_2O + 0.1% TFA (B) (0−2 min 40% A; 2−10 min 40 to 70% A; 10−20 min 70% A; 20−25 min 70 to 40% A; flow rate: 3 mL/min).

^{19}F NMR Spectroscopic Kinetic Analyses. A small quantity of the trifluoroborate salt (5 mg) was added to the NMR tube. At the start of the solvolysis reaction (t = 0 min), the trifluoroborate salt was dissolved in 0.5 mL of a buffer solution pH 7/acetonitrile-D_3 (8:2), and the decomposition was monitored by ^{19}F NMR spectroscopy. The buffer solution pH 7 with 200 mM strength was prepared by mixing in 100 mL H_2O, $Na_2HPO_4{\cdot}7H_2O$ (5.3 g) and $NaH_2PO_4{\cdot}H_2O$ (40 mg). ^{19}F NMR spectra were acquired at different times, and the integration was calculated on the spectra. Integrals corresponding to the trifluoroborate peak were divided by the sum of the trifluoroborate and the free fluoride integrations to calculate the fraction of ^{19}F existing as trifluoroborato moiety. The ratio of ^{19}F-signal existing as

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the trifluorborate to the total ^{19}F signal was plotted against time to determinate the kinetic of the hydrolysis. The kinetic curves reported in Figure 2 are the result of nonlinear regression analyses of the cumulative plot of all data sets for identical experiments, using excel 14.1.3 version.

(*R*)-α-Benzamido-β-iodo-propanoic Acid 9b. This compound has been synthesized from L-serine according a modified procedure.[15b] Under Ar atmosphere, oxazoline **8b** as sodium salt (0.5 g, 2.35 mmol), iodotrimethylsilane (1.34 mL, 9.39 mmol) and 85 μL of water were dissolved in 10 mL of chloroform stabilized by amylene. After 48 h of stirring at room temperature, the solvent was evaporated. The residue was dissolved in acetone and the NaI was removed by filtration. The filtrate was hydrolyzed by a $KHCO_3$ solution (1 M), and the aqueous phase was washed with AcOEt (2 × 30 mL) and acidified with $NaHSO_4$ solution (1 M) until pH 3. The aqueous layer was extracted by AcOEt (2 × 30 mL). The organic layer was dried over $MgSO_4$ and the solvent was evaporated to give 0.37 g of a yellow solid (yield = 50%). Mp = 98 °C; $[\alpha]_D$= −7.8 (*c* 0.4, acetone). ^1H NMR (300 MHz, acetone-D_6): δ 3.73 (dd, *J* = 6.9, *J* = 10.5 Hz, 1H), 3.86 (dd, *J* = 4.5, *J* = 10.5 Hz, 1H), 4.86−4.92 (m, 1H), 7.48−7.61 (m, 3H), 7.85−7.86 (m, 1H, NH), 7.93−7.96 (m, 2H). ^{13}C NMR (75 MHz, acetone-D_6): δ 5.2, 53.9, 127.3, 128.5, 131.7, 135.1, 166.5, 169.8. HRMS (ESI-Q-TOF) calcd for $C_{10}H_{10}INO_3$ $[M + Na]^+$, 341.95976; found, 341.95858. FT-IR (neat) cm^{-1}: 3282, 3032, 2973, 2925, 2598, 1965, 1903, 1707, 1643, 1603, 1578, 1520, 1487, 1446, 1419, 1331, 1295, 1244, 1192, 1169, 1096, 1026, 999, 929, 852, 818, 798, 754, 719, 691 Analysis calcd. for $C_{10}H_{10}INO_3$ (318.97): C 37.64, H 3.16, N 4.39; found C 37.54, H 3.31, N 4.66.

Allyl (*R*)-2-(Benzamido)-3-[2-(pinacolatoboronatophenyl)-diphenyl Phosphonium-iodide]propanoate 4a. To a solution of boronato-phosphine **10** (0.28 g, 0.72 mmol) in 1 mL of toluene under argon was added 0.28 g (0.6 mmol) of allyl (*R*)-α-benzamido-β-iodo-propanoate **9a**. After stirring 1 night at 60 °C, the solvent was evaporated and the residue was purified by chromatography on silica gel using a mixture of dichloromethane/acetone (2:1) as eluent, to afford 0.23 g of the product **4a** (yield = 55%). White solid. R_f: 0.43 (dichloromethane/acetone 2:1); mp = 132 °C; $[\alpha]_D$= −11.7 (c 0.3, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 0.96 (s, 6H), 0.99 (s, 6H), 4.56−4.74 (m, 4H), 5.09−5.19 (m, 2H), 5.23−5.25 (m, 1H), 5.77−5.81 (m, 1H), 7.37−8.02 (m, 18H), 8.23−8.25 (m, 1H), 9.01−9.03 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.2, 24.5, 26.9 (d, *J* = 52.2 Hz), 48.2 (d, *J* = 2.3 Hz), 66.9, 85.4, 118.5, 120.9 (d, *J* = 86.0 Hz), 121.7 (d, *J* = 87.5 Hz), 122.5 (d, *J* = 83.8 Hz), 128.1, 128.3, 129.9 (d, *J* = 10.6 Hz), 130.0 (d, *J* = 10.6 Hz), 131.3, 131.8, 132.1 (d, *J* = 16.6 Hz), 132.2, 133.5 (d, *J* = 9.3 Hz), 133.7 (d, *J* = 3.0 Hz), 133.9−134.0 (m), 136.8 (d, *J* = 12.8 Hz), 139.2 (d, *J* = 13.6 Hz), 167.4, 170.1 (d, *J* = 12.8 Hz), 1 C_q not observed. ^{31}P NMR (121 MHz, $CDCl_3$): δ +26.2. HRMS (ESI-Q-TOF) calcd. for $C_{37}H_{40}BNO_5P$ $[M - I]^+$, 620.27381; found, 620.27255. FT-IR (neat) cm^{-1}: 3229, 2981, 1981, 1733, 1658, 1582, 1520, 1483, 1436, 1375, 1340, 1272, 1219, 1169, 1140, 1108, 1052, 1028, 995, 962, 852, 826, 749, 713, 689. The enantiomeric excess of the phosphonium salt **4a** (>98% ee) was checked by ^{31}P NMR analysis in the presence of BINPHAT by comparison of a racemic sample.[15c]

(*R*)-2-(Benzamido)-3-[2-(pinacolatoboronatophenyl)-diphenyl Phosphonium-iodide] Propanoic Acid 4b. To a solution of boronato-phosphine **10** (0.22 g, 0.55 mmol) in 2 mL of acetonitrile under argon was added 0.13 g (0.4 mmol) of (*R*)-α-benzamido-β-iodo-propanoïc acid **9b**. After stirring 1 night at 60 °C, the solvent was evaporated. The residue was concentrated in dichloromethane and then precipitated with ether to afford 0.19 g of product **4b** as colorless solid (yield = 70%); mp: 152 °C; $[\alpha]_D$= −8.3 (c 0.3, acetone). ^1H NMR (500 MHz, $CDCl_3$): δ 0.94−0.98 (2s, 12H), 4.66−4.70 (m, 1H), 4.75−4.88 (m, 1H), 5.24−5.27 (m, 1H), 7.37−7.91 (m, 16H), 8.01−8.03 (m, 2H), 8.21−8.23 (m, 1H), 8.97 (d, *J* = 10.0 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 24.3, 24.4, 26.4 (d, *J* = 55.1 Hz), 49.4, 85.6, 120.6 (d, *J* = 88.5 Hz), 121.8 (d, *J* = 83.1 Hz), 122.1 (d, *J* = 88.5 Hz), 128.3, 128.4, 130.0 (d, *J* = 12.7 Hz), 130.2 (d, *J* = 12.7 Hz), 131.4, 132.3 (d, *J* = 13.0 Hz), 132.4, 133.2 (d, *J*= 9.3 Hz), 133.9 (d, *J*= 3.0 Hz), 134.0 (d, *J* = 10.0 Hz), 134.1 (d, *J* = 2.7 Hz), 134.2 (d, *J* = 2.7 Hz), 137.1 (d, *J* = 12.5 Hz), 139.2 (d, *J* = 14.0 Hz), 168.7, 170.8 (d, *J* = 10.7 Hz), 1 C_q not observed. ^{31}P NMR (202 MHz, $CDCl_3$): δ +25.4. HRMS (ESI-Q-TOF) calcd for $C_{34}H_{36}BNO_5P$ $[M - I]^+$, 580.24246; found, 580.24158. FTIR (neat) cm^{-1}: 3054, 2979, 2931, 1981, 1906, 1731, 1657, 1580, 1524, 1484, 1437, 1375, 1340, 1271, 1212, 1167, 1140, 1108, 1052, 997, 961, 852, 824, 746, 714, 690. The enantiomeric excess of the phosphonium salt **4b** (>90%) was checked by ^{31}P NMR analysis in the presence of (−)-*N*-methyl ephedrine by comparison with a racemic sample.

Allyl (*S*)-2-(*tert*-Butoxycarbonylamino)-4-[2(pinacolato-boronatophenyl)-diphenyl Phosphonium-iodide]butanoate 4c. To a solution of boronato-phosphine **10** (0.28 g, 0.72 mmol) in 5 mL of dry toluene was added 0.16 g (0.42 mmol) of allyl γ-iodo amino ester **9c**. After stirring 6 h at 76 °C, the solvent was evaporated and the residue was purified by chromatography on silica gel using a mixture dichloromethane/acetone (3:1) as eluent. After evaporation of the solvent, 0.28 g of phosphonium salt **4c** was obtained as a colorless solid (yield = 88%); R_f: 0.53 (dichloromethane/acetone 3:1); mp = 90 °C; $[\alpha]_D$= −16.7 (*c* 0.4, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ 0.99 (s, 6H), 1.02 (s, 6H), 1.41 (s, 9H), 2.15−2.19 (m, 1H), 2.34−2.38 (m, 1H), 3.78−3.81 (m, 1H), 4.04−4.08 (m, 1H), 4.55−4.62 (m, 3H), 5.17−5.30 (m, 2H), 5.80−5.94 (m, 1H), 6.42 (d, *J* = 5.0 Hz, 1H), 7.30−7.35 (m, 1H), 7.63−7.79 (m, 12H), 8.22−8.24 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.8 (d, *J* = 53.1 Hz), 24.3, 24.5, 25.7, 28.3, 53.6 (d, *J* = 17.7 Hz), 66.2, 79.9, 85.5, 118.5, 121.2 (d, *J* = 85.4 Hz), 121.5 (d, *J* = 88.5 Hz), 122.2 (d, *J* = 82.3 Hz), 130.3 (d, *J* = 3.6 Hz), 130.4 (d, *J* = 3.4 Hz), 131.8, 132.3 (d, *J* = 13.0 Hz), 133.0 (d, *J* = 6.2 Hz), 133.2 (d, *J* = 6.5 Hz), 134.0 (d, *J* = 2.6 Hz), 134.4 (d, *J* = 3.0 Hz), 134.4 (d, *J* = 2.9 Hz), 136.7 (d, *J* = 11.9 Hz), 139.2 (d, *J* = 13.6 Hz), 155.9, 170.7 (d, *J* = 1.4 Hz), 1 C_q not observed. ^{31}P NMR (121 MHz, $CDCl_3$): δ +28.0. HRMS (ESI-Q-TOF) calcd for $C_{36}H_{46}BNO_6P$ $[M - I]^+$, 630.31566; found, 630.31494. FTIR (neat) cm^{-1}: 2980, 2461, 2192, 1704, 1506, 1485, 1439, 1265, 1211, 1161, 1111, 1052, 993, 962, 911, 853, 786, 726, 690. Analysis calcd. for $C_{36}H_{46}BNO_6PI$ (757.44): C 57.08, H 6.12, N 1.85; found C 56.79, H 6.42, N 1.94. The enantiomeric excess of the phosphonium salt **4c** (>98% e.e.) was checked by ^{31}P NMR analysis in the presence of BINPHAT by comparison of a racemic sample.[15c]

Benzyl (*S*)-2-(*tert*-Butoxycarbonylamino)-4-[2-(pinacolato-boronato-phenyl)diphenyl Phosphonium-iodide]butanoate 4d. To a solution of boronato-phosphine **10** (0.315 g, 0.81 mmol) in 5 mL of dry toluene was added 0.21 g (0.50 mmol) of benzyl γ-iodo amino ester **9d**. After stirring 6 h at 76 °C, the solvent was evaporated, and the residue was purified by chromatography on silica gel using a mixture dichloromethane/acetone (3:1) as eluent. After evaporation of the solvent, 0.32 g of phosphonium salt **4d** was obtained as a colorless solid (yield = 80%); R_f: 0.54 (dichloromethane/acetone 3:1); mp = 97 °C; $[\alpha]_D$ = −10.0 (*c* 0.1, $CHCl_3$). ^1H NMR (600 MHz, $CDCl_3$): δ 0.99 (s, 6H), 1.04 (s, 6H), 1.36 (s, 9H), 2.17−2.27 (m, 1H), 2.40−2.50 (m, 1H), 3.75−3.86 (m, 1H), 4.08−4.19 (m, 1H), 4.56−4.63 (m, 1H), 5.15−5.18 (m, 2H), 6.52−6.54 (m, 1H), 7.29−7.37 (m, 5H), 7.63−7.81 (m, 13H), 8.23−8.25 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 21.8 (d, *J* = 53.6 Hz), 24.3, 24.6, 25.8 (d, *J* = 1.8 Hz), 28.3, 53.7 (d, *J* = 18.7 Hz), 67.9, 79.9, 85.5, 121.1 (d, *J* = 87.7 Hz), 121.4 (d, *J* = 86.5 Hz), 122.2 (d, *J* = 82.9 Hz), 128.2, 128.3, 128.4, 130.3 (d, *J* = 3.7 Hz), 130.4 (d, *J* = 3.6 Hz), 132.3 (d, *J* = 13.1 Hz), 133.1 (d, *J* = 10.6 Hz), 133.2 (d, *J* = 10.6 Hz), 134.0 (d, *J* = 3.2 Hz), 134.4 (d, *J* = 2.7 Hz), 134.5 (d, *J* = 3.1 Hz), 135.5, 136.7 (d, *J* = 12.4 Hz), 139.3 (d, *J* = 13.5 Hz), 155.8, 170.9, 1 C_q not observed. ^{31}P NMR (121 MHz, $CDCl_3$): δ +28.1. HRMS (ESI-Q-TOF) calcd for $C_{40}H_{48}BNO_6P$ $[M-I]^+$, 680.33039; found, 680.33137; FTIR (neat) cm^{-1}: 2977, 1702, 1605, 1500, 1348, 1340, 1254, 1212, 1161, 1110, 1052, 997, 962, 850, 732, 692. The enantiomeric excess of the phosphonium salt **4d** (>98% e.e.) was checked by ^{31}P NMR analysis in the presence of BINPHAT by comparison with a racemic sample.[15c]

(*S*)-2-(*tert*-Butoxycarbonylamino)-4-[2-(pinacolatoboronato-phenyl) Diphenylphosphonium-iodide]butanoic Acid 4e. A volume of 0.4 mL of NaOH 1 M was added to a solution of boronato−phosphonium amino ester **4d** (200 mg, 0.25 mmol) (or **4c**) in 4 mL of a mixture dioxane/water (8:2). After stirring overnight at room

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temperature, the aqueous layer was extracted with ether and acidified with acetic acid until pH= 3 and then extracted using dichloromethane. The organic layer was dried with $MgSO_4$ and the solvent was evaporated to afford a mixture of **4e** with the boronic acid derivative (120 mg, 88% yield) in ratio close to 1:1. ^{31}P NMR (121 MHz, $CDCl_3$): δ +29.6 (**4e**), +27.8 (boronic acid derivative). The LC−MS of the crude mixture **4e** was performed using C18 column and methanol as eluent. The chromatogram has showed two peaks at 7.3−7.8 min and 8.6−8.7 min which were characterized by ESI-Orbitrap (positive ion) as compounds **4e** which corresponds to the boronate $C_{33}H_{42}BNO_6P$ $[M - I]^+$: 590.39 and boronic acid derivative $C_{27}H_{30}BNO_5P$ $[M - I - H_2O]^+$: 490.34, respectively. The crude mixture of boronate **4e** with the boronic acid derivative was used without further purification in the following fluorination reaction.

Benzyl (*S*)-2-(Ammonium-chloride)-4-[2-(pinacolatoboronatophenyl) Diphenylphosphonium-iodide]butanoate 4f. To a solution of boronato−phosphonium amino ester **4d** (0.33 g, 0.4 mmol) in 2.5 mL of acetone was added 2 mL of HCl 6 M. After stirring 2 h at room temperature, the mixture was extracted with 2 × 10 mL of dichloromethane. The organic phase was dried with $MgSO_4$, and evaporated. The compound was obtained as a colorless solid (0.24 g, 78% yield); mp = 129 °C; $[\alpha]_D$ = +2.3 (*c* 0.4, $CHCl_3$). ^1H NMR (500 MHz, CD_3CN): δ 0.92 (d, *J* = 18.5 Hz, 12H), 2.29−2.32 (m, 1H), 2.45−2.50 (m, 1H), 3.96−4.03 (m, 2H), 4.36−4.39 (m, 1H), 5.11−5.21 (m, 2H), 7.28−7.91 (m, 18H), 8.18−8.20 (m, 1H). ^{13}C NMR (125 MHz, CD_3CN): δ 22.3 (d, *J* = 53.2 Hz), 24.3, 24.4, 25.0, 53.9 (d, *J* = 19.2 Hz), 68.6, 86.0, 121.0 (d, *J* = 86.3 Hz), 121.7 (d, *J* = 89.2 Hz), 121.8 (d, *J* = 87.1 Hz), 128.9, 129.13, 129.14, 129.20, 129.21, 130.1 (d, *J* = 11.4 Hz), 133.1 (d, *J* = 13.0 Hz), 133.7 (d, *J* = 9.8 Hz), 134.1 (d, *J* = 9.8 Hz), 134.9 (d, *J* = 4.9 Hz), 135.1 (d, *J* = 2.7 Hz), 135.2 (d, *J* = 2.8 Hz), 135.5, 137.7 (d, *J* = 12.4 Hz), 139.3 (d, *J* = 14.5 Hz), 168.6, 1 C_q not observed. ^{31}P NMR (202 MHz, CD_3CN): δ +26.6. ^{11}B NMR (160 MHz, CD_3CN): δ +30.1. HRMS (ESI-Q-TOF) calcd for $C_{35}H_{40}BNO_4P$ $[M-Cl-H-I]^+$, 580.27756; found, 580.27887. FTIR (neat) cm^{-1}: 2974, 2869, 2817, 2608, 1984, 1746, 1705, 1584, 1482, 1437, 1340, 1259, 1195, 1139, 1109, 1051, 995, 961, 852, 824, 731, 691.

Benzyl (*S*)-2-Amino-4-[2-(pinacolatoboronatophenyl)-diphenylphosphonium-iodide]butanoate 4g. To a solution of boronato−phosphonium **4f** (0.39 g, 0.52 mmol) in 1.5 mL of dichloromethane was added 1,4-diazabicyclo[2.2.2]octane (DABCO, 60 mg, 0.53 mmol). After stirring 1 h at room temperature and removing the precipitate, the solvent was evaporated to afford the amino compound **4g** as a colorless oil (0.32 g, yield 88%); $[\alpha]_D$= +2.8 (*c* 0.5, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 0.92 (s, 6H), 0.94 (s, 6H), 1.77−1.93 (m, 1H), 2.23−2.51 (m, 1H), 3.33−4.01 (m, 2H), 5.02−5.14 (m, 2H), 5.26 (br s, 2H), 7.21−7.31 (m, 5H), 7.31−7.40 (m, 1H), 7.61−7.74 (m, 12H), 8.17−8.21 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.4 (d, *J* = 51.5 Hz), 24.3, 24.4, 29.0 (d, *J* = 2.7 Hz), 53.8 (d, *J* = 16.7 Hz), 67.0, 85.4, 121.1 (d, *J* = 85.7 Hz), 121.2 (d, *J* = 87.1 Hz), 122.2 (d, *J* = 82.7 Hz), 128.3, 128.4, 128.6, 130.4 (d, *J* = 12.1 Hz), 132.4 (d, *J* = 12.5 Hz), 133.1 (d, *J* = 10.5 Hz), 134.0, 134.4, 135.4, 135.4, 136.7 (d, *J* = 12.2 Hz), 139.2 (d, *J* = 13.5 Hz), 173.5. ^{31}P NMR (121 MHz, $CDCl_3$): δ +27.8; HRMS (ESI-Q-TOF) calcd for $C_{35}H_{40}BNO_4P$ $[M - I]^+$, 580.27825; found, 580.27683.

Allyl (*R*)-2-(Benzamido)-3-[2-(trifluoroboratophenyl)-diphenyl Phosphonium-iodide]propanoate 5a. To a solution boronato−phosphonium **4a** (0.06 g, 0.08 mmol) in methanol (0.3 mL) was added a solution of KHF_2 (0.025 g, 0.32 mmol) in water (0.23 mL). After 1 h stirring at 50 °C, a precipitate was formed and analyzed by ^{31}P and ^{19}F NMR (CD_3CN), showing a complex mixture with two (δ +25.9 and +25.8) and four signals (δ −121.7, −137.0, −139.0 and −152.6), respectively.

(*R*)-2-(Benzamido)-3-[2-(trifluoroboratophenyl)diphenyl-phosphonium-iodide]propanoic Acid 5b. To a solution boronato−phosphonium **4b** (0.10 g, 0.10 mmol) in methanol (0.5 mL) was added a solution of KHF_2 (0.05 g, 0.64 mmol) in water (0.4 mL). After 1 h stirring at rt, the mixture was extracted with dichloromethane (2 × 5 mL), then the organic phase was dried with $MgSO_4$ and the solvent evaporated. The residue was dissolved in dichloromethane and then precipitated with ether. The trifluoroborate **5b** was obtained as a yellow solid with 71% yield (0.05 g); mp = 160 °C. ^1H NMR (500 MHz, CD_3CN): δ 3.57−3.67 (m, 1H), 4.34−4.42 (m, 1H), 4.77−4.83 (m, 1H), 7.17−7.25 (m, 5H), 7.35−7.42 (m, 3H), 7.49−7.56 (m, 7H), 7.66−7.82 (m, 3H), 7.94−7.97 (m, 1H). ^{13}C NMR (125 MHz, CD_3CN): δ 25.9 (dq, *J* = 5.7, 58.6 Hz), 48.3 (d, *J* = 5.2 Hz), 119.9 (d, *J* = 83.5 Hz), 120.7 (d, *J* = 84.8 Hz), 122.1 (d, *J* = 88.7 Hz), 127.4, 127.9 (d, *J* = 13.8 Hz), 128.9, 130.0 (d, *J* = 12.8 Hz), 130.3 (d, *J* = 12.8 Hz), 132.5, 133.2, 133.5 (d, *J* = 9.5 Hz), 133.7 (d, *J* = 3.3 Hz), 134.5 (d, *J* = 3.3 Hz), 134.7 (d, *J* = 9.5 Hz), 134.8 (d, *J* = 2.9 Hz), 135.9 (d, *J* = 14.7 Hz), 136.1 (dq, *J* = 3.4, 16.8 Hz), 167.9, 170.9 (d, *J* = 17.4 Hz), 1 C_q not observed. ^{31}P NMR (202 MHz, CD_3CN): δ +25.8. ^{11}B NMR (160 MHz, CD_3CN): δ +2.7. ^{19}F NMR (470 MHz, CD_3CN): δ −132.0. HRMS (ESI-Q-TOF) calcd $C_{28}H_{23}BF_2NO_3PNa$ $[M - H - F + Na]^+$, 524.13738; found, 524.13638. FTIR (neat) cm^{-1}: 3371, 3059, 3001, 2931, 1721, 1661, 1642, 1580, 1529, 1484, 1437, 1408, 1332, 1271, 1236, 1182, 1106, 1073, 1052, 1020, 980, 934, 825, 797, 744, 710, 688. The enantiomeric excess of the trifluoroborate **5b** (>90%) was checked by ^{31}P NMR analysis in the presence of (−)-*N*-methyl ephedrine by comparison with a racemic sample.

Allyl (*S*)-2-(*tert*-Butoxycarbonylamino)-4-[2-(trifluoroborato-phenyl)diphenylphosphonium-iodide]butanoate 5c. To a solution of boronato−phosphonium **4c** (0.35 g, 0.46 mmol) in methanol (1.4 mL) was added a solution of KHF_2 (0.14 g, 1.84 mmol) in water (1.1 mL). After stirring 1 h at 50 °C, 5 mL of dichloromethane was added, and the mixture was washed with H_2O. The organic phase was dried with $MgSO_4$ and the solvent was evaporated. The trifluoroborato−phosphonium **5c** (0.22 g) was obtained as a colorless solid (84% yield); mp = 75 °C; $[\alpha]_D$ = +14.4 (*c* 0.1, $CHCl_3$). ^1H NMR (500 MHz, DMSO D_6): δ 1.39 (s, 9H), 1.92−1.96 (m, 2H), 3.48−3.55 (m, 2H), 4.12−4.16 (m, 1H), 4.49−4.52 (m, 2H), 5.14−5.21 (m, 2H), 5.81−5.88 (m, 1H), 7.05−7.10 (m, 1H), 7.35−7.38 (m, 2H), 7.60−7.70 (m, 9H), 7.80−7.81 (m, 2H), 7.85−7.88 (m, 1H). ^{13}C NMR (75 MHz, DMSO-D_6): δ 20.31 (d, *J* = 48.1 Hz), 25.0, 28.1, 53.9 (d, *J* = 17.7 Hz), 64.8, 78.7, 117.4, 118.9 (d, *J* = 83.6 Hz), 121.7 (d, *J* = 85.5 Hz), 121.8 (d, *J* = 85.9 Hz), 126.9 (d, *J* = 13.5 Hz), 129.4 (d, *J* = 9.3 Hz), 129.6 (d, *J* = 9.3 Hz), 132.2, 132.8 (d, *J* = 3.3 Hz), 133.1 (d, *J* = 9.8 Hz), 133.3 (d, *J* = 9.7 Hz), 133.6 (d, *J* = 2.3 Hz), 133.7 (d, *J* = 2.8 Hz), 134.3 (d, *J* = 14.4 Hz), 135.0 (d, *J* = 14.9 Hz), 155.5, 171.1, 1 C_q not observed. ^{31}P NMR (202 MHz, DMSO-D_6): δ +29.3. ^{11}B NMR (160 MHz, DMSO-D_6): δ +2.5; ^{19}F NMR (470 MHz, DMSO-D_6): δ −132.0. HRMS (ESI-Q-TOF) calcd for $C_{30}H_{34}BClF_3NO_4P$ $[M + Cl]^-$, 606.19590; found, 606.19684. FTIR (neat) cm^{-1}: 3376, 2976, 1707, 1511, 1439, 1366, 1251, 1161, 1109, 1049, 1017, 991, 940, 858, 740, 690.

Benzyl (*S*)-2-(*tert*-Butoxycarbonylamino)-4-[2-(trifluoro-boratophenyl)diphenyl Phosphonium-iodide]butanoate 5d. To a solution of boronato−phosphonium **4d** (0.26 g, 0.32 mmol) in methanol (1 mL) was added a solution of KHF_2 (0.1 g, 1.3 mmol) in water (0.8 mL). After stirring 1 h at 50 °C, 5 mL of dichloromethane was added and the mixture was washed with H_2O. The organic phase was dried with $MgSO_4$ and the solvent evaporated. The trifluoroborato-phosphonium **5d** (0.18 g) was obtained as a colorless solid (yield 90%); mp = 80 °C; $[\alpha]_D$ = −20.2 (*c* 0.3, $CHCl_3$). ^1H NMR (500 MHz, DMSO D_6): δ 1.38 (s, 9H), 1.94−1.96 (m, 2H), 3.46−3.55 (m, 2H), 4.16−4.17 (m, 1H), 5.03−5.19 (m, 2H), 7.06−7.10 (m, 1H), 7.26−7.67 (m, 16H), 7.78−7.80 (m, 2H), 7.81−7.82 (m, 1H). ^{13}C NMR (75 MHz, DMSO-D_6): δ 19.3 (d, *J* = 48.0 Hz), 23.9, 27.0, 52.9 (d, *J* = 17.9 Hz), 64.9, 77.5, 117.8 (d, *J* = 84.8 Hz), 120.6 (d, *J* = 85.7 Hz), 121.7 (d, *J* = 84.8 Hz), 125.8 (d, *J* = 13.2 Hz), 126.5, 126.8, 127.2, 128.3 (d, *J* = 11.7 Hz), 128.4 (d, *J* = 11.7 Hz), 131.6 (d, *J* = 2.1 Hz), 130.0 (d, *J* = 8.5 Hz), 132.2 (d, *J* = 8.5 Hz), 132.5 (d, *J* = 2.3 Hz), 132.6 (d, *J* = 2.3 Hz), 133.2 (d, *J* = 14.5 Hz), 134.0 (d, *J* = 16.5 Hz), 134.6, 154.4, 170.2, 1 C_q not observed. ^{31}P NMR (202 MHz, DMSO-D_6): δ +29.3. ^{11}B NMR (160 MHz, DMSO-D_6): δ +2.7. ^{19}F NMR (470 MHz, DMSO -D_6): δ −131.9. HRMS (ESI-Q-TOF) calcd for $C_{34}H_{36}BF_3NNaO_4P$ $[M + Na]^+$, 644.23253; found, 644.23150. FTIR (neat) cm^{-1}: 3361, 2976, 1707, 1512, 1439, 1366, 1249, 1161, 1109, 1049, 1019, 942, 740, 693.

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(*S*)-2-(*tert*-Butoxycarbonylamino)-4-[2-(trifluoroborato-phenyl)diphenyl phosphonium-iodide]butanoic Acid 5e. The mixture of boronate (and boronic acid) phosphonium **4e** prepared as above was dissolved in MeOH (0.5 mL) and treated with a solution of KHF_2 (4 equiv, 0.5 mmol) in water (0.4 mL). The resulting solution was stirred for 1 h at room temperature. The mixture was extracted with dichloromethane (3 × 5 mL) and the organic layer was dried with $MgSO_4$. After evaporation, the compound **5e** is obtained as a colorless solid (50% overall yield from **4c**; 40% overall yield from **4d**); mp = 150 °C; $[\alpha]_D$ = +27.9 (*c* 0.3, $CHCl_3$). ^{1}H NMR (500 MHz, CD_3CN): δ 1.44 (s, 9H), 1.99−2.01 (m, 1H), 2.14−2.16 (m, 1H), 3.40−3.51 (m, 2H), 4.17 (br.s, 1H), 5.82 (br.s, 1H), 7.18 (dd, *J* = 8.0, 14.5 Hz, 1H), 7.36 (tdd, *J* = 1.5, 4.5, 7.5 Hz, 1H), 7.55−7.79 (m, 12H), 7.97−8.00 (m, 1H). ^{13}C NMR (125 MHz, CD_3CN): δ 21.3 (d, *J* = 45.8 Hz), 26.2, 28.2, 54.4 (d, *J* = 15.8 Hz), 79.8, 118.9 (d, *J* = 85.0 Hz), 123.2 (d, *J* = 85.0 Hz), 123.2 (d, *J* = 86.3 Hz,), 127.6 (d, *J* = 13.5 Hz), 130.1 (d, *J* = 12.0 Hz), 133.5 (d, *J* = 3.8 Hz), 133.6 (d, *J* = 11.3 Hz), 133.8 (d, *J* = 12.0 Hz), 134.1 (d, *J* = 1.5 Hz), 134.1 (d, *J* = 1.5 Hz), 135.5 (d, *J* = 15.0 Hz), 135.8 (dq, *J* = 2.3, 16.5 Hz), 156.4, 173.3, 1 C_q not observed. ^{31}P NMR (202 MHz, CD_3CN): δ +28.7. ^{11}B NMR (160 MHz, CD_3CN): δ +2.5. ^{19}F NMR (470 MHz, CD_3CN): δ −134.1. HRMS (ESI-Q-TOF) calcd for $C_{27}H_{29}BF_3NO_4P$ $[M - H]^-$, 530.18787; found, 530.19022. FTIR (neat) cm^{-1}: 2976, 2930, 1706, 1509, 1438, 1367, 1162, 1109, 1050, 1019, 943, 741, 691, 608, 531, 515. The enantiomeric excess of the trifluoroborato-phosphonium salt **5e** (>98% ee) was checked by ^{31}P NMR analysis in the presence of (−)-*N*-methyl ephedrine, by comparison with a racemic sample.

Benzyl (*S*)-2-(Ammonium-chloride)-4-[2-(trifluoroborato)-phenyl-diphenylphosphonium-iodide]butanoate 5f. To a solution of boronato−phosphonium **4f** (0.18 g, 0.24 mmol) in methanol (1 mL) was added a solution of KHF_2 (0.08 g, 1 mmol) in water (0.8 mL). After stirring 1 h at 50 °C, the mixture was extracted with dichloromethane (2 × 5 mL), then the organic phase was dried with $MgSO_4$, and the solvent evaporated. The residue was dissolved in dichloromethane and then precipitated with ether. The compound **5f** was obtained as a colorless solid (0.09 g, yield 67%); mp = 123 °C. ^{1}H NMR (500 MHz, CD_3CN): δ 2.22−2.30 (m, 2H), 3.49−3.64 (m, 2H), 4.13 (brs, 1H), 5.09−5.21 (m, 2H), 7.15−7.18 (m, 1H), 7.20−7.37 (m, 6H), 7.51−7.70 (m, 11H), 7.96−7.98 (m, 1H). ^{13}C NMR (125 MHz, CD_3CN): δ 20.90 (d, *J* = 55.9 Hz), 25.7, 54.0 (d, *J* = 19.6 Hz), 68.3, 122.32 (d, *J* = 87.5 Hz), 122.8 (d, *J* = 87.5 Hz), 127.8 (d, *J* = 13.6 Hz), 128.9, 129.0, 129.1, 130.1 (d, *J* = 10.6 Hz), 130.2 (d, *J* = 10.6 Hz), 133.7−134.0 (m), 134.36 (d, *J* = 11.7 Hz), 135.7, 136.0 (d, *J* = 14.8 Hz), 170.1, 1 C_q not observed. ^{31}P NMR (121 MHz, CD_3CN): δ +28.4. ^{11}B NMR (160 MHz, CD_3CN): δ +2.6. ^{19}F NMR (470 MHz, CD_3CN): δ −133.7. HRMS (ESI-Q-TOF) calcd for $C_{29}H_{28}BNO_2PClF_3$ $[M - Cl - H - F]^+$, 502.19075; found, 502.19184. FTIR (neat) cm^{-1}: 3055, 2929, 2890, 1982, 1952, 1743, 1587, 1523, 1498, 1486, 1438, 1184, 1109, 1071, 1049, 1017, 995, 940, 738, 691.

1-Benzyl-β-pentafluorophenyl L-Aspartate 12.[21] To an ice-cooled solution of 1-benzyl *N*-(*t*-butoxycarbonyl)-L-aspartate (646 mg, 2 mmol) and pentafluorophenol (366 mg, 2 mmol) in a mixture of ethyl acetate/DMF (5 mL, 0.16 mL) was added *N*,*N*′-dicyclohexylcarbodiimide (412 mg, 2 mmol). The mixture was stirred at 0 °C for 1h and then warmed at room temperature. After 1 h, the formed dicyclohexylurea was filtered off and the solvent was removed *in vacuo* to give the compound **12** as a white solid (940 mg, yield 96%); mp = 81 °C; $[\alpha]_D$ = +18.6 (*c* 0.5, $CHCl_3$); $[\alpha]_D$ = −9.1 (*c* 1, AcOEt).[21a] ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.43 (s, 9H), 3.30 (ABX, *J* = 4.8 Hz, *J* = 5.0 Hz, *J* = 17.2 Hz, 2H), 4.66−4.78 (m, 1H), 5.19 (s, 2H), 5.46 (d, *J* = 8.8, 1H), 7.30−7.39 (m, 5H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 28.2, 36.2, 50.1, 67.9, 80.6, 128.4, 128.6, 128.6, 134.9, 136.8, 138.8, 139.9, 140.7, 142.0, 155.2, 166.9, 170.0. ^{19}F NMR (286 MHz, $CDCl_3$): δ −152.2 (d, *J* = 17.5 Hz, 2F), −157.4 (t, *J* = 21.3 Hz, 1F), −162.0 (m, 2F).

Boronato−Phosphonium Dipeptide 13. To a solution of boronato−phosphonium amine **4g** (71 mg, 0.1 mmol) in 1.5 mL of dry acetonitrile was added the aspartate derivative **12** (49 mg, 0.1 mmol). After 6 h at 50 °C the acetonitrile was evaporated and the product was dissolved in dichloromethane and filtrated through Celite. After solvent removing, the residue was purified by column chromatography on silica gel using a mixture acetone/dichloromethane (1:9) as eluent to afford the dipeptide **13** as a viscous oil (62 mg, yield 61%); $[\alpha]_D$ = +10.5 (*c* 0.4, $CHCl_3$). ^{1}H NMR (300 MHz, CD_3CN): δ 0.91 (s, 6H), 0.93 (s, 6H), 1.32 (s, 9H), 2.03−2.10 (m, 2H), 2.71−2.97 (m, 2H), 3.43−3.59 (m, 2H), 4.47−4.65 (m, 2H), 5.01−5.17 (m, 4H), 5.95 (bd, *J* = 8.3 Hz, 1H), 7.18−7.48 (m, 10H), 7.55−7.94 (m, 13H), 8.22−8.25 (m, 1H); ^{13}C NMR (75 MHz, CD_3CN): δ 21.7 (d, *J* = 53.1 Hz), 24.2, 24.3, 26.2, 28.1, 37.5, 51.2, 53.0 (d, *J* = 17.9 Hz), 67.1, 67.5, 79.8, 85.9, 121.2 (d, *J* = 85.9 Hz), 121.7 (d, *J* = 87.9 Hz), 122.1 (d, *J* = 83.9 Hz), 128.3, 128.5, 128.6, 128.8, 129.0, 129.1, 130.8 (d, *J* = 11.9 Hz), 132.9 (d, *J* = 13.9 Hz), 133.5 (d, *J* = 9.5 Hz), 133.8 (d, *J* = 10.4 Hz), 134.8, 135.1, 136.4 (d, *J* = 19.5 Hz), 137.5 (d, *J* = 13.5 Hz), 139.3 (d, *J* = 13.5 Hz), 156.1, 170.6, 171.1, 172.2; ^{31}P NMR (121 MHz, CD_3CN): δ +27.0; HRMS (ESI-Q-TOF) calcd for $C_{51}H_{59}BN_2O_9P$ $[M - I]^+$, 885.40457; found, 885.40308.

Trifluoroborato−Phosphonium Dipeptide 14. To a solution of boronato−phosphonium peptide **13** (50 mg, 0.05 mmol) in methanol (0.8 mL) was added a solution of KHF_2 (15 mg, 0.2 mmol) in water (0.5 mL). After 30 min stirring at 50 °C, the mixture was extracted with dichloromethane (2 × 5 mL), then the organic phase was dried with $MgSO_4$ and the solvent evaporated. The trifluoroborato dipeptide **14** was obtained as colorless oil (31 mg, yield 78%); $[\alpha]_D$= +26 (*c* 0.5, $CHCl_3$). ^{1}H NMR (300 MHz, CD_3CN): δ 1.35 (s, 9H), 2.15−2.23 (brs, 2H), 2.64−2.89 (m, 2H), 3.29−3.45 (m, 2H), 4.45−4.51 (m, 2H), 5.04−5.15 (m, 4H), 5.87 (bd, *J* = 8.1 Hz, 1H), 7.12−7.21 (m, 1H), 7.25−7.34 (m, 10H), 7.42−7.66 (m, 12H), 7.92−8.00 (m, 1H); ^{13}C NMR (75 MHz, CD_3CN): δ 21.1 (d, *J* = 52.3 Hz), 25.7, 28.1, 37.4, 51.1, 53.1 (d, *J* = 19.5 Hz), 67.1, 67.4, 79.8, 119.0, 122.8 (d, *J* = 86.4 Hz), 122.8 (d, *J* = 87.6 Hz), 127.7 (d, *J* = 14.2 Hz), 128.4, 128.6, 128.8, 129.0, 129.1, 130.0 (d, *J* = 4.2 Hz, 130.2 (d, *J* = 3.6 Hz, 133.7 (d, *J* = 4.9 Hz), 133.9 (d, *J* = 4.9 Hz), 134.4, 135.8 (d, *J* = 14.3 Hz), 136.1, 136.5 (d, *J* = 14.8 Hz), 156.0, 171.0, 172.1; ^{31}P NMR (121 MHz, CD_3CN): δ +28.7; ^{19}F NMR (282 MHz, CD_3CN): δ −133.7; HRMS (ESI-Q-TOF) calcd for $C_{45}H_{47}BF_3N_2O_7P$ $[M + Na]^+$, 849.30582; found, 849.30704.

Radiofluorination of 4e into [^{18}F]-5e. $^{18}F^-$ aqueous solution (~180 MBq) prepared with an ABT biomarker generator cyclotron was dried at 100 °C for 5 min under compressed air flow and then briefly stirred (15 s) with 10 μL of 0.2 M KHF_2 in deionized water. Boronato phosphonium-amino acid **4e** (0.2 mg) diluted in deionized water (100 μL) was added to the [$^{18/19}$F]-KHF_2 solution and then allowed to react for 20 min at room temperature under constant stirring. The radiochemical purity of the resulting [^{18}F]-**5e** was assessed by analytical radio-HPLC using nonradiolabeled reference sample **5e** for comparison. The purification step was carried out via semipreparative HPLC to give final [^{18}F]-**5e** in >97% radiochemical purity, 10% radiochemical overall yield (decay corrected) and a specific activity of 130 MBq μmol^{-1} (Figure 3).

The **specific activity** of the radiolabeled product [^{18}F]-**5e** at the time of analysis was determined in MBq μmol^{-1}, according to the following calculation: first, the UV-HPLC calibration of the non-radioactive (cold) analogous precursor **5e** was made in order to determine the concentration of the product using the resulting UV peak area; second, the total amount of radioactivity at the end of the reaction and purification was measured in MBq using a dose calibrator. The specific activity of the product was calculated by dividing the total activity of the radiotracer recovered from the semiprep by the amount of product in μmol, based on the integration of the UV-HPLC.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^{1}H, ^{13}C, ^{31}P, ^{19}F NMR spectra, LC−MS of compound **4e**, kinetic hydrolysis data and radiolabeling HPLC of [^{18}F]-**5e**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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