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Biaryl Peptides from 4-Iodophenylalanine by Solid-Phase Borylation and Suzuki–Miyaura Cross-Coupling

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Resin-bound phenylalanine boronates were prepared by solid-phase Miyaura borylation of 4-iodophenylalanine peptides. Subsequent arylation through a Suzuki–Miyaura cross-coupling was carried out using a variety of aryl halides under conventional heating and under microwave irradiation. Microwaves greatly enhanced the arylation, shortening the reaction time and providing the biaryl peptides in higher purities.

Introduction

Nonproteinogenic amino acids play an important role in drug development. In particular, a great deal of research has been invested in the preparation of biaryl amino acids, such as arylphenylalanines. These moieties are widely present in natural products and constitute important structural elements for molecular recognition between pharmaceuticals and target receptors.[1] Moreover, their incorporation into biologically active peptides may lead to peptidomimetics with restricted conformational flexibility, increased proteolytic stability, and enhanced selectivity and biological activity.[2]

Despite the interest in these compounds, only a few 4-arylphenylalanines are commercially available. The synthesis of these compounds in solution has been accomplished by a Suzuki–Miyaura cross-coupling of either a 4-bromo- (or iodo- or triflyl-) phenylalanine with an aryl boronic acid[3] or a 4-boronophenylalanine with an aryl halide (or triflate).[4]

Even though the Suzuki–Miyaura coupling has been adapted to the solid phase and has found interesting applications in the discovery of novel compounds,[5] the modification of phenylalanine peptides through a solid-phase Suzuki–Miyaura reaction has only been described in two recent reports.[6] Moreover, these couplings are based on the reaction between a polymer-bound halogenated aromatic amino acid and an arylboron in solution. The alternative approach involving a polymer-bound amino acid boronate and an aryl halide has not been reported. Since the number of commercially available aryl and heteroaryl halides is larger than that of boronic acids, this approach would increase the diversity of biaryl peptides.

Based on these considerations and taking into account that the borylation on solid support of phenylalanine and, in general, of aromatic amino acids has not been disclosed, we envisioned that the solid-phase borylation of phenylalanine peptides would emerge as a successful approach for the preparation of modified peptides in a highly flexible manner. On the one hand, it would provide structurally diversified peptide boronic acids, for which there is a growing interest as potential pharmaceutical agents.[7] In fact, peptide boronic acids have been used as enzyme inhibitors, boron neutron capture agents for cancer therapy, and drug-delivery devices. Additionally, a Suzuki–Miyaura cross-coupling between polymer-bound borylated peptides and aryl or heteroaryl halides would provide a large variety of 4-arylphenylalanine peptides. In the present study, we describe the effectiveness of the solid-phase borylation of 4-iodophenylalanine peptides and their subsequent arylation by a Suzuki–Miyaura cross-coupling.

Results and Discussion

Solid-Phase Synthesis of Boronophenylalanines

We investigated the feasibility of the borylation on solid support of a 4-iodophenylalanine residue starting with the synthesis of the tripeptidyl resin Boc-Phe[4-pinacolatoboron (BPin)]-Leu-Leu-Rink-MBHA (**1a**) as a model system (Scheme 1). Thus, we prepared the resin Boc-Phe(4-I)-Leu-Leu-Rink-MBHA (**2a**) by coupling Boc-Phe(4-I)-OH[8] to H-Leu-Leu-Rink-MBHA, which was constructed from an Fmoc-Rink-MBHA resin (0.56 mmol/g) following an Fmoc/*t*Bu strategy of sequential coupling and deprotection steps under standard conditions. Treatment of an aliquot of the resulting resin **2a** with TFA/TIS/H_2O for 2 h at room temperature afforded H-Phe(4-I)-Leu-Leu-NH_2 (**3a**) in 95% purity, which was characterised by mass spectrometry.

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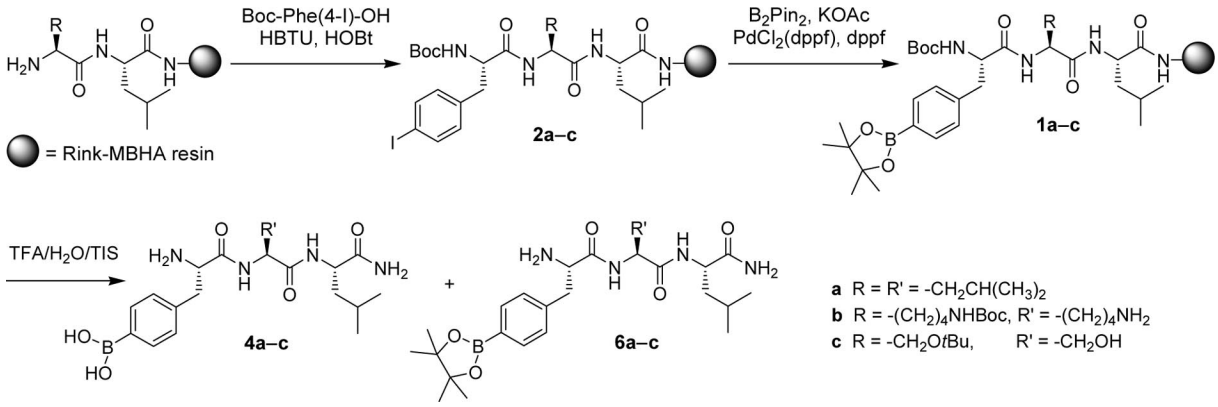
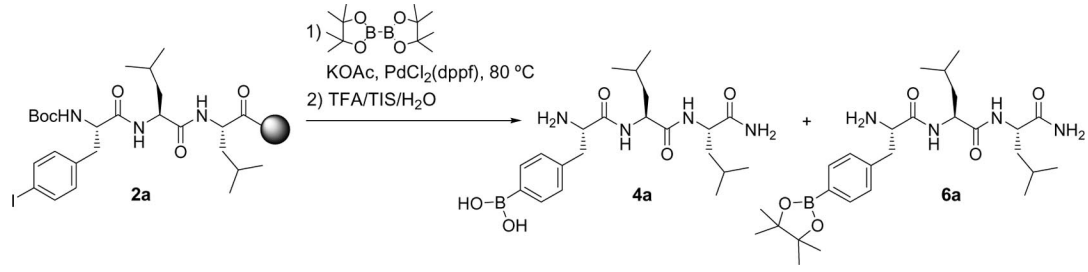


Scheme 1. Synthesis of boronopeptidyl resins **1a**–**c**. B_2Pin_2 = bis(pinacolato)diboron.

Among the methods of preparation of arylborons, the Miyaura reaction[4b,9] involves mild reaction conditions compatible with a variety of functional groups and, therefore, we considered it suitable for the solid-phase synthesis of boronophenylalanines. We investigated the Miyaura borylation of resin **2a** by treatment with B_2Pin_2, $PdCl_2$(dppf), and KOAc at 80 °C (Scheme 1, Table 1). The reaction conditions evaluated included the solvent, reaction time, amount of reagents, and the addition of 1,1′-bis(diphenylphosphanyl)ferrocene (dppf). After each experiment, an aliquot of resin was treated with TFA/TIS/H_2O, and the crude reaction mixture was analysed by HPLC and mass spectrometry. The formation of the boronate was also assessed by IR analysis of the resin, which would show a characteristic B–O band at 1362 cm^{-1}.

Firstly, we treated resin **2a** (5–10 mg) with B_2Pin_2 (2 equiv.), $PdCl_2$(dppf) (0.09 equiv.), and KOAc (3 equiv.) in DMF at 80 °C for 16 h (Table 1, Entry 1) and 24 h (Table 1, Entry 2). In both cases, the cleavage of the resin afforded three main compounds, as shown by HPLC. These compounds were identified by mass spectrometry analysis of the HPLC sample as the peptide boronic acid **4a** (32–43%), the iodinated tripeptide H-Phe(4-I)-Leu-Leu-NH_2 (**3a**, 30–43%), and H-Phe-Leu-Leu-NH_2 (**5a**, 25%) resulting from deiodination or protodeborylation. As previously reported, the peptide boronic acid **4a** could arise from the hydrolysis of the pinacol ester functionality of the corresponding boronate **6a** during HPLC analysis.[10] In fact, when the crude reaction mixture was dissolved and immediately analysed by mass spectrometry, only the boronate **6a** was observed. Increasing the amount of borylation reagents led to a decrease in the formation of H-Phe-Leu-Leu-NH_2 (**5a**, 8%), but it had only a marginal effect on the reaction efficiency (Table 1, Entry 3). An increase of the reaction time to 48 h or the addition of dppf did not improve the results (data not shown). Next, we analysed the use of dioxane and

Table 1. Miyaura borylation of Boc-Phe(4-I)-Leu-Leu-Rink-MBHA (**2a**).



Entry	B_2Pin_2 (equiv.)	KOAc (equiv.)	$PdCl_2$(dppf) (equiv.)	dppf (equiv.)	Solvent	Time [h]	Purity of **4a** [%][a]	Purity of **6a** [%]	Purity of **3a**[b] [%]	Purity of **5a**[c] [%]
1	2	3	0.09	0	DMF	16	32	0	43	25
2	2	3	0.09	0	DMF	24	43	0	30	25
3	4	6	0.18	0	DMF	24	48	3	26	8
4	4	6	0.18	0	dioxane	24	7	4	76	3
5	4	6	0.18	0	DMSO	24	38	0	55	7
6	4	6	0.18	0	DMSO	48	24	54	17	0
7	4	6	0.18	0.09	DMSO	24	21	63	0	4
8	8	12	0.36	0.18	DMSO	12	22	24	5	4
9[d]	4	6	0.18	0.09	DMSO	24	28	71	0	0

[a] Percentage determined by HPLC at 220 nm from the crude reaction mixture. [b] **3a** corresponds to H-Phe(4-I)-Leu-Leu-NH_2. [c] **5a** corresponds to H-Phe-Leu-Leu-NH_2. [d] This experiment was performed using 600 mg of resin **2a**.

DMSO as solvents (Table 1, Entries 4 and 5, respectively). While dioxane was inefficient, DMSO afforded **4a** in 38% purity. With DMSO, the borylation was significantly favoured by either increasing the reaction time to 48 h (78%, **4a** + **6a**, Table 1, Entry 6) or by adding dppf (84%, **4a** + **6a**, Table 1, Entry 7). Moreover, the latter conditions afforded only 4% of **5a**. Further increases in the amount of reagents failed to improve the results (Table 1, Entry 8). Interestingly, when the reaction conditions of Entry 7 were scaled up to 600 mg of resin **2a**, the borylated products were obtained in 99% purity (**4a** + **6a**, Table 1, Entry 9). The boronate **6a** was characterized by ^{1}H and ^{13}C NMR spectroscopy and mass spectrometry.

We next explored the compatibility of this reaction with common protecting groups used in solid-phase peptide synthesis. The iodophenylalanine peptidyl resins **2b**,**c** containing lysine (**2b**) and serine (**2c**) protected with Boc and *t*Bu, respectively, were prepared and subjected to the above optimal reaction conditions (Scheme 1). Thus, the resins **2b**,**c** were treated with B_2Pin_2 (4 equiv.), $PdCl_2$(dppf) (0.18 equiv.), and KOAc (6 equiv.) in DMSO at 80 °C for 24 h. Acidic cleavage yielded the corresponding boronopeptides (**4b** + **6b**) and (**4c** + **6c**) in 99% purity. These results clearly support the efficiency of our methodology.

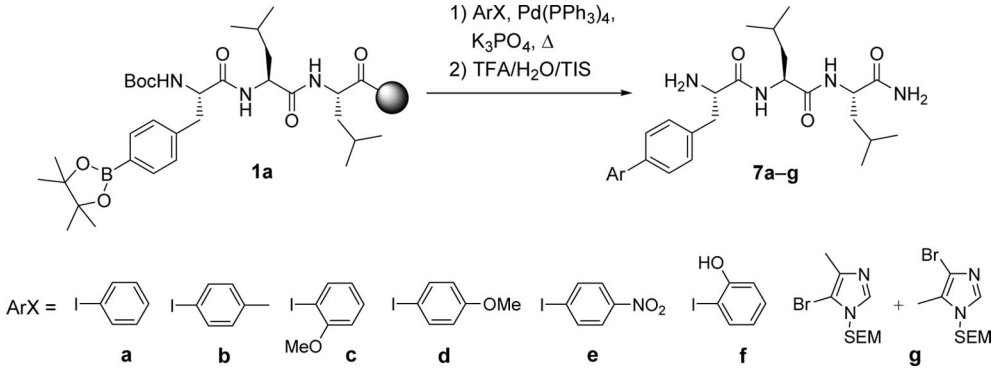
Solid-Phase Synthesis of Biaryl Peptides

We then studied the arylation of Boc-Phe(4-BPin)-Leu-Leu-Rink-MBHA (**1a**) by a Suzuki–Miyaura cross-coupling. For each experiment, aliquots of resin were subjected to the appropriate reaction conditions, and, after acidic cleavage, the crude product mixture was analysed by HPLC and mass spectrometry.

We initially screened the arylation under conventional heating using iodobenzene as the aryl halide for the survey of the reaction conditions. These results are summarised in Table 2. Treatment of resin **1a** with iodobenzene (5 equiv.), $Pd(PPh_3)_4$ (0.05 equiv.), and aq K_3PO_4 (2 M, 5 equiv.) in degassed DMF at 80 °C for 24 h provided H-Phe(4-Ph)-Leu-Leu-NH_2 (**7a**) but in low purity, and we also detected a large amount of boronic acid **4a** (Table 2, Entry 1). Using a degassed mixture of DME/EtOH/H_2O (9:9:2), the percentage of **7a** increased to 49% (Table 2, Entry 2). To avoid the evaporation of the solvent due to the high temperature, the long reaction time, and the low volume used (0.3 mL), we performed the cross-coupling at 60 °C for 48 h (Table 2, Entry 3). This experiment led to the best result, affording **7a** in 70% purity. It should be noted that these crude product mixtures proved to contain the homocoupling product **8** and the phenol **9** (6–14%), which are common side-products of the Suzuki–Miyaura cross-couplings (Figure 1).[11]

We next explored the scope of these conditions with different aryl halides including 4-iodotoluene, 2- and 4-iodoanisole, 1-iodo-4-nitrobenzene, 2-iodophenol, and [2-(trimethylsilyl)ethoxy]methyl (SEM) protected bromoimidazoles **g** (Table 2, Entries 4–9). All reactions afforded the desired 4-arylphenylalanine peptides **7b**–**g** in purities ranging from 35% to 87%. All arylpeptides were obtained with concurrent formation of the homocoupling product **8** and the phenol **9**. The couplings with 4-iodotoluene and the

Table 2. Arylation of Boc-Phe(4-BPin)-Leu-Leu-Rink-MBHA (**1a**) under conventional heating.[a]



Entry	ArX	Solvent[b]	Time [h]	*T* [°C]	Purity of **4a**[c] [%][d]	Purity of **8**+**9**[e] [%][d]	Peptide	Purity [%][d]
1	**a**	A	24	80	58	6	**7a**	26
2	**a**	B	24	80	14	14	**7a**	49
3	**a**	B	48	60	13	8	**7a**	70
4	**b**	B	48	60	43	14	**7b**	35
5	**c**	B	48	60	4	12	**7c**	83
6	**d**	B	48	60	0	20	**7d**	54
7	**e**	B	48	60	0	3	**7e**	87
8	**f**	B	48	60	0	26	**7f**	52
9	**g**	B	48	60	0	20	**7g**	36

[a] Reaction conditions: ArX (5 equiv.), $Pd(PPh_3)_4$ (0.05 equiv.), aq K_3PO_4 (2 M, 5 equiv.). [b] A: DMF; B: DME/EtOH/H_2O (9:9:2). [c] Its structure is shown in Scheme 1. [d] Percentage determined by HPLC at 220 nm from the crude reaction mixture. [e] These compounds coeluted during HPLC analysis and are depicted in Figure 1.

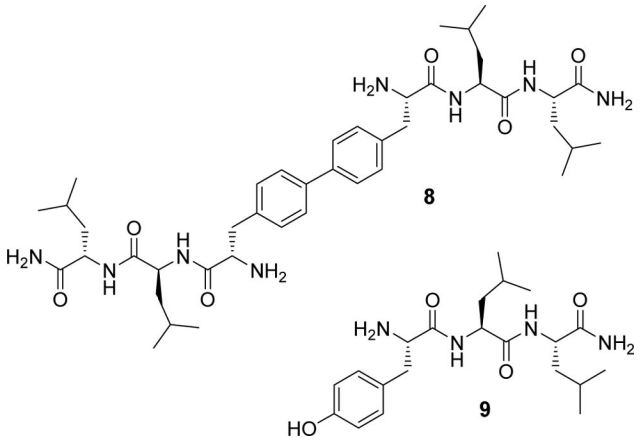
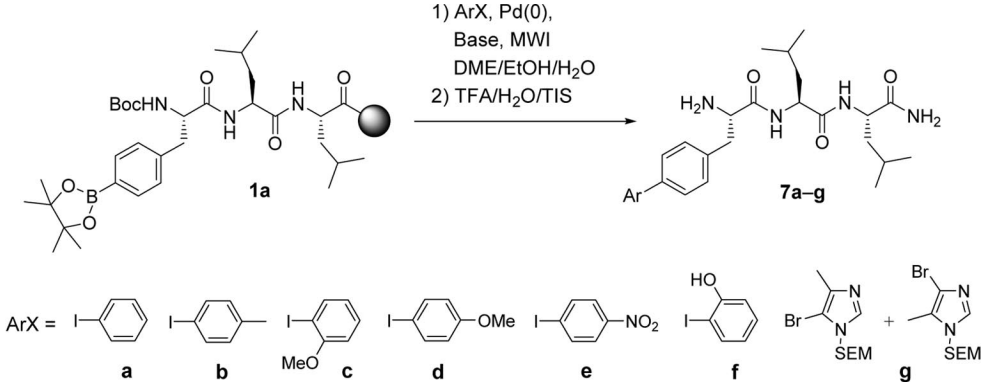


Figure 1. Structures of **8** and **9**.

bromoimidazoles **g** were the most difficult, affording the lowest purity percentages of the corresponding biaryl peptide **7b** and **7g** (≈ 35%, Table 2, Entries 4 and 9). In contrast, arylation with 2-iodoanisole and 1-iodo-4-nitrobenzene yielded the expected arylated products **7c** and **7e**, respectively, in significantly higher purities (≈ 85%, Table 2, Entries 5 and 7).

Taking into account that microwave heating has been employed to accelerate the rate of solid-phase Suzuki–Miyaura reactions,[12] the arylation of Boc-Phe(4-BPin)-Leu-Leu-Rink-MBHA (**1a**) was attempted under microwave irradiation (Table 3). As before, we first surveyed reaction conditions using iodobenzene. Thus, resin **1a** was treated with iodobenzene (5 equiv.), $Pd(PPh_3)_4$ (0.05 equiv.), and aq K_3PO_4 (2 M, 5 equiv.) in degassed DME/EtOH/H_2O (9:9:2) at different temperatures and for different reaction times (Table 3, Entries 1–5). Reactions carried out either at 80 °C or 120 °C for 30 min of irradiation afforded the best results, yielding the arylated peptide H-Phe(4-Ph)-Leu-Leu-NH_2 (**7a**) in 62–63% purity together with the homocoupling product **8** and the phenol **9** (8–9%, Table 3, Entries 3 and 4). Since the boronic acid **4a** was not detected at 120 °C, we selected this temperature for the following assays. It should also be noted that, in order to minimise the formation of phenol **9**, solvents must be thoroughly degassed before carrying out the reactions.

Table 3. Arylation of Boc-Phe(4-BPin)-Leu-Leu-Rink-MBHA (**1a**) under microwave irradiation.



Entry	ArX	Time [min]	*T* [°C]	Purity of **4a**[b] [%][c]	Purity of **8**+**9**[d] [%][c]	Peptide	Purity [%][c]
1[a]	**a**	15	60	15	10	**7a**	51
2[a]	**a**	15	80	12	11	**7a**	47
3[a]	**a**	30	80	9	8	**7a**	63
4[a]	**a**	30	120	0	9	**7a**	62
5[a]	**a**	30	140	2	15	**7a**	59
6[a]	**b**	30	120	0	15	**7b**	69
7[a]	**c**	30	120	0	5	**7c**	91
8[a]	**d**	30	120	0	14	**7d**	73
9[a]	**e**	30	120	4	6	**7e**	80
10[a]	**f**	30	120	0	4	**7f**	88
11[a]	**g**	30	120	0	49	**7g**	22
12[e]	**a**	30	120	0	8	**7a**	73 (27)[f]
13[e]	**b**	30	120	0	6	**7b**	79 (26)[f]
14[e]	**c**	30	120	0	0	**7c**	91 (63)[f]
15[e]	**d**	30	120	8	8	**7d**	77 (35)[f]
16[e]	**e**	30	120	5	6	**7e**	86 (49)[f]
17[e]	**f**	30	120	0	12	**7f**	60 (37)[f]
18[e]	**g**	30	120	0	5	**7g**	57 (10)[f]

[a] Reaction conditions (Entries 1–11): ArX (5 equiv.), $Pd(PPh_3)_4$ (0.05 equiv.), aq K_3PO_4 (2 M, 5 equiv.). [b] Its structure is shown in Scheme 1. [c] Percentage determined by HPLC at 220 nm from the crude reaction mixture. [d] These compounds coeluted during HPLC analysis and are depicted in Figure 1. [e] Reaction conditions (Entries 12–18): ArX (5 equiv.), $Pd_2(dba)_3$ (0.2 equiv.), P(*o*-tolyl)$_3$ (0.4 equiv.), KF (4 equiv.). [f] Isolated yield.

We then extended the selected conditions for the arylation under microwave irradiation to the reaction of resin **1a** with the aryl halides mentioned above (Table 3, Entries 6–11). This reaction yielded the biaryl peptides **7b**–**f** in moderate to good purities (69–91%). Homocoupling product **8** and phenol **9** were also formed as minor byproducts (4–15%). Compared to conventional heating, microwave irradiation significantly favoured the coupling of resin **1a** with 4-iodotoluene, 4-iodoanisole, and 2-iodophenol (35–54% vs. 69–88%). In contrast, arylation of resin **1a** with bromoimidazoles **g** yielded the biaryl peptide **7g** in only 22% purity (Table 3, Entry 11).

To improve the result obtained for the cross-coupling of resin **1a** with bromoimidazoles **g**, we assayed the conditions previously described for the solid-phase arylation of 5-bromohistidines.[13] Thus, this reaction was conducted by using $Pd_2(dba)_3$ (0.2 equiv.), P(*o*-tolyl)$_3$ (0.4 equiv.), and KF (4 equiv.) in degassed DME/EtOH/H_2O (9:9:2) yielding **7g** in 57% purity (Table 3, Entry 18). This finding is especially noteworthy because, to the best of our knowledge, this is the first example of the solid-phase synthesis of a 4-imidazol-4(5)-ylphenylalanine peptide. In view of this result, the arylation of resin **1a** was also performed with the aryl halides **a**–**f** under these conditions. Except for the reaction with 2-iodophenol (**f**, 60%, Table 3, Entry 17), all the cross-couplings yielded the biaryl peptides with comparable or better purities than those using $Pd(PPh_3)_4$ (73–91%, Table 3, Entries 12–16). Purification of the crude reaction mixtures by column chromatography afforded the corresponding biaryl peptides in 10–63% yield, and these products were characterised by ^1H and ^{13}C NMR spectroscopy and mass spectrometry. In agreement with previous results,[13] the NMR spectra showed the presence of one stereoisomer, revealing that no epimerisation occurred during the borylation and Suzuki–Miyaura cross-coupling steps.

Comparing the arylation of resin **1a** under conventional heating and microwave irradiation, the latter dramatically shortened the reaction time and facilitated the Suzuki–Miyaura cross-coupling, giving superior results. Moreover, in agreement with previous reports, this study revealed that, under both heating conditions, the electronic properties of the substituents on the aromatic ring cannot explain the reactivity of the aryl halide and, generally, the reaction proceeded smoothly for both electron-rich and -poor aryl halides.[6b]

Conclusions

In summary, we have developed a convenient strategy for the modification of phenylalanine peptides through solid-phase borylation and subsequent cross-coupling. This methodology yielded resin-bound phenylalanine boronates in good purities. Additionally, the cross-coupling between a polymer-bound phenylalanine boronate and different aryl halides led to a set of 4-arylphenylalanine tripeptides. These results constitute a new tool for post-synthesis peptide modification and are likely to have an impact on the generation of combinatorial libraries containing biaryl motifs.

Experimental Section

General Methods: Commercially available reagents were used throughout without purification. Solvents were purified and dried by passing them through an activated alumina purification system (MBraun SPS-800) or by conventional distillation techniques. IR spectra were recorded with a Mattson-Galaxy Satellite FT-IR spectrometer using a single-reflection ATR system as a sampling accessory.

Flash chromatography (FC) purifications were performed on C_{18}-reverse-phase silica gel 100 (>400 mesh, Fluka).

All compounds were analysed under standard analytical HPLC conditions with a Dionex liquid chromatography instrument composed of an UV/Vis Dionex UVD170U detector, a P680 Dionex bomb, an ASI-100 Dionex automatic injector, and CHROMELEON™ 6.60 software. Detection was performed at 220 nm. Method A: Analysis was carried out with a Kromasil 100 C_{18} (250 mm × 4.6 mm, 3.5 μm) column with a 2–100% B linear gradient over 28 min at a flow rate of 1 mL/min. Solvent A was 0.1% aq TFA, and solvent B was 0.1% TFA in CH_3CN. Method B: Analysis was carried out with a Kromasil 100 C_{18} (40 mm × 4.6 mm, 3.5 μm) column with a 2–100% B linear gradient over 7 min at a flow rate of 1 mL/min.

ESI-MS analyses were performed with an Esquire 6000 ESI ion Trap LC/MS (Bruker Daltonics) instrument equipped with an electrospray ion source. The instrument was operated in the positive ESI(+) ion mode. Samples (5 μL) were introduced into the mass spectrometer ion source directly through an HPLC autosampler. The mobile phase (80:20 CH_3CN/H_2O at a flowrate of 100 μL min^{-1}) was delivered by a 1100 Series HPLC pump (Agilent). Nitrogen was employed as both the drying and nebulising gas. HRMS were recorded under conditions of ESI with a Bruker MicroTof-Q instrument using a hybrid quadrupole time-of-flight mass spectrometer (University of Zaragoza). Samples were introduced into the mass spectrometer ion source directly through a 1100 Series Agilent HPLC autosampler and were externally calibrated using sodium formate. The instrument was operated in the positive ESI(+) ion mode.

^1H and ^{13}C NMR spectra were measured with a Bruker 300 or 400 MHz NMR spectrometer. Chemical shifts were reported as δ values (ppm) directly referenced to the solvent signal.

The microwave-assisted reactions were performed with an Ethos SEL labstation microwave (Milestone) equipped with a dual magnetron (1600 W). The time, temperature, and power were controlled with the EasyControl software. The temperature was monitored through the ATC-400FO Automatic Fiber Optic Temperature Control System immersed in a standard Milestone reference vessel. This equipment regulates the power to achieve and maintain the selected temperature.

Boc-Phe(4-I)-Leu-Leu-Rink-MBHA (2a): This peptidyl resin was synthesised manually by the solid-phase method using standard Fmoc chemistry. Fmoc-Rink-MBHA resin (0.56 mmol/g) was used as solid support. Couplings of Fmoc-Leu-OH (4 equiv.) and *N*-*tert*-butoxycarbonyl-4-iodo-L-phenylalanine[8] were performed using HBTU (3.8 equiv.), HOBt (4 equiv.), and DIEA (3 equiv.) in DMF at room temperature for 1 h. The completion of the reactions was monitored by the Kaiser test.[14] Fmoc group removal was achieved

with piperidine/DMF (3:7, 2 + 8 min). After each coupling and deprotection step, the resin was washed with DMF (3 × 1 min) and CH_2Cl_2 (3 × 1 min) and air-dried. An aliquot of Boc-Phe(4-I)-Leu-Leu-Rink-MBHA (**2a**) was cleaved with TFA/H_2O/TIS (95:2.5:2.5) whilst being stirred for 2 h at room temperature. After the reaction time, TFA evaporation and diethyl ether extraction afforded H-Phe(4-I)-Leu-Leu-NH_2 (**3a**, 95% purity). t_R = 6.93 min (Method B). HRMS (ESI): calcd. for $C_{21}H_{34}IN_4O_3$ 517.1670; found 517.1693; calcd. for $C_{21}H_{34}IN_4NaO_3$ 539.1490; found 539.1512.

Boc-Phe(4-I)-Lys(Boc)-Leu-Rink-MBHA (2b): This peptidyl resin was prepared following the procedure described for resin **2a**. Acidic cleavage of an aliquot of Boc-Phe(4-I)-Lys(Boc)-Leu-Rink-MBHA (**2b**) afforded H-Phe(4-I)-Lys-Leu-NH_2 (**3b**, 94% purity). t_R = 6.33 min (Method B).

Boc-Phe(4-I)-Ser(*t*Bu)-Leu-Rink-MBHA (2c): This peptidyl resin was prepared following the procedure described for resin **2a**. Acidic cleavage of an aliquot of Boc-Phe(4-I)-Ser(*t*Bu)-Leu-Rink-MBHA (**2c**) afforded H-Phe(4-I)-Ser-Leu-NH_2 (**3c**, 96% purity). t_R = 6.51 min (Method B).

Boc-Phe(4-BPin)-Leu-Leu-Rink-MBHA (1a): A 25 mL round-bottomed flask was charged with Boc-Phe(4-I)-Leu-Leu-Rink-MBHA (**2a**, 600 mg), B_2Pin_2 (4 equiv.), $PdCl_2$(dppf) (0.18 equiv.), and dppf (0.09 equiv.). A thoroughly sonicated solution of KOAc (6 equiv.) in anhydrous DMSO (12 mL) was then added, and the mixture was heated at 80 °C for 24 h. After the reaction time, the resin was washed with DMSO (6 × 1 min), MeOH (6 × 1 min), CH_2Cl_2 (6 × 1 min), and Et_2O (3 × 1 min). IR (neat): $\tilde{\nu}$ = 3316, 2953, 2928, 1650, 1505, 1453, 1362, 1209, 1159, 699 cm^{-1}.

An aliquot of Boc-Phe(4-BPin)-Leu-Leu-Rink-MBHA (**1a**) was cleaved with TFA/H_2O/TIS (95:2.5:2.5) whilst being stirred for 2 h at room temperature. After the reaction time, TFA evaporation and diethyl ether extraction afforded H-Phe(4-BPin)-Leu-Leu-NH_2 (**6a**, 99% purity). t_R = 7.23 min (Method B). ^{1}H NMR (400 MHz, CD_3CN): δ = 0.85–0.94 [m, 12 H, 4 CH_3(δ)-Leu], 1.31 [s, 12 H, 4 $(CH_3)_{BPin}$], 1.55–1.65 [m, 6 H, 2 CH(γ)-Leu, 2 CH_2(β)-Leu], 3.09–3.11 [m, 1 H, CH_2(β)-Phe], 3.26–3.29 [m, 1 H, CH_2(β)-Phe], 4.31–4.35 [m, 3 H, 2 CH(α)-Leu, CH(α)-Phe], 5.90 (s, 1 H, $CONH_2$), 6.64 (s, 1 H, $CONH_2$), 7.24 (d, J = 8.0 Hz, 1 H, CONH), 7.28 (d, J = 7.0 Hz, 2 H, 2-H_{arom}, 6-H_{arom}), 7.65 (d, J = 7.0 Hz, 2 H, 3-H_{arom}, 5-H_{arom}), 7.97 (d, J = 8.0 Hz, 1 H, CONH) ppm. ^{13}C NMR (100 MHz, CD_3CN): δ = 21.85 [2 CH_3(δ)-Leu], 23.17 [2 CH_3(δ)-Leu], 25.09 [$(CH_3)_{BPin}$], 25.24, 25.49 [2 CH(γ)-Leu], 37.72 [CH_2(β)-Phe], 41.52, 41.67 [2 CH_2(β)-Leu], 52.44, 53.36, 55.29 [3 CH(α)], 84.76 (C_{BPin}), 129.72 (C_{arom}-4), 130.08 (C_{arom}-2, C_{arom}-6), 135.81 (C_{arom}-3, C_{arom}-5), 138.59 (C_{arom}-1), 169.46, 172.66, 175.42 (3 CO) ppm. HRMS (ESI): calcd. for $C_{27}H_{46}BN_4O_5$ 517.3556; found 517.3559; calcd. for $C_{21}H_{45}BN_4NaO_5$ 539.3375; found 539.3375. During HPLC analysis, the pinacol boronic ester **6a** was partially hydrolysed to the boronic acid **4a**. t_R = 6.07 min (Method B). MS (ESI): m/z = 435.2 $[M + H]^+$.

Boc-Phe(4-BPin)-Lys-Leu-Rink-MBHA (1b): Starting from Boc-Phe(4-I)-Lys(Boc)-Leu-Rink-MBHA (**2b**, 100 mg), the procedure described for **1a** afforded boronate **1b**. IR (neat): $\tilde{\nu}$ = 3298, 2925, 1669, 1641, 1505, 1452, 1364, 1209, 1167 cm^{-1}. The corresponding acidic cleavage afforded H-Phe(4-BPin)-Lys-Leu-NH_2 (**6b**, 99% purity). t_R = 6.62 min (Method B). ^{1}H NMR (400 MHz, CD_3CN): δ = 0.89–0.93 [m, 6 H, 2 CH_3(δ)-Leu], 1.30 [s, 12 H, 4 $(CH_3)_{BPin}$], 1.58–1.65 [m, 9 H, CH(γ)-Leu, CH_2(β)-Leu, CH_2(β)-Lys, CH_2(γ)-Lys, CH_2(δ)-Lys], 2.88–2.92 [m, 2 H, CH_2(ε)-Lys], 3.06–3.09 [m, 1 H, CH_2(β)-Phe], 3.23–3.32 [m, 1 H, CH_2(β)-Phe], 4.32–4.48 [m, 3 H, CH(α)-Leu, CH(α)-Lys, CH(α)-Phe], 6.11 (s, 1 H, $CONH_2$), 6.98 (s, 1 H, $CONH_2$), 7.24 (d, J = 7.0 Hz, 2 H, 2-H_{arom}, 6-H_{arom}), 7.56 (s, 1 H, CONH), 7.62 (d, J = 7.0 Hz, 2 H, 3-H_{arom}, 5-H_{arom}), 8.27 (d, J = 8.0 Hz, 1 H, CONH) ppm. ^{13}C NMR (100 MHz, CD_3CN): δ = 21.95 [2 CH_3(δ)-Leu], 23.36 [CH_2(γ)-Lys], 25.19 [$(CH_3)_{BPin}$], 25.65 [CH(γ)-Leu], 32.58 [CH_2(β)-Lys, CH_2(δ)-Lys], 37.97 [CH_2(β)-Phe], 40.47 [CH_2(ε)-Lys], 41.54 [CH_2(β)-Leu], 52.96, 53.58, 55.18 [3 CH(α)], 84.88 (C_{BPin}), 129.81 (C_{arom}-4), 130.20 (C_{arom}-2, C_{arom}-6), 135.90 (C_{arom}-3, C_{arom}-5), 138.53 (C_{arom}-1), 172.73, 175.02, 176.35 (3 CO) ppm. MS (ESI): m/z = 532.3 $[M + H]^+$. HRMS (ESI): calcd. for $C_{27}H_{47}BN_5O_5$ 532.3669; found 532.3664; calcd. for $C_{27}H_{46}BN_5NaO_5$ 554.3489; found 554.3500. During HPLC analysis, the pinacol boronic ester **6b** was partially hydrolysed to the boronic acid **4b**. t_R = 5.50 min (Method B).

Boc-Phe(4-BPin)-Ser-Leu-Rink-MBHA (1c): Starting from Boc-Phe(4-I)-Ser(*t*Bu)-Leu-Rink-MBHA (**2c**, 100 mg), the procedure described for **1a** afforded boronate **1c**. IR (neat): $\tilde{\nu}$ = 3309, 2927, 1664, 1644, 1504, 1452, 1363, 1209, 1160 cm^{-1}. The corresponding acidic cleavage afforded H-Phe(4-BPin)-Ser-Leu-NH_2 (**6c**, 99% purity). t_R = 6.81 min (Method B). ^{1}H NMR (400 MHz, CD_3CN): δ = 0.85–0.99 [m, 6 H, 2 CH_3(δ)-Leu], 1.31 [s, 12 H, 4 $(CH_3)_{BPin}$], 1.58–1.70 [m, 3 H, CH(γ)-Leu, CH_2(β)-Leu], 3.09–3.11 [m, 1 H, CH_2(β)-Phe], 3.26–3.28 [m, 1 H, CH_2(β)-Phe], 3.68–3.79 [m, 2 H, CH_2(β)-Ser], 4.28–4.42 [m, 3 H, CH(α)-Phe, CH(α)-Leu, CH(α)-Ser], 5.86 (s, 1 H, $CONH_2$), 6.71 (s, 1 H, $CONH_2$), 7.04 (s, 1 H, CONH), 7.31 (d, J = 6.8 Hz, 2 H, 2-H_{arom}, 6-H_{arom}), 7.67 (d, J = 6.8 Hz, 2 H, 3-H_{arom}, 5-H_{arom}), 7.75 (s, 1 H, CONH) ppm. ^{13}C NMR (75 MHz, CD_3CN): δ = 22.47 [2 CH_3(δ)-Leu], 24.62 [$(CH_3)_{BPin}$], 24.65 [CH(γ)-Leu], 36.79 [CH_2(β)-Phe], 40.28 [CH_2(β)-Leu], 54.37, 54.88, 55.45 [3 CH(α)], 40.39 [CH_2(β)-Ser], 83.93 (C_{BPin}), 128.91 (C_{arom}-4), 129.19 (C_{arom}-2, C_{arom}-6), 134.98 (C_{arom}-3, C_{arom}-5), 137.52 (C_{arom}-1) ppm. MS (ESI): m/z = 491.2 $[M + H]^+$. HRMS (ESI): calcd. for $C_{24}H_{40}BN_4O_6$ 491.3040; found 491.3035; calcd. for $C_{24}H_{39}BN_4NaO_6$ 513.2859; found 513.2854. During HPLC analysis, the pinacol boronic ester **6c** was partially hydrolysed to the boronic acid **4c**. t_R = 5.53 min (Method B).

General Method for the Suzuki–Miyaura Reaction Under Conventional Heating: A 1 mL round-bottomed flask was charged with Boc-Phe(4-BPin)-Leu-Leu-Rink-MBHA (**1a**, 5–10 mg), and degassed DME/EtOH/H_2O (9:9:2, 0.3 mL) was added under nitrogen. The corresponding aryl halide (5 equiv.), a solution of 0.017 mmol/mL of $Pd(PPh_3)_4$ (0.05 equiv.) in DME/EtOH/H_2O (9:9:2), and degassed aq K_3PO_4 (2 M, 5 equiv.) were then added. The reaction mixture was heated at 60 °C for 48 h. After this time, the resin was washed with DMF (6 × 1 min), EtOH (6 × 1 min), CH_2Cl_2 (6 × 1 min), and diethyl ether (3 × 1 min). The arylphenylalanine peptides were released from the solid support by treatment with TFA/H_2O/TIS (95:2.5:2.5) with stirring for 2 h at room temperature. Following TFA evaporation and diethyl ether extraction, the crude peptides were dissolved in H_2O/CH_3CN, analysed by HPLC and characterised by mass spectrometry.

General Method for the Suzuki–Miyaura Reaction Under Microwave Irradiation. Protocol A: A 5 mL vial was charged with Boc-Phe(4-BPin)-Leu-Leu-Rink-MBHA (**1a**, 5–10 mg), and thoroughly degassed DME/EtOH/H_2O (9:9:2, 0.3 mL) was added under nitrogen. The corresponding aryl halide (5 equiv.), a solution of 0.017 mmol/mL of $Pd(PPh_3)_4$ (0.05 equiv.) in DME/EtOH/H_2O (9:9:2), and degassed aq K_3PO_4 (2 M, 5 equiv.) were then added. The reaction mixture was heated at 120 °C under microwave irradiation for 30 min. After this time, the resin was washed with DMF (6 × 1 min), EtOH (6 × 1 min), CH_2Cl_2 (6 × 1 min), and diethyl ether (3 × 1 min). The arylphenylalanine peptides were released from the solid support by treatment with TFA/H_2O/TIS (95:2.5:2.5) with stirring for 2 h at room temperature. Following TFA evaporation and diethyl ether

extraction, the crude peptides were dissolved in H_2O/CH_3CN and analysed by HPLC.

Protocol B: A 5 mL vial was charged with Boc-Phe(4-BPin)-Leu-Leu-Rink-MBHA (**1a**, 60–80 mg), the corresponding aryl halide (5 equiv.), $Pd_2(dba)_3$ (0.2 equiv.), P(*o*-tolyl)$_3$ (0.4 equiv.), and KF (4 equiv.). Thoroughly degassed DME/EtOH/H_2O (9:9:2, 1.2 mL) was then added under nitrogen. The reaction mixture was heated at 120 °C under microwave irradiation for 30 min. After this time, the resin was washed with DMF (6 × 1 min), EtOH (6 × 1 min), CH_2Cl_2 (6 × 1 min), and diethyl ether (3 × 1 min). The arylphenylalanine peptides were released from the solid support by treatment with TFA/H_2O/TIS (95:2.5:2.5) with stirring for 2 h at room temperature. Following TFA evaporation and diethyl ether extraction, an aliquot of the crude peptides was dissolved in H_2O/CH_3CN and analysed by HPLC. The pure biaryl peptides were obtained after purification by reverse-phase column chromatography.

Biaryl Peptide 7a: Starting from resin **1a** (50 mg), elution with H_2O/MeOH/TFA (50:50:0.2) afforded **7a** (3 mg, 27% yield). t_R = 21.13 min (Method A), 7.25 min (Method B). ^{1}H NMR (400 MHz, $CD_3CN + D_2O$): δ = 0.87–0.92 [m, 12 H, 4 CH_3(δ)-Leu], 1.52–1.64 [m, 6 H, 2 CH(γ)-Leu, 2 CH_2(β)-Leu], 3.11 [dd, J = 7.6, 14.4 Hz, 1 H, CH_2(β)-Phe], 3.30 [dd, J = 6.0, 14.4 Hz, 1 H, CH_2(β)-Phe], 4.23–4.34 [m, 3 H, 2 CH(α)-Leu, CH(α)-Phe], 7.35–7.39 (m, 3 H, 2-H_{arom}, 6-H_{arom}, 4′-H_{arom}), 7.46 (t, J = 7.4 Hz, 2 H, 3′-H_{arom}, 5′-H_{arom}), 7.61 (d, J = 8.2 Hz, 2 H, 3-H_{arom}, 5-H_{arom}), 7.64 (dt, J = 1.2, 7.4 Hz, 2 H, 2′-H_{arom}, 6′-H_{arom}) ppm. ^{13}C NMR (100 MHz, $CD_3CN + D_2O$): δ = 21.60, 21.63, 23.03, 23.09 [4 CH_3(δ)-Leu], 25.12, 25.32 [2 CH(γ)-Leu], 36.81 [CH_2(β)-Phe], 41.21, 41.29 [2 CH_2(β)-Leu], 52.12, 53.25, 54.97 [3 CH(α)], 127.56, 128.09 (C_{arom}-2′, C_{arom}-6′, C_{arom}-3, C_{arom}-5), 128.33 (C_{arom}-4′), 129.72 (C_{arom}-3′, C_{arom}-5′), 130.96 (C_{arom}-2, C_{arom}-6), 134.08 (C_{arom}-4), 140.90, 140.97 (C_{arom}-1, C_{arom}-1′), 168.54, 172.61, 175.48 (3 CO) ppm. MS (ESI): m/z = 467.2 [M + H]$^+$. HRMS (ESI): calcd. for $C_{27}H_{39}N_4O_3$ 467.3017; found 467.3016.

Biaryl Peptide 7b: Starting from resin **1a** (80 mg), elution with H_2O/MeOH/TFA (50:50:0.2) afforded **7b** (5 mg, 26% yield). t_R = 22.07 min (Method A), 7.47 min (Method B). ^{1}H NMR (400 MHz, $CD_3CN + D_2O$): δ = 0.85–0.88 [m, 12 H, 4 CH_3(δ)-Leu], 1.48–1.56 [m, 6 H, 2 CH(γ)-Leu, 2 CH_2(β)-Leu], 2.33 (s, 3 H, CH_3), 3.07 [dd, J = 8.0, 14.4 Hz, 1 H, CH_2(β)-Phe], 3.26 [dd, J = 5.6, 14.4 Hz, 1 H, CH_2(β)-Phe], 4.18–4.30 [m, 3 H, 2 CH(α)-Leu, CH(α)-Phe], 7.24 (d, J = 8.4 Hz, 2 H, 3′-H_{arom}, 5′-H_{arom}), 7.31 (d, J = 8.4 Hz, 2 H, 2-H_{arom}, 6-H_{arom}), 7.50 (d, J = 8.4 Hz, 2 H, 2′-H_{arom}, 6′-H_{arom}), 7.56 (d, J = 8.4 Hz, 2 H, 3-H_{arom}, 5-H_{arom}) ppm. ^{13}C NMR (100 MHz, $CD_3CN + D_2O$): δ = 20.71 (CH_3), 21.47, 21.50, 22.89, 22.95 [4 CH_3(δ)-Leu], 24.97, 25.18 [2 CH(γ)-Leu], 36.68 [CH_2(β)-Phe], 40.98, 41.11 [2 CH_2(β)-Leu], 52.00, 53.13, 54.79 [3 CH(α)], 127.29 (C_{arom}-2′, C_{arom}-6′), 127.72 (C_{arom}-3, C_{arom}-5), 130.21 (C_{arom}-2, C_{arom}-6), 130.78 (C_{arom}-3′, C_{arom}-5′), 133.72, 137.91, 138.14, 140.68 (C_{arom}-1, C_{arom}-4, C_{arom}-1′, C_{arom}-4′), 168.62, 172.70 (3 CO) ppm. MS (ESI): m/z = 481.3 [M + H]$^+$. HRMS (ESI): calcd. for $C_{28}H_{41}N_4O_3$ 481.3173; found 481.3155; calcd. for $C_{28}H_{40}N_4NaO_3$ 503.2993; found 503.2973.

Biaryl Peptide 7c: Starting from resin **1a** (60 mg), elution with H_2O/MeOH/TFA (60:40:0.2) afforded **7c** (9 mg, 63% yield). t_R = 21.16 min (Method A), 7.19 min (Method B). ^{1}H NMR (400 MHz, $CD_3CN + D_2O$): δ = 0.86–0.92 [m, 12 H, 4 CH_3(δ)-Leu], 1.51–1.66 [m, 6 H, 2 CH(γ)-Leu, 2 CH_2(β)-Leu], 3.07–3.15 [m, 1 H, CH_2(β)-Phe], 3.32 [dd, J = 3.6, 12.4 Hz, 1 H, CH_2(β)-Phe], 3.78 (s, 3 H, OCH_3), 4.30–4.39 [m, 3 H, 2 CH(α)-Leu, CH(α)-Phe], 7.03 (td, J = 0.8, 8.0 Hz, 1 H, 5′-H_{arom}), 7.08 (dd, J = 0.8, 8.0 Hz, 1 H, 3′-H_{arom}), 7.30 (td, J = 1.7, 8.0 Hz, 1 H, 4′-H_{arom}), 7.30 (d, J = 8.0 Hz, 2 H, 2-H_{arom}, 6-H_{arom}), 7.35 (dd, J = 1.7, 8.0 Hz, 1 H, 6′-H_{arom}), 7.47 (d, J = 8.0 Hz, 2 H, 3-H_{arom}, 5-H_{arom}) ppm. ^{13}C NMR (100 MHz, $CD_3CN + D_2O$): δ = 21.66, 22.91 [4 CH_3(δ)-Leu], 25.14, 25.33 [2 CH(γ)-Leu], 36.91 [CH_2(β)-Phe], 41.26, 41.34 [2 CH_2(β)-Leu], 52.21, 53.25, 55.03 [3 CH(α)], 55.91 (OCH_3), 112.34 (C_{arom}-3′), 121.61 (C_{arom}-5′), 129.77 (C_{arom}-4′), 130.06 (C_{arom}-3, C_{arom}-5), 130.46 (C_{arom}-1′), 130.64 (C_{arom}-2, C_{arom}-6), 131.31 (C_{arom}-6′), 133.55 (C_{arom}-4), 138.71 (C_{arom}-1), 157.19 (C_{arom}-2′), 168.57, 172.59, 175.44 (3 CO) ppm. MS (ESI): m/z = 497.3 [M + H]$^+$. HRMS (ESI): calcd. for $C_{28}H_{41}N_4O_4$ 497.3122; found 497.3125.

Biaryl Peptide 7d: Starting from resin **1a** (80 mg), elution with H_2O/MeOH/TFA (60:40:0.2) afforded **7d** (6.5 mg, 35% yield). t_R = 20.99 min (Method A), 7.20 min (Method B). ^{1}H NMR (300 MHz, $CD_3CN + D_2O$): δ = 0.85–0.90 [m, 12 H, 4 CH_3(δ)-Leu], 1.51–1.55 [m, 6 H, 2 CH(γ)-Leu, 2 CH_2(β)-Leu], 3.08 [dd, J = 7.8, 14.1 Hz, 1 H, CH_2(β)-Phe], 3.28 [dd, J = 9.0, 14.1 Hz, 1 H, CH_2(β)-Phe], 3.80 (s, 3 H, OCH_3), 4.19–4.32 [m, 3 H, 2 CH(α)-Leu, CH(α)-Phe], 7.01 (d, J = 8.9 Hz, 2 H, 3′-H_{arom}, 5′-H_{arom}), 7.32 (d, J = 8.1 Hz, 2 H, 2-H_{arom}, 6-H_{arom}), 7.56 (d, J = 8.1 Hz, 2 H, 3-H_{arom}, 5-H_{arom}), 7.58 (d, J = 8.9 Hz, 2 H, 2′-H_{arom}, 6′-H_{arom}) ppm. ^{13}C NMR (75 MHz, $CD_3CN + D_2O$): δ = 21.88, 21.91, 23.28, 23.36 [4 CH_3(δ)-Leu], 25.38, 25.60 [2 CH(γ)-Leu], 37.07 [CH_2(β)-Phe], 41.40, 41.52 [2 CH_2(β)-Leu], 52.43, 53.57, 55.24 [3 CH(α)], 56.06 (OCH_3), 115.36 (C_{arom}-3′, C_{arom}-5′), 127.86 (C_{arom}-3, C_{arom}-5), 128.93 (C_{arom}-2, C_{arom}-6), 129.10 (C_{arom}-1′), 131.16 (C_{arom}-2′, C_{arom}-6′), 133.58 (C_{arom}-4), 140.79 (C_{arom}-1), 160.49 (C_{arom}-4′), 168.78, 172.89, 175.79 (3 CO) ppm. MS (ESI): m/z = 497.3 [M + H]$^+$. HRMS (ESI): calcd. for $C_{28}H_{41}N_4O_4$ 497.3122; found 497.3101; calcd. for $C_{28}H_{40}N_4NaO_4$ 519.2942; found 519.2927.

Biaryl Peptide 7e: Starting from resin **1a** (60 mg), elution with H_2O/MeOH/TFA (60:40:0.2) afforded **7e** (7 mg, 49% yield). t_R = 21.09 min (Method A), 7.22 min (Method B). ^{1}H NMR (400 MHz, $CD_3CN + D_2O$): δ = 0.81–0.88 [m, 12 H, 4 CH_3(δ)-Leu], 1.49–1.58 [m, 6 H, 2 CH(γ)-Leu, 2 CH_2(β)-Leu], 3.09–3.14 [m, 1 H, CH_2(β)-Phe], 3.28–3.33 [m, 1 H, CH_2(β)-Phe], 4.23–4.31 [m, 3 H, 2 CH(α)-Leu, CH(α)-Phe], 7.39 (d, J = 7.8 Hz, 2 H, 2-H_{arom}, 6-H_{arom}), 7.65 (d, J = 7.8 Hz, 2 H, 3-H_{arom}, 5-H_{arom}), 7.82 (d, J = 8.8 Hz, 2 H, 2′-H_{arom}, 6′-H_{arom}), 8.25 (d, J = 8.8 Hz, 2 H, 3′-H_{arom}, 5′-H_{arom}) ppm. ^{13}C NMR (100 MHz, $CD_3CN + D_2O$): δ = 21.87, 21.89, 23.28, 23.34 [4 CH_3(δ)-Leu], 25.37, 25.57 [2 CH(γ)-Leu], 37.30 [CH_2(β)-Phe], 41.35, 41.48 [2 CH_2(β)-Leu], 52.41, 53.49, 55.11 [3 CH(α)], 125.12 (C_{arom}-3′, C_{arom}-5′), 128.85 (C_{arom}-3, C_{arom}-5, C_{arom}-2′, C_{arom}-6′), 131.49 (C_{arom}-2, C_{arom}-6), 136.30 (C_{arom}-4), 138.75 (C_{arom}-1), 147.72 (C_{arom}-1′), 148.30 (C_{arom}-4′), 169.38, 172.92, 175.86 (3 CO) ppm. MS (ESI): m/z = 512.2 [M + H]$^+$. HRMS (ESI): calcd. for $C_{27}H_{38}N_5O_5$ 512.2867; found 512.2846; calcd. for $C_{27}H_{37}N_5NaO_5$ 534.2687; found 534.2674.

Biaryl Peptide 7f: Starting from resin **1a** (60 mg), elution with H_2O/MeOH/TFA (60:40:0.2) afforded **7f** (5 mg, 37% yield). t_R = 19.84 min (Method A), 6.91 min (Method B). ^{1}H NMR (300 MHz, $CD_3CN + D_2O$): δ = 0.83–0.91 [m, 12 H, 4 CH_3(δ)-Leu], 1.49–1.60 [m, 6 H, 2 CH(γ)-Leu, 2 CH_2(β)-Leu], 3.09 [dd, J = 7.8, 14.1 Hz, 1 H, CH_2(β)-Phe], 3.21–3.28 [m, 1 H, CH_2(β)-Phe], 4.16–4.35 [m, 3 H, 2 CH(α)-Leu, CH(α)-Phe], 6.91–6.95 (m, 2 H, 3′-H_{arom}, 5′-H_{arom}), 7.17–7.35 (m, 4 H, 2-H_{arom}, 6-H_{arom}, 4′-H_{arom}, 6′-H_{arom}), 7.49 (d, J = 8.1 Hz, 2 H, 3-H_{arom}, 5-H_{arom}) ppm. ^{13}C NMR (75 MHz, $CD_3CN + D_2O$): δ = 21.88, 23.25 [4 CH_3(δ)-Leu], 25.32, 25.54 [2 CH(γ)-Leu], 37.27 [CH_2(β)-Phe], 41.41 [2 CH_2(β)-Leu], 52.37, 53.20, 55.21 [3 CH(α)], 117.13 (C_{arom}-3′), 121.18 (C_{arom}-5′), 128.27 (C_{arom}-4′), 129.90, 130.41, 130.79, 131.47 (C_{arom}-2, C_{arom}-6, C_{arom}-3, C_{arom}-5, C_{arom}-1′, C_{arom}-6′), 133.65 (C_{arom}-4), 138.97 (C_{arom}-1), 154.69 (C_{arom}-2′), 168.72, 172.96, 180.39 (3 CO) ppm.

MS (ESI): *m/z* = 483.3 $[M + H]^+$. HRMS (ESI): calcd. for $C_{27}H_{39}N_4O_4$ 483.2966; found 483.2951; calcd. for $C_{27}H_{38}N_4NaO_4$ 505.2785; found 505.2775.

Biaryl Peptide 7g: Starting from resin **1a** (80 mg), elution with H_2O/MeOH/TFA (80:20:0.2) afforded **7g** (2 mg, 10% yield). t_R = 15.70 min (Method A), 5.96 min (Method B). ^1H NMR (400 MHz, $CD_3CN + D_2O$): δ = 0.86–0.88 [m, 12 H, 4 CH_3(δ)-Leu], 1.45–1.57 [m, 6 H, 2 CH(γ)-Leu, 2 CH_2(β)-Leu], 2.40 (s, 3 H, CH_3), 3.11 [dd, *J* = 7.6, 14.6 Hz, 1 H, CH_2(β)-Phe], 3.24 [dd, *J* = 6.8, 14.6 Hz, 1 H, CH_2(β)-Phe], 4.16–4.21 [m, 3 H, 2 CH(α)-Leu, CH(α)-Phe], 7.37 (d, *J* = 8.4 Hz, 2 H, 2-H_{arom}, 6-H_{arom}), 7.47 (d, *J* = 8.4 Hz, 2 H, 3-H_{arom}, 5-H_{arom}), 8.50 (s, 1 H, CH_{imid}) ppm. ^{13}C NMR (100 MHz, $CD_3CN + D_2O$): δ = 10.44 (CH_3), 21.82, 21.87, 23.21, 23.25 [4 CH_3(δ)-Leu], 25.29, 25.51 [2 CH(γ)-Leu], 37.26 [CH_2(β)-Phe], 41.33 [2 CH_2(β)-Leu], 52.85, 53.49, 55.02 [3 CH(α)], 129.00 (C_{arom}-3, C_{arom}-5), 131.42 (C_{arom}-2, C_{arom}-6), 136.27 (CH_{imid}) ppm. MS (ESI): *m/z* = 471.3 $[M + H]^+$. HRMS (ESI): calcd. for $C_{25}H_{39}N_6O_3$ 471.3078; found 471.3073; calcd. for $C_{25}H_{38}N_6NaO_3$ 493.2898; found 493.2890.

Supporting Information (see also the footnote on the first page of this article): Experimental details, copies of IR spectra of boronopeptidyl resins **1a**–**c**, copies of ^1H and ^{13}C NMR, IR, ESI-MS, and HRMS spectra, and HPLC chromatograms of boronopeptides **6a**–**c** and biaryl peptides **7a**–**g**.

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[1] L. Feliu, M. Planas, *Int. J. Pept. Res. Ther.* **2005**, *11*, 53–97.
[2] a) A. Perdih, M. S. Dolenc, *Curr. Org. Chem.* **2007**, *11*, 801–832; b) D. Haldar, *Curr. Org. Synth.* **2008**, *5*, 61–80.
[3] a) W. Wang, M. Cai, C. Xiong, J. Zhang, D. Trivedi, V. J. Hruby, *Tetrahedron* **2002**, *58*, 7365–7374; b) S. Kotha, K. Lahiri, *Biopolymers* **2003**, *69*, 517–528; c) M. Limbach, M. Löweneck, J. V. Schreiber, J. Frackenpohl, D. Seebach, *Helv. Chim. Acta* **2006**, *89*, 1427–1441; d) M. Vilaró, G. Arsequell, G. Valencia, A. Ballesteros, J. Barluenga, *Org. Lett.* **2008**, *10*, 3243–3245.
[4] a) F. Firooznia, C. Gude, K. Chan, N. Marcopulos, Y. Satoh, *Tetrahedron Lett.* **1999**, *40*, 213–216; b) O. Skaff, K. A. Jolliffe, C. A. Hutton, *J. Org. Chem.* **2005**, *70*, 7353–7363; c) Y. Gong, J. K. Barbay, A. B. Dyatkin, T. A. Miskowski, E. S. Kimball, S. M. Prouty, M. C. Fisher, R. J. Santulli, C. R. Schneider, N. H. Wallace, S. A. Ballentine, W. E. Hageman, J. A. Masucci, B. E. Maryanoff, B. P. Damiano, P. Andrade-Gordon, D. J. Hlasta, P. J. Hornby, W. He, *J. Med. Chem.* **2006**, *49*, 3402–3411; d) P. Čapek, R. Pohl, M. Hocek, *Org. Biomol. Chem.* **2006**, *4*, 2278–2284.
[5] F. Alonso, I. P. Beletskaya, M. Yus, *Tetrahedron* **2008**, *64*, 3047–3101.
[6] a) B. E. Haug, W. Stensen, J. S. Svendsen, *Bioorg. Med. Chem. Lett.* **2007**, *17*, 2361–2364; b) N.-D. Doan, S. Bourgault, M. Létourneau, A. Fournier, *J. Comb. Chem.* **2008**, *10*, 44–51.
[7] a) W. Yang, X. Gao, B. Wang, *Med. Res. Rev.* **2003**, *23*, 346–368; b) P. J. Duggan, D. A. Offermann, *Aust. J. Chem.* **2007**, *60*, 829–834; c) I. B. Sivaev, V. I. Bregadze, *Arkivoc* **2008**, *iv*, 47–61.
[8] H. Lei, M. S. Stoakes, K. Herath, J. Lee, A. W. Shwabacher, *J. Org. Chem.* **1994**, *59*, 4206–4210.
[9] T. Ishiyama, M. Murata, N. Miyaura, *J. Org. Chem.* **1995**, *60*, 7508–7510.
[10] a) M. J. Schulz, S. J. Coats, D. J. Hlasta, *Org. Lett.* **2004**, *6*, 3265–3268; b) D. G. Hall, in: *Boronic Acids* (Ed.: D. G. Hall), Wiley-VCH, Weinheim, **2005**, pp. 1; c) D. Duran, N. Wu, B. Mao, J. Xu, *J. Liq. Chromatogr. Relat. Technol.* **2006**, *29*, 661–672.
[11] I. Cepanec, *Synthesis of Biaryls*, Elsevier, Amsterdam, **2004**.
[12] a) M. Lahred, G. Lindeberg, A. Hallberg, *Tetrahedron Lett.* **1996**, *37*, 8219–8222; b) C. O. Kappe, *Angew. Chem. Int. Ed.* **2004**, *43*, 6250–6284; c) C. O. Kappe, D. Dallinger, *Mol. Divers.* **2009**, *13*, 71–193.
[13] V. Cerezo, M. Amblard, J. Martinez, P. Verdié, M. Planas, L. Feliu, *Tetrahedron* **2008**, *64*, 10538–10545.
[14] E. Kaiser, R. L. Colescott, C. D. Bossinger, P. Cook, *Anal. Biochem.* **1970**, *34*, 595–598.

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