Suzuki-Miyaura diversification of amino acids and dipeptides in aqueous media

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Dedication ((optional))

The Suzuki-Miyaura derivatisation of free amino acids, peptides and proteins is an attractive area with much potential utility for medicinal chemistry and chemical biology. Here we report the modification of unprotected and Boc-protected aromatic amino acids and dipeptides in aqueous media, enabling heteroarylation and vinylation. We systematically investigate the impact of the peptide backbone and adjacent amino acid residues upon the reaction. Our studies reveal that whilst asparagine and histidine hinder the reaction, by utilising dppf, a ferrocene-based bidentate phosphine ligand, cross-coupling of halophenylalanine or halotryptophan adjacent to such a residue could be enabled. Our studies reveal dppf to have good compatibility with all unprotected, proteinogenic amino acid side chains.

Introduction

Since the discovery of palladium's catalytic potential, numerous reactions have been developed for the formation of carbon-carbon and carbon-heteroatom bonds.[1] Through the development of the Suzuki-Miyaura reaction, organoboron compounds were introduced as versatile coupling partners.[2] The use of boron as an organometallic partner provides several advantages such as its environmentally benign nature, commercial availability, high functional group tolerance and a compatibility with aqueous conditions.[3] The Suzuki-Miyaura reaction is therefore often the method of choice for the derivatisation of challenging substrates. It has been utilised for the derivatisation of biomolecules such as nucleosides,[4] amino acids,[5] peptides,[6] but also more complex natural products,[7] and proteins.[5c-d, 8] Site-selective derivatisation of peptides and proteins by bioorthogonal reactions[9] has received great attention as a key component of the chemical biology toolbox and for the labeling of bioactive products.[8c-d, 10] Additionally, one can explore structure-activity relationships for these biological substrates via the synthesis of related structures, enabled by the presence of a "derivatisation handle" in the amino acid sequence.

Introducing halogens onto the side chains of phenylalanine and tryptophan,[11] for example, opens opportunities for late-stage peptide functionalisation via palladium-catalysed cross-coupling reactions. Ideally, performing these derivatisations in a late stage of the synthetic pathway would provide a convergent method for rapid screening of structurally related compounds. However, when (partially) unprotected peptide substrates have to be derivatised, the envisaged Pd-catalysed reactions require aqueous conditions to mimic the natural environment of these biomolecules. To find catalytic systems that are compatible with water, various alterations to commonly used reaction conditions in organic solvents have been reported.[12] Unfortunately, when aiming at more complex substrates, (super)stoichiometric amounts of catalyst and ligand are often required.[5d,13] Clearly, catalytic amounts are preferred in view of the associated price of the Pd source and ligand used and in order to avoid large amounts of residual Pd to be scavenged after the reaction.[14] Herein, to address this issue, a compatibility study between Suzuki-Miyaura derivatisation and amino acid main and side chain functionalities was carried out via a systematic screening. By synthesis of dipeptide substrates containing a halogenated phenylalanine, the compatibility of various side chain functionalities could be screened. In this way, each side chain can be investigated individually, ultimately leading to a tool to make predictions for more complex substrates, i.e. polypeptides.

Results and Discussion

Evaluation of various Pd/Ligand systems on 4-bromophenylalanine as a model substrate

To achieve the required compatibility with aqueous conditions, an adaptation of the catalytic species is mandatory. Several examples of water soluble ligands have been reported. We screened complexes of 2-aminopyrimidine-4,6-diol disodium salt (Na_2ADHP, **1a**)[5d, 15], 2-(dimethylamino)pyrimidine-4,6-diol disodium salt (Na_2ADHP(Me_2), **1b**)[8d, 14a], 3,3′,3″-phosphanetriyltris(benzene sulfonic acid) trisodium salt (TPPTS, **2**)[4e, 5a], and sodium 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl-3'-sulfonate (sulfonated SPhos, **3**)[3c, 7a]. Beside precatalysts based on these ligands, we also evaluated $PdCl_2$dppf ([1,1′-bis(diphenylphosphino)ferrocene]palladium dichloride) (**5a**).[16a] This complex is considered to be insoluble in water, but has been used in aqueous media for the preparation of various biphenyls.[16b] Additionally, a

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biphenylamino-based Pd precatalyst featuring this ligand (**5b**) was also tested[17] as well as ligandless Pd salts (**4a**,**b**).[8d, 18]

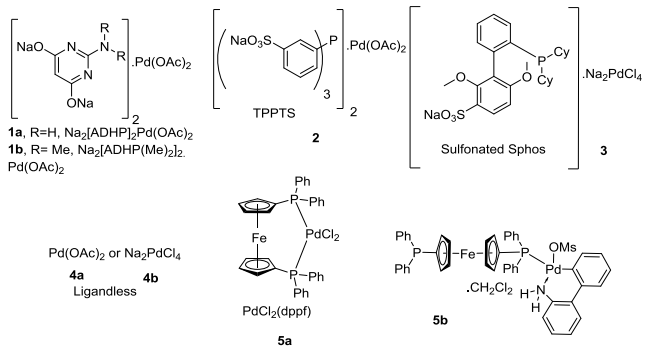
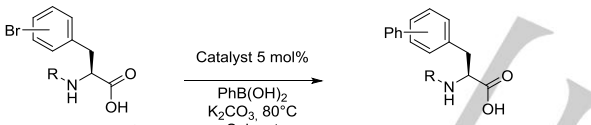


Figure 1. Various palladium(-ligand) sources tested during the initial screening with 4-bromophenylalanine.

A screening of these precatalysts was first performed on the model substrate 4-bromophenylalanine (**6a**) in a reaction with phenylboronic acid. Furthermore, in view of eventual SAR studies regioisomers, 3- (**6b**) and 2-bromophenylalanine (**6c**) were also evaluated in the Suzuki-Miyaura reactions with phenylboronic acid.

Table 1. Preliminary screening with regioisomeric bromophenylalanines (**6**) as substrates in a cross-coupling reaction with phenylboronic acid.



H-Phe(4-Br)-OH **6a**
H-Phe(3-Br)-OH **6b**
H-Phe(2-Br)-OH **6c**

H-Phe(4-phenyl)-OH **7a**
H-Phe(3-phenyl)-OH **7b**
H-Phe(2-phenyl)-OH **7c**

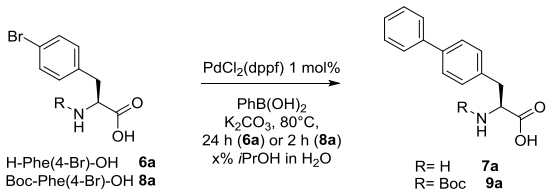
Entry	Cat.	Substrate	Solvent	Conv. /%[a,b], Time /h
1	**1a**	**6a**	H_2O	57% (2 h) - 90% (24 h)
2	**1b**	**6a**	H_2O	99% (3 h)
3	**2**	**6a**	H_2O	95% (4 h)
4[c]	**3**	**6a**	H_2O	10% (2 h) - 42% (24 h)
5	**4a**	**6a**	H_2O	53% (2 h) - 85% (24 h)
6	**4b**	**6a**	H_2O	50% (2 h) - 87% (24 h)
7	**5a**	**6a**	H_2O	2% (24 h)
8	**5a**	**6a**	aq. 5% *i*PrOH	80% (24 h)
9	**5a**	**6a**	aq. 50% *i*PrOH	99% (4 h)
10	**5b**	**6a**	aq. 50% *i*PrOH	78% (4 h)
11	**5a**	**6b**	aq. 50% *i*PrOH	49% (2 h) - 99% (4 h)
12	**5a**	**6c**	aq. 50% *i*PrOH	65% (4 h)

[a] Reaction conditions: bromophenylalanine (**6a-c**) (0.1 mmol), 5 mol% catalyst (**1-5**), phenylboronic acid (1.2 eq), K_2CO_3 (5 eq), H_2O or H_2O/*i*PrOH (2 mL), 80°C. [b] Measured by HPLC (215 nm, uncorrected). [c] Ratio ligand/Pd 2.5:1.

In pure water, the most promising results were obtained with precatalysts **1b** (entry 2) and **2** (entry 3). While incomplete conversion to the desired product was observed with **5a** in purely aqueous conditions (entry 7), changing to a mixed solvent system significantly improved the reaction outcome. Isopropanol (*i*PrOH) was selected as a green alternative[19] (entry 8 and 9) to more traditionally used organic solvents that are commonly applied in Suzuki-Miyaura transformations, such as toluene and DMF. No beneficial effect was found upon use of dppf based precatalyst **5b** (entry 10). The 2-bromo regioisomer **6c** (entry 12) required a longer reaction time to reach a high conversion, while the 3-bromo regioisomer **6b** (entry 11) converted at an intermediate rate. These derivatisations are highly interesting since ortho- and meta halogenated regioisomers are generally not considered in the derivatisation of halophenylalanine substrates.[20]

The use of **5a** is, to the best of our knowledge, hitherto limited to the derivatisation of protected (4-pinacolylborono)phenylalanine (BPA) with aromatic halides and triflates[16a] and has only been applied in aqueous conditions for the preparation of simple biphenyls.[16b] We therefore investigated the scope on unprotected and Boc-protected substrates, that can be directly applied in solid-phase peptide synthesis (SPPS). First, an optimisation of the *i*PrOH/water ratio was performed (Table 2). It was shown that for an unprotected substrate (**6a**), 50% *i*PrOH provided the highest conversion (entry 6) using 1 mol% of **5a**. To achieve short cross-coupling reaction times (4 h), 5 mol% of **5a** was required for complete conversion of **6a** (entry 6 vs Table 1, entry 9). On the *tert*-butyloxycarbonyl (Boc) protected substrate **8a**, nearly complete conversion can be reached with as little as 1 mol% of **5a** in a limited reaction time (2 h), while the amount of *i*PrOH required can be <5% (entry 2). As could be expected protected systems gave faster reaction but protection is interestingly not required. Avoiding these main chain protecting groups is a first step in the envisaged derivatisation of more complex peptide substrates in aqueous environment.

Table 2. *i*PrOH/H_2O ratio optimisation for unprotected (**6a**) and Boc-protected 4-bromophenylalanine (**8a**).



H-Phe(4-Br)-OH **6a**
Boc-Phe(4-Br)-OH **8a**

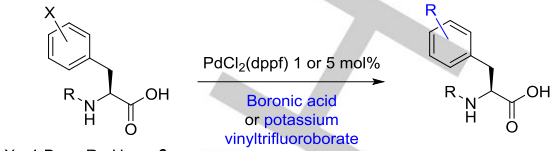
Entry	*i*PrOH /%	Substrate	Conv. /%[a,b]	Substrate	Conv. /%[a,b]
1	0%	**6a**	2	**8a**	94%
2	5%	**6a**	32	**8a**	99%
3	10%	**6a**	44	**8a**	99%
4	25%	**6a**	58	**8a**	99%
5	35%	**6a**	65	**8a**	99%
6	50%	**6a**	74	**8a**	99%
7	66%	**6a**	70	**8a**	99%
8	80%	**6a**	45	**8a**	99%
9	100%	**6a**	9	**8a**	71%

[a] Reaction conditions: 4-bromophenylalanine (**6a**) (0.2 mmol) or Boc-4-bromophenylalanine (**8a**) (0.15 mmol), 1 mol% **5a**, phenylboronic acid (1.2 eq), K_2CO_3 (5 eq), % *i*PrOH in H_2O (total 4 mL), 80°C. [b] Measured by HPLC (215 nm, uncorrected).

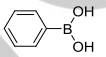
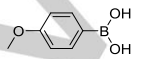
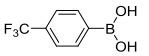
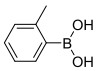
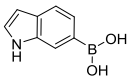
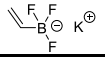
Boronic acid scope using the $PdCl_2$(dppf) (5a) catalytic system

Next the boronic acid scope was investigated with the optimised reaction conditions identified for reaction of **6a** and **8a** with phenylboronic acid using precatalyst **5a**. Gratifyingly, various (hetero)aromatic boronic acids (Table 3, entry 1-7) can be introduced on the halogenated phenylalanine substrates **6a** and **8a**, seemingly independent of the boronic acid. Although the reaction time was set at 2 hours during the initial solvent optimalisation experiments, complete conversion of **8a** was reached after only 1 hour at 80°C. Purification of the *N*-terminally unprotected cross-coupled products (**7a, d-j**) was performed by preparative HPLC, delivering lower yields characteristic for HPLC purification. Higher isolated yields were obtained for all protected products (**9a-h**) due to an easier isolation with flash chromatography. Boc protected 4-bromophenylalanine generally reacted faster with boronic acids as was also observed in the model cross-coupling with phenylboronic acid (Table 2). Next, 9-fluorenylmethyloxy-carbonyl protection (Fmoc) was also evaluated. On Fmoc-4-bromophenylalanine altered reaction conditions are required to avoid removal of the base-labile Fmoc-group observed at 80°C. Although, reaction at a lower temperature (40°C) under otherwise standard reaction conditions showed promising results, HPLC conversion only reached 80% after 24h (see supporting information).

Table 3. Suzuki-Miyaura reaction on unprotected (**6a**), Boc-protected 4-bromophenylalanine (**8a**), unprotected (**10a**), and Boc-protected 4-iodophenylalanine (**11a-c**).



X= 4-Br: R= H **6a**; R= Boc **8a**
X= 4-I: R= H **10a**; R= Boc **11a**
X= 3-I: R= Boc **11b**
X= 2-I: R= Boc **11c**

Entry	Substrate	Boronic acid	Time /h	Product	Conv. /%[a,b,c], Yield /%
1	**6a**		4 h	**7a**	93% (48%)[d]
	8a		1 h	**9a**	99% (83%)
2	**6a**		4 h	**7d**	99% (33%)[d]
	8a		1 h	**9b**	99% (88%)
3	**6a**		4 h	**7e**	79% (45%)[d]
	8a		1 h	**9c**	99% (79%)
4	**6a**		4 h	**7f**	95% (60%)[d]
	8a		1 h	**9d**	99% (85%)
5	**6a**		4 h	**7g**	98% (37%)[d]
	8a		1 h	**9e**	99% (89%)
6	**6a**		4 h	**7h**	94% (33%)[d]
	8a		1 h	**9f**	99% (84%)
7	**6a**		4 h	**7i**	97% (39%)[d]
	8a		1 h	**9g**	99% (89%)
8	**8a**		24 h	**9h**	11%
9	**10a**		2 h	**7j**	95% (40%)[d]
	11a		1 h	**9h**	99% (81%)
10	**11b**		1 h	**9i**	99% (89%)
11	**11c**		1 h	**9j**	99% (89%)

[a] Reaction conditions: R= H: halophenylalanine (**6a**, **10a**) (0.1 mmol), 5 mol% **5a**, boronic acid (1.2 eq), K_2CO_3 (5 eq), aq. 50% *i*PrOH (2 mL), 4 h, 80°C. [b] R= Boc: halophenylalanine (**8a**, **11a-c**) amino acid halide (2 mmol), 1 mol% **5a**, boronic acid (1.2 eq), K_2CO_3 (5 eq), aq. 5% *i*PrOH (20 mL), 1 h, 80°C. [c] Measured by HPLC (215 nm, uncorrected). [d] Isolated yields by preparative HPLC.

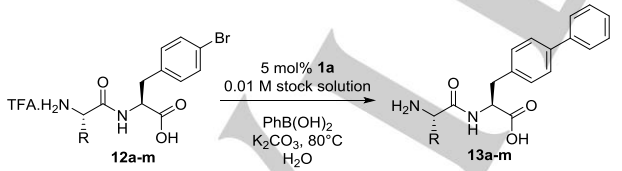
In addition to (hetero)aromatic boronic acids, we investigated several non-aromatic boronic acids (Table 3). Whereas little success was obtained for aliphatic boronic acids, a vinylic substituent can be efficiently introduced, as exemplified by the use of potassium vinyltrifluoroborate as reagent. We opted for this trifluoroborate as a convenient alternative to vinyl boronic acid,[21a] which is reported to readily undergo polymerisation.[2h, 21b] These potassium trifluoroborates can be used as bench-stable alternatives to their respective boronic acids.[2c] During cross-coupling in aqueous conditions, these trifluoroborates hydrolyse readily to the corresponding boronic acid.[22] To

achieve high conversions in an acceptable reaction time, 4-iodo-phenylalanine (**10a**) needed to be employed as the substrate (Table 3, entry 8 vs 9). Interestingly, the vinyl group permits a broad scope of further derivatisations, potentially allowing to obtain a variety of hitherto unknown functionalised Phe analogues. In addition to the preparation of *N*-Boc-4-vinylphenylalanine (**9h**), it was possible to perform the vinylation on the meta- and ortho-halogenated regioisomers (**11b**,**c**) as well, and with similar reactivities (entry 10 and 11). The preparation of protected vinylphenylalanine has primarily been described in organic solvents with vinylstannanes,[23] which suffer from several drawbacks such as poor atom-economy, toxicity and poor solubility in mixed aqueous conditions.[21a] To the best of our knowledge, this is the first reported vinylation reaction with trifluoroborates on (unprotected) halogenated aromatic amino acids that can be performed in mixed aqueous conditions. Only use of substituted alkenyl boronic acids has previously been reported by Davis and coworkers with **1a** on a protected iodinated tyrosine and a protein complex.[5d]

Evaluation of dipeptide substrates for Suzuki-Miyaura reactions

In order to determine the applicability of the catalytic systems (Figure 1) on increasingly difficult substrates, an explorative study on a slightly more elaborate substrate, H-Gly-Phe(4-Br)-OH (**12a**), was initially carried out (for experimental data, see supporting information). Similar to the results on halogenated phenylalanine substrates **6**, precatalysts **1a**, **1b** and **2** gave desirable conversions (>95%, see supporting information) in a limited amount of time (2 h) in water with only 5 mol% of catalyst. However, in this case 2.5 equivalents of boronic acid were required to achieve high conversion. While **5a** gave correspondingly high conversions in a mixed solvent (H_2O/*i*PrOH 1:1), the $[Na_2(ADHP)]_2Pd(OAc)_2$ (**1a**) system was selected as a convenient catalyst to perform a scope study on dipeptides **12** featuring side chain functionality (Table 4). Based on HPLC conversions we could determine combinations that inhibit or hamper cross-coupling.

Table 4. Suzuki-Miyaura reaction on 4-bromophenylalanine-containing dipeptide substrates (**12**) with $[Na_2ADHP]_2Pd(OAc)_2$ (**1a**) as the precatalyst.



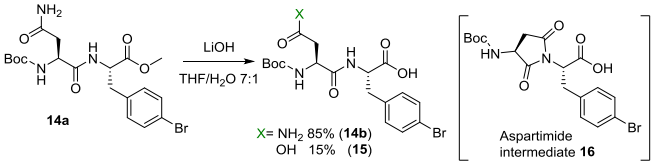
Entry	Substrate	Time /h	Conv. /%[a,b]
1	H-Gly-Phe(4-Br)-OH (**12a**)	2 h	>99%
2	H-Ala-Phe(4-Br)-OH (**12b**)	2 h	>99%
3	H-Leu-Phe(4-Br)-OH (**12c**)	2 h	>95%
4	H-Ser-Phe(4-Br)-OH (**12d**)	2 h	>99%
5	H-Asp-Phe(4-Br)-OH (**12e**)	2 h	>99%
6[c]	H-Lys-Phe(4-Br)-OH (**12f**)	2 h	>99%
7	H-Phe-Phe(4-Br)-OH (**12g**)	6 h	>99%
8	H-Tyr-Phe(4-Br)-OH (**12h**)	6 h	>95%
9	H-Trp-Phe(4-Br)-OH (**12i**)	6 h	>95%
10	**H-Asn-Phe(4-Br)-OH (12j)**	**24 h**	**0%**
11	H-Met-Phe(4-Br)-OH (**12k**)	2 h	>99%
12[c]	**H-His-Phe(4-Br)-OH (12l)**	**24 h**	**0%**
13[c]	H-Arg-Phe(4-Br)-OH (**12m**)	2 h	>99%

[a] Reaction conditions: dipeptide bromide (**12a-m**) (0.063 mmol), 5 mol% **1a** (0.01 M stock solution), phenylboronic acid (2.5 eq), K_2CO_3 (5 eq), H_2O (2 mL), 80°C. [b] Measured by HPLC (215 nm, uncorrected). [c] 6 eq instead of 5 eq. K_2CO_3.

As can be seen in Table 4, most amino acid side chains (aliphatic, aromatic, acidic and basic) do not interfere and readily allow cross-coupling reaction. The thioether functionality of Met (**12k**) is remarkable in this respect as sulphur is known to poison Pd^0.[5d, 24] However, for Asn (**12j**) and His (**12l**), containing a primary amide and imidazole moiety, respectively, no conversion was observed even after prolonged reaction times (Table 4, entry 10 and 12). A further evaluation of these substrates was performed by looking specifically at individual functionalities in the protected dipeptide substrates.

Synthesis of derivatised dipeptides with asparagine (Asn) and histidine (His)

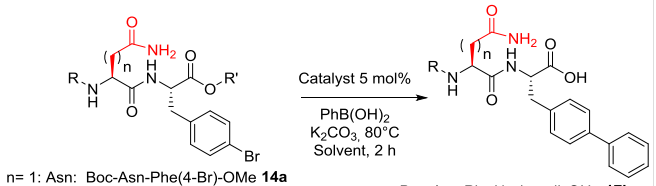
To allow cross-coupling with **12j** and **12l** both dipeptides were prepared as their *N*- and *C*-terminal protected derivatives. First, Boc-Asn-Phe(4-Br)-OMe (**14a**) was investigated as a substrate and subjected to various reaction conditions (Table 5). We observed that only with $PdCl_2$(dppf) (**5a**) a high conversion was obtained (Table 5, entry 6), although only the hydrolysed product **17b** was observed by HPLC analysis. Therefore the isolated yield could not be determined. In order to verify whether this smooth conversion could also be realised on partially deprotected dipeptides, a saponification was first carried out (Scheme 1). Since deprotection by hydrolysis in basic conditions led to aspartimide formation and resulted in a mixture of both the carboxylic acid (**15**) and primary amide side chain (**14b**), addition of formic acid (1.4 eq, 0.2 eq with respect to LiOH) was mandatory to avoid this side reaction.[25]



Scheme 1. Aspartimide formation occurring during basic hydrolysis of **14a**, giving rise to a mixture (85:15) of side chain amide (**14b**) and carboxylic acid. (**15**) via an aspartimide intermediate (**16**).

In fact, this aspartimide formation also occurred during the Suzuki-Miyaura derivatisation of **14b** (Table 5, entry 7) and fully deprotected dipeptide **12j**, yielding a 1:1 mixture of the carboxylic acid and primary amide in the side chain. Also here, a small amount of formic acid (0.2 eq with respect to K_2CO_3) solved the problem (entry 8 and 9).[25] This optimised procedure was then repeated with unprotected glutamine dipeptide **12n** (entry 10), yielding H-Gln-Phe(4-phenyl)-OH **13n**. As observed for amino acids, the lower isolated yields of the dipeptides can be explained by the necessity of purification by preparative HPLC.

Table 5. Evaluation of fully and partially protected Asn-Phe(4-Br) dipeptides (**14**) in Suzuki-Miyaura reactions.



n= 1: Asn: Boc-Asn-Phe(4-Br)-OMe **14a**; Boc-Asn-Phe(4-Br)-OH **14b**; H-Asn-Phe(4-Br)-OH **12j**
n= 2: Gln: H-Gln-Phe(4-Br)-OH **12n**

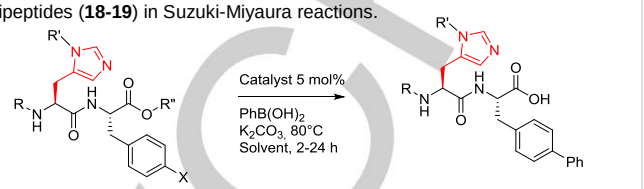
Boc-Asn-Phe(4-phenyl)-OH **17b**; H-Asn-Phe(4-phenyl)-OH **13j**; H-Gln-Phe(4-phenyl)-OH **13n**

Entry	Substrate	Cat.	Loading (mol%)	Solvent	Conv. (%)[a,b] Yield (%)
1	**14a**	**1a**	5 mol%	H_2O	No conv.
2	**14a**	**1b**	5 mol%	H_2O	No conv.
3	**14a**	**2**	10 mol%	H_2O	No conv.
4	**14a**	**1a**	100 mol%	H_2O	No conv.
5	**14a**	**4b**	5 mol%	H_2O	No conv.
6	**14a**	**5a**	5 mol%	aq. 50% *i*PrOH	99%[c]
7	**14b**	**5a**	5 mol%	aq. 50% *i*PrOH	99%[d]
8[e]	**14b**	**5a**	5 mol%	aq. 50% *i*PrOH	95% (66%)[f]
9[e]	**12j**	**5a**	5 mol%	aq. 50% *i*PrOH	95% (32%)[f]
10[e]	**12n**	**5a**	5 mol%	aq. 50% *i*PrOH	83% (36%)[f]

[a] Reaction conditions: Substrate (0.055 mmol, **14a**,**b**, **12j**,**n**), 5-100 mol% catalyst (0.01 M stock solution in case of **1a** and **1b**), phenylboronic acid (2.5 eq), K_2CO_3 (5 eq), solvent (2 mL), 80°C, 2 h. [b] Measured by HPLC (215 nm, uncorrected). [c] **17b** was formed instead of the expected methyl ester. [d] Side product (H-Asp-Phe(4-Ph)-OH, **13e**) formed due to aspartimide formation (see scheme 1). [e] Reaction conditions as described in [a], with 1 eq of formic acid. [f] Isolation by preparative HPLC.

In analogy to Asn, a stepwise deprotection was followed for histidine (Table 6). Dipeptide **18a**, featuring a benzyloxymethyl (BOM) protection on the N_π-position and methyl ester, was selected as BOM protecting allows selective *N*-Boc-removal by acidolysis. Similarly, whereas other catalytic systems fail to give conversion, $PdCl_2$(dppf) (**5a**) provided high conversion in a limited time (Table 6, entry 4). A concomitant hydrolysis of the methyl ester was however also observed in this case, and therefore no isolated yield was determined. The Suzuki-Miyaura derivatisation of partially deprotected **18b** (Table 6, entry 5) and **18c** (entry 6, unprotected main chain, imidazole protection was retained) was possible within 4h.

Table 6. Evaluation of fully and partially protected His-Phe(4-X) dipeptides and tripeptides (**18-19**) in Suzuki-Miyaura reactions.



Boc-His(BOM)-Phe(4-Br)-OMe **18a**; Boc-His(BOM)-Phe(4-Br)-OH **18b**; H-His(BOM)-Phe(4-Br)-OH **18c**; H-His-Phe(4-I)-OH **19a**; Ac-His-Phe(4-I)-OH **19b**; H-Gly-His-Phe(4-I)-OH **19c**; Ac-Gly-His-Phe(4-I)-OH **19d**

Boc-His(BOM)-Phe(4-phenyl)-OMe **20a**; Boc-His(BOM)-Phe(4-phenyl)-OH **20b**; H-His(BOM)-Phe(4-phenyl)-OH **20c**; H-His-Phe(4-phenyl)-OH **20d**; Ac-His-Phe(4-phenyl)-OH **20e**; H-Gly-His-Phe(4-phenyl)-OH **20f**; Ac-Gly-His-Phe(4-phenyl)-OH **20g**

Entry	Substrate	Cat.	Loading (mol%)	Solvent	Conv. (%)[a,b] Yield (%)
1	**18a**	**1a**	5 mol%	H_2O	No conv.
2	**18a**	**2**	10 mol%	H_2O	No conv.
3	**18a**	**1a**	100 mol%	H_2O	No conv.
4	**18a**	**5a**	5 mol%	aq.50% *i*PrOH	90%[c]
5	**18b**	**5a**	5 mol%	aq.50% *i*PrOH	95% (56%)[c]
6	**18c**	**5a**	5 mol%	aq.50% *i*PrOH	83% (42%)[d]
7	**19a**	**5a**	5 mol%	aq.50% *i*PrOH	25% (15%)[d]
8	**19b**	**5a**	5 mol%	aq.50% *i*PrOH	50% (19%)[d]
9	**19c**	**5a**	5 mol%	aq.50% *i*PrOH	18% (11%)[d]
10	**19d**	**5a**	5 mol%	aq.50% *i*PrOH	50% (29%)[d]

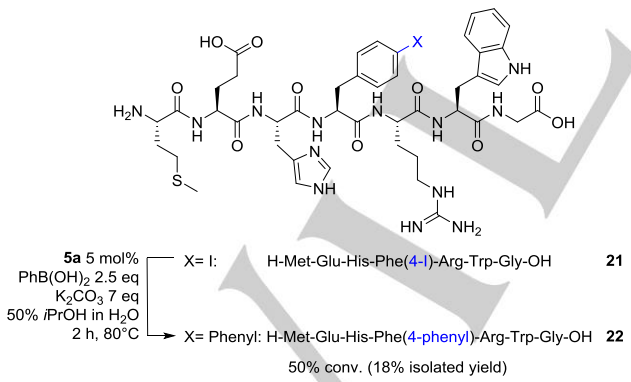
[a] Reaction conditions: Substrate (0.04 mmol, **18a-c** or 0.02 mmol **19a-d**), 5-100 mol% catalyst (0.01 M stock solution in case of **1a** and **1b**), phenylboronic acid (2.5 eq), K_2CO_3 (5 eq), solvent (2 mL, or 1 mL for **19a-d**), 80°C, 2-24 h. (standard 2 h, 4 h for **18c** and 24 h for **19b**,**d**. [b] Measured by HPLC (215 nm, uncorrected). [c] **20b** was formed instead of the expected methyl ester. [d] Isolation by preparative HPLC.

To avoid the need for a side chain protecting group on histidine, complexation of the imidazole with several metal halides was investigated (e.g. $MgCl_2$, $ZnCl_2$, $NiCl_2$). After all, addition of 0.1 equivalent of unprotected L-His to the successful reaction of 4-bromophenylalanine and phenylboronic acid (Table 1, entry 9) nearly completely blocked the reaction pointing to catalyst inhibition through imidazole coordination (see supporting information). These metal halides are potentially capable of coordinating with the interfering functionality and make it less available for disrupting the desired catalysis on peptide substrates such as **12l**.[13b, 26] Inhibition of typical Suzuki-Miyaura reactions by the presence of nitrogen-rich heterocycles, such as imidazole, has been reported in non-peptide systems.[27]

Unfortunately, when sacrificial metals were present in the reaction mixture, no improvement was observed. Interestingly, significant amounts (up to 1 eq) of Boc-His-OMe could be added to the standard reaction (Table 1, entry 9) with retention of acceptable reaction progress (see supporting information). It therefore seems that it is the combination of an unprotected α-nitrogen and imidazole ring which blocks the catalysis.

Subsequently, we turned towards the corresponding iodinated dipeptide substrate H-His-Phe(4-I)-OH (**19a**, Table 6, entry 7). Interestingly, upon use of this substrate it was possible to derivatise the fully deprotected dipeptide, albeit with a limited conversion and yield. To evaluate the effect of the free N^{α}-amine of His in combination with the imidazole moiety, the *N*-terminal amine was acetylated (**19b**). As expected, acylation of the *N*-terminus led to higher conversion (Table 6, entry 8). A similar trend was observed for tripeptide H-Gly-His-Phe(4-I)-OH (**19c**) and the acylated equivalent (**19d**) (Table 6, entry 9-10). These results further indicated that an unprotected N^{α}-amine in combination with the unprotected imidazole of His is problematic for Suzuki-Miyaura reaction.

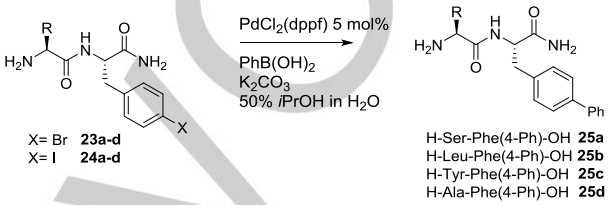
To check whether this dipeptide moiety is also problematic in longer peptide sequences, an earlier reported His-containing heptapeptide **21**[6a] was derivatised using $PdCl_2$(dppf) (**5a**) precatalyst (Scheme 2). Via use of 5 mol% of **2**, Barluenga and co-workers were able to achieve a HPLC conversion of 15-24% after 24 hours (depending on the boronic acid selected).[8a] Gratifyingly, using **5a** this unprotected peptide was functionalised with 50% conversion after 2 hours to **22**. Increased reaction times did, unfortunately, not further improve the conversion. This incomplete conversion is consistent with the results obtained for the unprotected His-Phe(4-I) containing dipeptides (**19a**,**b**) and tripeptides (**19c**,**d**) where no full conversion can be achieved (Table 6). This result shows that the imidazole moiety remains a troublesome functionality for palladium catalysed reactions, even upon elongation of the peptide substrates.



Scheme 2. Derivatisation of heptapeptide **21**, containing histidine and 4-iodophenylalanine using **5a** as precatalyst.

In addition to side chain primary amides, we verified whether *C*-terminal amides could also be used as substrates in the palladium-catalysed cross-coupling reactions (Table 7). With the classical catalyst systems (**1a**, **1b**, **2** or **4a**) we did not find any reaction product. This is all in line with the obtained results for Asn and Gln. However, by means of the ferrocene-based $PdCl_2$(dppf) (**5a**), conversion of H-Ser-Phe(4-X)-NH_2 (**23a** or **24a**) was only possible when the halogen moiety was iodine (entry 6). Excellent conversions were also observed with Leu, Tyr and Ala as the second amino acid component (entry 7-9). The brominated substrates (**23a-d**, entries 1-3) yielded side products only, whilst microwave heating did not improve the reaction outcome (entry 4 and 5).[28]

Table 7. Evaluation of *C*-terminal dipeptide amides (**23a-d**, **24a-d**) as substrates in Suzuki-Miyaura reaction.



Entry	Substrate	Conditions	Conv. (%)[a,b], Yield (%)
1	H-Ser-Phe(4-Br)-NH_2 (**23a**)	80°C, 24 h	No conv.
2	H-Leu-Phe(4-Br)-NH_2 (**23b**)	80°C, 24 h	No conv.
3	H-Tyr-Phe(4-Br)-NH_2 (**23c**)	80°C, 24 h	No conv.
4	H-Ala-Phe(4-Br)-NH_2 (**23d**)	MW, 140°C, 20 min	No conv.
5	H-Ala-Phe(4-Br)-NH_2 (**23d**)	MW, 140°C, 60 min	No conv.
6	H-Ser-Phe(4-I)-NH_2 (**24a**)	80°C, 6 h	95% (30%)[c]
7	H-Leu-Phe(4-I)-NH_2 (**24b**)	80°C, 2 h	99% (40%)
8	H-Tyr-Phe(4-I)-NH_2 (**24c**)	80°C, 2 h	95% (41%)
9	H-Ala-Phe(4-I)-NH_2 (**24d**)	80°C, 2 h	90% (49%)[c]

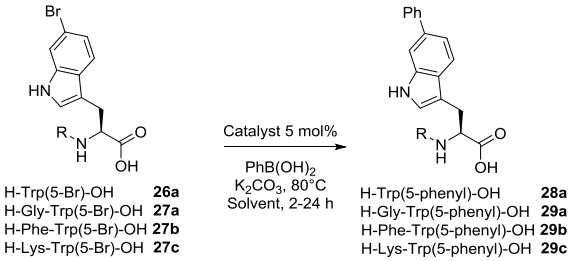
[a] Reaction conditions: Substrate (0.02 mmol, **23a-d** or **24 a**-**d**), 5 mol% **5a**, phenylboronic acid (2.5 eq), K_2CO_3 (5 eq), 50% *i*PrOH in H_2O (1 mL). [b] Measured by HPLC (215 nm, uncorrected). [c] Isolation by prep HPLC.

Evaluation of unprotected halotryptophan as substrates in Suzuki-Miyaura reactions.

In order to verify whether another aromatic core would present a similar reactivity, we evaluated brominated tryptophans that were readily available via a biotransformation protocol,[11a] and dipeptides containing this moiety as substrates (Table 8). Halotryptophans were previously investigated as substrates for Suzuki-Miyaura reaction.[5a,7a] In this work, various precatalysts on unprotected 5-bromotryptophan (**26a**) and selected tryptophan dipeptides were evaluated. High conversions on the unprotected dipeptides were obtained with the $[Na_2ADHP]_2Pd(OAc)_2$ precatalyst **1a** (Table 8, entry 1). In this case the $PdCl_2$(dppf) precatalyst **5a** however did not give rise to high conversions (Table 8, entry 6). In order to achieve

satisfactory conversion, the amount of $PhB(OH)_2$ had to be increased to 2.5 eq.

Table 8. Preliminary screening with 5-bromotryptophan (**26a**) and 5-bromotryptophan containing dipeptides (**27a-c**) as substrates in the Suzuki-Miyaura reaction.



H-Trp(5-Br)-OH **26a**
H-Gly-Trp(5-Br)-OH **27a**
H-Phe-Trp(5-Br)-OH **27b**
H-Lys-Trp(5-Br)-OH **27c**

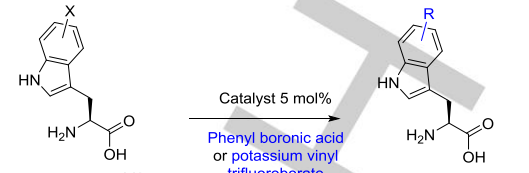
H-Trp(5-phenyl)-OH **28a**
H-Gly-Trp(5-phenyl)-OH **29a**
H-Phe-Trp(5-phenyl)-OH **29b**
H-Lys-Trp(5-phenyl)-OH **29c**

Entry	Cat.	Substrate	Solvent	Time /h	Conv. /% [a,b] Yield /%
1	**1a**	**26a**	H_2O	2 h	90% (54%)[c]
2	**1b**	**26a**	H_2O	2 h	57%
3	**2**	**26a**	H_2O	24 h	46%
4	**4a**	**26a**	H_2O	2 h	65%
5	**4b**	**26a**	H_2O	2 h	25%
6	**5a**	**26a**	aq. 50% *i*PrOH	2 h	9%
7	**1a**	**27a**	H_2O	2 h	89% (33%)[c]
8	**1a**	**27b**	H_2O	24 h	60% (24%)[c]
9	**1a**	**27c**	H_2O	4 h	80% (29%)[c]

[a] Reaction conditions: tryptophan bromide (**26a**, **27a-c**) (0.05-0.08 mmol), 5 mol% catalyst, phenylboronic acid (2.5 eq), K_2CO_3 (5 or 6 eq), H_2O (2 mL), 80°C. [b] Measured by HPLC (215 nm). [c] Isolated by preparative HPLC.

By using **1a** as a catalyst, it is now possible to isolate derivatised tryptophan dipeptides without protecting groups (**29a-c**). Furthermore, we verified whether this precatalyst was also able to perform the cross-coupling on other regioisomers of bromotryptophan (Table 9). Therefore, we tested 6-bromo- (**26b**) and 7-bromotryptophan (**26c**) and gratifyingly good conversions could be achieved (Table 9, entries 1 and 2). Access to 7-iodotryptophan (**30**)[11a] enabled the preparation of 7-vinyltryptophan (**31**), which in turn permits further derivatisation via the vinyl moiety (entry 4). In this case **5a** was a suitable precatalyst.

Table 9. Regioisomeric bromotryptophan (**26b**,**c**) and 7-IodoTrp (**30**) as substrates in the Suzuki-Miyaura reaction.



H-Trp(6-Br)-OH **26b**
H-Trp(7-Br)-OH **26c**
H-Trp(7-I)-OH **30**

H-Trp(6-Ph)-OH **28b**
H-Trp(7-Ph)-OH **28c**
H-Trp(7-vinyl)-OH **31**

Entry	Cat.	Substrate	Solvent	R	Conv. /% [a,b] Yield /%
1	**1a**	**26b**	H_2O	phenyl	70% (38%)[d]
2	**1a**	**26c**	H_2O	phenyl	95% (44%)[d]
3[c]	**5a**	**26c**	aq. 50% *i*PrOH	vinyl	No conversion
4[c]	**5a**	**30**	aq. 50% *i*PrOH	vinyl	80% (29%)[d]

[a] Reaction conditions: tryptophan halide (**26b-c**, **30**) (0.08 mmol), 5 mol% catalyst, phenylboronic acid (2.5 eq), K_2CO_3 (5 eq), H_2O (2 mL), 2 h, 80°C. [b] Measured by HPLC (215 nm, uncorrected). [c] Reaction time was 4 h. [d] Isolated by preparative HPLC.

Conclusions

A facile system for the derivatisation of unprotected halogenated phenylalanines, tryptophans and dipeptides, containing these amino acids, is described in water or mixed water/*i*PrOH as solvent. Compared to the previously reported catalytic systems for aqueous media, the $PdCl_2$(dppf) catalyst shows an increased tolerance for a broad range of side chain functionalities, including primary amide and imidazole moieties, without the need for protecting groups. Various (hetero)aromatic boronic acids reagents can be used and lead to molecules which can be used directly as building blocks in peptide synthesis. Interestingly, the $PdCl_2$(dppf) system also enabled access to unprotected vinylated amino acids.

Experimental Section

General

Column chromatography purifications were conducted with silica gel 60 (40-63 µm; Grace Davisil). TLC was carried out on glass plates precoated with silica gel 60F254 (Merck); the spots were visualised under UV light (λ= 254 nm) and/or a $KMnO_4$ (aq.) solution was used to reveal spots. The used HPLC system consisted of Waters 1525 Binary HPLC pumps and a Waters 2487 dual absorbance wavelength detector, with detection set at 215 nm and 254 nm, connected to an auto-sampler. All HPLC analyses were performed on this equipment, unless stated otherwise. Upon use of "system 2", a similar setup, without an auto-sampler, was used. A Grace Vydac C18 (25 cm x 4.6 mm x 5 µm) reversed phase column was employed in both systems. The solvent system consisted of water (with 0.1 % TFA)/acetonitrile (with 0.1 % TFA) mixtures. In general, the samples were dissolved in water/acetonitrile (1:1) and eluted with a standard gradient going from 3 % to 100 % AcN in 20 minutes, and with a flow rate of 1 ml/min. Preparative HPLC was conducted on a Gilson preparative HPLC system mounted with a Supelco Discovery Bio Wide Pore C18 column. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance DRX 250 console and a Bruker Avance II 500 console at 250 or 63 MHz and 500 or 126 MHz, respectively. The deuterated solvent is mentioned for each individual spectra. Chemical shifts (δ) are presented in parts per million (ppm), while coupling constants (*J*) are given in Hertz (Hz). High resolution mass spectrometry was conducted on a Waters Micromass QTof system in ES+ mode, using reserpine as the reference. Reagents were used as purchased from Sigma Aldrich (catalysts and general chemicals), Chemimpex (amino acid derivatives) or ABCR (general chemicals). The halogenated tryptophans were obtained via a biotransformation protocol as described in Smith. D. *et al.*[11a] The amino acids all possessed the L-configuration. The Suzuki-Miyaura reactions were run in mQ water and, where applicable, HPLC grade *i*PrOH was used.

Preparation of catalysts

All catalysts, except **1a**, **1b** and **3**, were used as obtained from their respective commercial source. Precatalyst **5b** was a kind gift from the ORSY research group, University of Antwerp. For **1a** and **1b,** the 0.01 M catalyst solution was prepared as described by Davis and coworkers.[5d] Sulfonated SPhos (**3**) was prepared starting from SPhos as described by Buchwald and coworkers.[3c] Spectra were consistent with literature data.[3c] Ligand **3** was obtained as a yellow solid in 82 % yield (102 mg). **MS (ES+):** 491 $[M+H^+]$ (MW 490.6 g/mol, as sulfonic acid; **^{1}H-NMR** (250 MHz, D_2O): δH 6.87-7.89 (6H, M), 3.70 (3H, s), 3.35 (3H, s), 0.87-2.01 (22H, m).

General procedure for the evaluation of ligands in the Suzuki-Miyaura coupling

To a solution of **6a-c** (25 mg, 0.102 mmol), K_2CO_3 (70.8 mg, 0.510 mmol) and phenylboronic acid (14.9 mg, 0.123 mol) in H_2O (2 mL) the respective catalyst (5 mol%, 5.1 µmol) was added. The solution was stirred for the reported reaction time (see Table 1) at 80°C in a sealed 10 mL vial. HPLC analysis was performed by taking an aliquot (10 µL) of the reaction mixture and further dilution to 1 mL with a H_2O/AcN (1:1) mixture.

Solvent ratio evaluation

A 10 mL microwave vial was charged with **6a** (50 mg, 0.205 mmol) or **8a** (50 mg, 0.145 mmol), phenylboronic acid (1.2 eq), K_2CO_3 (5 eq) and **5a** (1 mol%), and fitted with a stirring bar. A mixture of H_2O and *i*PrOH was added consecutively (to give a total volume of 4 mL, see Table 2). The reaction mixture was heated to 80°C for 24 (**6a**) or 2 hours (**8a**). HPLC analysis was performed by taking an aliquot (10 µL) of the reaction mixture and further dilution to 1 mL with a H_2O/AcN (1:1) mixture**.**

Evaluation of boronic acid scope with $PdCl_2$(dppf)

General procedure A

For unprotected substrates, **6a** (25 mg, 0.102 mmol) was dissolved together with the respective boronic acid (1.2 eq, 0.123 mmol), K_2CO_3 (70.8 mg, 0.510 mmol) and $PdCl_2$(dppf) **5a** (4.2 mg, 5.1 µmol) in a mixture of H_2O and *i*PrOH (1:1, total 2 mL). The 10 mL microwave vial was fitted with a stirring bar and closed with a crimp cap. The reaction mixture was heated to 80°C for 4 hours. After cooling to RT, the reaction mixture was concentrated by rotary evaporation. The residue was dissolved in H_2O (20 mL) and washed with CH_2Cl_2 (2x 10 mL). The aqueous phase was concentrated and redissolved in a mixture of H_2O and AcN (5:1) and purified by preparative HPLC (gradient 0-60 % AcN in H_2O over 20 mins, supplemented with 0.1 % TFA). The obtained solutions were lyophilised to obtain **7a-j** (TFA salts) as white powders.

General procedure B

For protected substrates, **8a** (688 mg, 2 mmol) was dissolved together with the respective boronic acid (1.2 eq, 2.4 mmol), K_2CO_3 (1.382 g, 10 mmol) and **5a** (16.5 mg, 0.02 mmol) in a mixture of H_2O and *i*PrOH (19:1, total 20 mL) in a 50 mL flask, equipped with a stirring bar and a reflux condenser. The reaction mixture was heated to 80°C for 60 mins. After cooling to RT, *i*PrOH was removed by rotary evaporation and carefully acidified with 5 N HCl to pH= 3, as indicated by pH paper. The aqueous phase was extracted with CH_2Cl_2 (4x 25 mL). The combined organic layers were dried over $MgSO_4$ and concentrated by evaporation. The crude was purified by column chromatography with a mixture of ethyl acetate and petroleum ether, supplemented with 2 % of acetic acid. The combined fractions were concentrated under high vacuum and lyophilised to obtain **9a-j** as white solids to yellow solids.

Preparation of H-Phe(4-phenyl)-OH (7a)

Compound **7a** was prepared via general procedure A to give a white powder in 48 % yield (16.6 mg). **HPLC:** t_R = 12.3 min; **HRMS:** $[M+H]^+$ calculated 242.1176 found 242.1177; **^{1}H-NMR** (500 MHz, CD_3OD): δH 7.59-7.65 (4H, m), 7.44 (2H, t, *J*= 7.6 Hz), 7.38 (2H, d, *J*= 8.1 Hz), 7.32-7.36 (1H, m), 4.24 (1H, t, *J*= 6.0 Hz), 3.37 (1H, dd, *J*=14.6 Hz, 5.0 Hz), 3.19 (1H, dd, *J*= 14.5 Hz, 7.7 Hz); **^{13}C-NMR** (63 MHz, DMSO-d_6): δC 170.4, 139.8, 139.1, 134.1, 130.1, 129.0, 127.5, 126.8, 126.6, 53.1, 35.5.

Preparation of H-Phe(3-phenyl)-OH (7b)

Compound **7b** was prepared according to general procedure A and obtained as a white powder in 41 % yield (14.3 mg). **HPLC:** t_R = 12.6 min; **HRMS:** $[M+H]^+$ calculated 242.1176 found 242.1190; **^{1}H-NMR** (500 MHz, DMSO-d_6): δH 7.66 (2H, d, *J*= 7.3 Hz), 7.54-7.58 (2H, m), 7.46 (2H, t, *J*= 7.6 Hz), 7.41 (1H, t, *J*= 7.9 Hz), 7.36 (1H, t, *J*= 7.3 Hz), 7.25 (1H, d, *J*= 7.5 Hz), 4.15 (1H, t, *J*= 6.1 Hz), 3.20 (1H, dd, *J*= 14.3 Hz, 5.6 Hz), 3.13 (1H, dd, *J*= 14.2 Hz, 6.7 Hz); **^{13}C-NMR** (126 MHz, DMSO-d_6): δC 170.4, 140.4, 140.1, 135.9, 129.1, 128.9, 128.6, 128.1, 127.5, 126.8, 125.5, 53.5, 36.0.

Preparation of H-Phe(2-phenyl)-OH (7c)

Compound **7c** was prepared according to general procedure A as a white powder in 38 % yield (13.0 mg). **HPLC:** t_R = 12.1 min; **HRMS:** $[M+H]^+$ calculated 242.1176 found 242.1167; **^{1}H-NMR** (500 MHz, DMSO-d_6): δH 8.13 (2H, br s), 7.26-7.47 (8H, M), 7.18 (1H, dd, *J*= 7.2 Hz, 1.4 Hz), 3.75 (1H, t, *J*= 7.6 Hz), 3.15 (1H, dd, *J*= 14.4 Hz, 7.6 Hz), 2.96 (1H, d, *J*= 14.4 Hz, 7.6 Hz); **^{13}C-NMR** (126 MHz, DMSO-d_6): δC 170.3, 142.1, 140.6, 132.7, 130.1, 129.7, 129.0, 128.3, 127.6, 127.1, 127.0, 52.6, 33.6.

Preparation of H-Phe(4-*p*-methoxyphenyl)-OH (7d)

Compound **7d** was prepared according to general procedure A as a white powder in 33 % yield (12.6 mg). **HPLC:** t_R = 12.3 min; **HRMS:** $[M+H]^+$ calculated 272.1281 found 272.1286. **^{1}H-NMR** (500 MHz, DMSO-d_6): δH 8.31 (2H, br s), 7.54-7.63 (4H, m), 7.31 (2H, d, *J*= 7.1 Hz), 7.01 (2H, d, *J*= 8.8 Hz), 4.21 (1H, t, *J*= 6.3 Hz), 3.78 (3H, s), 3.08-3.15 (2H, m);**^{13}C-NMR** (126 MHz, DMSO-d_6): δC 170.4, 158.9, 138.7, 133.2, 132.1, 130.0, 127.6, 126.3, 114.4, 55.2, 53.1, 35.4.

Preparation of H-Phe(4-*p*-trifluoromethylphenyl)-OH (7e)

Compound **7e** was prepared according to general procedure A as a white powder in 45 % yield (18.6 mg). **HPLC:** t_R = 14.1 min; **HRMS:** $[M+H]^+$ calculated 310.1049 found 310.1053. **^{1}H-NMR** (250 MHz, DMSO-d_6): δH ppm 8.36 (2H, br s), 7.89 (2H, d, *J*= 8.2 Hz), 7.80 (2H, d, *J*= 8.4 Hz), 7.72 (2H, d, *J*= 8.0 Hz), 7.40 (2H, d, *J*= 8.1 Hz), 4.24 (1H, t, *J*= 6.2 Hz), 3.16 (2H, d, *J*= 6.2 Hz); **^{13}C-NMR** (63 MHz, DMSO-d_6): δC 170.4, 143.7, 137.4, 135.4, 130.3, 127.3, 127.2, 125.8 (d, *J*= 3.7 Hz), 53.1, 35.5. Some quaternary carbons not observed.

Preparation of H-Phe(4-*o*-tolyl)-OH (7f)

Compound **7f** was prepared according to general procedure A as a white powder in 60 % yield (21.8 mg). **HPLC:** t_R = 12.8 min; **HRMS:** $[M+H]^+$ calculated 256.1332 found 256.1328; **^{1}H-NMR** (500 MHz, DMSO-d_6): δH 8.41 (2H, br s), 7.21-7.35 (7H, m), 7.16 (1H, d, *J*= 6.0 Hz), 4.13-4.20 (1H, m), 3.15 (2H, m), 2.22 (3H, s); **^{13}C-NMR** (126 MHz, DMSO-d_6): δC 170.5, 140.9, 140.0, 134.7, 133.7, 130.4, 129.3, 129.1, 127.3, 125.9, 53.4, 35.6, 20.2.

Preparation of H-Phe(4-indol-5-yl)-OH (7g)

Compound **7g** was prepared according to general procedure A as a white powder in 37 % yield (14.5 mg). **HPLC:** t_R = 11.7 min; **HRMS:** $[M+H]^+$ calculated 281.1285 found 281.1288; **^{1}H-NMR** (500 MHz, DMSO-d_6): δH 11.1 (1H, m), 10.98 (1H, s), 8.29 (2H, br s), 7.59-7.83 (2H, M), 7.52-7.57 (1H, m), 7.42-7.48 (1H, M), 7.22-7.41 (5H, M), 4.16-4.25 (1H, m), 3.06-3.15 (2H, m, overlap with H_2O); **^{13}C-NMR** (126 MHz, DMSO-d_6): δC 170.4, 140.8, 136.5, 135.5, 132.5, 129.9, 126.8, 126.1, 125.8, 120.2, 117.9, 111.8, 101.5, 53.2, 35.4.

Preparation of H-Phe(4-furan-3-yl)-OH (7h)

Compound **7h** was prepared according to general procedure A as a white powder in 33 % yield (11.0 mg). **HPLC:** t_R = 11.0 min; **HRMS:** $[M+H]^+$ calculated 232.0968 found 232.0965; **^{1}H-NMR** (500 MHz, DMSO-d_6): δH 8.25 (2H, br s), 8.18 (1 H, s), 7.73 (1H, s), 7.58 (1H, d, *J*= 7.9 Hz), 7.26 (2H, d, *J*= 8.1 Hz), 6.95 (1H, s), 4.16-4.24 (1 H, m), 3.05-3.12 (2H, m); **^{13}C-NMR** (63 MHz, DMSO-d_6): δC 170.4, 144.3, 139.2, 134.0, 130.8, 130.0, 125.7, 125.6, 108.7, 53.7, 35.8.

Preparation of H-Phe(4-thien-3-yl)-OH (7i)

Compound **7i** was prepared according to general procedure A as a white powder in 39 % yield (13.7 mg). **HPLC:** t_R = 11.9 min; **HRMS:** $[M+H]^+$ calculated 248.0740 found 248.0732; **^{1}H-NMR** (500 MHz, DMSO-d_6): δH 8.36 (2H, br s), 7.85 (1H, d, *J*= 1.5 Hz), 7.67 (2H, d, *J*= 7.9 Hz), 7.59-7.64 (1H, m), 7.49-7.58 (1H, d, *J*= 4.7 Hz), 7.29 (2H, d, *J*= 7.5 Hz), 4.11-4.25 (1H, m), 3.06-3.17 (2H, m); **^{13}C-NMR** (126 MHz, DMSO-d_6): δC 170.2, 141.0, 134.0, 133.6, 129.9, 127.0, 126.1, 126.0, 120.7, 53.1, 35.4.

Preparation of H-Phe(4-vinyl)-OH (7j)

Compound **7j** was prepared according to general procedure A from **10a** (29.8 mg, 0.102 mmol) as a white powder in 40 % yield (11.8 mg). **HPLC:** t_R = 11.7 min; **HRMS:** $[M+H]^+$ calculated 192.1019 found 192.1009; **^{1}H-NMR** (500 MHz, DMSO-d_6): δH 8.27 (2H, br s), 7.43 (2H, d, *J*= 7.9 Hz), 7.23 (2H, d, *J*= 7.9 Hz), 6.72 (2H, dd, *J*= 17.6 Hz, 11.0 Hz), 5.82 (1H, d, *J*= 17.5 Hz), 5.24 (1H, d, *J*= 11.1 Hz), 4.14 (1H, t, *J*= 6.3 Hz), 3.03-3.12 (2H, m); **^{13}C-NMR** (126 MHz, DMSO-d_6): δC 170.3, 136.3, 136.1, 134.6, 129.7, 126.3, 114.2, 53.2, 35.6.

Preparation of Boc-Phe(4-phenyl)-OH (9a)

Compound **9a** was prepared according to general procedure B as a white solid in 83 % yield (565 mg). The crude was purified with silica column chromatography with petroleumether/EtOAc 2:1 + 2 % AcOH. **R_f:** 0.26 (p.e./EtOAc 2:1 + 2 % AcOH); **HPLC:** t_R = 17.6 min; **HRMS:** $[M+Na]^+$ calculated 364.1519 found 364.1532; **^{1}H-NMR** (250 MHz, DMSO-d_6): δH 12.62 (1H, br s), 7.63 (2H, d, *J*= 8.0 Hz), 7.57 (2H, d, *J*= 8.0 Hz), 7.39-7.48 (2H, m), 7.27-38 (3H, m), 7.14 (1H, d, *J*= 8.4 Hz), 4.11 (1H, td, *J*= 9.2 Hz, 4.5 Hz), 3.05 (1H, dd, *J*= 13.7 Hz, 4.4 Hz), 2.85 (1H, dd, *J*= 13.4 Hz, 10.6 Hz), 1.31 (9H, s); **^{13}C-NMR** (63 MHz, DMSO-d_6): δC 173.6, 155.5, 140.0, 138.2, 137.3, 129.7, 128.9, 127.2, 126.5, 126.4, 78.1, 55.1, 36.0, 28.1.

Preparation of Boc-Phe(4-*p*-methoxyphenyl)-OH (9b)

Compound **9b** was prepared according to general procedure B as a white solid in 88 % yield (652 mg). The crude was purified with silica column chromatography with petroleumether/EtOAc 3:1 + 2 % AcOH). **R_f:** 0.30 (p.e./EtOAc 2:1 + 2 % AcOH); **HPLC:** t_R = 17.4 min; **HRMS:** $[M+Na]^+$ calculated 394.1625 found 394.1631; **^{1}H-NMR** (250 MHz, DMSO-d_6): δH 12.60 (1H, br), 7.57 (2H, d, *J*= 8.5 Hz), 7.51 (2H, d, *J*= 8.1 Hz), 7.29 (2H, d, *J*= 8.0 Hz), 7.11 (1H, d, *J*= 8.2 Hz), 6.99 (2H, d, *J*= 8.6 Hz), 4.03-4.17 (1H, m), 3.77 (3H, s), 3.03 (1H, dd, *J*= 13.7 Hz, 4.3 Hz), 2.84 (1H, dd, *J*= 13.4 Hz, 10.6 Hz), 1.31 (9H, s); **^{13}C-NMR** (63 MHz, DMSO-d_6): δC 173.6, 158.8, 155.5, 137.9, 136.5, 132.4, 129.6, 127.6, 125.9, 114.3, 78.0, 55.2, 55.1, 36.0, 28.2.

Preparation of Boc-Phe(4-*p*-trifluoromethylphenyl)-OH (9c)

Compound **9c** was prepared according to general procedure B as a white solid 79 % yield (644 mg). The crude was purified with silica column chromatography with petroleumether/EtOAc 4:1 +2 % AcOH). **R_f:** 0.30 (p.e./EtOAc 3:1 + 2 % AcOH); **HPLC:** t_R = 19.0 min; **HRMS:** $[M-Boc]^+$ calculated 310.1049 found 310.1062; **^{1}H-NMR** (250 MHz, DMSO-d_6): δH 12.65 (1H, s), 7.87 (2H, d, *J*= 8.4 Hz), 7.78 (2H, d, *J*= 8.5 Hz), 7.66 (2H, d, *J*= 8.1 Hz), 7.38 (2H, d, *J*= 8.1 Hz), 7.17 (1H, d, *J*= 8.5 Hz), 4.12 (1H, td, *J*= 9.5 Hz, 4.3 Hz), 3.07 (1H, dd, *J*= 13.8 Hz, 4.3 Hz), 2.87 (1H, dd, *J*= 13.6 Hz, 10.7 Hz), 1.30 (9H, s); **^{13}C-NMR** (63 MHz, DMSO-d_6): δC 173.5, 155.5, 144.0, 138.6, 136.6, 129.9, 127.3, 126.8, 125.8 (d, *J*= 3.7 Hz), 78.1, 55.1, 361, 28.2; **^{19}F-NMR** (236 MHz, DMSO-d_6) δF -60.83. Some quaternary carbons not observed.

Preparation of Boc-Phe(4-*o*-tolyl)-OH (9d)

Compound **9d** was prepared according to general procedure B as a white powder in 85 % yield (603 mg). The crude was purified with silica column chromatography with petroleumether/EtOAc 4:1 + 2 % AcOH). **R_f:** 0.31 (p.e./EtOAc 3:1 + 2 % AcOH); **HPLC:** t_R = 18.3 min; **HRMS:** $[M+Na]^+$ calculated 378.1676 found 378.1666; **^{1}H-NMR** (250 MHz, DMSO-d_6): δH 12.63 (1H, br s), 7.07-7.40 (9H, M), 4.03-4.24 (1H, m), 3.07 (1H, dd, *J*= 13.8 Hz, 4.2 Hz), 2.86 (1H, dd, *J*= 13.4 Hz, 11.0 Hz), 2.20 (3H, s), 1.31 (9H, s); **^{13}C-NMR** (63 MHz, DMSO-d_6): δC 173.6, 155.5, 141.1, 139.3, 136.7, 134.7, 130.3, 129.5, 129.0, 128.7, 127.2, 125.9, 78.0, 55.0, 36.2, 28.1, 20.2.

Preparation of Boc-Phe(4-indol-5-yl)-OH (9e)

Compound **9e** was prepared according to general procedure B as a white powder in 89 % yield (676 mg). The crude was purified with silica column chromatography with petroleumether/EtOAc 2:1 +2 % AcOH). **R_f:** 0.51 (p.e./EtOAc 1:1+ 2 % AcOH); **HPLC:** t_R = 16.2 min; **HRMS:** $[M+Na]^+$ calculated 403.1628 found 403.1622; **^{1}H-NMR** (250 MHz, DMSO-d_6): δH 12.67 (1H, br s), 11.12 (1H, br s), 7.77 (s, 1H), 7.56 (2H, d, *J*= 8.0 Hz), 7.41-7.48 (1H, m), 7.22-7.40 (4H, M), 7.09 (1H, d, *J*= 8.2 Hz), 6.46 (1H, s), 4.11 (1H, td, *J*= 9.0 Hz, 4.5 Hz), 3.05 (1H, dd, *J*= 13.7 Hz, 4.4 hz), 2.85 (1H, dd, *J*= 13.6 Hz, 10.3 Hz), 1.32 (9H, s); **^{13}C-NMR** (63 MHz, DMSO-d_6): δC 173.6, 155.5, 139.9, 135.9, 135.4, 131.2, 129.5, 128.2, 126.4, 126.0, 120.2, 117.9, 111.7, 101.5, 78.0, 55.3, 36.1, 28.2.

Preparation of Boc-Phe(4-furan-3-yl)-OH (9f)

Compound **9f** was prepared according to general procedure B as a white powder in 84 % yield (557 mg). The crude was purified with silica column chromatography with petroleumether/EtOAc 1:1 + 2 % AcOH). **R_f:** 0.20 (p.e./EtOAc 1:1 + 2 % AcOH); **HPLC:** t_R = 16.5 min; **HRMS:** $[M+Na]^+$ calculated 354.1312 found 354.1328; **^{1}H-NMR** (250 MHz, DMSO-d_6): δH 12.61 (1H, br s), 8.13 (1H, s), 7.71 (1H, s), 7.51 (2H, d, *J*= 8.0 Hz), 7.25 (2H, d, *J*= 8.0 Hz), 7.10 (1H, d, *J*= 8.3 Hz), 6.92 (1H, m), 4.09 (1H, m), 3.01 (1H, dd, *J*= 13.8 ,4.5 Hz), 2.83 (1H, dd, *J*= 13.8 ,10.4 Hz), 1.31 (9H, s); **^{13}C-NMR** (63 MHz, DMSO-d_6): δC 173.6, 155.5, 144.2, 139.0, 136.7, 130.0, 129.6, 125.7, 125.3, 108.7, 78.1, 55.2, 36.1, 28.2.

Preparation of Boc-Phe(4-thien-3-yl)-OH (9g)

Compound **9g** was prepared according to general procedure B as a white powder in 89 % yield (618 mg). The crude was purified with silica column chromatography with petroleumether/EtOAc 2:1 + 2 % AcOH). **R_f:** 0.39 (p.e./EtOAc 1:1 + 2 % AcOH); **HPLC:** t_R = 17.1 min; **HRMS:** $[M+Na]^+$ calculated 370.1083 found 370.1070; **^{1}H-NMR** (250 MHz, DMSO-d_6): δH 12.62 (1H, s), 7.81 (1H, m), 7.50-7.65 (4H, M), 7.27 (2H, d, *J*= 8.0 Hz), 7.11 (1H, d, *J*= 8.4 Hz), 4.03-4.14 (1H, m), 3.02 (1H, dd, *J*= 13.6 Hz, 4.3 Hz), 2.83 (1H, dd, *J*= 13.4 Hz, 10.7 Hz), 1.31 (9H, s); **^{13}C-NMR** (63 MHz, DMSO-d_6): δC 173.6, 155.5, 141.3, 136.9, 133.3, 129.6, 127.0, 126.1, 125.9, 120.5, 78.1, 55.2, 36.1, 28.2.

Preparation of Boc-Phe(4-vinyl)-OH (9h)

Compound **11a** was dissolved (782 mg, 2 mmol) together with potassium vinyltrifluoroborate (321 mg, 2.4 mmol), K_2CO_3 (1.382 mg, 10 mmol) and **5a** (16.5 mg, 0.02 mmol) in a mixture of H_2O and *i*PrOH (1:1, total 20 mL). The solution was heated to 80°C for 1 hour. Work-up was similar as described in general procedure B. The crude was purified by silica column chromatography (CH_2Cl_2/MeOH/AcOH 97:1:2) and lyophilised. **9h** was obtained as a yellow solid in 81 % yield (471 mg). **R_f:** 0.25 (CH_2Cl_2/MeOH/AcOH 97:1:2). **HPLC:** t_R = 16.9 min; **HRMS:** $[M+Na]^+$ calculated 314.1363 found 314.1378; **^{1}H-NMR** (500 MHz, DMSO-d_6): δH 12.56 (1H, br s), 7.36 (2H, d, *J*= 7.5 Hz), 7.20 (2H, d, *J*= 7.5 Hz), 7.07 (1H, d, *J*=8.3 Hz), 6.68 (1H, dd, *J*= 17.4 Hz, 11.0 Hz), 5.77 (1H, d, *J*= 17.5 Hz), 5.19 (1H, d, *J*= 10.9 Hz), 4.01-4.12 (1H, m), 2.98 (1H, dd, *J*=13.7 Hz, 3.9 Hz), 2.80 (1H, dd, *J*= 12.9 Hz, 10.8 Hz,) 1.30 (9H, s). **^{13}C-NMR:** (126 MHz, DMSO-d_6): δC: 173.6, 137.9, 136.5, 135.3, 129.4, 126.0, 113.7, 78.1, 55.1, 36.2, 28.2.

Preparation of Boc-Phe(3-vinyl)-OH (9i)

Compound **9i** was prepared starting from **11b** following the procedure as described for **9h**. After column chromatography, the product was obtained as a white solid in 89 % yield (520 mg). **R_f:** 0.22 (CH_2Cl_2/MeOH/AcOH 97:1:2); **HPLC:** t_R = 16.9 min; **HRMS:** $[M+Na]^+$ calculated 314.1363 found 314.1377; **^{1}H-NMR** (500 MHz, $CDCl_3$): δH 10.72 (1H, br s), 7.23-7.32 (3H, M), 7.10 (1H, s), 6.70 (1H, dd, *J*= 17.5 Hz, 10.9 Hz), 6.58-6.63 (1H, m, [B])*, 5.75 (1H, d, *J*= 17.5 Hz), 5.25 (1H, d, *J*= 10.9 Hz), 5.02 (1H, d, *J*= 6.2 Hz, [A])*, 4.59-4.67 (1H, m, [A])*, 4.38-4.46 (1H, m, [B])*, 3.17-3.25 (1H, m), 3.05-3.12 (1H, m, [A])*, 2.87-2.95 (1H, m, [B])*, 1.43 (9H, s, [A])*, 1.29 (9H, s, [B])*; **^{13}C-NMR** (126 MHz, $CDCl_3$): δC 176.7 [A] and 176.3 [B]*, 156.8 [B] and 155.6 [A]*, 137.8, 136.6, 136.1, 129.0, 128.7, 127.3, 124.9 [A] and 124.8 [B]*, 114.0, 81.6 [B] and 80.3 [A]*, 56.0 [A] and 54.2 [B]*, 39.2 [A] and 37.7 [B]*, 28.3 [A] and 27.9 [B]*. *Rotamers observed on ^{1}H-NMR and ^{13}C-NMR. At 25°C, two rotamers ([A]: major, [B]: minor) in approximately 64:36 ratio were visible**.**

Preparation of Boc-Phe(2-vinyl)-OH (9j)

Compound **9j** was prepared starting from **11c** following the procedure as described for **9h**. After column chromatography, the product was obtained as a white solid in 89 % yield (517 mg). **R_f:** 0.24 (CH_2Cl_2/MeOH/AcOH 97:1:2); **HPLC:** t_R = 17.0 min; **HRMS:** $[M+Na]^+$ calculated 314.1363 found 314.1367; **^{1}H-NMR** (500 MHz, $CDCl_3$): δH 11.56 (1H, br s), 7.52-7.59 (1H, m), 7.18-7.32 (4H, M), 7.04-7.16 (1H, m), 5.68-5.77 (1H, m), 5.38 (1H, d, *J*= 10.9 Hz), 5.05 (1H, d, *J*= 7.3 Hz, [B]), 4.61 (1H, m, [B]), 4.45-4.52 (1H, m, [A]),1.44 (9H, s, [B]), 1.17 (9 H, s, [A]); **^{13}C-NMR** (63 MHz, DMSO-d_6): δC 176.6 [B] and 175.5 [A]*, 156.7 [A] and 155.2 [B]*, 137.5 [B] and 137.2 [A]*, 134.4 [A] and 133.4 [B]*, 134.2 [B] and 133.9 [A]*, 131.1 [A] and 130.3 [B]*, 127.8, 127.4 [B] and 127.2 [A], 126.2 [B] and 125.7 [A]*, 116.6 [B] and 116.1 [A]*, 81.3 [A] and 80.1 [B]*, 55.2 [A] and 54.2 [B]*, 38.1 [A] and 35.3 [B]*, 28.5 [B] and 28.0 [A]*. *Rotamers observed on ^{1}H-NMR and ^{13}C-NMR. At 25°C, two rotamers ([A]: major, [B]: minor) in approximately 66:33 ratio were visible.

Dipeptide experiments with 0.01 M $[Na_2(ADHP)]_2.Pd(OAc)_2$

Dipeptide synthesis of H-AA-Phe(4-Br)-OH (12a-12m)

Dipeptide carboxylic acids were synthesised on 2-Cl-tritylchloride resin (obtained from GL Biochem or Chemimpex) following standard Fmoc-based solid-phase peptide synthesis (SPPS) in a polypropylene syringe with polyethylene frit using SPPS grade CH_2Cl_2 or DMF. The protocol was started by swelling the resin in DMF for 30 mins and followed by coupling the first amino acid (Fmoc-4-Br-Phe, 2 eq) with DIPEA (4 eq) in DMF for 90 mins. Reagents were filtered and the resin was washed with DMF, *i*PrOH and CH_2Cl_2 (each 3x 1 min). The resin was treated with a mixture of MeOH, CH_2Cl_2 and DIPEA (2:17:1) for endcapping (4x 5 min). After washing, the Fmoc protecting group was removed by treating the resin with 20 % 4-methylpiperidine in DMF (5 min, 15 min). After washing, the second amino acid (either as Boc-AA-OH or Fmoc-AA(Pg)-OH was coupled (3 eq) with HCTU (3 eq) in 0.4 M NMM for 60 mins. The excess reagents were removed by filtration and the resin was washed. The Kaiser ninhydrin test was used to check for complete conversion. If complete coupling was observed, the resin was treated with 20 % 4-methylpiperidine in DMF (in the case Boc-AA-OH was coupled, this

deprotection step was not necessary) for 5 mins and 15 mins. Upon completion of the peptide assembly, the resin was washed and treated with a standard cleavage cocktail (95 % TFA and 5 % H_2O)[1] for 2 hours.[2] The deprotected peptide was collected by filtration, concentrated in vacuo and purified over a C-18 cartridge (Supelco) while eluting with H_2O/AcN (5:1). Afterwards, the dipeptides were lyophilised and obtained as white to off-white powders, identification and purity were determined by HPLC and LC/MS analysis. As such, the dipeptides were prepared as their corresponding TFA salts.

[1]In the case of Trp, Asn, His, Arg the cleavage cocktail was altered to 95 % TFA, 2.5 % H_2O and 2.5 % triethylsilane.
[2]3 hours in the case of Arg for complete pbf deprotection.

Entry	Peptide	MW (g/mol)	LC/MS $[M+H,^{81}Br]^+$	HPLC (min) [a]
1	H-Gly-Phe(4-Br)-OH **12a**	301.1	303	9.2
2	H-Ala-Phe(4-Br)-OH **12b**	315.2	317	9.2
3	H-Leu-Phe(4-Br)-OH **12c**	357.2	359	10.5
4	H-Ser-Phe(4-Br)-OH **12d**	331.2	333	9.1
5	H-Asp-Phe(4-Br)-OH **12e**	359.2	361	9.3
6	H-Lys-Phe(4-Br)-OH **12f**	372.3	374	8.6
7	H-Phe-Phe(4-Br)-OH **12g**	391.3	393	10.7
8	H-Tyr-Phe(4-Br)-OH **12h**	407.3	409	9.9
9	H-Trp-Phe(4-Br)-OH **12i**	430.3	432	11.2
10	H-Asn-Phe(4-Br)-OH **12j**	358.2	360	9.1
11	H-Met-Phe(4-Br)-OH **12k**	375.3	377	10.2
12	H-His-Phe(4-Br)-OH **12l**	381.2	383	8.6
13	H-Arg-Phe(4-Br)-OH **12m**	400.3	402	8.9

[a] Measured by HPLC system 2 (215 nm).

Suzuki-Miyaura derivatisation of dipeptides 12a-12m

In a 10 mL vial, dipeptide bromide (**12a-12m**, 0.063 mmol) was dissolved in H_2O (1.7 mL) together with phenylboronic acid (19.1 mg, 0.157 mmol), K_2CO_3 (43.4 mg, 0.312 mmol or 52.1 mg, 0.374 mmol for entries 6, 12 and 13). The vial was fitted with a stirring bar and the 0.01 M **1a** solution (315 µL, 3.15 µmol) was added with a syringe. The reaction mixture was heated to 80°C. Reaction follow-up was performed by HPLC analysis at 215 nm. For this analysis, 10 µL aliquot of the reaction mixture was diluted to 1 mL with H_2O/AcN (1:1). Conversion was calculated based on the area under the curve (at 215 nm) by comparison of starting product and cross-coupled product peak surface area. LC/MS analysis was performed on the crude mixtures to identify the cross-coupled products.

Entry	Peptide	MW (g/mol)	LC/MS $[M+H]^+$	HPLC (min) [a]
1	H-Gly-Phe(4-phenyl)-OH **13a**	298.3	299	10.8
2	H-Ala-Phe(4-phenyl)-OH **13b**	312.4	313	10.9
3	H-Leu-Phe(4-phenyl)-OH **13c**	354.5	355	11.7
4	H-Ser-Phe(4-phenyl)-OH **13d**	328.4	329	10.7
5	H-Asp-Phe(4-phenyl)-OH **13e**	356.4	357	10.9
6	H-Lys-Phe(4-phenyl)-OH **13f**	369.5	370	10.2
7	H-Phe-Phe(4-phenyl)-OH **13g**	388.5	389	12.0
8	H-Tyr-Phe(4-phenyl)-OH **13h**	404.5	405	11.4
9	H-Trp-Phe(4-phenyl)-OH **13i**	427.7	428	12.3
10	H-Asn-Phe(4-phenyl)-OH **13j**	**No coupling observed**		
11	H-Met-Phe(4-phenyl)-OH **13k**	372.5	373	11.6
12	H-His-Phe(4-phenyl)-OH **13l**	**No coupling observed**		
13	H-Arg-Phe(4-phenyl)-OH **13m**	397.4	398	10.4

[a] Measured by HPLC system 2 (215 nm).

Synthesis and derivatisation of protected and partially unprotected Asn-Phe(4-Br) and His-Phe(4-X) dipeptides

Preparation of Boc-Asn-Phe(4-Br)-OMe (14a)

Compound **6a** (2.44 g, 10 mmol) was dissolved in MeOH (20 mL, HPLC grade) in a 50 mL flask, equipped with a stirring bar. The reaction mixture was cooled to 0°C by means of water/ice bath and distilled $SOCl_2$ (2.5 eq, 1.82 mL, 25 mmol) was added dropwise. After complete addition, the water/ice bath was removed and the flask was equipped with a reflux condenser and heated to 45°C for overnight reaction. Conversion was checked by HPLC and the reaction mixture was concentrated by rotary evaporation. The pale yellow solid was washed thoroughly with cold diethylether and dried overnight with a high vacuum pump. H-Phe(4-Br)-OMe was obtained as a pale white solid in 97 % yield (2.86 g, obtained as the HCl salt). **HPLC:** t_R = 9.3 min (system 2); **MS (ES+):** 260 $[M+H^+, {}^{81}Br]$, 258 $[M+H^+, {}^{79}Br]$ (MW 258.1 g/mol); **^{1}H-NMR** (250 MHz, $CDCl_3$): δH 7.45 (2H, d, *J*= 15.0 Hz), 7.06 (2H, d, *J*= 15.0 Hz), 4.22 (1H, t, *J*= 4.0 Hz), 3.70 (3H, s), 3.20 (2H, d, *J*= 4.0 Hz); **^{13}C-NMR** (63 MHz, $CDCl_3$): 169.2, 132.3, 132.2, 130.9, 122.2, 54.0, 53.3, 35.6.

Spectra for HCl.H-Phe(4-Br)-OMe were consistent with literature data.[29]

To a solution of HCl.H-Phe(4-Br)-OMe (1.5 g, 5.09 mmol), Boc-Asn-OH (1.42 g, 6.11 mmol) and HOBt (1.25 g, 8.15 mmol) in CH_2Cl_2 (20 mL, SPPS grade) was added DIPEA (2.66 mL, 15.28 mmol). The reaction mixture was cooled with a water/ice bath to 0°C and a solution of EDC.HCl (1.56 g, 8.15 mmol) in CH_2Cl_2 (5 mL, SPPS grade) was added dropwise. After complete addition, the reaction mixture was allowed to warm to room temperature and stirred for 16 h. The obtained cloudy solution was diluted with CH_2Cl_2 (25 mL) and filtered over a glass frit. The organic phase was washed with saturated NH_4Cl (2x 25 mL), aq. sat. $NaHCO_3$ (2x 25 mL), water (2x 25 mL) and brine (1x 25 mL). The solution was dried over $MgSO_4$ and concentrated by evaporation. The crude was suspended in a minimal amount of methanol and filtered over a glass frit. After drying overnight with a high vacuum pump, **14a** was obtained as a white solid in 65 % yield (1.65 g). **HPLC:** t_R = 14.8 min; **MS (ES+):** 474 $[M+H^+, {}^{81}Br]$, 472 $[M+H^+, {}^{79}Br]$ (MW: 472.3 g/mol); **^{1}H-NMR** (250 MHz, DMSO-d_6): δH 8.14 (1H, d, *J*= 7.4 Hz), 7.43 (2H, d, *J*= 8.2 Hz), 7.28 (1H, br s), 7.16 (2H, d, *J*= 9.0 Hz), 6.85-6.90 (2H, M), 4.44 (1H, dd, *J*= 13.8 Hz, 6.9 Hz), 4.24 (1H, dd, *J*= 13.8 Hz, 7.8 Hz), 3.58 (3H, s), 2.86-3.03 (2H, m), 2.30 (2H, m), 1.35 (9H, s); **^{13}C-NMR** (63 MHz, DMSO-d_6): δC 171.8, 171.5, 171.3, 155.0, 136.4, 131.5, 131.1, 119.8, 78.2, 53.2, 51.9, 51.2, 37.2, 35.8, 28.2.

Preparation of Boc-Asn-Phe(4-Br)-OH (14b)

Compound **14a** (150 mg, 0.318 mmol) was dissolved in a mixture of THF/H_2O (total 2 mL, 7:1) in a 10 mL flask. To this solution was added LiOH monohydrate (93 mg, 2.223 mmol) and formic acid (17 µL, 0.445 mmol). The reaction mixture was stirred for 16 hours. After complete conversion of starting material, the reaction mixture was concentrated by evaporation and resuspended in H_2O (10 mL). The aqueous phase was washed with CH_2Cl_2 (2x 5 mL) and was acidified with 1 N HCl to pH = 3, as indicated by pH paper. The aqueous layer was extracted with CH_2Cl_2 (4x 10 mL) and the combined organic layers were collected and washed with brine (1x 20 mL) and dried over $MgSO_4$. The product was concentrated by evaporation and dissolved in water with a minimal amount of AcN. After lyophilisation, **14b** was obtained as a white powder in 74 % yield (107 mg). **HPLC**: t_R = 13.9 min; **MS (ES+):** 460 $[M+H^+, {}^{81}Br]$, 458 $[M+H^+, {}^{79}Br]$ (MW: 458.3 g/mol); **^{1}H-NMR** (250 MHz, DMSO-d_6): δH 7.27-7.39 (4H, M), 7.03 (2H, d, *J*= 8.2 Hz), 6.86 (1H, s), 4.09-4.17 (1H, m), 3.87 (1H, dd, *J*= 10.2 Hz, 4.7 Hz), 3.02 (1H, dd, *J*= 13.1 Hz, 4.9 Hz), 2.90 (1H, dd, *J*= 13.0 Hz, 4.6 Hz), 2.28-2.44 (2H, m), 1.34 (9H, s); **^{13}C-**

NMR (63 MHz, DMSO-d_6): 171.8, 171.3, 170.2, 155.0, 138.4, 132.1, 130.2, 118.7, 78.2, 55.1, 51.8, 37.2, 36.1, 28.1.

Suzuki-Miyaura derivatisation of Asn-Phe dipeptides (14a,b and 12j, n): General procedure C

In a 10 mL MW vial, the dipeptide bromide (0.055 mmol) was dissolved together with phenylboronic acid (16.6 mg, 0.136 mmol) and K_2CO_3 (37.7 mg, 0.273 mmol or 45.6 mg, 0.330 mmol for **12j, n**) in a mixture of H_2O and *i*PrOH (1:1, total 2 mL). Formic acid (2 µL, 0.055 mmol) was added to the reaction mixture. The catalyst was added in the respective amount (5 mol% to 100 mol%, see Table 5). The vial was equipped with a stirring bar, closed with a crimp cap and heated to 80°C. Conversion of the reaction was monitored by HPLC (215 nm). If satisfactory conversion was obtained (only with **5a**), the reaction mixture was allowed to cool to room temperature, concentrated and redissolved in 5 mL of H_2O.

Preparation of Boc-Asn-Phe(4-phenyl)-OMe (17a)

Derivatisation of **14a** (26 mg, 0.055 mmol) was performed as described in general procedure C. The aqueous phase was extracted with CH_2Cl_2 (3x 5 mL). The combined organic layers were combined and dried over $MgSO_4$. The reaction mixture was concentrated by evaporation and resuspended in H_2O with a minimal amount of AcN (total 4 mL). The product was purified by prep HPLC and obtained as a white powder after lyophilisation. Concomitant hydrolysis to **14b** was observed by LC/MS analysis. Further characterisation indicated that the product was hydrolysed.

Preparation of Boc-Asn-Phe(4-Phenyl)-OH (17b)

Derivatisation of **14b** (25 mg, 0.055 mmol) was performed as described in general procedure C using **5a** (5 mol%, 2.3 mg, 2,75 µmol). After redissolving the crude in H_2O, the mixture was acidified with 1N HCl to pH= 3, as indicated by pH paper and extracted with CH_2Cl_2 (3x 5 mL). The combined organic layers were dried over $MgSO_4$, concentrated by evaporation and redissolved in in H_2O with a minimal amount of AcN (total 4 mL). The product **17b** was purified by prep HPLC and obtained as a white powder after lyophilisation in 66 % yield (16.6 mg). **HPLC:** t_R = 15.0 min; **HRMS:** $[M+Na]^+$ calculated 478.1949 found 478.1942.

Preparation of H-Asn-Phe(4-phenyl)-OH (13j)

Derivatisation of **12j** (25 mg, 0.055 mmol), prepared by Fmoc-based SPPS (*vide supra*), was performed as described in general procedure C using **5a** (5 mol%, 2.3 mg, 2,75 µmol). The obtained aqueous phase was washed with CH_2Cl_2 (1x 5 mL), concentrated by rotary evaporation and resuspended in H_2O with a minimal amount of AcN (total 4 mL). The crude was purified by prep HPLC and lyophilised to obtain **13j** as a white powder in 32 % yield (7.9 mg). **HPLC:** t_R = 12.2 min; **HRMS:** $[M+H]^+$ calculated 356.1605 found 356.1632.

Preparation of H-Gln-Phe(4-phenyl)-OH (13n)

Derivatisation of **12n** (26 mg, 0.055 mmol), prepared by Fmoc-based SPPS (*vide supra*), was performed as described in general procedure C using **5a** (5 mol%, 2.3 mg, 2,75 µmol). Isolation of **13n** was performed as described for **13j** The crude was purified by prep HPLC and lyophilised to obtain **12n** as a white powder in 36 % yield (9.3 mg). **HPLC:** t_R = 12.3 min; **HRMS:** $[M+H]^+$ calculated 370.1761 found 370.1750.

Preparation of Boc-His(BOM)-Phe(4-Br)-OMe (18a)

To a solution of HCl.H-Phe(4-Br)-OMe (600 mg, 2.04 mmol), Boc-His(BOM)-OH (918 mg, 2.44 mmol) and HOAt (444 mg, 3.26 mmol) in CH_2Cl_2 (15 mL, SPPS grade) was added DIPEA (1.06 mL, 6.11 mmol). The reaction mixture was cooled with a water/ice bath to 0°C and a solution of EDC.HCl (625 mg, 3.26 mmol) in CH_2Cl_2 (5 mL, SPPS grade) was added dropwise. After complete addition, the reaction mixture was allowed to warm to room temperature and stirred for 16 h. The obtained cloudy solution was diluted with CH_2Cl_2 (25 mL) and filtered over a glass frit. The organic phase was washed with saturated NH_4Cl (2x 25 mL), aq. sat. $NaHCO_3$ (2x 25 mL), water (2x 25 mL) and brine (1x 25 mL). The solution was dried over $MgSO_4$ and concentrated by evaporation. After drying overnight under high vacuum, **18a** was obtained as a white solid in 99 % yield (1.237 g). **HPLC:** t_R = 15.8 min; **MS (ES+):** 617 $[M+H, {}^{81}Br]^+$, 615 $[M+H, {}^{79}Br]^+$ (MW= 615.5 g/mol); **^{1}H-NMR** (250 MHz, $CDCl_3$): δH 7.54 (1H, s), 7.28-7.44 (7H, M), 6.85-6.95 (3H, m), 6.75-6.84 (1H, d, *J*= 7.6 Hz), 5.23-5.38 (3H, m), 4.73 (1H, dd, *J*= 13.8 Hz, 6.2 Hz), 4.49 (2H, s), 4.33-4.45 (1H, m), 3.68 (3H, s), 2.97-3.14 (3H, m), 2.90 (1H, dd, *J*= 14.0 Hz, 6.5 Hz), 1.42 (9H, s); **^{13}C-NMR** (63 MHz, $CDCl_3$): 171.1, 170.5, 155.3, 138.2, 135.8, 134.8, 131.6, 130.9, 128.9, 128.7, 128.4, 128.1, 127.1, 121.0, 80.4, 73.1, 70.0, 53.8, 53.0, 52.4, 37.2, 28.2, 26.6.

Preparation of Boc-His(BOM)-Phe(4-Br)-OH (18b)

Compound **18b** (200 mg, 0.373 mmol) was prepared starting from **18a** according to a similar procedure as described for **13b** with LiOH monohydrate (78 mg, 1.864 mmol) in THF/H_2O (7:1; total 2 mL). After lyophilisation, a white powder was obtained in 68 % (133 mg). **HPLC:** t_R = 15.1 min; **MS (ES+):** 603 $[M+H, {}^{81}Br]^+$, 601 $[M+H, {}^{79}Br]^+$ (MW= 601.5 g/mol). **^{1}H-NMR** (500 MHz, DMSO-d_6): δH 8.20 (1H, s), 8.15 (1H, d, *J*= 7.5 Hz), 7.41 (2H, d, *J*= 7.7 Hz), 7.26-7.35 (5H, M), 7.17 (2H, d, *J*= 7.7 Hz), 7.01 (1H, d, *J*= 8.3 Hz), 6.92 (1H, br s), 5.50 (2H, s), 4.46 (3H, m), 4.28 (1H, m), 2.94-3.08 (2H, M), 2.78-2.93 (2H, M), 1.32 (9H, s); **^{13}C-NMR** (126 MHz, DMSO-d_6): 172.3, 170.8, 155.1, 137.5, 137.0, 136.7, 131.5, 131.0, 128.7, 128.3, 127.7, 127.7, 124.6, 119.7, 78.3, 74.2, 69.7, 53.1, 53.1, 35.9, 28.1, 26.0.

Preparation of H-His(BOM)-Phe(4-Br)-OH (18c)

To a solution of **15c** (54 mg, 0.090 mmol) in CH_2Cl_2 (4 mL) was added trifluoroacetic acid (1 mL). The reaction mixture was stirred for 2 hours and concentrated by evaporation. After lyophilisation of the product, a white powder was obtained in quantitative yield (53.7 mg) as the trifluoroacetic acid salt. **HPLC:** t_R = 11.8 min; **MS (ES+):** 503 $[M+H^+, {}^{81}Br]$, 501 $[M+H^+, {}^{79}Br]$ (MW= 501.4 g/mol). **^{1}H-NMR** (500 MHz, DMSO-d_6): δH 9.19 (1H, s), 8.93 (1H, d, *J*= 7.5 Hz), 8.42 (2H, br s), 7.50 (1H, s), 7,45 (2H, d, *J*= 8.1 Hz), 7.26-7.37 (5H, M), 7.20 (2H, d, *J*= 8.3 Hz), 5.69 (2H, q, *J*= 10.4 Hz), 4.51-4.59 (3H, M), 4.19 (1H, t, *J*= 6.4 Hz), 3.29 (1H, dd, *J*= 15.7 Hz, 5.7Hz), 3.20 (1H, dd, *J*= 15.8 Hz, 8.0 Hz), 3.07 (1H, dd, *J*= 14.0 Hz, 4.8 Hz), 2.94 (1H, dd, *J*= 14.0 Hz, 8.4 Hz); **^{13}C-NMR** (126 MHz, DMSO-d_6): 171.9, 167.4, 136.9, 136.5, 136.5, 131.4, 131.1, 128.4, 128.0, 127.8, 127.2, 121.1, 120.0, 75.8, 70.6, 53.6, 50.8, 35.7, 24.8.

Preparation of 19a-d

Histidine-containing dipeptides (**19a-b**) and tripeptides (**19c-d**) were prepared by standard Fmoc-based SPPS (*vide supra*). Acylation of the C-terminus (**19b** and **19d**) was performed by treating the resin with a mixture of acetic anhydride (10 eq) and DIPEA (20 eq) in DMF (3 mL) for 30 mins. Kaiser ninhydrin test was performed to confirm complete acylation of the peptide. Afterwards, the resin was washed consecutively with DMF, *i*PrOH and CH_2Cl_2 (each 3x 1 min). For final cleavage, the resin was treated with a cleavage cocktail (3 mL), consisting of TFA

(95 %), H_2O (2.5 %) and triethylsilane (2.5 %) for 2 hours. The obtained crude peptides were purified by preparative HPLC and obtained as white powders after lyophilisation.

H-His-Phe(4-I)-OH (**19a**): **HPLC:** t_R = 10.7 min; **HRMS:** $[M+H]^+$ calculated 429.0418 found 429.0400.

Ac-His-Phe(4-I)-OH (**19b**): **HPLC:** t_R = 11.6 min; **HRMS:** $[M+H]^+$ calculated 471.0524 found 471.0520.

H-Gly-His-Phe(4-I)-OH (**19c**): **HPLC:** t_R = 10.7 min; **HRMS:** $[M+H]^+$ calculated 486.0633 found 486.0637.

Ac-Gly-His-Phe(4-I)-OH (**19d**): **HPLC:** t_R = 11.5 min; **HRMS:** $[M+H]^+$ calculated 528.0739 found 528.0738.

Suzuki-Miyaura derivatisation of His-Phe dipeptides (18a-d, 19a-b) and tripeptides (19c-d): General procedure D

In a 10 mL MW vial, the dipeptide halide (0.02 mmol-0.042 mmol) was dissolved together with phenylboronic acid (2.5 eq) and K_2CO_3 (5-6 eq) in a mixture of H_2O and *i*PrOH (1:1, total 2 mL). The catalyst was added in the respective amount (5 mol% to 100 mol%, see Table 6). Conversion of the reaction was monitored by HPLC (215 nm). The vial was fitted with a stirring bar, closed with a crimp cap and heated to 80°C for the respective time. Conversion of the reaction was monitored by HPLC (215 nm). If satisfactory conversion was obtained (only with catalyst **5a**), the reaction mixture was allowed to cool to room temperature, concentrated and redissolved in 5 mL of H_2O.

Preparation of Boc-His(BOM)-Phe(4-phenyl)-OMe (20a)

Derivatisation of **18a** (25 mg, 0.041 mmol) was performed according to general procedure D with **5a** (5 mol%, 1.7 mg, 2.03 µmol) and K_2CO_3 (28.1 mg, 0.203 mmol) for 2 hours. Isolation of the product was similar to the purification of **14a**, correspondingly, hydrolysis to **20b** was observed by LC/MS and ^{1}H-NMR analysis, consistent with data found for **20b**.

Preparation of Boc-His(BOM)-Phe(4-phenyl)-OH (20b)

Derivatisation of **18b** (25 mg, 0.042 mmol) was performed according to general procedure D with **5a** (5 mol%, 1.7 mg, 2.08 µmol) and K_2CO_3 (28.7 mg, 0.208 mmol) for 2 hours. The purification was performed as described for **14b**. After preparative HPLC and lyophilisation, **20b** was obtained as a pale brown powder in 56 % yield (14.0 mg). **HPLC**: t_R = 15.9 min; **HRMS:** $[M+H]^+$ calculated 599.2864 found 599.2869.

Preparation of H-His(BOM)-Phe(4-phenyl)-OH (20c)

Derivatisation of **18c** (25 mg, 0.042 mmol) was performed according to general procedure D with **5a** (5 mol%, 1.7 mg, 2.09 µmol) and K_2CO_3 (34.6 mg, 0.251 mmol) for 2 hours. Isolation of **20c** was performed as described for **12j**. The product was purified by preparative HPLC and obtained as a white powder in 42 % yield (10.4 mg). **HPLC:** t_R = 12.7 min; **HRMS:** $[M+H]^+$ calculated 499.2340 found 499.2332.

Preparation of H-His-Phe(4-phenyl)-OH (20d)

Derivatisation of **19a** (12.5 mg, 0.020 mmol) was performed according to general procedure D with phenylboronic acid (6.1 mg, 0.05 mmol), **5a** (5 mol%, 0.8 mg, 1.00 µmol) and K_2CO_3 (16.6 mg, 0.121 mmol) in 1 mL of a mixture of H_2O and *i*PrOH (1:1) for 24 hours. Isolation of **20d** was performed as described for **12j**. After purification by preparative HPLC and lyophilisation, the product was obtained as a white powder in 15 % yield (1.7 mg). **HPLC:** t_R = 11.9 min; **HRMS:** $[M+H]^+$ calculated 379.1765 found 379.1774.

Preparation of Ac-His-Phe(4-phenyl)-OH (20e)

Derivatisation of **19b** (12.5 mg, 0.022 mmol) was performed according to general procedure D with phenylboronic acid (6.7 mg, 0.055 mmol), **5a** (5 mol%, 0.9 mg, 1.10 µmol) and K_2CO_3 (15.2 mg, 0.110 mmol) in 1 mL of a mixture of H_2O and *i*PrOH (1:1) for 2 hours. Isolation of **20e** was performed as described for **12j.** After purification by preparative HPLC and lyophilisation, the product was obtained as a white powder in 19 % yield (1.7 mg). **HPLC:** t_R = 12.4 min; **HRMS:** $[M+H]^+$ calculated 421.1870 found 421.1877.

Preparation of H-Gly-His-Phe(4-phenyl)-OH (20f)

Derivatisation of **19c** (14.0 mg, 0.020 mmol) was performed according to general procedure D with phenylboronic acid (6.1 mg, 0.050 mmol), **5a** (5 mol%, 0.8 mg, 1.00 µmol) and K_2CO_3 (16.6 mg, 0.120 mmol) in 1 mL of a mixture of H_2O and *i*PrOH (1:1) for 24 hours. Isolation of **20f** was performed as described for **12j.** After purification by preparative HPLC and lyophilisation, the product was obtained as a white powder in 11 % yield (1.4 mg). **HPLC:** t_R = 11.5 min; **HRMS:** $[M+H]^+$ calculated 436.1979 found 436.1971.

Preparation of Ac-Gly-His-Phe(4-phenyl)-OH (20g)

Derivatisation of **19d** (12.5 mg, 0.020 mmol) was performed according to general procedure D with phenylboronic acid (6.1 mg, 0.050 mmol), 5a (5 mol%, 0.8 mg, 1.00 µmol) and K_2CO_3 (13.8 mg, 0.120 mmol) in 1 mL of a mixture of H_2O and *i*PrOH (1:1). Isolation of **20g** was performed as described for **12j**. After purification by preparative HPLC and lyophilisation, the product was obtained as a white powder in 29 % yield (3.3 mg). **HPLC:** t_R = 11.5 min; **HRMS:** $[M+H]^+$ calculated 478.2085 found 478.2077.

Synthesis and derivatisation of halogenated phenylalanine containing heptapeptide

Preparation of H-Met-Glu-His-Phe(4-I)-Arg-Trp-Gly-OH (21)

Heptapide **21** was synthesised following standard Fmoc-based SPPS on 2-Cl-tritylchloride resin (*vide infra*) and deprotected with a cleavage cocktail (TFA/TES/H_2O 95:2.5:2.5) for 3 hours. The resulting crude was precipitated in diethylether and purified by preparative HPLC and obtained as a white powder after lyophilisation in 19 % yield. (40 mg). **HPLC:** t_R = 11.5 min; **HRMS:** $[M+H]^+$ calculated 1088.3268 found 1088.3222.

Preparation of H-Met-Glu-His-Phe(4-phenyl)-Arg-Trp-Gly-OH (22)

The heptapide **21** (10.0 mg, 7.3 µmol) was dissolved with phenylboronic acid (2.2 mg, 0.018 mmol), K_2CO_3 (7.0 mg, 0.051 mmol) and **5a** (5 mol%, 0.3 mg, 0.36 µmol) in a mixture of H_2O and *i*PrOH (1:1, total 1 mL) in a microwave vial (10 mL). The vial was equipped with a stirring bar and sealed with a crimp cap. The mixture was heated to 80°C with an oil bath for 2 hours. The mixture was allowed to cool to room temperature and concentrated by evaporation. The crude was redissolved in H_2O, with a minimal amount of AcN, and purified by preparative HPLC to yield **22** as a white powder in 18 % yield (1.7 mg). **HPLC:** t_R = 12.4 min; **HRMS:** $[M+H]^+$ calculated 1038.4614 found 1038.4651.

Synthesis and derivatisation of *C*-terminal amide dipeptides

Preparation of H-AA-Phe(4-Br)-NH_2 (23a-d)

Dipeptides amides (**23a-d**) were synthesised on Rink Amide resin, following standard Fmoc-based SPPS protocols (*vide infra*). The first amino acid (Fmoc-4-Br-Phe, 3 eq) was coupled together with HCTU (3 eq) for 60 mins after Fmoc deprotection (20 % 4-methylpiperidine solution for 5 minutes and 15 minutes) of the resin. Subsequent couplings, deprotection and final cleavage were performed as described for 2-Cl-tritylchloride resin. Dipeptides were identified by LC/MS analysis and purified by preparative HPLC.

Entry	Peptide	MW (g/mol)	LC/MS $[M+H, {}^{81}Br]^+$	HPLC (min)[a]
1	H-Ser-Phe(4-Br)-NH_2 **23a**	330.2	332	9.9
2	H-Leu-Phe(4-Br)-NH_2 **23b**	356.3	358	11.3
3	H-Tyr-Phe(4-Br)- NH_2 **23c**	406.3	408	10.8
4	H-Ala-Phe(4-Br)- NH_2 **23d**	314.3	316	10.1

[a] Measured by HPLC (215 nm).

Preparation of H-AA-Phe(4-I)-NH_2 (24a-d)

Dipeptide amides (**24a**-**d**) containing 4-iodophenylalanine were synthesised as described for **23a-d** with Fmoc-4-I-Phe. After cleavage, the peptides were purified by preparative HPLC and obtained as white powders.

H-Ser-Phe(4-I)-NH_2 (**24a**): **HPLC:** t_R = 10.5 min; **HRMS:** $[M+H]^+$ calculated 378.0309 found 378.0281.

H-Leu-Phe(4-I)-NH_2 (**24b**): **HPLC:** t_R = 11.6 min; **HRMS:** $[M+H]^+$ calculated 404.0829 found 404.0786.

H-Tyr-Phe(4-I)-NH_2 (**24c**): **HPLC:** t_R = 11.1 min; **HRMS:** $[M+H]^+$ calculated 454.0622 found 454.0618.

H-Ala-Phe(4-I)-NH_2 (**24d**): **HPLC:** t_R = 10.6 min; **HRMS:** $[M+H]^+$ calculated 362.0360 found 362.0344.

Derivatisation of *C*-terminal amides 23a-d and 24a-d

The *C*-terminal amide (0.026 mmol) was dissolved in a 10 mL MW vial together with phenylboronic acid (8.0 mg, 0.066 mmol), K_2CO_3 (18.2 mg, 0.132 mmol) and **5a** (1.1 mg, 1.32 µmol) in a mixture of H_2O and *i*PrOH (1:1, total 1 mL). The solution was heated to 80°C for the respective time, conversion was determined by HPLC analysis. For the 4-iodophenylalanine containing dipeptides (**24a-d**), high conversion was observed after 2 hours (6 hours for **24a**) and the crudes were purified by preparative HPLC yielding the derivatised dipeptides as white powders.

H-Ser-Phe(4-phenyl)-NH_2 (**25a**) was obtained in 30 % yield (3.3 mg). **HPLC:** t_R = 12.1 min; **HRMS:** $[M+H]^+$ calculated 328.1656 found 328.1666.

H-Leu-Phe(4-phenyl)-NH_2 (**25b**) was obtained in 40 % yield (4.7 mg). **HPLC:** t_R = 12.6 min; **HRMS:** $[M+H]^+$ calculated 354.2176 found 354.2205.

H-Tyr-Phe(4-phenyl)-NH_2 (**25c**) was obtained in 41 % yield (5.3 mg). **HPLC:** t_R = 12.2 min; **HRMS:** $[M+H]^+$ calculated 404.1969 found 404.1960.

H-Ala-Phe(4-phenyl)-NH_2 (**25d**) was obtained in 49 % yield (5.5 mg). **HPLC:** t_R = 12.0 min; **HRMS:** $[M+H]^+$ calculated 312.1707 found 312.1720.

Synthesis and derivatisation of halogenated tryptophan and dipeptides containing halogenated tryptophan

Brominated tryptophans (**26a-c**) and 7-iodotryptophan (**30**) were synthesised via a biotransformation reaction.[11a] No further purification was performed.

Preparation of Fmoc-5-bromotryptophan

Compound **26a** (500 mg, 1.57 mmol) and Na_2CO_3 (199 mg, 1.88 mmol) were dissolved in H_2O (10 mL). To this solution was added a solution of Fmoc-OSu (581 mg, 1.72 mmol) in dioxane (10 mL). The suspension was stirred overnight at room temperature. The aqueous phase was acidified with 1 N HCl to pH= 1, as indicated by pH paper, and extracted with CH_2Cl_2 (4x 30 mL). The combined organic layers were washed with 1 N HCl (1x 100 mL) and dried over $MgSO_4$. The resultant crude was triturated with a mixture of CH_2Cl_2/hexane (1:1) and the resulting pink solid was further purified with silica column chromatography (CH_2Cl_2/MeOH/AcOH 97:2:1) and concentrated to obtain Fmoc-5-bromotryptophan as a white solid in 71 % yield (561 mg). **R_f:** 0.19 (CH_2Cl_2/MeOH/AcOH 97:2:1). **HPLC:** t_R = 18.9 min; **HRMS:** $[M+Na, {}^{81}Br]^+$ calculated 529.0560 found 529.0552; **^{1}H-NMR** (500 MHz, DMSO-d_6): δH 12.65 (1H, br s), 11.06 (1H, s), 7.87 (2H, d, *J*= 7.7 Hz), 7.75 (1H, d, *J*= 1.3 Hz), 7.70 (1H, d, *J*= 8.1 Hz), 7.63 (2H, dd, *J*= 15.6 Hz, 7.5 Hz), 7.39 (2H, q, *J*= 7.1 Hz), 7.22-7.32 (4H, M), 7.17 (1H, dd, *J*= 8.5 Hz, 1.7 Hz), 4.14-4.22 (4H, m, 3.15 (2H, dd, *J*= 14.5 Hz, 4.6 Hz), 2.99 (2H, dd, *J*= 14.5 Hz, 9.8 Hz).

Spectra were consistent with literature data.[30]

Dipeptides containing 5-bromotryptophan were prepared according to standard Fmoc-based SPPS (*vide infra*) on 2-Cl-tritylchloride resin with Fmoc-5-bromotryptophan. After coupling with the second Fmoc-protected amino acid followed Fmoc deprotection and cleavage of the resin, the unprotected dipeptides (**27a-c**) were purified by preparative HPLC and lyophilised.

Entry	Peptide	MW (g/mol)	HRMS $[M+H, {}^{81}Br]^+$	HPLC (min)[a]
1	H-Gly-Trp(5-Br)-OH **27a**	340.2	Calc: 342.0272 Found: 342.0291	11.3
2	H-Phe-Trp(5-Br)-OH **27b**	430.3	Calc: 432.0743 Found: 432.0734	12.7
3	H-Lys-Trp(5-Br)-OH **27c**	411.3	Calc: 413.1006 Found: 413.0999	10.9

[a] Measured by HPLC (215 nm).

Preparation of 5-phenyltryptophan (28a)

Compound **26a** (HCl-salt, 25 mg, 0.078 mmol) was dissolved with phenylboronic acid (23.9 mg, 0.196 mmol) and K_2CO_3 (54.1 mg, 0.391 mmol) in 1.6 mL H_2O. To this was added 0.01 M **1a** solution (0.391 µL, 3.91 µmol). The reaction mixture was stirred for 2h at 80°C. The reaction mixture was cooled to room temperature and concentrated by evaporation. The crude was redissolved in H_2O with a minimal amount of AcN and purified by preparative HPLC. The product was obtained as a brown oil after lyophilisation in 54 % yield (16.0 mg). **HPLC:** t_R = 12.4 min; **HRMS:** $[M+H]^+$ calculated 281.1285 found 281.1282; **^{1}H-NMR** (250 MHz, DMSO-d_6): δH 11.12 (1H, br s), 8.18 (2H, br s), 7.84 (1H, s), 7.62-7.74 (2H, m), 7.16-7.54 (7H, M), 4.16 (1H, t, *J*= 5.9 Hz), 3.25-3.33 (2H, m, overlap with H_2O peak); **^{13}C-NMR** (63 MHz, DMSO-d_6): δC 171.0, 142.0, 135.9, 131.3, 128.7, 127.7, 126.8, 126.2, 125.8, 120.6, 116.6, 111.9, 107.4, 52.9, 26.1.

Spectra were consistent with literature data.[5a]

Preparation of H-Gly-Trp(5-phenyl)-OH (29a)

Compound **27a** (25 mg, 0.066 mmol) was dissolved with phenylboronic acid (20.2 mg, 0.166 mmol) and K_2CO_3 (45.9 mg, 0.332 mmol) in 1.7 mL H_2O. To this was added 0.01 M **1a** solution (332 µL, 3.32 µmol). The reaction mixture was stirred for 2h at 80°C. The reaction mixture was cooled to room temperature and concentrated by evaporation. The crude was redissolved in H_2O with a minimal amount of AcN and purified by preparative HPLC. After lyophilisation, **29a** was obtained as a white powder in 33 % yield (9.6 mg). **HPLC:** t_R = 13.8 min; **HRMS:** $[M+H]^+$ calculated 338.1499 found 338.1504.

Preparation of H-Phe-Trp(5-phenyl)-OH (29b)

Compound **29b** was prepared starting from **27b** (25 mg, 0.054 mmol) following the procedure as described for **29a**. The product was obtained as a white powder after lyophilisation in 24 % yield (5.9 mg). **HPLC:** t_R = 13.8 min; **HRMS:** $[M+H]^+$ calculated 428.1969 found 428.1963.

Preparation of H-Lys-Trp(5-phenyl)-OH (29c)

Compound **29c** was prepared starting from **27c** (25 mg, 0.052 mmol) following the procedure as described for **29a**. The product was obtained as a white powder after lyophilisation in 29 % yield (8.9 mg). **HPLC:** t_R = 11.9 min; **HRMS:** $[M+H]^+$ calculated 409.2234 found 409.2206.

Preparation of 6-phenyltryptophan (28b)

Compound **28b** was prepared starting from **26b** according to the procedure described for **28a**. The product was obtained as a white powder after preparative HPLC in 38 % yield. (11.2 mg). **HPLC:** t_R = 12.6 min; **HRMS:** $[M+H]^+$ calculated 281.1285 found 281.1289; **^{1}H-NMR** (500 MHz, DMSO-d_6): δH 11.12 (1H, s), 8.13 (2H, br s), 7.58-7.70 (4H, M), 7.38-7.49 (3H, M), 7.28-7.35 (2H, M), 7.24-7.27 (1H, m), 4.10-4.18 (1H, m), 3.21-3.27 (2H, M, partial overlap with H_2O peak); **^{13}C-NMR** (126 MHz, DMSO-d_6): δC 170.8, 141.6, 136.9, 133.7, 128.8, 128.7, 126.7, 126.5, 125.8, 118.7, 118.1, 109.5, 106.9, 52.8, 26.2.

Preparation of 7-phenyltryptophan (28c)

Compound **28c** was prepared starting from **26c** according to the procedure described for **28a**. The product was obtained as a white powder after preparative HPLC in 44 % yield. (12.9 mg). **HPLC:** t_R = 12.6 min; **HRMS:** $[M+H]^+$ calculated 281.1285 found 281.1279; **^{1}H-NMR** (250 MHz, CD_3OD): δH 7.59-7.68 (3H, m), 7.46-7.54 (2H, m), 7.35-7.43 (1H, m), 7.24 (1H, s), 7.16-7.19 (2H, m), 4.21 (3H, dd, *J*= 8.2 Hz, 4.7 Hz), 3.55 (1H, dd, *J*= 15.1 Hz, 4.5 Hz) 3.33-3.40, (1H, m); **^{13}C-NMR** (126 MHz, DMSO-d_6): δC 170.6, 138.7, 133.4, 128.9, 128.1, 128.0, 127.2, 125.6, 125.3, 121.3, 119.2, 117.7, 107.9, 53.0, 26.3.

Spectra were consistent with literature data.[5a]

Preparation of 7-vinyltryptophan (31)

Compound **31** was prepared by dissolving **30** (29 mg, 0.078 mmol), potassium vinyltrifluoroborate (26 mg, 0.195 mmol), K_2CO_3 (54 mg, 0.390 mmol) and **5a** (5 mol%, 3.2 mg, 3.90 µmol) in a mixture of H_2O and *i*PrOH (1:1, total 2 mL). The reaction mixture was stirred for 2 hours at 80°C, allowed to cool to room temperature. The aqueous phase was washed with CH_2Cl_2 (2x 5 mL) and was acidified with 1N HCl to pH = 3, as indicated by pH paper. The aqueous layer was extracted with CH_2Cl_2 (4x 10 mL) and the combined organic layers were collected and washed with brine (1x 20 mL) and dried over $MgSO_4$. The product was concentrated by evaporation and dissolved in water with a minimal amount of AcN. The crude was purified by preparative HPLC and obtained as a white powder after lyophilisation in 51 % yield (13.0 mg). **HPLC:** t_R = 11.1 min; **HRMS:** $[M+H]^+$ calculated 231.1128 found 231.1131; **^{1}H-NMR** (500 MHz, DMSO-d_6): δH 11.19 (1H, s), 8.19 (2H, br s), 7.51 (1H, d, *J*= 7.9 Hz), 7.31 (1H, d, *J*= 7.5 Hz), 7.25 (1H, d, *J*= 2.1 Hz), 7.17 (1H, dd, *J*= 17.6 Hz, 11.2 Hz), 7.02 (1H, t, *J*= 7.6 Hz), 5.90 (1H, d, *J*= 17.7 Hz), 5.36 (1H, d, *J*= 11.1 Hz), 4.09 (1H, t, *J*= 6.2 Hz), 3.28 (1H, dd, *J*= 15.0 Hz, 5.5 Hz), 3.22 (1H, dd, *J*= 15.0 Hz, 6.8 Hz); **^{13}C-NMR** (126 MHz, DMSO-d_6): 170.8, 134.0, 132.6, 127.9, 125.2, 121.3, 119.0, 118.1, 118.0, 114.3, 107.4, 52.7, 26.2.

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Keywords: Amino acids • C-C coupling • Palladium • Peptides • Homogenous catalysis

Abbreviations

AA: amino acid; **ADHP**: 2-aminopyrimidine-4,6-diol; **ADHP(Me$_2$)**: 2-(dimethyl)aminopyrimidine-4,6-diol **Boc**: *tert*-butyloxycarbonyl; **BOM:** benzyloxymethyl; **BPA**: 4-pinacolylborono)phenylalanine ; **DIPEA:** *N*,*N'*-diisiopropylethylamine; **dppf**: 1,1'-bis(diphenylphosphino)ferrocene; **EDC**: *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide; **Fmoc**: 9-fluorenylmethyloxycarbonyl; **HCTU**: *O*-(6-chlorobenzotriazol-1-yl)-*N*,*N*,*N'*,*N'*-tetramethyluronium hexafluorophosphate ; HOAt: 1-Hydroxy-7-azabenzotriazole; **HOBt**: 1-hydroxybenzotriazole; **NMM**: *N*-methylmorpholine; **MW**: microwave; **pbf**: 2,2,4,6,7-pentamethyldihydrobenzofuran-5-sulfonyl; **Pg**: protecting group; **SAR:** structure-activity relationships; **sulfonated SPhos**: sodium 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl-3'-sulfonate; **SPPS**: solid-phase peptide synthesis; **TES**: triethylsilane; **TFA**: trifluoroacetic acid; **TPPTS**: 3,3′,3″-phosphanetriyltris(benzene sulfonic acid).

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Entry for the Table of Contents

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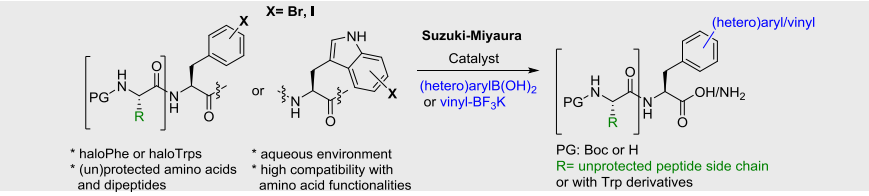

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Suzuki-Miyaura diversification of amino acids and dipeptides in aqueous media

The palladium-catalysed Suzuki-Miyaura derivatisation of (un)protected Phe or Trp, and peptide substrates containing halogenated Phe or Trp, is performed via use of various water-compatible catalytic systems. Problems associated to the unprotected side chains of Asn and His could be circumvented. By mimicking the natural aqueous environment of peptides, halogenated moieties are transformed to a variety of (hetero)aryl and vinyl subtituents.

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