Synthesis of Boron- and Silicon-containing Amino Acids through Cu-Catalyzed Conjugate Additions to Dehydroalanine Derivatives

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Abstract: A copper-based catalytic technique for the regioselective hydroboration and hydrosilylation of dehydroalanine derivatives has been developed. This method introduces synthetically versatile boron and silicon groups, while simultaneously performing a catalytic anti-Markovnikov hydrofunctionalization of dehydroalanines and dehydropeptides for the synthesis of amino acids and peptides bearing unnatural side chains. The products obtained were expediently converted into valuable nonproteinogenic amino acid building blocks for polypeptide synthesis.

Introduction

Recently, there has been considerable interest in the generation of small molecules with organoboron and organosilicon functionalities due to their extensive applications in organic synthesis (organometallic partners in cross-coupling reactions), chemical biology, and even as diagnostic and therapeutic agents.[1] Applications such as inhibitor design, imaging, drug-release technology, and mapping inhibitor binding are also known.[2] The approval of bortezomib (marketed as Velcade® by Millennium Pharmaceuticals), a proteosome inhibitor containing a boronic acid group, for the treatment of multiple myeloma in humans highlights the successful application of unnatural functional groups in a therapeutically relevant manner.[3]

Of particular significance is the incorporation of silicon and boron into amino acids as well as peptides to afford improved physiochemical properties and in vivo activity (Figure 1). Additionally, boronic acid-containing amino acids remain one of the more promising classes of boron neutron capture therapy (BNCT) agents.[4] Boron- and silicon-containing amino acids are most often prepared via alkylation of glycinimine or another synthetic equivalent with halomethyl boronate or halomethyl silane electrophiles[5] or the transmetalation of highly reactive organolithium/organomagnesium reagents (alanine anion equivalents) with electrophilic boron/silicon species.[6] These methods have significant limitations, such as a difficult preparation, requirements of cryogenic conditions and additional steps, and functional group incompatibility in the case of transmetalations.

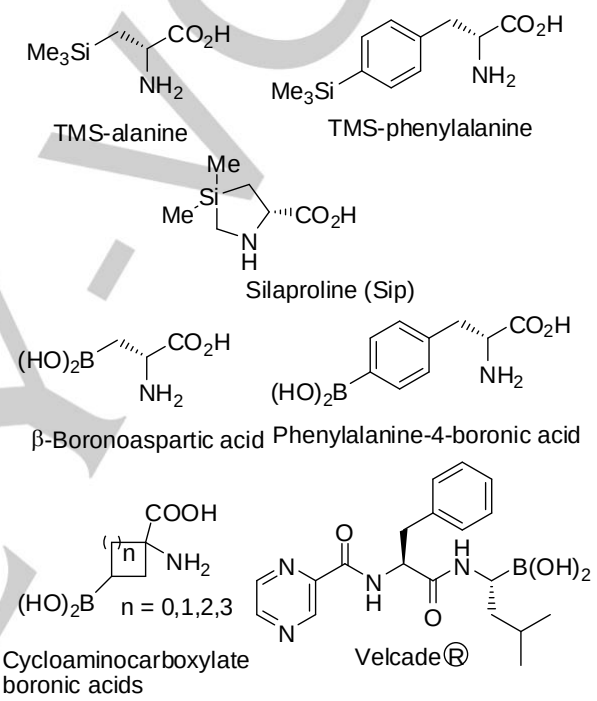

Figure 1. Examples of silyl- and boronic acid-containing amino acids.

Results and Discussion

During the past several years, we have endeavored to enlarge the scope, utilization, and application of dehydroalanine derivatives in synthesis.[7] Until now, we have focused our attention exclusively on C−C bond-forming processes, establishing that an array of indoles can be coupled efficiently with different dehydroalanine electrophiles using a stoichiometric amount of a strong Lewis Acid in an organocatalytic manner.[7c,e] We recently decided to attempt to expand these coupling reactions to generate bonds other than C−C bonds in a catalytic manner. In view of the need for additional complementary methods for the synthesis of boron- and silicon-containing amino acids, we undertook the challenge of achieving borylation and silylation of dehydroalanine derivatives to provide C−B and C−Si bonds, a transformation that could enable regiospecific and late-stage incorporation of boron and silicon into dehydroamino acids and dehydropeptides in an umpolung process. At the time that we initiated this

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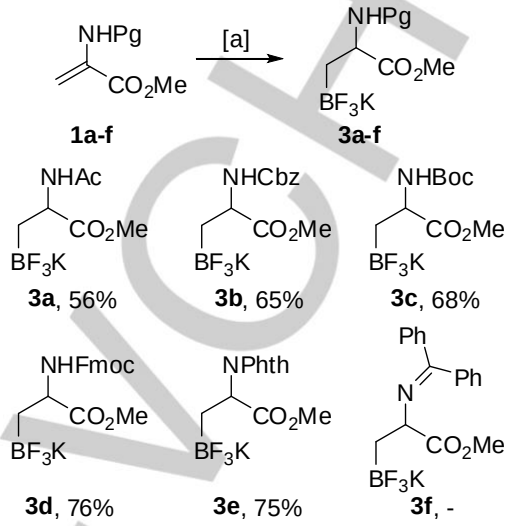
investigation, there were no reports of such reactions; however, last year, Lin and co-workers described copper catalysts that result in borylation of β-substituted α-dehydroamino acid derivatives at room temperature or above.[8]

In this report, we provide a copper(I)-catalyzed method that accomplishes borylation and silylation reactions of an array of unactivated protected dehydroalanine derivatives. Particularly noteworthy is our observation that, for the first time, small dehydropeptide electrophiles can serve as effective coupling partners for borylations and silylations. In addition, we report experimental details demonstrating the capability of *N*-Boc β-pinacolboronate- and (dimethyl)phenylsilyl-alanine methyl ester, to be selectively deprotected to give either the free amine or the free acid under mild reaction conditions, and then, undergo some of the typical coupling associated with peptide synthesis.

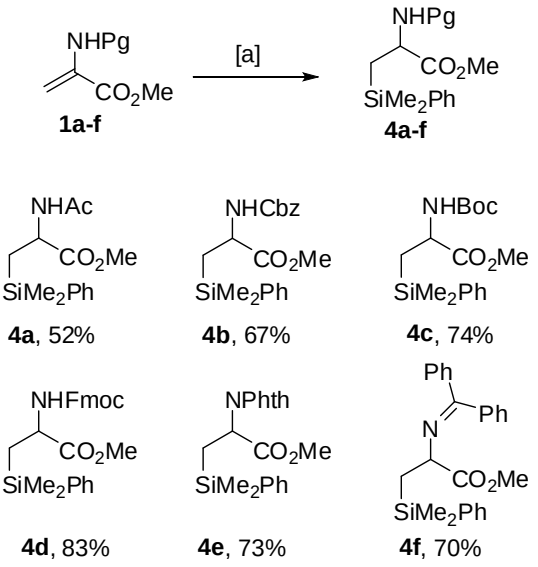
The C–B bond functionalization of acrylates and acrylamide mediated by copper is well established.[9] We recognized that the methodology described by Yun 2006[9d] could be applied to selectively functionalize protected dehydroalanines, formally a hydroboration reaction, by employing bis(pinacolato)diboron (B_2pin_2) as the "boron" source, MeOH as the "hydrogen" source, a catalytic amount of CuCl to generate copper(I) *tert*-butoxide as the active catalyst, and a phosphine ligand in THF. Yun's reaction conditions were initially applied to the commercially available methyl *N*-acetamidoacrylate. Changes to the reaction conditions included modifying the Cu catalyst and loading, solvent, inert atmosphere, and reaction temperature; however, no increase in yield was recorded. Optimal turnover numbers and yields were seen with 5 mol-% CuCl. The reaction proceeded at room temperature in 20 h, and the addition of the phosphine ligand 1,2-bis(diphenylphosphino)benzene (dppbz) proved to be important for full conversion, based on ^{1}H NMR data (see SI). Generally, isolation of the resulting β-pinacolboronate-α-amino acid intermediate was not successful because of its instability during flash chromatography.[8] Therefore, it was transformed quantitatively into the corresponding potassium organotrifluoroborate by treating the crude reaction mixture with KHF_2. The non-Lewis acidic, salt-like potassium trifluoroboronate amino acid thus prepared was a nonhygroscopic, free-flowing powder or crystalline solid that was indefinitely stable to the atmosphere. The resultant crude potassium trifluoroborate was recrystallized from acetone/diethyl ether to afford the pure product, free of pinacol. A significant advantage of the organotrifluoroborate product over the corresponding boronate is the easy purification of the former product via acetone−ether precipitation.[10]

We first studied the extension of this reaction to a diverse array of *N*-protected dehydroamino esters (**1a-f**) not only to access differently protected useful amino acids containing boron but also to evaluate their influence on reaction yields. From the tested amino protecting groups (Scheme 1), acetyl (**1a**), Cbz (**1b**), Boc (**1c**) and Fmoc (**1d)** protecting groups gave good yields of β-trifluoroborate alanine derivatives (**3a-d**) with equally high yields. Concerning the phthalimido (**1e**) protecting groups, we obtained very efficient addition. In contrast, the diphenylmethylene group (**1f**) was not compatible with the reaction conditions, giving a byproduct during the trifluoroborate formation.



Scheme 1. Borylation of α-Dehydroamino Acid Derivatives (**1a-f**). Reagents and conditions: [a] 1. CuCl (5 mol-%), KO-*t*-Bu (15 mol-%), dppbz (5 mol-%), B_2pin_2 (1.3 equiv), MeOH (2 equiv), THF, r.t., 20 h; 2. KHF_2 (4 equiv), THF, H_2O, r.t., 20 h..

Next, we evaluated the transfer of silicon nucleophiles onto the same dehydroalanine derivatives (**1a-f**) under copper(I)-catalyzed standard conditions by employing Suginome's reagent ($Me_2PhSiBpin$)[11] as the silicon pronucleophile. While silylboranes have been employed extensively to promote silylborylation of various α,β-unsaturated carbonyl and carboxyl compounds, conjugated alkynes, aldehydes, and imines,[12] to the best of our knowledge their utilization en route to silane-containing amino acids has not been explored. As shown in Scheme 2, employing commercially available **1a**, CuCl as the catalyst, and dppbz as the supporting ligand afforded promising results but required heating at 50 °C to achieve reasonable reaction times. Several simple *N*-protected dehydroalanine methyl esters, such as *N*-Cbz (**1b**), *N*-Boc (**1c**), *N*-Fmoc (**1d**) and phthalimido (**1e**) showed no variation in terms of yield or reactivity. Even the diphenylmethylene protecting group (**1f**) was compatible with the silylation reaction conditions, giving the product (**4f**) in good yield.

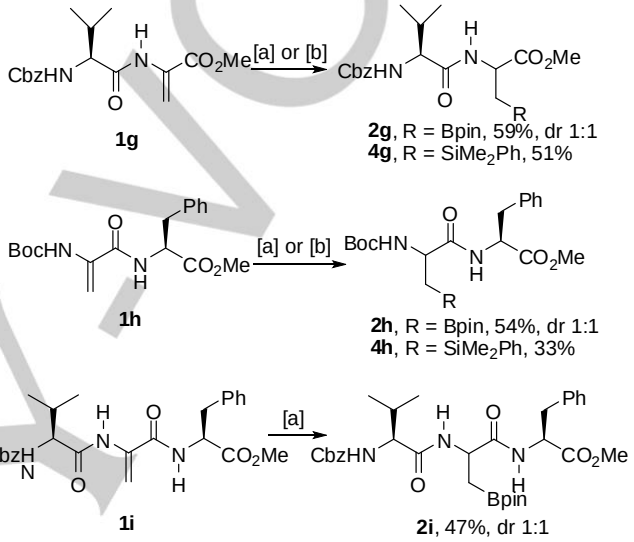


Scheme 2. Silylation of α-Dehydroamino Acid Derivatives (**1a-f**). *Reagents and conditions:* [a] CuCl (5 mol-%), KO-*t*-Bu (15 mol-%), dppbz (5 mol-%), $Me_2PhSiBpin$ (1.3 equiv), MeOH (2 equiv), THF, 50 °C, 20 h.

Based on these results, it appeared that a great variety of boryl and silyl alanine derivatives were readily obtained using this tandem metalation/protonation process. The scope of our racemic copper(I)-catalyzed enamine addition is certainly broad, as documented by its compatibility with common protecting groups at the nitrogen atom (Schemes 1 and 2). However, our attempts to render this reaction enantioselective with representative chiral ligands did not meet with success. The regiochemical outcomes of these reactions are definitively governed by the mode of addition of the boryl- or silyl-copper species, derived from B_2pin_2 or $Me_2PhSiBpin$ and a copper(I) complex, across the unsaturated C–C bond, and anti-Markovnikov selectivities were observed as depicted in Schemes 1 and 2.

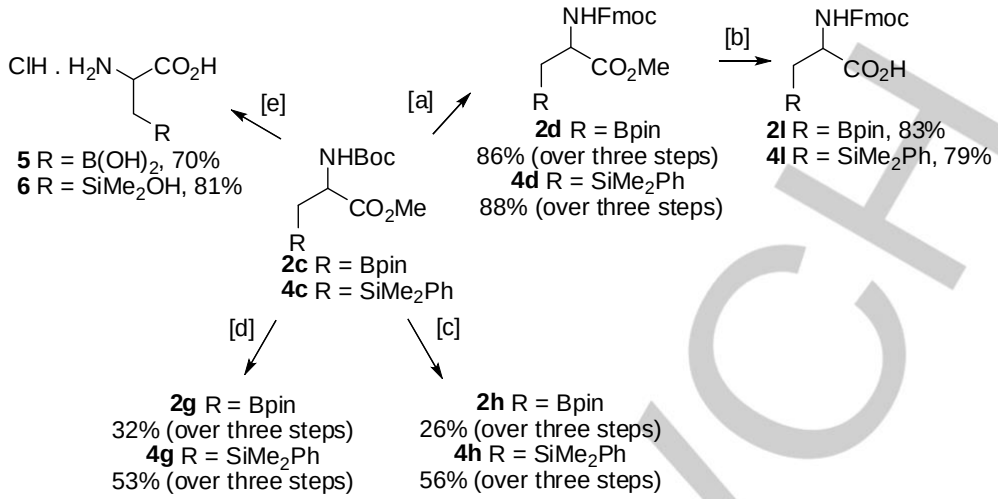
In consideration of the importance of applications for site-specific peptide labeling and chemically modified peptides,[13] we next tested the versatility of the optimized reaction conditions for the direct borylation and silylation of some dehydropeptides. All these dehydropeptides (**1g-i**) were easily prepared in good yields from serine derivatives by a coupling reaction with the appropriate protected amino acid and hydroxy elimination (see SI, Schemes S1 and S2), without intermediate purification steps. We successfully applied our optimized reaction conditions to the borylation and silylation of dehydroalanine-containing dipeptides **1g** and **1h** (Scheme 3), providing nonracemic **2g,h** and **4g,h** as a mixture of diastereoisomers, respectively. For compounds **4g,h** the two diastereomers were separable. When applied to the three residue dehydroalanine-containing peptide **1i**, it was necessary to increase the catalyst loading to 9 mol-% for Cu to obtained **2i** in decent yield**.** Notably, these reactions proceeded with a comparable efficiency and selectivity for both N- and C-terminal as well as internal dehydroalanine residues under an ambient atmosphere of air, highlighting the robust nature of this user-friendly protocol. The potential of this approach for late-stage diversification of enantiomerically pure peptides offering a unique reactive handle for further modifications or modulating the activity needs to be highlighted in future studies.

These reactions achieved rather poor diastereoselectivity, which clearly indicates and confirms the lack of stereocontrol in the protonation step and further attests to the difficulties in enantioselective protonation of enamines.[14]



Scheme 3. Extended Scope of the Borylation and Silylation. Reaction to Polypeptides (**1g-i**). *Reagents and conditions:* [a] CuCl (5 mol-%), KO-*t*-Bu (15 mol-%), dppbz (5 mol-%), B_2pin_2 (1.3 equiv), MeOH (2 equiv), THF, r.t., 20 h, For **1i** CuCl (9 mol-%), KO-*t*-Bu (27 mol-%), dppbz (9 mol-%), B_2pin_2 (1.3 equiv), MeOH (2 equiv), THF, rt, 20 h; [b] CuCl (5 mol-%), KO-*t*-Bu (15 mol-%), dppbz (5 mol-%), $Me_2PhSiBpin$ (1.3 equiv), MeOH (2 equiv), THF, 50 °C, 20 h.

The broader utility of this protocol for the rapid synthesis of bisprotected boron- and silicon-containing amino acids, such as **2c** and **4c,** is highlighted by their facile conversion to useful amino acid building blocks for solid-phase peptide synthesis, and their ability of undergoing typical reactions associated with peptide synthesis (Scheme 4). The *N*-Boc-protected borylated and silylated alanine **2c** and **4c** were coupled, after selective methyl ester hydrolysis using lithium hydroxide, with L-phenylalanine methyl ester using EDCI/HOBT coupling conditions to produce the dipeptides **2h** and**4h** in good yield. Removal of the *N*-Boc group and coupling with *N*-Cbz-valine yielded the dipeptides **2g** and **4g**, again in decent yield. These results, along with those of Walkup[6c] on (trimethylsily1)alanine, indicate that at least the simple β- borylated and β-sylilated alanines **2c** and **4c** are not affected by the coupling and deprotection conditions usually associated with solution peptide synthesis.[15] Interchange of *N*-protections is relevant when a switch over of the chemoselectivity of protecting groups is required due to a change in the synthetic methods. Thus, *N*-Boc-protected borylated and silylated alanines **2c** and **4c** where fully



Scheme 4. Functionalization of *N*-Boc-β-boronate alanine methyl ester (**2c**) and *N*-Boc β-(dimethyl)phenylsilyl-alanine methyl ester (**4c**). *Reagents and conditions:* [a] 1. TFA, DCM, r.t., 2 h, 2. FmocOSu, $NaHCO_3$, H_2O, dioxane, r.t., 20h; [b] Me_3SnOH, DCE, 80 °C, 6h ; [c] 1. LiOH, THF, r.t., 16 h, 2. L-Phe (OMe), HOBt, TEA, DCM, EDCI, r.t., 20 h; [d] 1. TFA, DCM, r.t., 2 h, 2. Z-Val, HOBt, TEA, DCM, EDCI, r.t., 20 h; [e] HCl 6N, 70 °C, 16 h.

compatible with standard Boc-deprotection and then Fmoc-reprotection sequence, to afford **2d** and **4d** (obtainable also by direct hydrofunctionalization of **1d**) almost in very good yields. Equally intriguing was the fact that the Fmoc protecting group in **2d** and **4d** remained intact throughout the methyl ester hydrolysis with trimethyltin hydroxide,[16] yielded to their corresponding carboxylic acids **2l** and **4l** in sufficiently pure form for direct use as nonproteinogenic amino acid building blocks in Fmoc solid-phase peptide synthesis (SPPS). Finally, heating **2c** and **4c** with 6 N HCl at 70 °C led to the completely unprotected boron and silicon-containing α-amino acid **5**[5f] and **6**[5e] respectively, with the simultaneous hydrolysis of the pinacolboronate for **2c**, and Si-C(Ph) bond cleavage for **4c.**

Conclusions

In summary, we have reported herein the regioselective transfer of boron and silicon nucleophiles onto dehydroalanine derivatives as well as dehydropeptides, affording β-boronated and silylated amino acids and peptides in a catalyst-controlled reaction for the first time. The value of this strategy as an expedient means for a rapid, general, and mild synthetic route to a novel class of orthogonally N- and C-protected boron- and silicon-containing amino acids was underscored by the ability of these amino acids to be selectively deprotected and incorporated into peptides by solution-phase methodology. Moreover, they can be easily converted in suitable noncanonical amino acid building blocks for specific incorporation into a peptide framework by SPPS. While the majority of the reported products are α-amino acid pinacolboranes and dimethylphenylsilyl, a succinct method towards the corresponding and more stable trifluoroborate derivatives as a novel nucleophilic alanine equivalent also has been reported. This transformation can serve as a starting point for the construction of borono and silicon amino acid-derived peptides. Further studies addressing the scope and utility of this process are in progress.

Experimental Section

General Methods. All reactions were run in air unless otherwise noted. Column chromatography purifications were performed in flash chromatography conditions using Merck 230-400 Mesh silica gel. Analytical thin layer chromatography (TLC) was carried out on Merck silica gel plates (Silica Gel 60 F254), that were visualized by exposure to ultraviolet light and an aqueous solution of cerium ammonium molybdate (CAM) or $KMnO_4$. ^1H NMR ,^{13}C NMR and ^{11}B NMR spectra were recorded on a Bruker Avance 200 or 400 spectrometer, using $CDCl_3$, CD_3OD, DMSO-d_6, Acetone- d_6 or D_2O as solvent. Chemical shifts (δ scale) are reported in parts per million (ppm) relative to the central peak of the solvent. Coupling constants (J values) are given in hertz (Hz). In ^{13}C NMR carbon adjacent to boron was not observed. ESI-MS spectra was taken on a Waters Micromass ZQ instrument. IR spectra were obtained on a Nicolet Avatar 360 FT-IR spectrometer, absorbance are reported in cm-1. Melting points were determined on a Buchi SMP-510 capillary melting point apparatus and are uncorrected. Elemental analyses were performed on a Carlo Erba analyzer, and the results are within ± 0.4 of the theoretical values (C, H, N). See Supporting Information for other details.

General Procedure for the Copper(I)-Catalyzed Borylation of Dehydroalanine (1a-e) and Dehydropeptides (1g-i): A mixture of CuCl (1 mg, 0.01 mmol), KO-*t*-Bu (3.5 mg, 0.03 mmol), and 1,2-bis(diphenylphosphino)benzene (ddpbz) (5 mg, 0.01 mmol) in anhydrous THF (0.12 mL) was stirred for 30 min in a seal tube. B_2pin_2 (66 mg, 0.26 mmol) in THF (0.12 mL) was added. The reaction mixture was stirred for 10 min and then the appropriate dehydroalanine (**1a-e**) or dehydropeptide (**1g-i**) (0.2 mmol) in THF (0.12 mL) was added to the

reaction mixture, followed by MeOH (16 μL, 0.4 mmol). The reaction mixture was stirred at the room temperature for 20 hours and then filtered through a short plug of silica gel and used for the following reaction without further purification (**2a-e**) or purified by flash chromatography (**2g-i**).

(Notice: the hydroboration products were unstable, so the purification operation should be quick).

Methyl 2-(((9H-fluoren-9-yl)methoxy)carbonylamino)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propanoate (2d): The title compounds (**2d**) was obtained following the general procedure for the Cu(I)-catalyzed borylation using methyl 2-(((9*H*-fluoren-9-yl)methoxy)carbonylamino)acrylate **(1d)**. The residue obtained was purified by flash chromatography (gradient from cyclohexane /EtOAc 9:1 to cyclohexane /EtOAc 7:3) yielding **2d** as colourless oil (71 mg, 79%); TLC (cyclohexane /EtOAc 7:3) R_f = 0.23 (CAM); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, J = 7.5 Hz, 2H), 7.62 (t, J = 7.5 Hz, 2H), 7.41 (t, J = 7.5 Hz, 2H), 7.323 (t, J = 7.5, 1H), 7.320 (t, J = 7.5, 1H), 5.65 (br d, J = 8.5 Hz, 1H), 4.58 (dd, J_1 = 15.0 and J_2 = 6.5 Hz, 1H), 4.43-4.34 (m, 2H), 4.26 (t, J = 7.0 Hz, 1H), 3.75 (s, 3H), 1.36 (t, J = 6.5 Hz, 2H), 1.27 (d, J = 4.0 Hz, 12H).^{13}C NMR (100 MHz, $CDCl_3$) δ 173.4, 155.8, 143.8, 141.28, 141.27, 127.6, 127.0, 125.2, 125.1, 119.9, 83.7, 67.0, 52.3, 50.6, 47.1, 24.8, 24.6 (carbon adjacent to boron was not observed); ^{11}B NMR (128 MHz, $CDCl_3$, BF_3•OEt_2): 33.0; IR (film): 3311, 1728, 1712, cm^{-1}; MS(ESI) m/z : 452 (M+1); Anal. calcd for $C_{25}H_{30}BNO_6$ (451.22): C, 66.53; H, 6.70; N, 3.10; found: C, 66.71; H, 6.63; N, 3.18.

(*R*)-Methyl 2-((*S*)-2-(benzyloxycarbonylamino)-3-methylbutanamido)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propanoate and (*S*)-methyl 2-((*S*)-2-(benzyloxycarbonylamino)-3-methylbutanamido)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propanoate (2g): The title compounds (**2g**) was obtained following the general procedure for the Cu(I)-catalyzed borylation using Z-L-Val-ΔAla-OMe **(1g)**. The residue obtained was purified by flash chromatography (CH_2Cl_2/acetone 9:1) yielding **2g** as a mixture of two diastereomers (55 mg, 59%); yellowish oil; TLC (CH_2Cl_2/acetone 9:1) R_f = 0.5 (CAM); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.35 (s, 10H), 6.78 (br d, J = 8.0 Hz, 1H), 6.68 (br d, J = 8.0 Hz, 1H), 5.50 (br d, J = 9.0 Hz, 1H), 5.43 (br d, J = 9.0 Hz, 1H), 5.18-5.05 (m, 4H), 4.81-4.71 (m, 2H), 4.14-4.02 (m, 2H), 3.70 (s, 6H), 2.24-2.09 (m, 2H), 1.36-1.22 (m, 4H), 1.22 (s, 24H), 1.01-0.90 (m, 12H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 172. 9, 170.4, 156.2, 136.2, 128.5, 128.1, 128.0, 83.9, 83.8, 67.0, 60.1, 52.3, 48.8, 31.6, 31.3, 24.8, 24.6, 19.1, 18.8, 17.8, 17.6 (carbon adjacent to boron was not observed); ^{11}B NMR (64 MHz, $CDCl_3$, BF_3•OEt_2): 33.4; IR (film): 3316, 1736, 1708, 1658 cm^{-1}; MS(ESI) m/z : 463 (M+1); Anal. calcd for $C_{23}H_{35}BN_2O_7$ (462.25): C, 59.75; H, 7.63; N, 6.06; found: C, 59.48; H, 7.69; N, 6.02.

(*S*)-Methyl 2-((*R*)-2-(tert-butoxycarbonylamino)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propanamido)-3-phenylpropanoate and (*S*)-methyl 2-((*S*)-2-(tert-butoxycarbonylamino)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propanamido)-3-phenylpropanoate (2h): The title compounds (**2h**) was obtained following the general procedure for the Cu(I)-catalyzed borylation, using *N*-Boc-ΔAla-L-Phe-OMe (**1h**). The residue obtained was purified by flash chromatography (CH_2Cl_2/MeOH 96:4) yielding **2h** as a mixture of two diastereomers (51 mg, 54%); yellowish oil; TLC (CH_2Cl_2/MeOH 96:4) R_f = 0.2 (CAM); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29-7.20 (m, 6H), 7.11-7.10 (m, 4H), 7.03 (br d, J = 7.0 Hz, 1H), 6.95 (d, J = 7.0 Hz, 1H), 5.38 (d, J = 8.0 Hz, 1H), 5.32 (d, J = 8.0 Hz, 1H), 4.82-4.78 (m, 2H), 4.37-4.31 (m, 2H), 3.67 (s, 3H), 3.66 (s, 3H), 3.13 (dd, J_1 = 14.0 and J_2 = 6.0 Hz, 1H), 3.11 (dd, J_1 = 14.0 and J_2 = 6.0 Hz, 1H), 3.07 (dd, J_1 = 14.0 and J_2 = 6.0 Hz, 1H), 3.04 (dd, J_1 = 14.0 and J_2 = 6.0 Hz, 1H), 1.42 (s, 9H), 1.40 (s, 9H), 1.25 (dd, J_1 = 16.0 and J_2 = 5.0 Hz, 2H), 1.21 (s, 12H), 1.20 (s, 12H), 1.11 (dd, J_1 = 16.0 and J_2 = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.4, 172.3, 171.6, 171.5, 155.8, 155.6, 135.9, 129.30, 129.28, 128.50, 128.47, 127.0, 83.7, 83.6, 79.9, 79.8, 53.44, 53.36, 52.13, 52.09, 50.9, 38.0, 37.8, 28.3, 24.9, 24.8, 24.6, 24.5 (carbon adjacent to boron was not observed); ^{11}B NMR (128 MHz, $CDCl_3$, BF_3•OEt_2): 32.9; IR (film): 3334, 1740, 1716, 1686 cm^{-1}; MS(ESI) m/z : 477 (M+1); Anal. calcd for $C_{24}H_{37}BN_2O_7$ (476.27): C, 60.51; H, 7.83; N, 5.88; found: C, 60.73; H, 7.90; N, 5.93.

(5*S*, 8*R*, 11*S*)-Methyl 11-benzyl-5-isopropyl-3,6,9-trioxo-1-phenyl-8-((4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl)-2-oxa-4,7,10-triazadodecan-12-oate and (5*S*, 8*S*, 11*S*)-methyl 11-benzyl-5-isopropyl-3,6,9-trioxo-1-phenyl-8-((4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl)-2-oxa-4,7,10-triazadodecan-12-oate (2i): The title compounds (**2i**) was obtained following the general procedure for the Cu(I)-catalyzed borylation, using Z-L-Val-ΔAla-L-Phe-OMe (**1i**) CuCl (1.8 mg, 0.018 mmol), KO-*t*-Bu (6 mg, 0.054 mmol), and (ddpbz) (8 mg, 0.018 mmol). The residue obtained was purified by flash chromatography (CH_2Cl_2/acetone 9:1) yielding **2i** as a mixture of two diastereoisomers (57 mg, 47%); yellowish oil; TLC (CH_2Cl_2/acetone 9:1) R_f = 0.46 (CAM); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.20 (m, 16H), 7.17-7.07 (m, 4H), 6.96-6.93 (m, 4H), 5.32 (br d, J = 8.5 Hz, 2H), 5.14-5.06 (m, 4H), 4.78-4.74 (m, 2H), 4.62-4.57 (m, 2H), 4.04-4.00 (m, 2H), 3.66 (s, 6H), 3.10-3.02 (m, 2H), 2.17-2.04 (m, 2H), 1.29 (dd, J_1 = 16.0 and J_2 = 8.0 Hz, 2H), 1.25 (s, 24H), 1.08 (dd, J_1 = 16.0 and J_2 = 8.0 Hz, 2H), 0.83 (d, J = 7.0 Hz, 6H), 0.80 (d, J = 7.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.5, 170.7, 156.3, 136.2, 135.9, 129.25, 129.22, 128.55, 128.52, 128.51, 128.2, 128.07, 128.04, 127.07, 127.01, 83.8, 83.7, 67.0, 60.1, 53.6, 53.5, 52.2, 52.1, 49.8, 37.9, 37.8, 31.3, 30.8, 25.0, 24.8, 24.6, 24.5, 19.0, 17.6 (carbon adjacent to boron was not observed); ^{11}B NMR (132 MHz, $CDCl_3$, BF_3•OEt_2): 36.2; δ IR (film): 3302, 1736, 1703, 1648 cm^{-1}; MS(ESI) m/z : 610 (M+1); Anal. calcd for $C_{32}H_{44}BN_3O_8$ (609.32): C, 63.06; H, 7.28; N, 6.89; found: C, 62.83; H, 7.21; N, 6.95.

General Procedure for the Synthesis of Potassium β-Trifluoroborate Alanine (3a-e): To a solution of crude boronate derivatives (**2a-e**) (0.2 mmol) in THF (2 mL) was added a 4.5 M aqueous solution of KHF_2 (62.5 mg, 0.8 mmol). The mixture was stirred at room temperature for 20 h. The solvents were evaporated under reduced pressure and the residue obtained was triturated with hot acetone, then was crystallized by acetone/Et_2O.

***N*-Acetyl potassium β-trifluoroborate alanine methyl ester (3a):** Following the general procedure, for the synthesis of potassium β-trifluoroborate alanine, compound **3a** was obtained as white solid (28 mg, 56% over two steps); ^{1}H NMR (200 MHz, Acetone-d_6) δ 6.86 (br s, 1H), 4.18 (ddd, J_1 = 11.5 and J_2 = 8.5, J_3 = 6.0, Hz, 1H), 3.56 (s, 3H), 1.83 (s, 3H), 0.56 (br s, 2H); ^{13}C NMR (50 MHz, Acetone-d_6) δ 175.7, 168.7, 51.4, 50.5, 22.0 (carbon adjacent to boron was not observed); ^{11}B NMR (64 MHz, Acetone-d_6, BF_3•OEt_2): 4.7; IR (film): 3283, 1739, 1645 cm^{-1}; MS(ESI) m/z : 212 (M-K); Anal. calcd for $C_6H_{10}BF_3KNO_3$ (251.03): C, 28.70; H, 4.01; N, 5.58; found: C, 28.48; H, 3.93; N, 5.52.

***N*-Benzyloxycarbonyl potassium β-trifluoroborate alanine methyl ester (3b):** Following the general procedure, for the synthesis of potassium β-trifluoroborate alanine, compound **3b** was obtained as white solid (45 mg, 65% over two steps); ^{1}H NMR (200 MHz, CD_3OD) δ 7.24 (s, 6H), 4.96 (s, 2H), 4.02 (t, J = 7.0 Hz, 1H), 3.57 (s, 3H), 0.65-0.53 (m, 2H); ^{13}C NMR (50 MHz, CD_3OD) δ 176.5, 156.9, 136.8, 128.0, 127.5, 127.3, 66.0, 52.6, 50.9; (carbon adjacent to boron was not observed); ^{11}B NMR (64 MHz, CD_3OD, BF_3•OEt_2): 4.2; IR (film): 3340, 1749, 1720 cm^{-1}; MS(ESI) m/z : 304 (M-K); Anal. calcd for $C_{12}H_{14}BF_3KNO_4$ (343.06): C, 42.00; H, 4.11; N, 4.08; found: C, 42.18; H, 4.16; N, 4.15.

***N*-*tert*-Butoxycarbonyl potassium β-trifluoroborate alanine methyl ester (3c):** Following the general procedure, for the synthesis of potassium β-trifluoroborate alanine, compound **3c** was obtained as white solid (42 mg, 68% over two steps); ^{1}H NMR (200 MHz, Acetone-d_6) δ 5.66 (br s, 1H), 3.89 (dd, J_1 = 13.0 and J_2 = 6.5 Hz, 1H), 3.46 (s, 3H), 1.25 (s, 9H), 0.48–0.42 (m, 2H);^{13}C NMR (50 MHz, Acetone-d_6) δ 176.0, 155.4, 77.7, 52.4, 50.6, 27.7 (carbon adjacent to boron was not observed); ^{11}B NMR (64 MHz, Acetone-d_6, BF_3•OEt_2): 4.0; IR (film): 3332, 1735, 1715 cm^{-1}; MS(ESI) m/z : 270 (M-K); Anal. calcd for $C_9H_{16}BF_3KNO_4$ (309.08): C, 34.97; H, 5.22; N, 4.53;found: C, 35.16; H, 5.31; N, 4.45.

***N*- ((9*H*-fluoren-9-yl)methoxy)carbonylamino potassium β-trifluoroborate alanine methyl ester (3d):** Following the general procedure, for the synthesis of potassium β-trifluoroborate alanine, compound **3d** was obtained as white solid (65 mg, 76% over two steps); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.89 (d, J = 7.5 Hz, 2H), 7.69 (d, J = 7.5 Hz, 2H), 7.42 (t, J = 7.5 Hz, 2H), 7.34 (t, J = 7.5 Hz, 2H), 6.44 (br d, J = 2.5 Hz, 1H), 4.22 (s, 3H), 3.91-3.86 (m, 1H), 3.54 (s, 3H), 0.51-0.39 (m, 2H).^{13}C NMR (100 MHz, DMSO-d_6) δ 175.7, 156.0, 144.4, 144.3, 141.1, 129.4, 128.1, 127.7, 127.5, 125.7, 121.8, 120.5, 66.1, 53.1, 51.5, 47.1 (carbon adjacent to boron was not observed); ^{11}B NMR (128 MHz, DMSO-d_6, BF_3•OEt_2): 4.4; IR (film): 3305, 1740, 1722 cm^{-1}; MS(ESI) m/z : 392 (M-K); Anal. calcd for $C_{19}H_{18}BF_3KNO_4$ (431.09): C, 52.92; H, 4.21; N, 3.25;found: C, 52.81; H, 4.16; N, 3.32.

***N*-Phthalimido potassium β-trifluoroborate alanine methyl ester (3e):** Following the general procedure, for the synthesis of potassium β-trifluoroborate alanine, compound **3e** was obtained as white solid (51 mg, 75% over two steps); ^{1}H NMR (200 MHz, DMSO-d_6) δ 7.82 (s, 1H), 4.77 (dd, J_1 = 13.0 and J_2 = 3.5 Hz, 1H), 3.59 (s, 3H), 1.20-1.01 (m, 1H), 0.77-0.65 (m, 1H); ^{13}C NMR (50 MHz, DMSO-d_6) δ 173.2, 167.6, 134.6, 132.3, 123.2, 52.4, 51.2 (carbon adjacent to boron was not observed); ^{11}B NMR (64 MHz, DMSO-d_6, BF_3•OEt_2): 4.8; IR (film): 1742, 1722 cm^{-1}; MS(ESI) m/z : 300 (M-K); Anal. calcd for $C_{12}H_{10}BF_3KNO_4$ (339.03): C, 42.50; H, 2.97; N, 4.13; found: C, 42.28; H, 2.89; N, 4.06.

General Procedure for the Copper(I)-Catalyzed Silylation of Dehydroalanine (1a-f) and Dehydropeptides (1g-i): A mixture of CuCl (1 mg, 0.01 mmol), KO-*t*-Bu (3.5 mg, 0.03 mmol), and ddpbz (5 mg, 0.01 mmol) in anhydrous THF (0.18 mL) was stirred for 30 min in a seal tube. Me_2PhSi-Bpin (71 µl, 0.26 mmol) was added. The reaction mixture was stirred for 10 min and then the appropriate dehydroalanine (**1a-f**) or dehydropeptide (**1g-i**) (0.2 mmol) in THF (0.18 mL) was added to the reaction mixture, followed by MeOH (16 µL, 0.4 mmol). The reaction mixture were stirred at 50 °C for 20 h. The solvent was evaporated under reduced pressure, to give a residue that was purified by flash chromatography.

Methyl 2-acetamido-3-(dimethyl(phenyl)silyl)propanoate (4a): The residue obtained following the general procedure for Cu(I)-catalyzed silylation was purified by flash chromatography (CH_2Cl_2/acetone 9:1) to obtained **4a** as a colourless oil (29 mg, 52%); TLC (CH_2Cl_2/acetone 9:1) R_f = 0.3 ($KMnO_4$);^{1}H NMR (200 MHz, $CDCl_3$) δ 7.53–7.46 (m, 2H), 7.41–7.35 (m, 3H), 5.64 (br d, J = 7.5 Hz, 1H), 4.61 (ddd, J_1 = 15.0, J_2 = 9.0 and J_3 = 6.0, 1H), 3.58 (s, 3H), 1.73 (s, 3H), 1.41 (dd, J_1 = 15.0 and J_2 = 6.0 Hz, 1H), 1.23 (dd, J_1 = 15.0 and J_2 = 9.0 Hz, 1H), 0.36 (s, 3H), 0.34 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 174.0, 169.4, 138.1, 133.5, 129.3, 128.0, 52.1, 49.2, 22.8, 20.2, -2.8, -3.2; IR (film): 3285, 1744, 1650 cm^{-1}; MS(ESI) m/z : 280 (M+1), 202 (M-77); Anal. calcd for $C_{14}H_{21}NO_3Si$ (279.13): C, 60.18; H, 7.58; N, 5.01; found: C, 60.39; H, 7.63; N, 5.06.

Methyl 2-(benzyloxycarbonylamino)-3-(dimethyl(phenyl)silyl)propanoate (4b): The residue obtained following the general procedure for Cu(I)-catalyzed silylation was purified by flash chromatography (gradient from cyclohexane/CH_2Cl_2 1:1 to cyclohexane/CH_2Cl_2 2:8) to obtained **4b** as a colourless oil (50 mg, 67%); TLC (CH_2Cl_2) R_f = 0.52 (CAM);^{1}H NMR (200 MHz, $CDCl_3$) δ 7.51–7.42 (m, 2H), 7.38–7.27 (m, 8H), 5.14 (d, J = 7.0 Hz, 1H), 5.07 (s, 2H), 4.49-4.37 (m, 1H), 3.57 (s, 3H), 1.43 (dd, J_1 = 15.0 and J_2 = 6.5 Hz, 1H), 1.24 (dd, J_1 = 15.0 and J_2 = 9.0 Hz, 1H), 0.37 (s, 3H), 0.36 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 173.8, 155.4, 137.8, 136.3, 133.5, 129.2, 128.5, 128.1, 128.0, 127.9, 66.8, 52.1, 51.1, 20.6, -2.8, -2.9; IR (film): 3346, 1748, 1724 cm^{-1}; MS(ESI) m/z : 372 (M+1), 294 (M-77); Anal. calcd for $C_{20}H_{25}NO_4Si$ (371.16): C, 64.66; H, 6.78; N, 3.77; found: C, 64.89; H, 6.71; N, 3.83.

Methyl 2-(*tert*-butoxycarbonylamino)-3-(dimethyl(phenyl)silyl)propanoate (4c):[6d] The residue obtained following the general procedure for Cu(I)-catalyzed silylation was purified by flash chromatography (gradient from cyclohexane/CH_2Cl_2 1:9 to CH_2Cl_2) to obtained **4c** as a colourless oil (50 mg, 74%); TLC (CH_2Cl_2) R_f = 0.5 ($KMnO_4$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.54-7.49 (m, 2H), 7.40-7.28 (m, 3H), 4.86 (br d, J = 8.0 Hz, 1H), 4.41-4.29 (m, 1H), 3.57 (s, 3H), 1.43 (s, 9H), 1.38 (dd, J_1 = 15.0 and J_2 = 6.5 Hz, 1H), 1.19 (dd, J_1 = 15.0 and J_2 = 9.0 Hz, 1H), 0.37 (s, 3H), 0.36 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 174.3, 154.9, 138.1, 133.5, 129.2, 127.9, 79.73, 52.0, 50.5, 28.3, 20.6, -2.7, -2.9; IR (film): 3358, 1740, 1720 cm^{-1}; MS(ESI) m/z : 338 (M+1), 204 (M-134); Anal. calcd for $C_{17}H_{27}NO_4Si$ (337.17): C, 60.50; H, 8.06; N, 4.15; found: C, 60.26; H, 8.12; N, 4.11.

Methyl 2-(((9*H*-fluoren-9-yl)methoxy)carbonylamino)-3-(dimethyl(phenyl)silyl)propanoate (4d): The residue obtained following the general procedure for Cu(I)-catalyzed silylation was purified by flash chromatography (cyclohexane/EtOAc 8:2) to obtained **4d** as a colourless oil (76 mg, 83%); TLC (cyclohexane/EtOAc 8:2) R_f = 0.5 (CAM); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, J = 7.5 Hz, 2H), 7.42 (t, J = 8.0 Hz, 2H), 7.37-7.36 (m, 2H), 7.30-7.16 (m, 7H), 5.00 (br d, J = 8.5 Hz, 1H), 4.32-4.25 (m, 1H), 4.22-4.19 (m, 2H), 4.04 (t, J = 7.0 Hz, 1H), 3.45 (s, 1H), 1.31-1.26 (m, 1H), 1.13 (dd, J_1 = 15.0 and J_2 = 9.0 Hz, 1H), 0.22 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.0, 155.5, 143.9, 143.8, 141.3, 137.8, 133.5, 129.3, 128.0, 127.7, 127.0, 125.1, 120.0, 66.9, 52.2, 51.1, 47.1, 20.4, -2.80, -2.83; IR (film): 3323, 1725, 1712 cm^{-1}; MS(ESI) m/z : 460 (M+1), 382 (M-77); Anal. calcd for $C_{27}H_{29}NO_4Si$ (459.19): C, 70.56; H, 6.36; N, 3.05; found: C, 70.68; H, 6.27; N, 2.96.

Methyl 3-(dimethyl(phenyl)silyl)-2-(1,3-dioxoisoindolin-2-yl)propanoate (4e): The residue obtained following the general procedure for Cu(I)-catalyzed silylation was purified by flash chromatography (gradient from cyclohexane/CH_2Cl_2 1:1 to cyclohexane/CH_2Cl_2 2:8) to obtained **4e** as a colourless oil (54 mg, 73%); TLC (CH_2Cl_2) R_f = 0.5 ($KMnO_4$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.62 (s, 4H), 7.33-7.28 (m, *2*H), 7.02 – 6.89 (m, 3H), 4.95 (dd, J_1 = 12.5 and J_2 = 3.5 Hz, 1H), 3.69 (s, 3H), 2.08 (dd, J_1 = 15.0 and J_2 = 12.5 Hz, 1H), 1.69 (dd, J_1 = 15.0 and J_2 = 3.5 Hz, 1H), 0.39 (s, 3H), 0.26 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 171.0, 167.3, 137.0, 133.6, 133.23, 131.6, 128.5, 127.5, 123.1, 52.8, 48.7, 16.3, -2.3, -4.4; IR (film): 1744, 1716 cm^{-1}; MS(ESI) m/z : 368 (M+1), 290 (M-77); Anal. calcd for $C_{20}H_{21}NO_4Si$ (367.12): C, 65.37; H, 5.76; N, 3.81; found: C, 65.14; H, 5.69; N, 3.87.

Methyl 3-(dimethyl(phenyl)silyl)-2-(diphenylmethyleneamino)propanoate (4f): The residue obtained following the general procedure for Cu(I)-catalyzed silylation was purified by flash chromatography (cyclohexane/ EtOAc 95:5) to obtained **4f** as a colourless oil (56 mg, 70%); TLC (cyclohexane/ EtOAc 9:1) R_f = 0.5 ($KMnO_4$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.64-7.60 (m, 2H), 7.47-7.30 (m, 11H), 7.09-7.05 (m, 2H), 4.27 (dd, J_1 = J_2 = 7.0 Hz, 1H), 3.63 (s, 3H), 1.65 (dd, J_1 = 14.5 and J_2 = 7.0 Hz, 1H), 1.45 (dd, J_1 = 14.5 and J_2 = 7.0

Hz, 1H), 0.28 (s, 3H), 0.27 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 173.8, 169.3, 139.3, 138.8, 136.2, 133.6, 130.3, 130.1, 128.9, 128.6, 128.5, 128.0, 127.7, 127.6, 62.4, 52.0, 21.6, -2.1, -2.3.; IR (film): 1739, 1661 cm^{-1}; MS(ESI) m/z : 402 (M+1), 324 (M-77); Anal. calcd for $C_{25}H_{27}NO_2Si$ (401.18): C, 74.77; H, 6.78; N, 3.49; found: C, 74.98; H, 6.69; N, 3.42.

(*S*)- Methyl 2-((*S*)-2-(benzyloxycarbonylamino)-3-methylbutanamido)-3-(dimethyl(phenyl)silyl)propanoate and (*R*)-Methyl 2-((*S*)-2-(benzyloxycarbonylamino)-3-methylbutanamido)-3-(dimethyl(phenyl)silyl)propanoate (4g): The residue obtained following the general procedure for Cu(I)-catalyzed silylation using Z-L-Val-ΔAla-OMe **(1g)** was purified by flash chromatography (Et_2O/ petroleum ether 1:1) to obtained the less polar diastereoisomer as a white solid (26 mg) and the more polar distereoisomer as white solid (22 mg). Total yield 51%.

4g (less polar diastereoisomer): TLC (Et_2O/ petroleum ether 1:1) R_f = 0.39 (CAM); mp: 122 °C; $[\alpha]_D^{25}$ = +14.6 (c = 0.48, CH_2Cl_2); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.52-7.47 (m, 2H), 7.38-7.37 (m, 8H), 5.97 (br d, *J* = 7.0 Hz, 1H), 5.24 (br d, *J* = 9.0 Hz, 1H), 5.12 (s, 2H), 4.57 (dd, J_1 = 15.0 and J_2 = 7.0 Hz, 1H), 3.84-3.77 (m, 1H), 3.55 (s, 3H), 2.04-1.88 (m, 1H), 1.37-1.17 (m, 2H), 0.89 (d, *J* = 6.5 Hz, 3H), 0.83 (d, *J* = 6.5 Hz, 3H), 0.34 (s, 3H), 0.33 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 173.3, 170.6, 156.2, 137.8, 136.3, 133.5, 129.5, 128.5, 128.2, 128.13, 128.06, 67.0, 59.8, 52.1, 49.5, 31.3, 19.9, 18.9, 17.6, -3.0, -3.1; IR (film): 3269, 1747, 1715, 1662 cm^{-1}; MS(ESI) m/z: 471 (M+1), 393 (M-77); Anal. calcd for $C_{25}H_{34}N_2O_5Si$ (470.22): C, 63.80; H, 7.28; N, 5.95; found: C, 63.62; H, 7.19; N, 6.02.

4g (more polar distereoisomer**):** TLC (Et_2O/ petroleum ether 1:1) R_f = 0.37 (CAM); mp: 121 °C; $[\alpha]_D^{25}$ = -13.6 (c = 0.51, CH_2Cl_2); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.52-7.48 (m, 2H), 7.40-7.33 (m, 8H), 6.32 (br d, *J* = 7.5 Hz, 1H), 5.25 (br d, *J* = 8.5 Hz, 1H), 5.12 (s, 2H), 4.54 (dd, J_1 = 15.0 and J_2 = 7.5 Hz, 1H), 4.01-3.94 (m, 1H), 3.51 (s, 3H), 2.09-1.96 (m, 1H), 1.36-1.27 (m, 2H), 0.92 (d, *J* = 7.0 Hz, 3H), 0.84 (d, *J* = 7.0 Hz, 3H), 0.35 (s, 3H), 0.33 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 173.3, 170.9, 156.4, 137.7, 136.1, 133.5, 129.4, 128.5, 128.2, 128.12, 128.07, 67.2, 60.0, 52.1, 49.6, 30.6, 19.9, 19.4, 17.1, -2.6, -3.0; δ IR (film): 3270, 1749, 1714, 1662 cm^{-1}; MS(ESI) m/z: 471 (M+1), 393 (M-77); Anal. calcd for $C_{25}H_{34}N_2O_5Si$ (470.22): C, 63.80; H, 7.28; N, 5.95; found: C, 63.59; H, 7.36; N, 5.87.

(*S*)-Methyl 2-((*S*)-2-(tert-butoxycarbonylamino)-3-(dimethyl(phenyl)silyl)propanamido)-3-phenylpropanoate and (*S*)-methyl 2-((*R*)-2-(tert-butoxycarbonylamino)-3-(dimethyl(phenyl)silyl)propanamido)-3-phenylpropanoate (4h): The residue obtained following the general procedure for Cu(I)-catalyzed silylation using *N*-Boc-ΔAla-L-Phe-OMe (**1h**) was purified by flash chromatography (gradient from Et_2O/ petroleum ether 4:6 to Et_2O/ petroleum ether 1:1) to obtained the less polar diastereoisomer as a yellowish oil (18 mg) and the more polar diastereoisomer as a yellowish oil (14 mg). Total yield 33%.

4h (less polar diastereoisomer**):** TLC (Et_2O/ petroleum ether 1:1) R_f = 0.27 (CAM); $[\alpha]_D^{25}$ = +31.1 (c = 0.77, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50-7.48 (m, 2H), 7.37-7.35 (m, 3H), 7.25-7.23 (m, 3H), 7.09-7.07 (m, 2H), 6.49 (br d, *J* = 3.5 Hz, 1H), 4.75-4.70 (m, 1H), 4.65 (br d, *J* = 3.5 Hz, 1H), 4.14-4.10 (m, 1H), 3.70 (s, 3H), 3.12 (dd, J_1 = 7.0 and J_2 = 3.0 Hz, 1H), 3.03 (dd, J_1 = 7.0 and J_2 = 3.0 Hz, 1H), 1.40 (s, 9H), 1.40-1.35 (m, 1H), 1.14-1.08 (m, 1H), 0.33 (s, 3H), 0.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.6, 171.6, 155.1, 138.1, 135.8, 133.5, 129.3, 129.2, 128.5, 128.0, 127.0, 80.0, 53.2, 52.2, 51.8, 37.9, 28.2, 19.6, -2.6, -3.1; δ IR (film): 3309, 1746, 1724, 1663 cm^{-1}; MS(ESI) m/z : 485 (M+1); Anal. calcd for $C_{26}H_{36}N_2O_5Si$ (484.24): C, 64.43; H, 7.49; N, 5.78; found: C, 64.65; H, 7.41; N, 5.86.

4h (more polar diastereoisomer**):** TLC (Et_2O/ petroleum ether 1:1) R_f = 0.25 (CAM); $[\alpha]_D^{25}$ = +35.9 (c = 0.32, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48-7.46 (m, 2H), 7.36-7.33 (m, 3H), 7.25-7.18 (m, 3H), 7.08-7.06 (m, 2H), 6.62 (br d, *J* = 3.5 Hz, 1H), 4.78 (dd, J_1 = 7.0 and J_2 = 3.0 Hz, 1H), 4.58 (br d, *J* = 3.5 Hz, 1H), 4.13 (br s, 1H), 3.68 (s, 3H), 3.10-3.00 (m, 2H), 1.38 (s, 9H), 1.37 (dd, J_1 = 7.5 and J_2 = 2.5 Hz, 1H), 1.06 (dd, J_1 = 7.5 and J_2 = 5.0 Hz, 1H), 0.31 (s, 3H), 0.29 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.9, 171.8, 155.2, 138.2, 135.8, 133.5, 129.2, 128.6, 128.0, 127.1, 80.0, 53.1 52.2, 51.6, 37.9, 28.2, 19.6, -2.6, -3.3; δ IR (film): 3382, 1750, 1706, 1642 cm^{-1}; MS(ESI) m/z : 485 (M+1); Anal. calcd for $C_{26}H_{36}N_2O_5Si$ (484.24): C, 64.43; H, 7.49; N, 5.78; found: C, 64.67; H, 7.56; N, 5.85.

General procedure for the hydrolysis of esters 2d and 4d: The carboxylic ester **2d** or **4d** (0.15 mmol) was dissolved in 1,2-dichloroethane (0.7 mL) and after addition of trimethyltin hydroxide (54 mg, 0.3 mmol), the mixture was heated at 80 °C for 6 h. After completion of the reaction, the mixture was concentrated in vacuo, and the residue was taken up in ethyl acetate (1 mL). The organic layer was washed with aqueous $KHSO_4$ (0.01n) (3 x 10 mL) and brine (1 x 10 mL) and dried over Na_2SO_4. Removal of the solvent in vacuo afforded the carboxylic acid in sufficiently pure form, often in >98% purity (by ^{1}H NMR spectroscopy).

2-(((9*H*-Fluoren-9-yl)methoxy)carbonylamino)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propanoic acid (2l): Following the general procedure, for the hydrolysis of esters compound **2l** was obtained as white solid (54 mg, 83%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, *J* = 7.5 Hz, 2H), 7.61 (t, *J* = 7.5 Hz, 2H), 7.41 (t, *J* = 7.5 Hz, 2H), 7.31 (t, *J* = 7.5 Hz, 2H), 5.71 (br d, *J* = 8.0 Hz, 1H), 4.59 (dd, J_1 = 14.0 and J_2 = 6.5 Hz, 1H), 4.44-4.35 (m, 2H), 4.25 (t, *J* = 7.0 Hz, 1H), 1.40 (d, *J* = 6.5 Hz, 2H), 1.26 (d, *J* = 4.0 Hz, 12H).^{13}C NMR (100 MHz, $CDCl_3$) δ 177.4, 156.1, 143.9, 143.7, 141.3, 127.7, 127.0, 125.2, 125.1, 120.0, 84.0, 67.2, 50.6, 47.1, 24.8, 24.6 (carbon adjacent to boron was not observed); ^{11}B NMR (128 MHz, $CDCl_3$, BF_3•OEt_2): 7.16; IR (film): 3415, 3321, 1729, 1721 cm^{-1}; MS(ESI) m/z : 438 (M+1), 436 (M-1).

2-(((9*H*-Fluoren-9-yl)methoxy)carbonylamino)-3-(dimethyl(phenyl)silyl)propanoic acid (4l): Following the general procedure, for the hydrolysis of esters compound **4l** was obtained as white solid (53 mg, 79%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.73 (br s, 1H), 7.76 (d *J* = 7.5 Hz, 2H) 7.55-7.29 (m, 11H), 5.09 (br s, 1H), 4.36-4.29 (m, 2H), 4.15-4.12 (m, 1H), 1.46-1.43 (m, 1H), 1.28-1.25 (m, 1H), 0.35 (s, 3H), 0.33 (s, 3H);^{13}C NMR (100 MHz, $CDCl_3$) 178.9, 155.8, 143.8, 143.7, 141.3, 137.8, 133.5, 129.3, 128.0, 127.7, 127.0, 125.1, 120.0, 67.0, 51.2, 47.1, 20.0, -2.7, -3.1; IR (film): 3411, 3313, 1723 cm^{-1}; MS(ESI) m/z : 444 (M-1).

Synthesis of β-boronoaspartic acid (5):[5f] The crude **2c** obtained using general procedure for the copper(I)-catalyzed borylation of methyl 2-(*tert*-butoxycarbonylamino)acrylate (**1c**) (0.2 mmol) was heating at 70 °C for 16 h in the presence of 6 N HCl (4 mL). The organic by-products were removed by washing the aqueous layer repeatedly with CH_2Cl_2 (3 × 20 mL). The aqueous layer was concentrated in vacuum at 40 °C to afford a brownish powder. Trituration with acetone and CH_2Cl_2 provided pure β-boronoaspartic acid **5** (24 mg, 70%). ^{1}H NMR (200 MHz, D_2O) δ; 4.10 (dd, J_1= 10.0 and J_2 = 8.0 Hz, 1H), 1.30 (dd, J_1= 14.0 and J_2 = 8.0 Hz, 1H), 1.05 (dd, J_1= 14.0 and J_2 = 10.0 Hz, 1H).

Synthesis of 2-amino-3-(hydroxydimethylsilyl)propanoic acid hydrochloride (6):[5e] The crude **4c** obtained using general procedure for the copper(I)-catalyzed silylation of methyl 2-(*tert*-butoxycarbonylamino)acrylate (**1c**) (0.2 mmol) was heating at 70 °C for 16 h in the presence of 6 N HCl (4 mL). The organic by-products were

removed by washing the aqueous layer repeatedly with CH_2Cl_2 (3 × 20 mL). The aqueous layer was concentrated in vacuum at 40 °C to afford a yellowish powder as pure 2-amino-3-(hydroxydimethylsilyl)propanoic acid hydrochloride (**6**) (32 mg, 81%). ^{1}H NMR (400 MHz, D_2O) δ; 4.10 (dd, J_1= 10.0 and J_2 = 6.0 Hz, 1H), 1.28 (dd, J_1= 14.5 and J_2 = 10.0 Hz, 1H), 1.19 (dd, J_1= 14.5 and J_2 = 6.0 Hz, 1H).

Keywords: Copper (I) / Boron / Silicon / Amino acids / Catalysis

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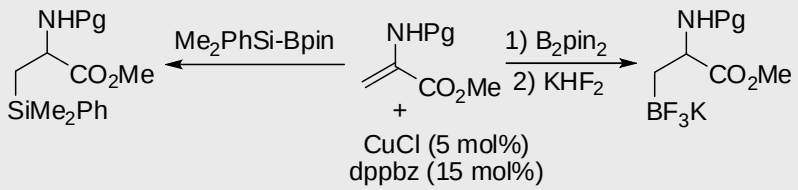

Copper mediated β-boration and β-silylation of a variety of dehydroalanine and dehydropeptide compounds provides ready access to orthogonally *N*- and *C*-protected boron- and silicon-containing amino acid and small peptides.

Conjugate Addition

*Francesca Bartoccini, Silvia Bartolucci, Simone Lucarini and Giovanni Piersanti**

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Synthesis of Boron- and Silicon-containing Amino Acids through Cu-Catalyzed Conjugate Additions to Dehydroalanine Derivatives