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Peptide modification through site-selective residue interconversion: application of the rhodium-catalysed 1,4-addition of aryl siloxanes and boronates

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ABSTRACT

The site-selective interconversion of serine and cysteine residues of di- and tripeptides into phenylalanine derivatives, bearing a range of functionalities, has been achieved in high yield and selectivity through the common dehydroalanine intermediate. Through the application and development of the rhodium-catalysed 1,4-addition to α,β-dehydroamino acid moieties with organometallic nucleophiles, a variety of peptides have been successfully modified to contain unnatural amino acid residues in predesignated residue positions.

1. Introduction

Proteins and peptides are fundamental in life with an extensive array of functions born of the multitude of possible structures. Consisting of common fragments the primary, secondary and tertiary structures formed through intra- and inter-molecular interactions provide innumerable variations of structure and resultant activity in biological systems. However, the serial nature of synthetic peptide synthesis leads to the perpetual problem of long synthetic routes when investigating residue effects through analogue synthesis. Whilst the ability to modify individual residues of peptides and complex molecules selectively and reliably leads to a number of exciting possibilities in chemical biology and synthetic strategies. Currently, the majority of methods applied to the modification of biological systems are based on biochemical techniques,[1] however, examples of modifications achieved through small molecule (chemical) reactivity is increasing.[2,3]

The rhodium-catalysed 1,4-addition of aryl boronates to α,β-unsaturated carbonyl derivatives has developed in recent years from Miyaura[4] and Hayashi's[5] primary publications to a highly selective and synthetically robust method for the formation of β-aryl ketones and their related structures.[6] Previously, ourselves and others have reported the rhodium-catalysed 1,4-conjugate addition of aryl boronates[7] and siloxanes[8] to α-substituted activated alkenes and dehydroalanine (ΔAla) derivatives. Within this article, we highlight catalytic methodology facilitating the elaboration of peptides and pseudo-peptide fragments through site-selective modification of common natural amino acid residues. Moreover, we show that the diastereoselectivity can be switched through the application of chiral rhodium complexes.

2. Results and discussion

The preparation of an array of unnatural phenylalanine residues within a preformed peptide allows for the rapid variation of complex biomolecules and the possibility to explore residue effects quickly through shrewd alteration at individual sites. To this end, we envisaged the combination of the, previously described transformation of serine or cysteine residues to dehydroalanine together with the rhodium-catalysed conjugate addition reactio, would provide a simple and efficient technique to introduce variation to complex molecules (Scheme 1).

The dehydroalanine (ΔAla) residue itself is of significant interest in protein chemistry due to the rigid nature of the conjugate system and the associated effects imparted on the peptide chain.[9] Synthetic routes to dehydroamino acid containing peptides include a variety of approaches. The elimination of water from serine is a well established route with the activation of the hydroxyl group enabling elimination by various reagents including: carbodiimide/copper(I) chloride,[10] dichloroacetyl chloride/triethylamine,[11] tosyl anhydride/1,4-diazabicyclo[2.2.2]octane (DABCO),[12] triphenyl phosphine/diethyl azodicarboxylate (DEAD),[13] Boc-anhydride/4-(*N*,*N*-dimethylamino)pyridine (DMAP),[14] *O*-Cbz or *O*-Eoc/potassium carbonate,[15] and exchange to form the selenoether with diphenyl diselenide followed by oxidation and elimination though thermolysis.[16] Similarly, cysteine thioethers can be oxidised and eliminated through thermolysis in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) or sodium hydroxide.[17] Recently, Davis and co-workers have successfully modified a peptide

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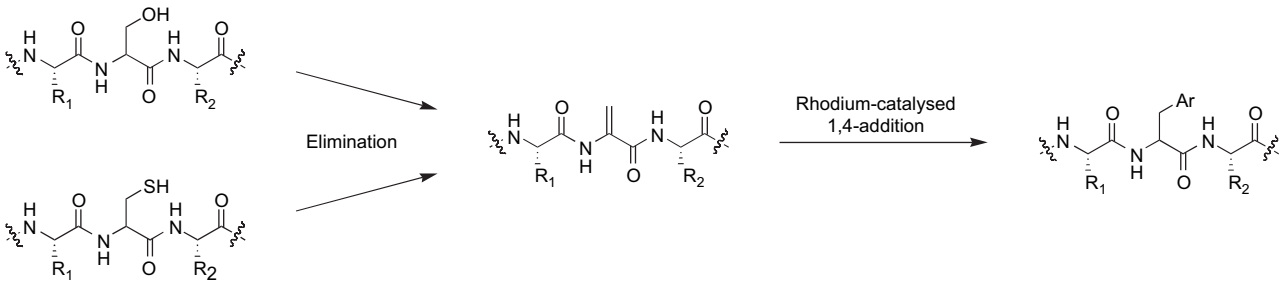
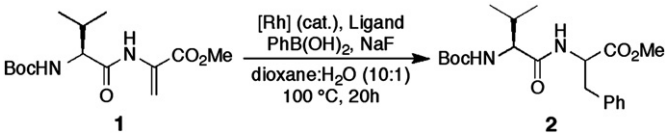


Scheme 1. Proposed route for site-selective modification of peptides though selective residue elimination and sequential rhodium-catalysed 1,4-addition.

through the application of the *O*-mesitylenesulfonylhydroxylamine (MSH) mediated conversion of cysteine to dehydroalanine subunits under mild aqueous conditions.[18]

Our initial investigations focused on the dipeptide Boc-Val-ΔALa-OMe **1** with the Δ-alanine portion present as the acrylate ester, prepared in 91% yield from Boc-Val-Ser-OMe though the application of 1-ethyl-3-(3′-dimethylaminopropyl)carbodiimide (EDCI)/CuCl. In comparison with our previously described work on methyl 2-acetamidoacrylate,[7c] exchange of the *N*-acetyl group for Boc-valine produced no detrimental effect concerning the reactivity of the substrate. However, unlike with Ac-ΔAla-OMe, application of a (*Rac*)-BINAP derived catalyst provided the minimal natural selectivity of 8% de in preference to the formation of the unnatural D-phenylalanine (Table 1, entry 3).[19] Application of chiral

Table 1
Ligand effects on the rhodium-catalysed 1,4-addition with phenyboronic acid[a]

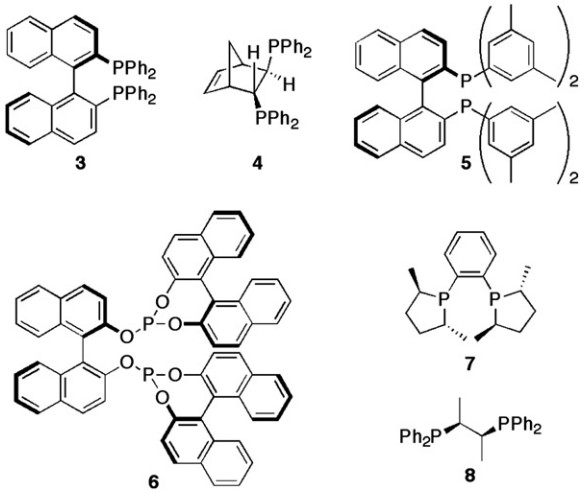


1 **2**

Entry	Catalyst	Ligand	Conv. (d.e.)[c] (%)
1	$[Rh(acac)(C_2H_4)_2]$	(*R*)-BINAP **3**	100 (39 *R*)
2	$[Rh(acac)(C_2H_4)_2]$	(*S*)-BINAP	100 (23 *S*)
3	$[Rh(acac)(C_2H_4)_2]$	(*Rac*)-BINAP	100 (8 *R*)
4	$[RhCl(C_2H_4)_2]_2$	(*S*)-BINAP	83[b] (29 *S*)
5	$[RhCl(C_2H_4)_2]_2$	(*S,S*)-Chiraphos **8**	33 (NR)
6	$[RhCl(C_2H_4)_2]_2$	(*R,R,R*)-**1**	82[b] (22 *S*)
7	$[RhCl(C_2H_4)_2]_2$	(*R,R*)-Norphos **4**	97 (37 *S*)
8	$[RhCl(C_2H_4)_2]_2$	(*R,R*)-DUPHOS **7**	21 (NR)
9	$[RhCl(C_2H_4)_2]_2$	(*R*)-3,5-Xylyl-BINAP **5**	89 (40 *R*)

[a] Conditions: [Rh] (3 mol % Rh), ligand (1.1 equiv to Rh), $PhB(OH)_2$ (4 equiv), NaF (3 equiv), dioxane/H_2O 10:1, 100 °C, 20 h.
[b] Isolated yield.
[c] Diastereoselectivity calculated from proton NMR spectroscopy, configuration of new stereocentre of the major diastereomer.

BINAP catalysts provided marginal enhancements in selectivity with (*R*)-BINAP affording the matched pair with 39% de (D-(*R*)-selectivity) and (*S*)-BINAP the mis-matched pair with 23% de (L-(*S*)-selectivity). Disappointingly, the application of a variety of bisphosphine ligands provided no significant enhancement in selectivity including diphosphite ligand (*R,R,R*)-**6**, which had previously afforded up to 72% ee when applied to the addition of boronic acids to methyl 2-acetamidoacrylate.[7c] The rhodium source used in the reaction had little effect on the reactivity and selectivity of the reaction with the presence of sodium fluoride having a greater effect reducing the undesired side reactions and providing cleaner products.



Elaboration of the method with a variety of organometallic nucleophiles proved successful (Table 2). However, only low diastereoselectivities could be achieved using BINAP as the chiral ligand. Both aryl siloxanes and boronic acids were efficiently coupled to provide an assortment of functionalised phenylalanine derivatives. Of note, 4-formylphenyl boronic acid was successfully coupled to afford the corresponding aldehyde functionalised peptide in 33% isolated yield. The low yield of this reaction, when

Table 2
Additions to Boc-Val-ΔAla-OMe

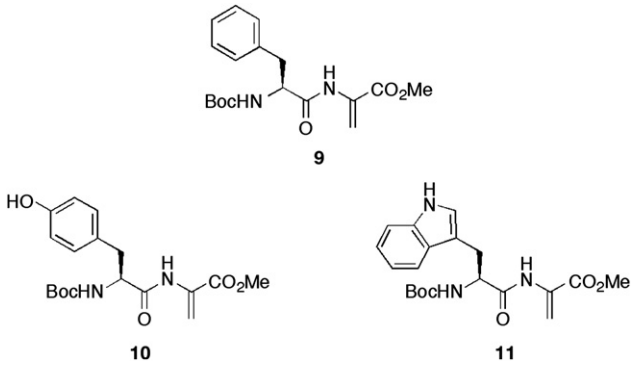
1

Entry	Conditions[a]	Organometallic	Yield (d.e.)[b] (%)
1	A	4-Cl-$PhB(OH)_2$	86 (39 *R*)
2	A	4-Ac-$PhB(OH)_2$	86 (37 *R*)
3	A	1-Naphthyl-$PhB(OH)_2$	62 (21 *R*)
4	A	3-Br-$PhB(OH)_2$	86 (33 *R*)
5	A	4-CHO-$PhB(OH)_2$	33 (34 *R*)
6	B	$PhSi(OMe)_3$	68 (<1)
7	B	4-OMe-$PhSi(OMe)_3$	85 (ND)
8	B	4-CF_3-$PhSi(OMe)_3$	61 (22 *S*)
9	B	4-Me-$PhSi(OMe)_3$	66 (2 *S*)
10	B	4-Cl-$PhSi(OMe)_3$	53 (12 *S*)
11	B	2,3,4,5,6-F-$PhSi(OMe)_3$	0 (0)

[a] Conditions: (A) $[RhCl(C_2H_4)_2]_2$ (1.5 mol %), (*R*)-BINAP (3.3 mol %), $ArB(OH)_2$ (3 equiv), NaF (3 equiv), dioxane/H_2O 10:1, 100 °C, 20 h; (B) $[Rh(COD)_2][BF_4]$ (3 mol %), $ArSi(OMe)_3$ (2 equiv), dioxane/H_2O 10:1, 110 °C, 24 h.
[b] Diastereoselectivity calculated from proton NMR spectroscopy, configuration of new stereocentre of the major diastereomer.

compared to previous studies,[7b] was attributed to the dimerisation of the boronic acid to itself via the rhodium-catalysed 1,2-addition to the aldehyde, a reaction, which is hindered in the absence of organic solvent. Whilst addition of phenylsiloxane provided no natural selectivity, the more electron deficient 4-trifluorophenyl and 4-chlorophenyl siloxanes afforded 22% and 12% diastereoselectivity, respectively. Intriguingly, a reversal in natural selectivity from *R* to *S* is also observed possibly as a result of the coordination orientation during the all important protonation step. However, throughout our previous studies, we have observed no switch in selectivity.[8b]

Variation of the N-terminal amino acid was also possible and provided equivalent reactivity. The three tripeptides Boc-Phe-ΔAla-OMe **9**, Boc-Tyr-ΔAla-OMe **10** and Boc-Trp-ΔAla-OMe **11** were prepared from the corresponding serine precursors. Dehydration was performed using EDCI and Cu(I) Cl with the Boc-Phe-ΔAla-OMe dipeptide isolated in >75% yield. The presence of the phenolic OH of tyrosine proved problematic, however, with yields decreasing to around 45%. A comparable loss of reactivity was observed with tryptophan providing average yields of 55%.



However, the reactivity of the rhodium-catalysed addition to these substrates was comparable to those with Boc-Val-ΔAla-OMe with a range of siloxanes and boronic acids coupled in 33–86% yield (Table 3). The proximity of the phenol and indole groups to the reactive centre affected the selectivity with little or no natural diastereoselectivity observed for the addition to Boc-Trp-ΔAla-OMe and Boc-Tyr-ΔAla-OMe (Table 3, entries 10–15).

Further to these dipeptides, we also synthesised Boc-Val-Cys(SMe)-Ser-OMe **12** with a view to investigate the resilience of the methodology to the presence of a thioether, which would also allow for the subsequent elimination through oxidation to sulfoxide. Pleasingly, the serine residue can be dehydrated with CuCl and EDCI to provide the dehydroalanine containing peptide Boc-Val-Cys-ΔAla-OMe **13** in 83% yield, and the 1,4-addition can be performed albeit in low yield and selectivity with 4-*tert*-butylphenyl boronic acid, 30% and 23%, respectively (Scheme 2). The ability to perform the selective elimination and 1,4-addition provides a viable route to the sequential modification of a peptide chain or complex organic molecule at a late stage of the synthesis.

Whilst the addition to a dehydroalanine ester as a dipeptide is noteworthy, the greater challenge would be the selective addition

Table 3
Additions to dipeptides **9**–**11**

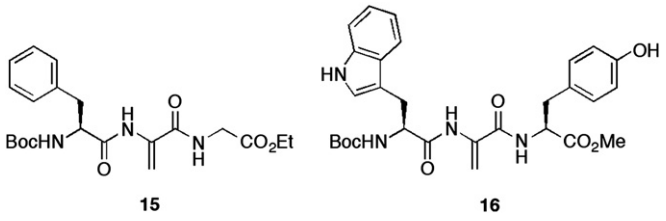
Entry	Substrate	Conditions[a]	Organometallic	Yield (d.e.)[b] %
1	**9**	A	$PhB(OH)_2$	66 (23 *R*)
2	**9**	B	$3\text{-}NO_2\text{-}PhB(OH)_2$	43 (20 *S*)
3	**9**	B	$4\text{-Ac-}PhB(OH)_2$	65 (22 *S*)
4	**9**	B	$4\text{-CHO-}PhB(OH)_2$	33 (38 *S*)
5	**9**	C	$PhSi(OMe)_3$	80 (<1)
6	**9**	C	$4\text{-Cl-}PhSi(OMe)_3$	60 (<1)
7	**9**	C	$2\text{-Me-}PhSi(OMe)_3$	81 (4 *S*)
8	**9**	C	$9\text{-phenanthrene-Si}(OMe)_3$	76 (15 *S*)
9	**9**	C	$4\text{-OMe-}PhSi(OMe)_3$	78 (<1)
10	**10**	D	$4\text{-CN-}PhB(OH)_2$	86 (<1)
11	**10**	D	$4\text{-OMe-}PhB(OH)_2$	65 (<1)
12	**10**	D	$4\text{-Cl-}PhB(OH)_2$	57 (<1)
13	**11**	D	$4\text{-CN-}PhB(OH)_2$	65 (<1)
14	**11**	D	$4\text{-Cl-}PhB(OH)_2$	68 (<1)
15	**11**	D	$4\text{-F-}PhB(OH)_2$	50 (<1)

[a] Conditions: (A) $[RhCl(C_2H_4)_2]_2$ (3 mol %), (*R*,*R*,*R*)-**6** (6.6 mol %), $PhB(OH)_2$ (4 equiv), NaF (3 equiv), dioxane/H_2O 10:1, 100 °C, 20 h; (B) $[RhCl(C_2H_4)_2]_2$ (1.5 mol %), (*R*)-BINAP (3.3 mol %), $ArB(OH)_2$ (3 equiv), NaF (3 equiv), dioxane/H_2O 10:1, 100 °C, 20 h; (C) $[Rh(COD)_2][BF_4]$ (3 mol %), $ArSi(OMe)_3$ (2 equiv), dioxane/H_2O 10:1, 110 °C, 24 h; (D) $Rh(acac)(C_2H_4)_2$ (6 mol %), (*Rac*)-BINAP (6.6 mol %), $ArB(OH)_2$ (4 equiv), NaF (3 equiv), dioxane/H_2O 10:1, 100 °C, 20 h.

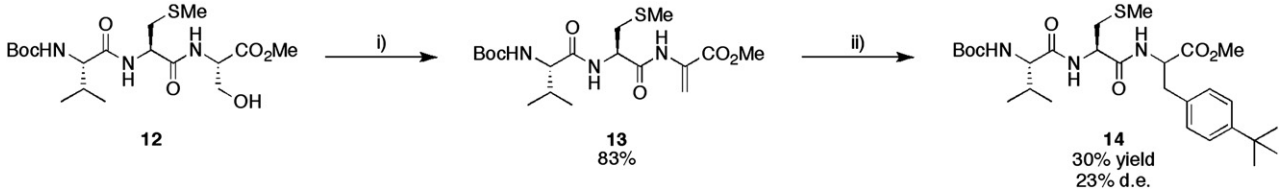
[b] Calculated from proton NMR spectroscopy, configuration of new stereocentre of the major diastereomer.

to a dehydroalanine fragment encased in a tripeptide or polypeptide. To this end, we investigated the addition to tripeptide substrates with an α,β-unsaturated amide. These substrates provide a number of interesting facets including an expected drop in reactivity of the acrylate and steric effects provided on either side of the acrylate.

Dehydration of Boc-Phe-Ser-Gly-OMe with EDCI and CuCl afforded the desired ΔAla containing peptide **15** in 82%. However, as with the dipeptide series where tyrosine or tryptophan residues were adjacent to the serine, problems were encountered during dehydration with little product isolated. Further attempts at progressing via *O*-acetyl serine with elimination under basic conditions also failed to provide significant quantities of the desired peptide. Pleasingly, application of oxidative elimination of cysteine ethers allowed for the preparation of Boc-Trp-ΔAla-Tyr-OMe **16** in 67% yield over three steps.



Initial additions to the simple tripeptide Boc-Phe-ΔAla-Gly-OEt **15** with phenyl boronic acid provided a pleasing level of reactivity, with the $Rh(acac)(C_2H_4)_2$/*Rac*-BINAP catalyst providing 85% isolated yield. Cyclooctadiene based rhodium catalysts, $[Rh(COD)_2][BF_4]$, $[RhCl(COD)]_2$, $[Rh(OH)(COD)]_2$, provided significantly lower yields



Scheme 2. Chemoselective modification of tripeptide **12**. (i) EDCI, Cu(I) Cl, CH_2Cl_2, rt, 18 h; (ii) $[RhCl(C_2H_4)_2]_2$ (3 mol %), (*S*)-BINAP (6.6 mol %), 4-*t*-Bu-$PhB(OH)_2$ (4 equiv), NaF (3 equiv), dioxane/H_2O (10:1), 100 °C, 20 h.

compared to the bisphosphine/Rh(ethylene) based systems $Rh(acac)(C_2H_4)_2$ and $[RhCl(C_2H_4)_2]_2$ in the reaction. Disappointingly, addition of phenylsiloxanes could not be achieved with these α,β-unsaturated amide substrates. Whilst no natural selectivity was observed in the addition of phenyl boronic acid with *Rac*-BINAP based catalysts, additions performed with 4-fluorophenylboronic acid provided a selectivity of 8% de. In similar fashion to the dipeptide substrates, the use of chiral BINAP complexes provided marginal selectivity with (*R*)-BINAP yielding a 28% de and (*S*)-BINAP 44% de. Significantly, the reversal in ligand selectivity should be highlighted from that obtained with the Boc-Val-ΔAla-OMe system with in this case (*S*)-BINAP rather than (*R*)-BINAP providing the matched pair and the higher diastereoselectivity. The presence of a chiral centre on either side of the dehydroalanine residue affords only a single diastereomeric product (Table 4).

Table 4
Additions to tripeptides **15** and **16**

Entry	Substrate	Conditions[a]	Organometallic	Yield (d.e.)[b] %
1	**15**	(*Rac*)-A	$PhB(OH)_2$	85
2	**15**	(*R*)-A	4-F-$PhB(OH)_2$	61c (28 −)
3	**15**	(*S*)-B	4-F-$PhB(OH)_2$	82c (44 +)
4	**15**	(*Rac*)-A	4-F-$PhB(OH)_2$	79 (8 +)
5	**15**	C	$PhSi(OMe)_3$	0
6	**15**	(*Rac*)-A	4-Cl-$PhB(OH)_2$	82
7	**15**	(*Rac*)-A	3-NO_2-$PhB(OH)_2$	43
8	**15**	(*Rac*)-A	4-Br-$PhB(OH)_2$	35
9	**16**	(*Rac*)-A	4-F-$PhB(OH)_2$	54 (>99 +)
10	**16**	(*Rac*)-A	4-CN-$PhB(OH)_2$	14 (>99 +)
11	**16**	(*Rac*)-A	3,5-di-CF_3-$PhB(OH)_2$	38 (>99)

[a] Conditions: (A) $Rh(acac)(C_2H_4)_2$ (6 mol %), BINAP (6.6 mol %), $ArB(OH)_2$ (4 equiv), NaF (3 equiv), dioxane/H_2O 10:1, 100 °C, 20 h; (B) $[RhCl(C_2H_4)_2]_2$ (1.5 mol %), BINAP (3.3 mol %), $ArB(OH)_2$ (3 equiv), NaF (3 equiv), dioxane/H_2O 10:1, 100 °C, 20 h; (C) $[Rh(COD)_2][BF_4]$ (3 mol %), $ArSi(OMe)_3$ (2 equiv), dioxane/H_2O 10:1, 110 °C, 24 h.
[b] Calculated from proton NMR spectroscopy, configuration of new stereocentre of the major diastereomer.

To further explore the scope of this result and the limits of the methodology, we investigated its application as an efficient procedure to synthesise analogues of the urotensin receptor agonists recently described by Hirschmann and co-workers (Scheme 3).[20] We elected to investigate the lower portion as a viable test substrate, in which to modify the β-naphthylalanine residue. One can easily imagine the preparation of a ΔAla residue from which multiple analogues can be prepared to investigate interactions with the binding pocket of the urotensin. Synthesis of the lower half of the cyclic hexapeptide was performed by standard peptide coupling techniques to provide the tripeptide Boc-Lys(Cbz)-Ser-Ala-OMe **19**, which was subsequently dehydrated at the serine residue in 89% yield to afford the dehydroalanine containing tripeptide **18**. Preliminary studies looking at the addition of phenyl boronic acid proved fruitful with *Rac*-BINAP providing the desired product in 34% yield and a natural selectivity of 19% de in preference to the L-phenylalanine being formed. Application of the chiral BINAP complexes provided more promising results with (*S*)-BINAP providing a 45% yield of solely the D-phenylalanine addition product, whilst (*R*)-BINAP provided a 50% yield of the L-phenylalanine adduct together with an 8% yield of the unnatural D-isomer also isolated by flash column chromatography. Similarly, the addition of three further boronic acids with (*R*)-BINAP based catalysts provided single isomers of the products in 32–68% isolated yield as single diastereoisomers (Table 5). These results further confirm this methodology as a plausible method for the late stage modification of peptides and complex organic molecules.

Table 5
Additions to the lower portion of Urotensin agonist substrate **18**

18

Entry	Conditions[a]	Boronic acid	Yield (%)
1	(*R*)-A	$PhB(OH)_2$	50 L(*S*)+8 D(*R*)
2	(*R*)-B	$PhB(OH)_2$	31 L(*S*)
3	(*S*)-A	$PhB(OH)_2$	45 D(*R*)
4	(*Rac*)-A	$PhB(OH)_2$	34 (19% d.e. L(*S*))
5	(*R*)-B	1-NaphthylB$(OH)_2$	56 L(*S*)[b]
6	(*R*)-B	2-NaphthylB$(OH)_2$	68 L(*S*)[b]
7	(*R*)–B	3,5-di(F)-$PhB(OH)_2$	32 L(*S*)[b]

[a] Conditions: (A) $[RhCl(C_2H_4)_2]_2$ (3 mol %), BINAP (6.6 mol %), $PhB(OH)_2$ (4 equiv), NaF (3 equiv), dioxane/H_2O 10:1, 100 °C, 20 h; (B) $[Rh(acac)(C_2H_4)_2]_2$ (1.5 mol %), BINAP (3.3 mol %), $ArB(OH)_2$ (3 equiv), NaF (3 equiv), dioxane/H_2O 10:1, 100 °C, 20 h.
[b] Assigned by comparison of proton NMR spectroscopy and selectivity in other reactions.

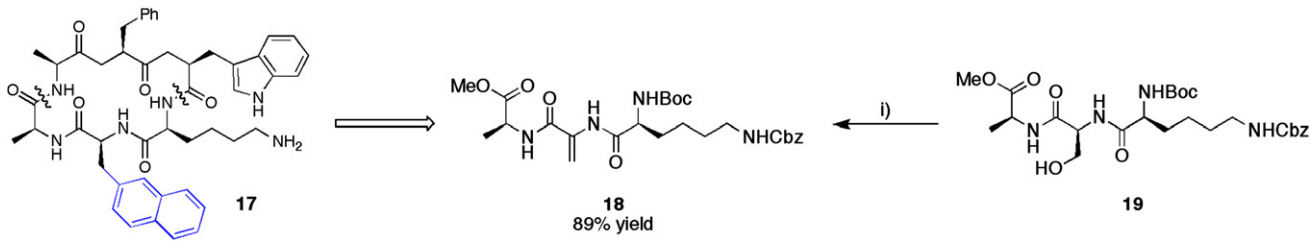
3. Conclusion

In conclusion, we have selectively modified peptides at designated residues through an efficient process enabling the incorporation of diversity both quickly and with high diastereoselectivity. The preparation of a common intermediate, which can be modified, from a range of different primary residues enables the highly selective alteration of complex molecules. We have shown that this methodology can be applied to a range of peptide substrates with high selectivity and yield, enabling the rapid interjection of an array of chemical variation in a molecule from a common beginning. Efforts are ongoing to further appreciate the mechanism and understanding of the chirality inducing protonation phase.

4. Experimental

4.1. General procedure for the rhodium-catalysed 1,4-addition of aryl boronic acids to ΔAla containing peptides

An oven dried flask was charged with peptide (0.2 mmol), $Rh(acac)(C_2H_4)_2$ (6 mol %, 1.2×10^{-5} mol), *Rac*-BINAP (6.6 mol %,



Scheme 3. Urotensin agonist **17** provides a worthy test substrate for the application of the residue selective modification of proteins. (i) CuCl, EDCI, DCM, 18 h.

1.3×10^{-5} mol), $ArB(OH)_2$ (4 equiv 0.8 mmol) and dioxane (2 mL), evacuated and backfilled with argon and stirred at room temperature for 10 min. Water (0.2 mL) was added and the mixture heated at 100 °C for 20 h. After cooling to room temperature, the resulting mixture was diluted with ethyl acetate (5 mL) and extracted with water (10 mL). The aqueous wash was back extracted with ethyl acetate (2×5 mL) and the combined organics washed with saturated $NaHCO_3$ solution (10 mL), brine (10 mL), dried over $MgSO_4$ and evaporated in vacuo. The residue was purified by column chromatography to afford the desired compound.

4.2. General procedure for the rhodium-catalysed 1,4-addition of organosiloxanes to ΔAla containing peptides

An oven dried carousel tube was charged with $[Rh(COD)_2][BF_4]$ (3 mol %) and the corresponding peptide (0.25 mmol) in anhydrous dioxane (2 mL) under an atmosphere of nitrogen, followed by the appropriate siloxane (0.5 mmol, 2 equiv) and water (0.2 mL). The resulting solution was heated to reflux for 24 h at 110 °C and allowed to cool to room temperature. Solvents were removed under reduced pressure, the residue re-dissolved in ethyl acetate (20 mL) and washed with water (20 mL), saturated $NaHCO_3$ solution (20 mL) and brine (20 mL). The organic extract was dried over $MgSO_4$ and concentrated in vacuo to afford the crude product, which was further purified by flash chromatography to afford the desired compound.

4.3. Dipeptides

4.3.1. Boc-Val-ΔAla-OMe (**1**)

An oven dried flask was charged with Boc-Val-Ser-OMe (3.31 g, 10.4 mmol) dissolved in degassed dichloromethane (80 mL) under an atmosphere of nitrogen, copper(I) chloride (309 mg, 3.12 mmol) and EDCI (2.19 g, 11.4 mmol) were subsequently added and the resultant suspension stirred for 18 h at ambient temperature. The solution was washed with two portions of water (20 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by flash column chromatography (petroleum ether/ethyl acetate 5:1) gave the title compound as a colourless foam in 91% yield (2.85 g). $[\alpha]_D^{20}$ −23.19 (*c* 0.69, $CHCl_3$); IR (film, cm^{-1}) ν 3281, 3045, 2956, 2254, 1824, 1743, 1667, 1536, 1437, 1389, 1364, 1297, 1247, 1155, 1043, 1018, 992, 909, 882, 867, 800, 718; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.23 (1H, s), 6.60 (1H, s), 5.89 (1H, d, *J*=1.5), 5.12 (1H, d, *J*=8.1), 4.06 (1H, m), 3.83 (3H, s), 2.19 (1H, app octet, *J*=6.9), 1.43 (9H, s), 0.97 (3H, d, *J*=6.9), 0.91 (3H, d, *J*=6.9); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 171.0, 164.6, 156.1, 130.9, 109.6, 80.4, 60.9, 53.3, 31.1, 28.6, 19.6, 17.8; HRMS (ESI^+) calcd for $C_{14}H_{24}N_2NaO_5$: 323.1583 $[M+Na]^+$, found: 323.1585 $[M+Na]^+$.

4.3.2. Boc-Val-Phe-OMe (**2**)

In accordance with the representative procedure for 1,4-additions with boronic acids, Boc-Val-ΔAla-OMe (60 mg, 0.2 mmol) was reacted with phenyl boronic acid (97.5 mg, 0.8 mmol). The title compound was obtained as a mixture of diastereomers in 83% yield (63 mg) as a colourless solid. Mp 93–96 °C; IR (film, cm^{-1}) ν 3422, 2968, 1742, 1654, 1551, 1498, 1456, 1391, 1367, 1298, 1169, 1106, 1044, 1017, 911, 872, 839, 697; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.3–7.2 (3H, m), 7.11 (2H, dd, *J*=1.7, 7.8), 6.57 and 6.45 (1H, d, *J*=7.8), 5.2–5.0 (1H, m), 4.9–4.8 (1H, m), 4.0–3.9 (1H, m), 3.70 (3H, s), 3.13 (1H, dd, *J*=5.4, 13.8), 3.05 (1H, d, *J*=6.9, 14.1), 2.1–2.0 (1H, m), 1.44 and 1.43 (9H, s), 0.91 (1H, d, *J*=6.9), 0.86 (3H, app d, *J*=6.9), 0.78 (2H, d, *J*=6.9); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 172.5 and 172.0 (minor), 171.6, 156.1 and 156.0 (minor), 136.1 and 136.0 (minor), 129.5 (minor) and 129.4, 128.91 and 128.89 (minor), 127.4, 80.2, 60.1 (minor) and 59.9, 53.4 (minor) and 53.3, 52.63 and 52.59 (minor), 38.3 and 38.2 (minor), 31.2 (minor) and 31.0, 28.6, 19.5 and 19.4 (minor), 18.0 (minor) and 17.5; HRMS (ESI^+) calcd for $C_{20}H_{30}N_2NaO_5$: 401.2041 $[M+Na]^+$, found: 401.2052 $[M+Na]^+$.

4.3.3. Boc-Val-Phe(4-Cl)-OMe

In accordance with the representative procedure for 1,4-additions with boronic acids, Boc-Val-ΔAla-OMe (150 mg, 0.5 mmol) was reacted with 4-chlorobenzene boronic acid (235 mg, 1.5 mmol). The title compound was obtained as a mixture of diastereomers in 86% yield (177 mg) as an off white solid. Mp 121–123 °C; IR (film, cm^{-1}) ν 4215, 3429, 3332, 3019, 2970, 2934, 2875, 2401, 1742, 1668, 1494, 1447, 1436, 1410, 1392, 1368, 1218, 1173, 1093, 1016, 928, 869, 841, 758, 668; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.25 (2H, dd, *J*=2.1, 8.7), 7.05 (2H, dd, *J*=2.1, 8.7), 6.50 and 6.38 (1H, d, *J*=7.8), 5.01–4.83 (2H, m), 4.00–3.95 and 3.87 (1H, m and dd, *J*=6.3, 8.4), 3.72 (3H, s), 3.17–3.02 (2H, m), 2.21–2.04 (1H, m), 1.45 and 1.44 (9H, s), 0.90–0.80 (6H, m); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 171.9 and 171.8, 171.67 (minor) and 171.65, 156.18, 134.57 and 134.53 (minor), 133.42, 130.96 (minor) and 130.89, 129.11 and 129.08, 80.69, 60.04, 53.31 (minor) and 53.17, 52.81 and 52.80 (minor), 37.72 and 37.69 (minor), 31.02 (minor) and 30.77, 28.61, 19.66 and 19.56 (minor), 17.46 and 17.44 (minor); HRMS (ESI^+) calcd for $C_{20}H_{29}ClN_2NaO_5$: 435.1663 $[M+Na]^+$, found: 435.1661 $[M+Na]^+$.

4.3.4. Boc-Val-Phe(4-Ac)-OMe

In accordance with the representative procedure for 1,4-additions with boronic acids, Boc-Val-ΔAla-OMe (150 mg, 0.5 mmol) was reacted with 4-acetylbenzene boronic acid (246 mg, 01.5 mmol). The title compound was obtained as a mixture of diastereomers in 86% yield (181 mg) as a colourless solid. Mp 123–126 °C; IR (film, cm^{-1}) ν 3340, 3008, 2967, 2934, 2875, 1744, 1652, 1608, 1520, 1436, 1415, 1392, 1366, 1269, 1175, 1120, 1043, 1018, 958, 928, 870, 850, 822, 755, 666, 596; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.86 (2H, d, *J*=8.4), 7.21 (2H, d, *J*=8.4), 6.61 and 6.49 (1H, d, *J*=7.5), 5.03–4.85 (2H, m), 3.98–3.85 (1H, m), 3.70 (3H, s), 3.21 and 3.20 (1H, dd, *J*=5.7, 14.1), 3.12 and 3.11 (1H, dd, *J*=5.7, 14.1), 2.56 and 2.55 (3H, s), 2.17–2.03 (1H, m), 1.43 and 1.41 (9H, s), 0.92–0.83 (4H, m), 0.79 (2H, d, *J*=6.9); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 198.0 and 197.9 (minor), 171.81, 171.75 (minor) and 171.71, 156.1, 141.84 and 141.79 (minor), 136.3, 129.85 (minor) and 129.80, 129.0, 80.4, 60.3 (minor) and 60.0, 53.23 (minor) and 53.11, 52.79 and 52.77 (minor), 38.3, 31.0 and 30.8, 28.58, 26.9, 19.6 and 19.5 (minor), 17.5; HRMS (ESI^+) calcd for $C_{22}H_{32}N_2NaO_6$: 443.2158 $[M+Na]^+$, found: 443.2152 $[M+Na]^+$.

4.3.5. Boc-Val-1-Nal-OMe

In accordance with the representative procedure for 1,4-additions with boronic acids, Boc-Val-ΔAla-OMe (150 mg, 0.5 mmol) was reacted with 1-naphthyl boronic acid (258 mg, 1.5 mmol). The title compound was obtained as a mixture of diastereomers in 62% yield (132 mg) as a colourless solid. Mp 119–122 °C; IR (film, cm^{-1}) ν 3431, 3018, 2969, 2091, 1740, 1665, 1501, 1456, 1438, 1392, 1368, 1283, 1216, 1163, 1018, 927, 757; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.13 and 8.12 (1H, d, *J*=8.4), 7.85 (1H, d, *J*=8.1), 7.76 (1H, d, *J*=8.1), 7.59–7.46 (2H, m), 7.38 (1H, app t, *J*=8.7), 7.27 (1H, app t, *J*=6.3), 6.84 and 6.72 (1H, d, *J*=7.8), 5.16 (1H, app t, *J*=9.0), 5.01 (1H, app q, *J*=7.5), 4.03–3.94 (1H, m), 3.60 and 3.59 (3H, s), 3.57–3.52 (2H, m), 1.46 and 1.44 (9H, s), 0.94–0.75 (6H, m); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 172.5 (minor) and 172.3, 171.8 and 171.7 (minor), 156.1 and 156.0 (minor), 134.12 and 134.10 (minor), 132.5, 132.3 (minor) and 132.2, 129.1, 128.20 and 128.19 (minor), 127.7, 126.7 and 126.6 (minor), 126.0, 125.50 (minor) and 125.45, 123.7 (minor) and 123.6, 80.0, 60.0 (minor) and 59.8, 53.4 (minor) and 53.3, 52.5 and 52.4 (minor), 35.8 and 35.6 (minor), 31.2 (minor) and 31.1, 19.42 and 19.38 (minor), 17.86 (minor) and 17.52; HRMS (ESI^+) calcd for $C_{24}H_{33}N_2O_5$: 429.2389 $[M+H]^+$, found: 429.2374 $[M+H]^+$.

4.3.6. Boc-Val-Phe(3-Br)-OMe

In accordance with the representative procedure for 1,4-additions with boronic acids, Boc-Val-ΔAla-OMe (150 mg, 0.5 mmol) was reacted with 3-bromobenzene boronic acid (301 mg, 1.5 mmol). The title compound was obtained as a mixture of diastereomers in 86% yield (196 mg) as a colourless foam. IR (film, cm^{-1}) ν 3344, 2962, 2872, 1734, 1688, 1649, 1552, 1521, 1476, 1435, 1390, 1366, 1349, 1299, 1245, 1177, 1121, 1073, 1044, 1020, 851, 818, 697; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.35 (1H, dt, J=7.8, 1.5), 7.28 (1H, s), 7.14 (1H, app t, J=7.8), 7.06 (1H, dt, J=7.8, 1.5), 6.66 and 6.60 (1H, d, J=7.5), 5.08 (1H, d, J=8.7), 4.90–4.81 (1H, m), 4.01–3.89 (1H, m), 3.71 (3H, s), 3.11 (1H, dd, J=13.8, 5.7), 3.00 (1H, dd, J=13.8, 8.1), 2.15–2.02 (1H, m), 1.44 and 1.42 (9H, s), 0.93–0.80 (6H, m); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 171.9, 171.8 and 171.7 (minor), 156.1, 138.6 and 138.5 (minor), 132.64 and 132.63 (minor), 130.5, 130.41 and 130.40 (minor), 128.2 (minor) and 128.1, 122.85 and 122.82 (minor), 80.2, 60.4 (minor) and 59.9, 53.4 (minor) and 53.3, 52.8 and 52.7 (minor), 37.9, 31.1 and 30.0 (minor), 28.6, 19.6 and 19.5 (minor), 18.1 (minor) and 17.5; HRMS (ESI^+) calcd for $C_{20}H_{30}BrN_2O_5$: 457.1338 $[M+H]^+$, found: 457.1329 $[M+H]^+$.

4.3.7. Boc-Val-Phe(4-CHO)-OMe

In accordance with the representative procedure for 1,4-additions with boronic acids, Boc-Val-ΔAla-OMe (150 mg, 0.5 mmol) was reacted with 4-formylbenzene boronic acid (225 mg, 1.5 mmol). The title compound was obtained as a mixture of diastereomers in 33% yield (45 mg) as an off white foam. IR (film, cm^{-1}) ν 3425, 3316, 3019, 2968, 2934, 2875, 1743, 1702, 1670, 1610, 1578, 1507, 1455, 1438, 1420, 1392, 1368, 1216, 1171, 1118, 1043, 1019, 851, 759, 668; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.94 and 9.93 (1H, s), 7.78 (2H, d, J=8.1), 7.30 (2H, d, J=8.1), 6.74 and 6.64 (1H, d, J=4.8), 5.09–5.03 (1H, m), 4.92–4.87 (1H, m), 3.99–3.86 (1H, m), 3.702 and 3.699 (3H, s), 3.23 (1H, dd, J=5.7, 13.8), 3.13 and 3.12 (1H, dd, J=6.9, 13.8), 2.15–2.02 (1H, m), 1.43 and 1.41 (9H, s), 0.91–0.77 (6H, m); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 192.13 (minor) and 192.08, 171.9 (minor) and 171.84, 171.77 and 171.6 (minor), 156.2 and 156.1 (minor), 143.54 and 143.47 (minor), 135.63 and 135.61 (minor), 130.27, 130.25, 80.3, 60.3 (minor) and 60.0, 53.2 (minor) and 53.1, 52.79 and 52.77 (minor), 38.5, 31.0 (minor) and 30.8, 28.6, 19.6 and 19.5 (minor), 18.3 (minor) and 17.5; HRMS (ESI^+) calcd for $C_{21}H_{31}N_2O_6$: 407.2182 $[M+H]^+$, found: 407.2159 $[M+H]^+$.

4.3.8. Boc-Val-Phe(4-OMe)-OMe

In accordance with the representative procedure for 1,4-additions with siloxanes, Boc-Val-ΔAla-OMe (75 mg, 0.25 mmol) was reacted with triethoxy(4-methoxyphenyl)silane (196 μL, 0.75 mmol). The title compound was isolated as a mixture of diasteromers as a colourless solid (87 mg, 85%). Mp 98–99 °C; IR ($CDCl_3$, cm^{-1}) ν 3054, 2964, 2935, 2874, 2838, 2253, 1743, 1706, 1664, 1612, 1513, 1465, 1437, 1367, 1265, 1250, 1178, 1117, 1036, 909, 840, 733; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.01 (2H, d, J=8.6), 6.80 (2H, d, J=8.6), 6.49 and 6.37 (1H, d, J=7.9), 5.12–4.96 (1H, m), 4.86–4.77 (1H, m), 4.00–3.85 (1H, m), 3.76 and 3.75 (3H, s), 3.69 (3H, s), 3.05–3.01 (2H, m), 2.17–2.03 (1H, m), 1.43 and 1.41 (9H, s), 0.96–0.84 (6H, m); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 172.3 and 172.1, 171.6 and 171.5, 159.1, 156.1, 130.6 and 130.5, 128.0 and 127.9, 114.4 and 114.4, 80.3, 60.2 and 60.0, 55.5 and 55.5, 53.6 and 53.5, 52.9 and 52.8, 37.5 and 37.4, 31.3 and 31.1, 28.6, 19.6 and 19.5; HRMS (ESI^+) calcd for $C_{21}H_{32}N_2NaO_6$: 401.2158 $[M+Na]^+$, found: 431.2145 $[M+Na]^+$.

4.3.9. Boc-Val-Phe(4-CF_3)-OMe

In accordance with the representative procedure for 1,4-additions with siloxanes, Boc-Val-ΔAla-OMe (75 mg, 0.25 mmol) was reacted with triethoxy(4-(trifluoromethyl)phenyl)silane (210 mg, 0.75 mmol). The title compound was isolated as a mixture of diasteromers as a colourless solid (68 mg, 61%). Mp 122–124 °C; IR ($CDCl_3$, cm^{-1}) ν 3430, 3018, 2967, 1740, 1685, 1656, 1521, 1438, 1392, 1368, 1325, 1299, 1216, 1165, 1125, 1067, 1018, 757, 666; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.47 (2H, d, J=7.9), 7.18 (2H, d, J=7.9), 6.54 and 6.43 (1H, d, J=7.8), 4.98–4.78 (2H, m), 3.84–3.78 and 4.00–3.86 (1H, m), 3.65 (3H, s), 3.16 (1H, dd, J=5.6, 13.9), 3.04 (1H, dd, J=6.4, 13.9), 1.94–2.20 (1H, m), 1.37 and 1.34 (9H, s), 0.96–0.70 (6H, m); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 171.8 and 171.8, 171.8 and 171.7, 156.1, 140.4, 129.6, 125.9, 122.7, 80.4, 60.5 and 60.1, 53.2 and 53.1, 52.8 and 52.8, 38.1, 30.5, 28.6, 19.7 and 19.6; ^{19}F NMR ($CDCl_3$, 376.4 MHz) −62.48 and −62.54; HRMS (ESI^+) calcd for $C_{21}H_{29}F_3N_2O_5$: 447.2029 $[M+H]^+$, found: 447.2106 $[M+H]^+$.

4.3.10. Boc-Val-Phe(4-Me)-OMe

In accordance with the representative procedure for 1,4-additions with siloxanes, Boc-Val-ΔAla-OMe (75 mg, 0.25 mmol) was reacted with triethoxy(*p*-tolyl)silane (193 μL, 0.75 mmol). The title compound was isolated as a mixture of diasteromers as a colourless oil (98 mg, 66%). Mp 92–94 °C; IR ($CDCl_3$, cm^{-1}) ν 3312, 3053, 2963, 2929, 2873, 2251, 1745, 1702, 1656, 1542, 1515, 1458, 1435, 1390, 1366, 1291, 1248, 1176, 1119, 1043, 1017, 910, 880, 731, 647; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.08 (2H, d, J=7.9), 6.99 (2H, d, J=7.9), 6.40 and 6.28 (1H, d, J=7.9), 5.08–4.90 (1H, m), 4.84 (1H, app dq, J=7.9, 6.0), 4.00–3.85 (1H, m), 3.71 (3H, s), 3.14–2.99 (2H, m), 2.30 (3H, s), 2.16–2.01 (1H, m), 1.44 and 1.43 (9H, s) 0.93–0.8 (6H, m); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 172.2 and 172.1, 171.6 and 171.5, 156.1, 137.1, 132.9, 130.2, 129.7 and 129.4, 80.2, 60.2 and 60.0, 53.5 and 53.4, 52.9 and 52.6, 37.9, 31.2 and 31.0, 28.6, 21.8 and 21.4, 21.2; HRMS (ESI^+) calcd for $C_{21}H_{32}N_2NaO_5$: 415.2209 $[M+Na]^+$, found: 415.2224 $[M+Na]^+$.

*4.3.11. Boc-Phe-ΔAla-OMe (**9**)*

An oven dried flask was charged with Boc-Phe-Ser-OMe (1.80 g, 4.91 mmol) dissolved in degassed dichloromethane (60 mL) under an atmosphere of nitrogen, copper(I) chloride (145 mg, 1.47 mmol) and EDCI (1.04 g, 5.40 mmol) were subsequently added and the resultant suspension stirred for 18 h at ambient temperature. The solution was washed with two portions of water (20 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by flash column chromatography (petroleum ether/ethyl acetate 5:1) gave the title compound as a colourless foam in 77% yield (1.32 g). $[\alpha]_D^{20}$ −17.58 (*c* 0.46, $CHCl_3$); mp 94–96 °C; IR ($CDCl_3$, cm^{-1}) ν 3362, 3019, 2088, 1748, 1687, 1527, 1443, 1392, 1368, 1326, 1252, 1221, 1172, 1057, 1030, 988, 746, 702, 668; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.22 (1H, br s), 7.34–7.18 (5H, m), 6.62 (1H, s), 5.90 (1H, d, J=1.5), 5.11 (1H, br d, J=7.2), 4.55–4.39 (1H, br m), 3.80 (3H, s), 3.16 (1H, dd, J=6.6, 14.1), 3.13–3.04 (1H, m), 1.42 (9H, s); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 170.6, 164.3, 155.6, 136.6, 130.9, 129.5, 129.0, 127.3, 109.6, 80.7, 56.8, 53.2, 38.4, 28.5; HRMS (ESI^+) calcd for $C_{18}H_{24}N_2NaO_5$: 371.1583 $[M+Na]^+$, found: 371.1569 $[M+Na]^+$.

4.3.12. Boc-Phe-Phe-OMe

In accordance with the representative procedure for 1,4-additions with boronic acids, Boc-Phe-ΔAla-OMe (70 mg, 0.2 mmol) was reacted with phenyl boronic acid (98 mg, 0.8 mmol). The title compound was obtained as a mixture of diastereomers in 66% yield (55 mg) as a colourless solid. Mp 108–110 °C; IR (film, cm^{-1}) ν 3312, 3088, 3065, 3030, 3008, 2980, 2953, 2932, 2864, 1950, 174, 1660, 1498, 1455, 1438, 1392, 1367, 1251, 1218, 1171, 1116, 1080, 1049, 1023, 918, 887, 856, 817, 756, 700, 666; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.32–7.15 (8H, m), 7.02–6.94 (2H, m), 6.48 and 6.37 (1H, d, J=7.5), 4.98–5.05 (1H, m), 4.88–4.76 (1H, m), 4.42–4.32 (1H, m), 3.67 (3H, s), 3.12–2.94 (4H, m), 1.41 and 1.39 (9H, s); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 171.8 (minor) and 171.6, 171.2 and 171.1 (minor), 155.6, 136.9 and 136.8 (minor), 135.95 and 135.87 (minor), 129.64 and 129.63 (minor), 129.50 and 129.45 (minor), 128.9 (minor) and 128.8, 127.42 (minor) and 127.37, 127.2, 80.4, 53.6, 53.4, 52.5, 38.7, 38.3 and 38.2

(minor), 28.5; HRMS (ESI^+) calcd for $C_{24}H_{31}N_2O_5$: 427.2233 $[M+H]^+$, found: 427.2219 $[M+H]^+$.

4.3.13. Boc-Phe-Phe(3-NO_2)-OMe

In accordance with the representative procedure for 1,4-additions with boronic acids, Boc-Phe-ΔAla-OMe (174 mg, 0.5 mmol) was reacted with 3-nitrobenzene boronic acid (250 mg, 1.5 mmol). The title compound was obtained as a mixture of diastereomers in 43% yield (101 mg) as an off white solid. Mp 95–99 °C; IR (film, cm^{-1}) ν 3316, 3065, 3028, 3009, 2979, 2956, 2932, 2868, 1746, 1671, 1531, 1455, 1438, 1392, 1367, 1352, 1317, 1252, 1219, 1170, 1082, 1054, 1028, 988, 920, 885, 855, 820, 756, 700, 667; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.08 (1H, dm, J=7.5), 7.91–7.89 (1H, m), 7.40 (1H, app t, J=7.8), 7.3–7.1 (6H, m), 6.63 and 6.53 (1H, d, J=7.5), 4.92 (1H, d, J=8.1), 4.9–4.8 (1H, m), 4.4–4.3 (1H, m), 3.79 and 3.70 (3H, s), 3.3–2.9 (4H, m) 1.38 and 1.36 (9H, s); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 171.49 (minor) and 171.45, 171.1, 155.7, 148.54 and 148.53 (minor), 138.3 (minor) and 138.2, 136.8 and 136.7 (minor), 135.92 (minor) and 135.86, 129.79 and 129.75 (minor), 129.7 (minor) and 129.6, 129.0, 127.4, 124.5 (minor) and 124.4, 122.5, 80.8, 56.1, 53.4 (minor) and 53.3, 52.9, 38.3, 37.9, 28.6 (minor) and 28.5; HRMS (ESI^+) calcd for $C_{24}H_{29}N_3NaO_7$: 494.1903 $[M+Na]^+$, found: 494.1899 $[M+Na]^+$.

4.3.14. Boc-Phe-Phe(4-Ac)-OMe

In accordance with the representative procedure for 1,4-additions with boronic acids, Boc-Phe-ΔAla-OMe (174 mg, 0.5 mmol) was reacted with 4-acetylbenzene boronic acid (246 mg, 1.5 mmol). The title compound was obtained as a mixture of diastereomers in 65% yield (152 mg) as a colourless foam. IR (film, cm^{-1}) ν 4064, 3672, 3303, 3063, 3029, 3807, 2979, 2964, 2932, 2866, 1744, 1682, 1608, 1521, 1455, 1438, 1415, 1392, 1366, 1269, 1219, 1170, 1121, 1079, 1048, 1019, 959, 888, 853, 823, 755, 700, 666, 597; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.83 and 7.52 (2H, d, J=8.1), 7.32–7.05 (7H, m), 6.68 and 6.56 (1H, d, J=7.5), 5.08 (1H, d, J=8.1), 4.90–4.89 (1H, m), 4.44–4.34 (1H, m), 3.67 (3H, s), 3.19–2.94 (4H, m), 2.564 and 2.559 (3H, s), 1.40 and 1.38 (9H, s); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 197.92 (minor) and 197.87, 171.5, 171.33 and 171.29 (minor), 155.6, 141.7 (minor) and 141.6, 136.8 and 136.7 (minor), 136.21 and 136.20 (minor), 129.6, 128.9, 128.84 and 128.79 (minor), 127.2, 80.5, 56.0, 53.3 (minor) and 53.1, 52.6, 38.4 and 38.2 (minor) and 38.1, 28.5, 26.8; HRMS (ESI^+) calcd for $C_{26}H_{33}N_2O_6$: 469.2339 $[M+H]^+$, found: 469.2340 $[M+H]^+$.

4.3.15. Boc-Phe-Phe(4-CHO)-OMe

In accordance with the representative procedure for 1,4-additions with boronic acids, Boc-Phe-ΔAla-OMe (174 mg, 0.5 mmol) was reacted with 4-formylbenzene boronic acid (225 mg, 1.5 mmol). The title compound was obtained as a mixture of diastereomers in 33% yield (76 mg) as a colourless foam. IR (film, cm^{-1}) ν 3316, 3063, 3031, 2978, 2931, 2860, 2738, 2361, 1746, 1698, 1608, 1577, 1529, 1454, 1437, 1392, 1367, 1274, 1252, 1171, 1118, 1052, 1025, 986, 887, 852, 751, 700, 646; ^1H NMR ($CDCl_3$, 300 MHz) δ 9.95 (1H, s), 7.75 and 7.74 (2H, d, J=8.1), 7.36–7.10 (7H, m), 6.61 and 6.50 (1H, d, J=7.5), 5.99 (1H, d, J=8.4), 4.91–4.81 (1H, m), 4.39–4.30 (1H, m), 3.672 and 3.668 (3H, s), 3.21–2.95 (4H, m), 1.40 and 1.37 (9H, s); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 192.12 (minor) and 192.09, 171.43, 171.38, 155.7, 143.3 (minor) and 143.2, 136.8 and 136.7 (minor), 135.6, 130.2, 129.6, 129.0, 127.3, 80.7, 56.0, 53.3 (minor) and 53.1, 52.7, 38.43, 38.37, 28.5; HRMS (ESI^+) calcd for $C_{25}H_{31}N_2O_6$: 455.2182 $[M+H]^+$, found: 455.2172 $[M+H]^+$.

4.3.16. Boc-Phe-Phe(4-Cl)-OMe

In accordance with the representative procedure for 1,4-additions with siloxanes, Boc-Phe-ΔAla-OMe (87 mg, 0.25 mmol) was reacted with triethoxy(4-chlorophenyl)silane (185 mg, 0.75 mmol). The title compound was obtained as a mixture of diastereomers in 60% yield (69 mg) as a colourless oil. IR (film, cm^{-1}) ν 3331, 2987, 2933, 1740, 1651, 1614, 1583, 1512, 1475, 1418, 1491, 1378, 1313, 1257, 1227, 1175, 1111, 1033, 931; ^1H NMR (250 MHz, $CDCl_3$) δ 7.30–7.05 (7H, m), 6.82 (2H, dd, J=6.8), 6.35 and 6.25 (1H, d, J=7.8), 4.9–4.65 (2H, m), 4.45–4.40 and 4.28–2.20 (1H, m), 3.61 and 3.60 (3H, s), 3.1–2.8 (4H, m), 1.34 and 1.31 (9H, s); ^{13}C NMR (75.5 MHz, $CDCl_3$) 170.2 and 170.1, 169.9 and 169.8, 154.3, 135.5 and 135.4, 133.1 and 133.0, 132.1 and 132.0, 129.6 and 129.5, 128.34 and 128.31, 127.7 and 127.6, 126.04 and 125.99, 79.4, 52.1 and 51.9, 51.5 and 51.4, 47.1 and 46.9, 37.2 and 31.1, 36.3 and 36.2, 27.2; HRMS (ESI^+) calcd for $C_{24}H_{29}N_2NaO_5Cl$: 483.1663 $[M+Na]^+$, found: 483.1646 $[M+Na]^+$.

4.3.17. Boc-Phe-Phe(2-Me)-OMe

In accordance with the representative procedure for 1,4-additions with siloxanes, Boc-Phe-ΔAla-OMe (87 mg, 0.25 mmol) was reacted with triethoxy(*o*-tolyl)silane (127 mg, 0.5 mmol). The title compound was obtained as a mixture of diastereomers in 81% yield (90 mg) as a colourless oil. IR (film, cm^{-1}) ν 3054, 2984, 1741, 1712, 1678, 1497, 1255, 1438, 1368, 1211, 1167, 1049; ^1H NMR (300 MHz, $CDCl_3$) δ 7.35–7.05 (8H, m), 7.00–6.89 (1H, m), 6.55 and 6.40 (1H, dd, J=7.6), 5.10–5.05 (1H, m), 4.75 (1H, m), 4.40–4.30 (1H, m), 3.64 (3H, s), 2.88–3.14 (4H, m), 2.32 and 2.31 (3H, s), 1.41 and 1.39 (9H, s); ^{13}C NMR (75.5 MHz, $CDCl_3$) 172.5, 172.2, 171.2, 137.0, 136.9, 134.4, 131.0, 130.1, 130.1, 129.7, 129.7, 129.0, 127.6, 127.3, 126.4, 80.5, 60.8, 52.8, 38.7, 36.3, 36.1, 28.6, 21.4, 19.7, 19.6, 14.6; HRMS (CI^+) calcd for $C_{25}H_{33}N_2O_5$: 441.2384 $[M+H]^+$, found: 441.2385 $[M+H]^+$.

4.3.18. Boc-Phe-Anthtra-OMe

In accordance with the representative procedure for 1,4-additions with siloxanes, Boc-Phe-ΔAla-OMe (87 mg, 0.25 mmol) was reacted with triethoxy(phenanthren-10-yl)silane (170 mg, 0.5 mmol). The title compound was obtained as a mixture of diastereomers in 76% yield (100 mg) as a colourless solid. Mp 199–201 °C; IR (film, cm^{-1}) ν 3320, 1744, 1659, 1523, 1497, 1455, 1391, 1357, 1213, 1123, 1022, 856; ^1H NMR (300 MHz, $CDCl_3$) δ 8.64–8.63 (1H, m, Ar), 8.60–8.56 (1H, d, J=8.1), 8.10–8.04 (1H, m), 7.72–7.70 (1H, m), 7.63–7.40 (4H, m), 7.41–7.34 (1H, d, J=15.2), 7.00–7.18 (5H, m), 6.42 and 6.30 (1H, dd, J=7.4), 4.9 (2H, m), 4.28 (1H, m), 3.42 (3H, s), 3.41–3.30 (2H, m), 2.90 (2H, m), 1.28 (9H, s); ^{13}C NMR (75.5 MHz, $CDCl_3$) 172.4, 172.1, 171.4, 136.8, 131.7, 131.2, 131.2, 131.1, 131.1, 130.8, 130.5, 129.7, 129.6, 129.0, 128.9, 128.6, 127.4, 127.3, 127.2, 127.0, 124.5, 124.4, 123.7, 122.9, 79.1, 53.3, 53.3, 52.6, 36.4, 28.6, 14.1; HRMS (ESI^+) calcd for $C_{32}H_{35}N_2O_5$: 527.2540 $[M+H]^+$, found: 527.2542 $[M+H]^+$.

4.3.19. Boc-Phe-Phe(4-OMe)-OMe

In accordance with the representative procedure for 1,4-additions with siloxanes, Boc-Phe-ΔAla-OMe (87 mg, 0.25 mmol) was reacted with triethoxy(4-methoxyphenyl)silane (148 mg, 0.75 mmol). The title compound was obtained as a mixture of diastereomers in 78% yield (90 mg) as a colourless oil. IR (film, cm^{-1}) ν 3315, 2978, 2934, 1743, 1659, 1613, 1584, 1513, 1455, 1441, 1391, 1367, 1301, 1249, 1216, 1173, 1118, 1032, 911, 838, 789, 732, 700, 647; ^1H NMR (300 MHz, $CDCl_3$) δ 7.26–7.08 (5H, m), 6.85–6.65 (4H, m), 6.27 and 6.17 (1H, d, J=7.5), 4.86–4.80 (1H, m), 4.75–4.65 (1H, m), 4.45–4.20 (1H, m), 3.70 and 3.69 (3H, s), 3.60 (3H, s), 3.04–2.88 (4H, m), 1.34 and 1.31 (9H, s); ^{13}C NMR (75.5 MHz, $CDCl_3$) 171.9 and 171.8, 171.1 and 171.0, 159.1 and 159.0, 155.9, 137.0 and 136.9, 130.6 and 130.5, 129.7 and 129.7, 129.0, 127.9 and 127.8, 127.3, 114.4 and 114.3, 80.6, 55.5, 53.8 and 53.5, 52.8 and 52.6, 48.3, 38.7, 37.4 and 37.4, 28.6; HRMS (ESI^+) calcd for $C_{25}H_{32}N_2NaO_6$: 479.2158 $[M+Na]^+$, found: 479.2158 $[M+Na]^+$.

4.3.20. Boc-Tyr-ΔAla-OMe (**10**)

To an oven dried flask were added Boc-Tyr-Ser-OMe (0.28 g, 0.73 mmol) in degassed dichloromethane (10 mL), copper(I) chloride (22 mg, 0.22 mmol) and EDCI (154 mg, 0.80 mmol, 1.1 equiv),

the flask was sealed and the solution stirred under an atmosphere of nitrogen for 18 h at ambient temperature. The solution was diluted with dichloromethane (5 mL) and washed with two portions of water (10 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by flash column chromatography (ethyl acetate/petroleum ether 1:5) gave the title compound as a colourless solid (119 mg, 45%). $[\alpha]_D^{20}$ −10.6 (*c* 0.47, CH_2Cl_2); mp 128–130 °C; IR (KBr) 3415 (br), 3218 (br), 3015, 2929, 1736, 1687, 1665, 1634, 1593, 1544, 1515, 1479, 1440, 1400, 1368, 1269, 1199, 1163 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.04 (1H, br s), 6.98 (2H, d, *J*=8.1), 6.69 (2H, d, *J*=8.1), 6.60 (1H, s), 6.10–5.90 (1H, br s), 5.82 (1H, br s), 4.92 (1H, br s), 4.15–4.02 (1H, m), 3.73 (3H, s), 2.99–2.94 (2H, m), 1.35 (9H, s); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 170.8, 164.4, 155.9, 130.9, 130.7, 128.1, 116.1, 116.0, 109.9, 81.1, 57.1, 53.4, 49.7, 28.6; MS (ESI^+) *m/z* 265.2 $[M+H]^+$; HRMS (ESI^+) calcd for $C_{18}H_{25}N_2O_6$: 365.1707 $[M+H]^+$, found: 365.1706 $[M+H]^+$.

4.3.21. Boc-Tyr-Phe(4-CN)-OMe

In accordance with the representative procedure for 1,4-additions with boronic acids, Boc-Tyr-ΔAla-OMe (55 mg, 0.15 mmol) was reacted with 4-cyanobenzene boronic acid (87 mg, 0.6 mmol, 4 equiv) in the presence of sodium fluoride (19 mg, 0.45 mmol). The title compound was obtained as a mixture of diastereoisomers in 86% yield (60 mg) as an off white foam. IR (film, cm^{-1}) ν 3408 (br), 3020, 2983, 2231, 1742, 1666, 1614, 1516, 1443, 1368, 1217, 1171, 1119, 1052, 1022, 850, 826, 756, 669; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.53 (1H, d, *J*=8.3), 7.51 (1H, d, *J*=8.1), 7.13 (1H, d, *J*=8.3), 7.05 (1H, d, *J*=8.1), 7.02 (2H, app d, *J*=8.4), 6.74 (1H, d, *J*=8.4), 6.72 (1H, d, *J*=8.4), 6.55 and 6.37 (1H, d, *J*=6.3 and 7.8), 5.6–5.3 (1H, br s, O*H*), 4.99–4.73 (2H, m), 4.33–4.21 (1H, m), 3.69 and 3.68 (3H, s), 3.20–2.86 (4H, m), 1.42 and 1.40 (9H, s); ^{13}C NMR ($CDCl_3$, 75.5 MHz, mixture of diastereoisomers) δ 171.71 and 171.67, 171.4 and 171.2, 155.9, 155.5, 141.9 and 141.8, 132.72 and 132.67, 130.86 and 130.83, 130.54 and 130.45, 129.1, 128.3, 127.8, 119.2, 116.0, 111.4, 81.1, 53.4, 53.2, 53.0, 38.4 and 38.3, 37.7, 28.6; HRMS (ESI^-) calcd for $C_{25}H_{28}N_3O_6$: 466.1978 $[M-H]^-$, found: 466.1977 $[M-H]^-$.

4.3.22. Boc-Tyr-Phe(4-OMe)-OMe

In accordance with the representative procedure for 1,4-additions with boronic acids, Boc-Tyr-ΔAla-OMe (73 mg, 0.2 mmol) was reacted with 4-methoxybenzene boronic acid (122 mg, 0.8 mmol, 4 equiv). The title compound was obtained as a mixture of diastereomers in 65% yield (79 mg) as an off white foam. IR (film, cm^{-1}) ν 3413 (br), 2254, 1655, 1516, 1446, 1368, 1249, 1166, 908, 733, 650; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.05–6.82 (1H, br s), 6.99–6.85 (4H, m), 6.78–6.70 (4H, m), 6.51 and 6.38 (1H, d, *J*=7.2), 5.11–5.01 (1H, m), 4.80–4.69 (1H, m), 4.42–4.23 (1H, m), 3.75 and 3.74 (3H, s), 3.66 and 3.65 (3H, s), 3.01–2.87 (4H, m), 1.40 and 1.39 (9H, s); ^{13}C NMR ($CDCl_3$, 75.5 MHz, mixture of diastereoisomers) δ 172.1, 171.7, 159.1, 155.9, 130.8, 130.63 and 130.56, 129.83, 127.9 and 127.8, 116.1, 114.5 and 114.4, 80.7, 55.6, 53.9, 53.7,52.7, 37.9, 37.47 and 37.36, 28.7; HRMS (ESI^+) calcd for $C_{25}H_{33}N_2O_7$: 473.2288 $[M+H]^+$, found: 473.2280 $[M+H]^+$.

4.3.23. Boc-Tyr-Phe(4-Cl)-OMe

In accordance with the representative procedure for 1,4-additions with boronic acids, Boc-Tyr-ΔAla-OMe (55 mg, 0.15 mmol) was reacted with 4-chlorobenzene boronic acid (70 mg, 0.45 mmol, 3 equiv). The title compound was obtained as a mixture of diastereomers in 57% yield (41 mg) as an off white foam. IR (film, cm^{-1}) ν 4214, 3419 (br), 3020, 2983, 2401, 1742, 1665, 1615, 1516, 1493, 1445, 1369, 1216, 1166, 1093, 1017, 929, 756, 669; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.32 and 1.34 (9H, s), 2.78–3.00 (4H, m), 3.58 and 3.59 (3H, s), 4.11–4.32 (1H, m), 4.64–4.77 (1H, m), 4.91–5.06 (1H, m), 6.38 and 6.54 (1H, d, *J*=7.5), 6.64 (2H, dd, *J*=2.1, 8.7), 6.68 (1H, br s), 6.78–6.92 (4H, m), 7.12 (2H, dd, *J*=1.5, 8.4); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 171.8, 171.7, 171.6, 155.9, 155.7, 134.5, 134.4, 133.5, 133.4, 131.0, 130.9, 130.8, 129.2, 129.1, 128.1, 116.0, 81.0, 53.8, 53.5, 52.8, 37.8, 37.7, 37.6, 28.6; HRMS (ESI^+) calcd for $C_{24}H_{30}ClN_2O_6$: 477.1787 $[M+H]^+$, found: 477.1788 $[M+H]^+$.

4.3.24. Boc-Trp-ΔAla-OMe (**11**)

To an oven dried flask were added Boc-Trp-Ser-OMe (0.50 g, 1.23 mmol) in degassed dichloromethane (10 mL), copper(I) chloride (37 mg, 0.3 mmol) and EDCI (260 mg, 1.35 mmol, 1.1 equiv), the flask was sealed and the solution stirred under an atmosphere of nitrogen for 18 h at ambient temperature. The solution was diluted with dichloromethane (5 mL) and washed with two portions of water (10 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by flash column chromatography (ethyl acetate/petroleum ether 1:5) gave the title compound as a colourless solid (260 mg, 55%). Mps–$[\alpha]_D^{20}$ −35.8 (*c* 2.4, CH_2Cl_2); mp 78–80 °C; IR (KBr) 3371 (br), 3067, 2977, 2931, 2852, 1710, 1682, 1636, 1517, 1439, 1328, 1250, 1166, 1098, 1054, 1010, 961, 906, 742 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.23 (1H, br s), 8.06 (1H, br s), 7.53 (1H, d, *J*=9.0), 7.26 (1H, d, *J*=9.0), 7.11 (1H, t, *J*=6.9), 7.05 (1H, t, *J*=6.9), 6.95 (1H, br s), 6.52 (1H, br s), 5.78 (1H, br s), 5.07 (1H, br s), 4.45 (1H, br s), 3.64 (3H, s), 3.24–3.13 (2H, m), 1.32 (9H, s); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 171.2, 164.3, 155.9, 136.7, 131.1, 127.8, 123.6, 122.7, 120.2, 119.1, 111.6, 110.6, 109.7, 80.9, 56.4, 53.2, 49.6, 28.6; MS (ESI^+) *m/z* 388.2 $[M+H]^+$; HRMS (ESI^+) calcd for $C_{20}H_{26}N_3O_5$: 388.1867 $[M+H]^+$; found: 388.1870 $[M+H]^+$.

4.3.25. Boc-Trp-Phe(4-CN)-OMe

In accordance with the representative procedure for 1,4-additions with boronic acids, Boc-Trp-ΔAla-OMe (58 mg, 0.15 mmol) was reacted with 4-cyanobenzene boronic acid (89 mg, 0.6 mmol, 4 equiv). The title compound was obtained as a mixture of diastereomers in 65% yield (48 mg) as an off white foam. IR (film, cm^{-1}) ν 3409 (br), 3018, 2928, 2856, 1680, 1612,1514, 1457, 1442, 1368, 1249, 1216, 1165, 1119, 1093, 1026, 855, 757, 669; ^1H NMR ($CDCl_3$, 300 MHz, mixture of diastereoisomers) δ 8.35 (1H, br s), 7.63 (1H, app t, *J*=8.7), 7.36 (3H, app d, *J*=8.4), 7.23–7.16 (1H, m), 7.15–7.09 (1H, m), 7.02 (1H, dd, *J*=10.5, 2.0), 6.89 (2H, d, *J*=8.1), 6.43 and 6.32 (1H, d, *J*=7.2), 5.00–5.18 (1H, m), 4.84–4.67 (1H, m), 4.52–4.36 (1H, m), 6.60 and 3.59 (3H, s), 3.07–3.38 (2H, m), 2.84–3.06 (2H, m), 1.43 and 1.39 (9H, s); ^{13}C NMR ($CDCl_3$, 75.5 MHz, mixture of diastereoisomers) δ 171.86 and 171.81, 171.13 and 170.98, 155.8, 141.69 and 141.60, 136.62 and 136.56, 132.46 and 132.38, 130.30 and 130.27, 127.71 and 127.63, 123.6, 123.4, 122.72 and 122.68, 120.16 and 120.12, 119.21 and 119.12, 119.01 and 118.99, 111.62 and 111.58, 111.21 and 111.17, 110.7, 80.7, 53.2, 53.0, 52.7, 38.21, 38.15, 28.58 and 28.56; HRMS (ESI^+) calcd for $C_{27}H_{31}N_4O_5$: 491.2294 $[M+H]^+$, found: 491.2285 $[M+H]^+$.

4.3.26. Boc-Trp-Phe(4-Cl)-OMe

In accordance with the representative procedure for 1,4-additions with boronic acids, Boc-Trp-ΔAla-OMe (58 mg, 0.15 mmol) was reacted with 4-chlorobenzene boronic acid (70 mg, 0.45 mmol, 3 equiv). The title compound was obtained as a mixture of diastereomers in 68% yield (51 mg) as an off white foam. IR (film, cm^{-1}) ν 3416 (br), 3019, 1742, 1671, 1492, 1458, 1438, 1368, 1216, 1167, 1093, 1016, 842, 757, 669; ^1H NMR ($CDCl_3$, 300 MHz, mixture of diastereoisomers) δ 8.24 (1H, br s), 7.64 (1H, app t, *J*=8.4), 7.36 (1H, dm, *J*=7.8), 7.21 (1H, tm, *J*=7.2), 7.14 (1H, dm, *J*=7.2), 7.12–7.05 (2H, m), 7.00 and 6.97 (1H, d, *J*=2.4), 6.71 (2H, app dd, *J*=5.4, 8.4), 6.33 and 6.26 (1H, d, *J*=7.5), 5.20–5.00 (1H, m), 4.81–4.66 (1H, m), 4.52–4.38 (1H, m), 3.60 (3H, s), 3.33–3.21 (1H, m), 3.23 and 3.12 (1H, dd, *J*=7.2, 14.4), 2.95–2.83 (1H, m), 2.89 and 2.78 (1H, dd, *J*=5.7, 13.8 and m), 1.43 and 1.40 (9H, s); ^{13}C NMR ($CDCl_3$, 75.5 MHz) 171.6, 171.5, 171.3, 171.2, 136.4, 136.3, 134.3, 134.1, 133.1, 133.0, 130.6, 130.6, 128.8, 128.7, 127.6, 123.4, 123.2, 122.5, 120.0, 119.9, 119.0, 119.0, 111.4,

111.4, 80.4, 55.3, 53.2, 53.0, 52.4, 37.3, 37.2, 28.4; HRMS (ESI^+) calcd for $C_{26}H_{31}O_5N_3Cl$: 500.1947 $[M+H]^+$, found: 500.1946 $[M+H]^+$.

4.3.27. Boc-Trp-Phe(4-F)-OMe

In accordance with the representative procedure for 1,4-additions with boronic acids, Boc-Trp-ΔAla-OMe (58 mg, 0.15 mmol) was reacted with 4-fluorobenzene boronic acid (84 mg, 0.6 mmol, 4 equiv). The title compound was obtained as a mixture of diastereomers in 50% yield (36 mg) as an off white foam. IR (film, cm^{-1}) ν 3414 (br), 3018, 2968, 1742, 1672, 1602, 1510, 1458, 1439, 1368, 1216, 1160, 1093, 1047, 1016, 927, 846, 755, 668; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.14 (1H, br s), 7.65 (1H, app t, J=6.6), 7.36 (1H, d, J=8.1), 7.21 (1H, app tdd, J=7.2, 3.0, 1.2), 7.13 (1H, app tdd, J=7.2, 1.8, 1.2), 7.04 and 7.00 (1H, d, J=2.1), 6.84–6.71 (4H, m), 6.28 and 6.21 (1H, d, J=7.8), 5.15–5.00 (1H, m), 4.78–4.65 (1H, m), 4.49–4.38 (1H, m), 3.61 (3H, s), 3.37–3.06 (2H, m), 2.93–2.85 (1H, m), 2.76 and 2.90 (1H, dd, J=5.4, 13.8), 1.43 and 1.40 (9H, s); ^{13}C NMR ($CDCl_3$, 75.5 MHz, mixture of diastereoisomers) δ 171.7 and 171.58, 171.56 and 171.5, 163.9, 155.72 and 155.70, 136.59 and 136.55, 131.60 and 131.56 (d, J=7.6), 131.98 and 130.95 (d, J=7.6), 127.8, 123.6, 123.3, 122.7, 120.21 and 120.19, 119.3 and 19.2, 115.71 and 115.60 (d, J=21.9), 111.6 and 111.5, 111.0, 80.6, 53.5, 53.3, 52.6, 37.4, 37.3, 28.6; ^{19}F NMR ($CDCl_3$, 376.5 MHz) δ −115.84; HRMS (ESI^+) calcd for $C_{26}H_{31}FN_3O_5$: 484.2248 $[M+H]^+$, found: 484.2247 $[M+H]^+$.

4.4. Difunctionalised peptides

*4.4.1. Boc-Val-Cys(Me)-ΔAla-OMe (**13**)*

An oven dried flask was charged with Boc-Val-Cys(Me)-Ser-OMe (349 mg, 0.8 mmol) dissolved in degassed dichloromethane (10 mL) under an atmosphere of nitrogen. Copper(I) chloride (24 mg, 0.24 mmol) and EDCI (169 mg, 0.88 mmol) were added and the resultant suspension stirred for 18 h at ambient temperature. The solution was diluted with dichloromethane (10 mL) and washed with two portions of water (10 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by flash column chromatography (Petroleum ether/ethyl acetate 1:1) gave the title compound as a colourless foam in 83% yield (371 mg). $[\alpha]_D^{20}$ −9.6 (*c* 0.73, $CHCl_3$); IR (film, cm^{-1}) ν 3682, 3297, 3019, 2968, 2932, 2875, 2401, 1743, 1662, 1504, 1449, 1392, 1368, 1295, 1216, 1168, 1043, 1016, 967, 928, 909, 868, 850, 755, 669; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.71 (1H, s), 7.09 (1H, d, J=8.7), 6.56 (1H, s), 5.91 (1H, d, J=1.5), 5.20 (1H, d, J=10.5), 4.69 (1H, dd, J=7.2, 8.4), 4.06–3.99 (1H, m), 3.83 (3H, s), 2.98–2.79 (2H, m), 2.22–2.09 (1H, m), 2.14 (3H, s), 1.42 (9H, s), 0.96 (3H, d, J=8.1), 0.90 (3H, d, J=8.1); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 172.4, 169.2, 164.3, 156.2, 131.1, 110.3, 80.4, 53.7, 53.3, 36.1, 31.0, 28.6, 19.6, 17.9, 16.2; HRMS (ESI^+) calcd for $C_{18}H_{32}N_3O_6S$: 418.2012 $[M+H]^+$, found: 418.1991 $[M+H]^+$.

*4.4.2. Boc-Val-Cys(Me)-Phe(4-t-Bu)-OMe (**14**)*

In accordance with the representative procedure for 1,4-additions with boronic acids, Boc-Val-Cys(Me)-ΔAla-OMe (167 mg, 0.4 mmol) was reacted with 4-*tert*-butylbenzene boronic acid (341 mg, 1.9 mmol). The title compound was obtained as a mixture of diastereomers in 30% yield (66 mg) as a colourless foam. ^1H NMR ($CDCl_3$, 300 MHz) δ 7.32–7.27 (2H, m), 7.08–6.99 (3H, m), 6.92 and 6.91 (1H, d, J=7.5), 5.05–5.02 (1H, m), 4.79 (1H, dt, J=7.5, 6), 4.58–4.46 (1H, m), 3.99–3.91 (1H, m), 3.71 and 3.69 (3H, s), 3.18–3.00 (2H, m), 2.92–2.83 (1H, m), 2.79–2.59 (1H, m), 2.20–2.10 (1H, m), 2.09 (3H, s), 1.44 (9H, s), 1.29 and 1.28 (9H, s), 0.95–0.87 (6H, m); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 171.97 (minor) and 171.89, 171.80 and 171.77 (minor), 170.2 and 170.1 (minor), 156.4 and 156.2 (minor), 150.4 and 150.3 (minor), 133.0 (minor) and 132.8, 129.3 (minor) and 129.2, 125.9 and 125.8 (minor), 80.6 (minor) and 80.5, 60.5 (minor) and 60.3, 54.0 and 53.7 (minor), 52.7 and 52.6 (minor), 52.1 and 51.9 (minor), 37.5 (minor) and 37.4, 36.4 and 36.3 (minor), 34.8 and 34.4 (minor), 31.6, 31.1 and 30.9 (minor), 28.6, 19.64 (minor) and 19.61, 17.9 and 17.8 (minor), 16.0 and 15.9 (minor); HRMS (ESI^+) calcd for $C_{28}H_{46}N_3O_6S$: 552.3107 $[M+H]^+$, found: 552.3111 $[M+H]^+$.

4.5. Tripeptides

*4.5.1. Boc-Phe-ΔAla-Gly-OEt (**15**)*

An oven dried flask was charged with Boc-Phe-Ser-Gly-OMe (2.00 g, 4.57 mmol) dissolved in degassed dichloromethane (40 mL) under an atmosphere of nitrogen. Copper(I) chloride (136 mg, 1.37 mmol) and EDCI (964 mg, 5.03 mmol) were added and the resultant suspension stirred for 18 h at ambient temperature. The solution was washed with three portions of water (15 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by flash column chromatography (petroleum ether/ethyl acetate 1:1) gave the title compound as an off white solid in 82% yield (1.57 g). Mp 134–137 °C; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.49 (1H, br s), 7.32–7.16 (5H, m), 6.84 (1H, app t, J=4.8), 6.48 (1H, s), 538 (1H, s), 5.04 (1H, d, J=7.2), 4.49–4.43 (1H, m), 4.23 (2H, q, J=7.2), 4.06 (2H, app t, J=4.8), 3.16 (1H, dd, J=13.8, 6.0), 3.06–2.99 (1H, m), 1.38 (9H, s), 1.29 (3H, t, J=7.2); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 170.8, 169.9, 164.0, 155.7, 136.5, 133.7, 129.5, 129.0, 127.3, 103.5, 80.7, 62.1, 56.7, 42.1, 38.6, 28.5, 14.4; HRMS (ESI^+) calcd for $C_{21}H_{29}N_3NaO_6$: 442.1949 $[M+Na]^+$; found: 442.1948 $[M+Na]^+$. Anal. Calcd for C 60.13, H 6.97, N 10.02; found C 60.2, H 7.05, N 9.96%.

4.5.2. Boc-Phe-Phe-Gly-OEt

In accordance with the representative procedure for 1,4-additions with boronic acids, Boc-Phe-ΔAla-Gly-OEt (105 mg, 0.25 mmol) was reacted with benzene boronic acid (121 mg, 1.0 mmol). The title compound was obtained as a mixture of diastereomers in 85% yield (105 mg) as a colourless foam. IR (film, cm^{-1}) ν 3418, 2090, 1751, 1645, 1554, 1497, 1455, 1392, 1368, 1250, 1194, 1029, 700; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.33–7.20 (6H, m), 7.17–7.08 (3H, m), 7.00 (1H, d, J=6.0), 6.96 and 6.59 (1H, br s), 6.46 and 6.40 (1H, d, J=5.4), 5.14 and 4.92 (1H, d, J=6.3), 4.79–4.70 (1H, m), 4.30 and 4.14 (1H, m), 4.18 and 4.16 (2H, q, J=7.4), 4.02 and 3.96 (1H, dd, J=18.0, 5.4), 3.81 and 3.80 (1H, dd, J=18.0, 5.4), 3.14–2.80 (4H, m), 1.36 and 1.35 (9H, s), 1.27 and 1.25 (3H, t, J=7.4); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 171.8 and 171.6 (minor), 171.3 and 171.2 (minor), 169.8 and 169.6, 156.1, 136.8, 136.7 and 136.6 (minor), 129.8, 129.70, 129.67, 129.2, 129.1, 129.0, 127.5, 127.40 and 127.37 (minor), 81.0 (minor) and 80.8, 61.77 and 61.75 (minor), 57.0 and 56.4 (minor), 54.2, 41.7, 38.4, 38.0 and 37.7 (minor), 28.62 and 28.59, 14.53 and 14.52; HRMS (ESI^+) calcd for $C_{27}H_{36}N_3O_6$: 498.2599 $[M+H]^+$; found: 498.2595 $[M+H]^+$. Anal. calcd for C 65.17, H 7.09, N 8.44; found C 64.7, H 7.04, N 8.23%.

4.5.3. Boc-Phe-Phe(4-F)-Gly-OEt

In accordance with the representative procedure for 1,4-additions with boronic acids, Boc-Phe-ΔAla-Gly-OEt (63 mg, 0.15 mmol) was reacted with 4-fluorobenzene boronic acid (84 mg, 0.6 mmol). The title compound was obtained as a mixture of diastereomers in 79% yield (61 mg) as a colourless solid. Mp 137–140 °C; IR (film, cm^{-1}) ν 3446, 2991, 2092, 1755, 1645, 1560, 1510, 1485, 1392, 1271, 1192, 1122, 1061, 1029, 827, 700; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.35–7.25 (3H, m), 7.18–7.14 (2H, m), 7.07–7.02 (1H, m), 6.97–6.87 (3H, m), 7.05 and 6.58 (1H, br s), 6.46 and 6.38 (1H, d, J=8.4), 5.12 and 4.93 (1H, d, J=6.9), 4.73 and 4.70 (1H, q, J=6.6), 4.30 and 4.16 (1H, q, J=6.6), 4.18 and 4.17 (2H, q, J=7.2), 4.02 and 3.96 (1H, dd, J=18, 6.0), 3.84 and 3.78 (1H, app t, J=6.0), 3.12–2.77 (4H, m), 1.37 and 1.36 (9H, s), 1.27 and 1.26 (3H, t, J=7.2); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 171.7 and 171.5 (minor), 171.0 and 170.9 (minor), 169.7 and 169.6, 162.5 (d, J=245), 156.1, 136.7 (minor) and 136.6, 132.2 (q, J=3), 131.3 (q, J=5), 129.7, 129.2, 129.1, 127.6, 115.98

(minor) and 115.97, 115.70 (minor) and 115.69, 81.1 (minor) and 81.0, 61.8, 57.3, 56.5, 54.0, 41.7, 38.2, 37.1, 36.7, 28.60 and 28.56, 14.53 (minor) and 14.51; HRMS (ESI^+) calcd for $C_{27}H_{34}FN_3O_6$: 516.2504 $[M+H]^+$, found: 516.2502 $[M+H]^+$.

4.5.4. Boc-Phe-Phe(4-Cl)-Gly-OEt

In accordance with the representative procedure for 1,4-additions with boronic acids, Boc-Phe-ΔAla-Gly-OEt (63 mg, 0.15 mmol) was reacted with 4-chlorobenzene boronic acid (93 mg, 0.6 mmol). The title compound was obtained as a mixture of diastereomers in 85% yield (105 mg) as a colourless solid. Mp 163–166 °C; IR (film, cm^{-1}) ν 2361, 1756, 1708, 1645, 1562, 1555, 1475, 1409, 1290, 1193, 1091, 1016, 978, 889, 841; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.23–7.17 (3H, m), 7.14–7.06 (4H, m), 6.94 (1H, d, J=8.4), 6.84 (1H, d, J=7.2), 7.05 and 6.58 (1H, m), 6.68 and 6.39 (1H, d, J=7.2), 5.01 and 4.92 (1H, d, J=7.2), 4.67 (1H, app pentet, J=6.9), 4.24 and 4.12 (1H, q, J=6.9), 4.11 and 4.08 (2H, q, J=6.9), 3.93 and 3.88 (1H, dd, J=16.8, 5.7), 3.77 and 3.71 (1H, app t, J=5.7), 3.00–2.71 (4H, m), 1.29 and 1.28 (9H, s), 1.20 and 1.18 (3H, t, J=7.2); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 170.5 and 170.2 (minor), 169.7 and 169.6 (minor), 168.3 and 168.2, 154.7, 135.3 (minor) and 135.2, 133.7 (minor) and 133.6, 131.9 and 131.8 (minor), 129.8 (minor) and 129.7, 128.3, 127.8 (minor) and 127.7, 126.1, 79.7 (minor) and 79.5, 60.4, 55.7 and 55.0, 52.5, 40.3, 36.9, 35.9 and 35.6, 27.20 (minor) and 27.17, 13.12 (minor) and 13.10; HRMS (ESI^+) calcd for $C_{27}H_{35}ClN_3O_6$: 532.2209 $[M+H]^+$, found: 532.2204 $[M+H]^+$.

4.5.5. Boc-Phe-Phe(3-NO_2)-Gly-OEt

In accordance with the representative procedure for 1,4-additions with boronic acids, Boc-Phe-ΔAla-Gly-OEt (63 mg, 0.15 mmol) was reacted with 3-nitrobenzene boronic acid (100 mg, 0.6 mmol). The title compound was obtained as a mixture of diastereomers in 43% yield (35 mg) as a colourless solid. Mp 142–144 °C; IR (film, cm^{-1}) ν 3432, 2983, 2930, 2861, 2361, 2093, 1750, 1704, 1646, 1531, 1498, 1454, 1352, 1251, 1195, 1167, 1122, 1023, 700; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.01–7.97 (1H, m), 7.88 (1H, br s), 7.43 and 7.33 (1H, m), 7.38–7.32 (1H, m), 7.23–7.15 (4H, m), 7.10–7.04 (2H, m), 6.77–6.68 (1H, m), 5.13–4.96 (1H, d, J=6.9), 4.80–4.72 (1H, m), 4.25–4.15 (1H, m), 4.10 and 4.08 (2H, q, J=6.9), 3.97–3.73 (2H, m), 3.18–2.80 (4H, m), 1.27 (9H, s), 1.20 and 1.18 (3H, t, J=6.9); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 172.2 and 171.9 (minor), 170.8 and 170.6 (minor), 169.8 (minor) and 169.7, 156.1, 148.7 and 148.6 (minor), 138.92 (minor) and 138.89, 137.1, 136.7 (minor) and 136.6, 136.2 and 136.1 (minor), 129.9 and 129.8 (minor), 129.7, 129.63 and 129.60 (minor), 129.2, 129.1 and 129.0 (minor), 127.50 and 127.48 (minor), 127.35, 124.8 and 124.7 (minor), 122.5 and 122.4 (minor), 81.1 (minor) and 80.9, 61.93 and 61.91 (minor), 57.0 and 56.5 (minor), 53.8 and 53.7 (minor), 41.7, 38.8 and 38.3, 37.8 and 37.5, 28.58 (minor) and 28.56, 14.51 and 14.49 (minor); HRMS (ESI^+) calcd for $C_{27}H_{35}N_4O_8$: 543.2449 $[M+H]^+$, found: 543.2451 $[M+H]^+$.

4.5.6. Boc-Phe-Phe(4-Br)-Gly-OEt

In accordance with the representative procedure for 1,4-additions with boronic acids, Boc-Phe-ΔAla-Gly-OEt (63 mg, 0.15 mmol) was reacted with 4-bromobenzene boronic acid (120 mg, 0.6 mmol). The title compound was obtained as a mixture of diastereomers in 35% yield (30 mg) as a colourless solid. Mp 159–161 °C; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.37–7.26 (5H, m), 7.17–7.13 (2H, m), 7.02 and 6.58 (1H, m), 6.94 (1H, d, J=8.4), 6.84 (1H, d, J=7.8), 6.39 and 6.28 (1H, d, J=8.4), 5.08 and 4.90 (1H, d, J=6.3), 4.73 and 4.70 (1H, q, J=6.6), 4.28 and 4.14 (1H, q, J=6.9), 4.18 and 4.16 (2H, q, J=7.2), 4.00 and 3.95 (1H, dd, J=18, 5.7), 3.83 and 3.77 (1H, dd, J=7.2, 5.7), 3.10 and 2.76 (1H, m), 3.09–2.85 (3H, m), 1.36 and 1.35 (9H, s), 1.27 and 1.25 (3H, t, J=7.2); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 170.4 and 170.1 (minor), 169.6 and 169.5 (minor), 168.2 and 168.1, 154.8, 135.3 (minor) and 135.1, 134.13 (minor) and 134.06, 130.7, 130.2 and 130.1 (minor), 128.3, 127.8 (minor) and 127.7, 126.2, 79.8 (minor) and 79.6, 60.4, 55.8 and 55.0, 52.4, 40.4, 37.0, 35.7 and 35.6, 27.22 (minor) and 27.18, 13.14; HRMS (ESI^+) calcd for $C_{27}H_{35}BrN_3O_6$: 576.1704 $[M+H]^+$, found: 576.1703 $[M+H]^+$.

4.5.7. Preparation of Boc-Trp-ΔAla-Tyr-OMe (**16**)

4.5.7.1. Mixture of Boc-Trp-Cys(SOBzl)-Tyr-OMe and Boc-Trp-Cys-(SO_2Bzl)-Tyr-OMe. The thioether of Boc-Trp-Cys(SBzl)-Tyr-OMe was oxidised as described in the literature.[17a] Sodium metaperiodate (1.47 g, 6.88 mmol, 2.2 equiv) was dissolved in water (50 mL) and cooled in an ice bath. Boc-Trp-Cys(Bzl)-Tyr-OMe (2.11 g, 3.13 mmol) was dissolved in dioxane (100 mL) and added dropwise to the oxidant. The reaction mixture was stirred on ice for 2 h and at 40 °C for 6 h, then concentrated to ~50 mL, water (50 mL) was added and the product extracted into DCM (3×50 mL). The combined organics were washed with water (50 mL), brine (50 mL), dried ($MgSO_4$) and concentrated in vacuo to give a colourless glass, which was progressed to the next step without further purification. MS (ESI^-) m/z 705.3 and 689.3 $[M-H]^-$ sulfone and sulfoxide, respectively.

4.5.7.2. Boc-Trp-ΔAla-Tyr-OH. Boc-Trp-Cys(SOBzl)-Tyr-OMe (2 g, 2.83 mmol), was dissolved in methanol (120 mL) and cooled on an ice–salt bath. Aqueous NaOH (1 M, 14 mL, 5 equiv) was added dropwise and the reaction mixture allowed to warm to room temperature over 2 h. The reaction mixture was concentrated in vacuo to approx 3 mL, acidified to pH 4 with 2 M $KHSO_4$ and the product extracted into DCM (3×50 mL), washed with water (100 mL) and brine (50 mL), dried ($MgSO_4$) and concentrated to dryness to afford the title compound as a gummy foam. ^1H NMR (DMSO-d_6, 250 MHz) δ 12.81 (1H, br s), 10.84 (1H, d, J=1.8), 9.23 (1H, s), 9.11 (1H, s), 8.68 (1H, d, J=8.3), 7.58 (1H, d, J=7.8), 7.34 (1H, d, J=8.0), 7.28 (1H, d, J=8.0), 7.15 (1H, d, J=1.8), 7.12–6.94 (4H, m), 6.67 (2H, d, J=8.5), 6.29 (1H, s), 5.59 (1H, s), 4.49–4.36 (1H, m), 4.32–4.19 (1H, m), 3.24–2.84 (4H, m), 1.30 (9H, s); HRMS (ESI^-) calcd for $C_{28}H_{31}N_4O_7$: 535.2198 $[M-H]^-$; found 535.2207 $[M-H]^-$.

*4.5.7.3. Boc-Trp-ΔAla-Tyr-OMe (**16**).* To a suspension of $NaHCO_3$ (250 mg, 2.97 mmol, 1.1 equiv) in anhydrous DMF (10 mL) were added Boc-Trp-ΔAla-Tyr-OH (1.45 g, 2.7 mmol) and methyl iodide (186 μL, 2.97 mmol). This mixture was stirred at 25 °C for 20 h. Distilled water was added and the product extracted with ethyl acetate (3×20 mL). The combined organic phases were washed with distilled water, dried over $MgSO_4$ and concentrated in vacuo to the crude product, which was purified by flash chromatography (ethyl acetate/petroleum ether 1:1) to afford the titled compound as an off white solid (930 mg, 67% over three steps).[21] Mp 205 °C; $[\alpha]_D^{20}$ +9.38 (c 0.21, CH_2Cl_2); IR (film, cm^{-1}) ν 4214, 3362 (br), 3019, 2980, 2933, 2856, 2401, 1887, 1738, 1694, 1633, 1616, 1515, 1455, 1369, 1216, 1171, 1109, 1060, 1022, 988, 963, 892, 843, 755, 699, 668; ^1H ($CDCl_3$, 300 MHz) δ 8.31 (1H, s), 8.30 (1H, s), 7.57 (1H, d, J=7.8), 7.32 (1H, d, J=8.1), 7.16 (1H, dt, J=0.9, 7.8), 7.08 (1H, dt, J=0.9, 8.1), 6.96 (1H, d, J=1.8), 6.88 (2H, AB d, J=8.4), 6.74 (2H, AB d, J=8.4), 6.54 (1H, d, J=7.8), 6.40 (1H, br s), 6.35 (1H, s), 5.19 (1H, s), 5.16 (1H, s), 4.76 (1H, dt, J=5.7, 7.4), 4.51 (1H, br s), 3.73 (3H, s), 3.33–3.19 (2H, m), 3.06 (1H, dd, J=5.7, 14.1), 2.98 (1H, dd, J=6, 14.1), 1.40 (9H, s); ^{13}C ($CDCl_3$, 75.5 MHz) δ 172.1, 171.4, 163.4, 155.9, 155.8, 136.6, 133.8, 130.7, 127.8, 127.2, 123.5, 122.6, 120.0, 119.0, 116.1, 111.6, 110.3, 103.8, 80.9, 56.5, 54.1, 52.9, 37.2, 37.1, 28.6; HRMS (ESI^+) calcd for $C_{29}H_{34}N_4NaO_7$: 573.2325 $[M+Na]^+$, found: 573.2309 $[M+Na]^+$.

4.5.8. Boc-Trp-Phe(4-F)-Tyr-OMe

In accordance with the representative procedure for 1,4-additions with boronic acids, Boc-Trp-ΔAla-Tyr-OMe (110 mg, 0.2 mmol) was reacted with 4-fluorobenzene boronic acid (122 mg,

0.8 mmol, 4 equiv) in the presence of sodium fluoride (25 mg, 0.6 mmol, 3 equiv). The title compound was obtained in 54% yield (70 mg) as an off white solid. Mp 92–94 °C; $[\alpha]_D^{20}$ +6.8 (*c* 0.15, CH_2Cl_2); IR (film, cm^{-1}) ν 4214, 3390 (br), 3020, 2982, 2932, 2854, 2401, 1893, 1737, 1664, 1615, 1512, 1439, 1369, 1216, 1172, 1114, 1054, 1015, 929, 844, 757, 669, 621, 575, 538; ^{1}H NMR ($CDCl_3$, 300 MHz) 8.28 (1H, s), 7.62 (1H, d, *J*=7.8), 7.35 (1H, d, *J*=7.8), 7.22–7.06 (2H, m), 6.85 (1H, d, *J*=2.1), 6.9–6.66 (8H, m), 6.29 (1H, d, *J*=8.1), 6.20 (1H, d, *J*=8.1), 5.06 (1H, d, *J*=7.8), 4.66 (1H, dt, *J*=6.9, 6.0), 4.53–4.34 (2H, m), 3.70 (3H, s), 3.14–2.96 (3H, m), 2.83–2.73 (3H, m), 1.40 (9H. s); ^{13}C NMR ($CDCl_3$, 75.5 MHz) 172.1, 172.0, 170.3, 155.7, 152.0, 136.6, 132.2 and 132.1, 131.2 (d, *J*=8.0), 130.7, 127.7 and 127.6, 124.1, 123.7 and 123.6, 122.9, 120.3, 119.2, 116.2, 115.7 (d, *J*=21.9), 111.7, 110.6, 81.1, 54.1, 53.8, 52.9, 52.8, 37.3, 37.2, 30.1, 28.7; ^{19}F NMR ($CDCl_3$, 376.5 MHz) δ −115.80; HRMS (ESI^+) calcd for $C_{35}H_{39}FN_4NaO_7$: 669.2700 $[M+Na]^+$, found: 669.2699 $[M+Na]^+$.

4.5.9. Boc-Trp-Phe(4-CN)-Tyr-OMe

In accordance with the representative procedure for 1,4-additions with boronic acids, Boc-Trp-ΔAla-Tyr-OMe (110 mg, 0.2 mmol) was reacted with 4-cyanobenzene boronic acid (122 mg, 0.8 mmol, 4 equiv) in the presence of sodium fluoride (25 mg, 0.6 mmol, 3 equiv). The title compound was obtained in 14% yield (14 mg) as an off white foam. $[\alpha]_D^{20}$ +6.8 (*c* 0.15, CH_2Cl_2); IR (film, cm^{-1}) ν 3413 (br), 2254, 1655, 1516, 1368, 1249, 1175, 908, 733, 650; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.32 (1H, s), 7.58 (1H, d, *J*=7.8), 7.40–7.13 (5H, m), 6.98–6.67 (8H, m), 6.65–6.28 (1H, br s), 6.14 (1H, d, *J*=7.2), 5.13 (1H, d, *J*=4.5), 4.69–4.60 (2H, m), 4.27 (1H, q, *J*=6.9), 3.69 (3H, s), 3.19–3.12 (2H, m), 3.00–2.82 (3H, m), 2.55 (1H, dd, *J*=13.8, 6.9), 1.39 (9H, s); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 172.6, 172.2, 170.1, 155.7, 155.6, 141.9, 136.6, 132.6, 130.7, 130.6, 127.8, 127.7, 123.7, 122.9, 120.4, 119.2, 119.0, 116.1, 111.9, 111.1, 110.3, 80.2, 56.4, 54.1, 53.5, 52.8, 37.4, 37.2, 30.1, 28.7; HRMS (ESI^+) calcd for $C_{36}H_{39}N_5NaO_7$: 676.2747 $[M+Na]^+$, found 676.2740 $[M+Na]^+$.

4.5.10. Boc-Trp-Phe(3,5-di-CF_3)-OMe

In accordance with the representative procedure for 1,4-additions with boronic acids, Boc-Trp-ΔAla-Tyr-OMe (110 mg, 0.2 mmol) was reacted with 3,5-bis-trifluoromethylbenzene boronic acid (206 mg, 0.8 mmol, 4 equiv) in the presence of sodium fluoride (25 mg, 0.6 mmol, 3 equiv). The title compound was obtained in 38% yield (59 mg) as an off white foam. IR (film, cm^{-1}) ν 4214, 3411 (br), 3020, 1651, 1516, 1440, 1379, 1280, 1216, 1177, 1138, 1013, 902, 757, 707, 682, 668; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.31 (1H, d, *J*=0.9), 7.68 (1H, s), 7.61 (1H, d, *J*=7.8), 7.41 (2H, s), 7.33 (1H, d, *J*=8.1), 7.20–7.06 (2H, m), 6.94 (1H, d, *J*=2.1), 6.77 (2H, d, *J*=8.4), 6.8–6.5 (1H, br s), 6.68 (1H, d, *J*=8.4), 6.46–6.30 (2H, m), 5.02 (1H, d, 7.5), 4.68–4.57 (2H, m), 4.36 (1H, dd, *J*=14.4, 6.6), 3.69 (3H, s), 3.25 (1H, dd, *J*=5.4, 14.4), 3.11 (1H, dd, *J*=6.9, 14.4), 3.01–2.77 (4H, m), 1.37 (9H, s); ^{13}C NMR ($CDCl_3$, 75.5 MHz) 172.4, 171.9, 169.4, 156.1, 155.7, 139.1, 136.7, 132.1, 131.7, 131.2, 130.7, 130.1, 127.6, 127.4, 125.4, 123.5, 122.9, 121.8, 121.3, 120.2, 119.3, 116.2, 111.8, 110.4, 81.3, 55.7, 53.8, 53.7, 52.8, 37.6, 37.2, 30.1, 28.5; ^{19}F NMR ($CDCl_3$, 376.5 MHz) δ −62.92; HRMS (ESI^+) calcd for $[M+H]^+$ $C_{37}H_{39}F_6N_4O_7$: 765.2723, found: 765.2716$[M+H]^+$.

4.6. Synthesis of urotensin receptor agonist fragments

4.6.1. Boc-Lys(Cbz)-ΔAla-Ala-OMe (**18**)

An oven dried flask was charged with Boc-Lys(Cbz)-Ser-Ala-OMe (3.31 g, 10.4 mmol) dissolved in degassed dichloromethane (40 mL) under an atmosphere of nitrogen. Copper(I) chloride (117 mg, 1.18 mmol) and EDCI (831 mg, 4.33 mmol) were subsequently added and the resultant suspension stirred for 18 h at ambient temperature. The solution was washed with two portions of water (15 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by flash column chromatography (petroleum ether/ethyl acetate 1:1) gave the title compound as a colourless foam in 89% yield (1.88 g). $[\alpha]_D^{20}$ −5.5 (*c* 1.3, $CHCl_3$); IR (film, cm^{-1}) ν 3435, 3019, 2083, 1696, 1653, 1512, 1455, 1368, 1223, 1167, 1054, 772, 733, 668; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.61 (1H, s), 7.33–7.30 (5H, m), 7.02 (1H, d, *J*=6.0), 6.43 (1H, s), 5.36 (1H, s), 5.32 (1H, d, *J*=7.5), 5.07 (2H, s), 5.02 (1H, m), 4.59 (1H, app pentet, *J*=7.2), 4.21–4.18 (1H, m), 3.75 (3H, s), 3.16 (2H, q, *J*=6.0), 1.84–1.76 (1H, m), 1.69–1.38 (5H, m), 1.44 (3H, s), 1.41 (9H, s); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 173.9, 172.0, 163.9, 157.0, 156.3, 137.0, 134.1, 128.8, 128.4, 103.91, 80.5, 66.9, 55.6, 53.0, 49.0, 40.8, 32.2, 29.7, 28.7, 23.0, 18.0; HRMS (ESI^+) calcd for $C_{26}H_{38}N_4NaO_8$: 557.2587 $[M+Na]^+$, found: 557.2553 $[M+Na]^+$.

4.6.2. Boc-Lys(Cbz)-L-Phe-Ala-OMe

In accordance with the representative procedure for 1,4-additions with boronic acids, Boc-Lys(Cbz)-ΔAla-Ala-OMe (107 mg, 0.2 mmol) was reacted with benzene boronic acid (98 mg, 0.8 mmol) and (*R*)-BINAP. The title compound was isolated as a single diastereomer in 50% yield (61 mg) as a colourless glass. $[\alpha]_D^{20}$ −21.2 (*c* 0.33, $CHCl_3$); mp 126–129 °C; IR (film, cm^{-1}) ν 3434, 2094, 1652, 1511, 1162, 806; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.37–7.18 (10H, m), 6.67 (2H, d, *J*=7.8), 5.22 (1H, br s), 5.10 (2H, s), 5.08–5.03 (1H, m), 4.70 (1H, dt, *J*=7.8, 6.6), 4.48 (1H, app pent, *J*=7.2), 4.05–3.98 (1H, m), 3.69 (3H, s), 3.19–3.02 (4H, m), 1.80–1.70 (1H, m), 1.64–1.40 (3H, m), 1.40 (9H, s), 1.32 (3H, d, *J*=7.2), 1.33–1.25 (2H, m); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 173.1, 172.4, 170.7, 157.1, 156.2, 137.0, 136.7, 129.7, 128.9, 128.8, 128.5, 128.4, 127.3, 80.5, 67.0, 55.1, 54.3, 52.7, 48.5, 40.5, 38.3, 31.9, 29.8, 28.6, 22.6, 18.3; HRMS (ESI^+) calcd for $C_{32}H_{44}N_4NaO_8$: 635.3057 $[M+Na]^+$, found: 635.3035 $[M+Na]^+$.

4.6.3. Boc-Lys(Cbz)-D-Phe-Ala-OMe

In accordance with the representative procedure for 1,4-additions with boronic acids, Boc-Lys(Cbz)-ΔAla-Ala-OMe (107 mg, 0.2 mmol) was reacted with benzene boronic acid (98 mg, 0.8 mmol) and (*S*)-BINAP. The title compound was isolated as a single diastereomer in 45% yield (55 mg) as a colourless glass. $[\alpha]_D^{20}$ +11.8 (*c* 0.085, $CHCl_3$); IR (film, cm^{-1}) ν 3423, 3018, 2088, 1700, 1669, 1517, 1455, 1368, 1225, 1208, 1165, 1057, 1028, 925, 853, 778, 741, 699, 668; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.36–7.19 (10H, m), 6.86 (1H, d, *J*=8.1), 6.80 (1H, d, *J*=8.1), 5.18 (1H, d, *J*=6.9), 5.09 (2H, s), 4.96–4.93 (1H, m), 4.74 (1H, app q, *J*=7.5), 4.50 (1H, app pent, *J*=7.2), 3.94 (1H, dt, *J*=6.3, 7.2), 3.69 (3H, s), 3.19–3.01 (4H, m), 1.70–1.10 (6H, m), 1.40 (9H, s), 1.28 (3H, d, *J*=7.2); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 173.5, 172.6, 170.7, 156.9, 156.1, 137.0, 136.9, 129.7, 129.0, 128.9, 128.6, 128.5, 127.3, 80.5, 67.0, 55.1, 54.4, 52.8, 48.4, 40.7, 38.2, 31.9, 29.7, 28.6, 22.6, 18.1; HRMS (ESI^+) calcd for $C_{32}H_{44}N_4NaO_8$: 635.3057 $[M+Na]^+$, found: 635.3035 $[M+Na]^+$.

4.6.4. Boc-Lys(Cbz)-Phe(3,5-di-F)-Ala-OMe

In accordance with the representative procedure for 1,4-additions with boronic acids, Boc-Lys(Cbz)-ΔAla-Ala-OMe (107 mg, 0.2 mmol) was reacted with 3,5-difluorobenzene boronic acid (126 mg, 0.8 mmol) and (*R*)-BINAP. The title compound was isolated as a single diastereomer in 32% yield (42 mg) as a colourless glass. $[\alpha]_D^{20}$ −17.8 (*c* 0.51, $CHCl_3$); IR (film, cm^{-1}) ν 4213, 3419, 3019, 2100, 1660, 1518, 1222, 1208, 1164, 1119, 786, 732, 668; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.37–7.31 (5H, m), 6.81–6.63 (5H, m), 5.31 (1H, d, *J*=6.6), 5.10 (2H, s), 5.08–5.01 (1H, m), 4.72 (1H, dt, *J*=6.9, 7.8), 4.50 (1H, pent, *J*=7.2), 4.05–3.98 (1H, m), 3.72 (3H, s), 3.22–3.13 (2H, m), 3.09–3.06 (2H, m), 1.81–1.72 (1H, m), 1.65–1.58 (1H, m), 1.50–1.31 (4H, m), 1.41 (9H, s), 1.35 (3H, d, *J*=7.2); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 173.1, 172.5, 170.0, 164.9 (d, *J*=12.8), 161.7 (d, *J*=12.8), 157.2, 140.8 (d, *J*=9.1), 136.9, 128.9, 128.5, 112.8, 112.5, 102.9 (t, *J*=25.1), 80.8, 67.0, 55.2, 53.8, 52.8, 48.6, 40.3, 37.9, 31.4, 29.8, 28.6, 22.5, 18.3; HRMS (ESI^+) calcd for $C_{32}H_{43}F_2N_4O_8$: 649.3049 $[M+H]^+$, found: 649.3042 $[M+H]^+$.

4.6.5. Boc-Lys(Cbz)-1-Nal-Ala-OMe

In accordance with the representative procedure for 1,4-additions with boronic acids, Boc-Lys(Cbz)-ΔAla-Ala-OMe (107 mg, 0.2 mmol) was reacted with 1-naphthyl boronic acid (138 mg, 0.8 mmol) and (*R*)-BINAP. The title compound was isolated as a single diastereomer in 56% yield (75 mg) as a colourless glass. $[\alpha]_D^{20}$ −31.58 (*c* 0.19, $CHCl_3$); IR (film, cm^{-1}) ν 4211, 3414, 3011, 2085, 1701, 1654, 1499, 1454, 1368, 1242, 1163, 1057, 1027, 926, 802; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.20 (1H, d, *J*=8.4), 7.85 (1H, dd, *J*=1.2, 8.1), 7.75 (1H, dd, *J*=2.1, 7.2), 7.59–7.46 (2H, m), 7.38–7.30 (7H, m), 6.81 (1H, d, *J*=7.2), 6.35 (1H, d, *J*=7.2), 5.17–5.13 (1H, m), 5.09 (2H, s), 4.99 (1H, t, *J*=6.0), 4.80 (1H, dt, *J*=7.2, 7.5), 4.38 (1H, pent, *J*=7.2), 4.05–3.99 (1H, m), 3.63 (3H, s), 3.61–3.46 (2H,m), 3.15 (2H, q, *J*=6.3), 1.80–1.42 (4H, m), 1.39 (9H, s), 1.24 (3H, d, *J*=7.2), 1.24–1.15 (2H, m); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 172.7, 172.2, 170.5, 157.0, 156.2, 136.9, 134.2, 132.9, 132.3, 129.2, 128.8, 128.4, 128.2, 126.9, 126.2, 125.7, 124.0, 80.6, 67.0, 55.1, 54.3, 52.7, 48.6, 40.4, 35.5, 31.7, 29.8, 28.6, 22.4, 18.3; HRMS (ESI^+) calcd for $C_{36}H_{47}N_4O_8$: 663.3394 $[M+H]^+$, found: 663.3363 $[M+H]^+$.

4.6.6. Boc-Lys(Cbz)-2-Nal-Ala-OMe

In accordance with the representative procedure for 1,4-additions with boronic acids, Boc-Lys(Cbz)-ΔAla-Ala-OMe (107 mg, 0.2 mmol) was reacted with 2-naphthyl boronic acid (138 mg, 0.8 mmol) and (*R*)-BINAP. The title compound was isolated as a single diastereomer in 68% yield (90 mg) as a colourless glass. $[\alpha]_D^{20}$ −15.56 (*c* 0.45, $CHCl_3$); IR (film, cm^{-1}) ν 4214, 3418, 3018, 2399, 2096, 1693, 1667, 1515, 1455, 1438, 1368, 1226, 1206, 1162, 1027, 929, 794, 721, 665, 629; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.79–7.74 (3H, m), 7.61 (1H, s), 7.45–7.42 (2H, m), 7.38–7.33 (6H, m), 6.73–6.68 (2H, m), 5.28 (1H, br s), 5.11 (1H, d, *J*=18.6), 5.08 (1H, d, *J*=18.6), 4.92 (1H, t, *J*=6.0), 4.81 (1H, dt, *J*=6.6, 7.8), 3.98 (1H, m), 3.60 (3H, s), 3.35–3.19 (2H, m), 3.11–3.02 (2H, m), 1.75–1.64 (1H, m), 1.60–1.49 (1H, m), 1.38–1.10 (16H, m); ^{13}C NMR ($CDCl_3$; 75.5 MHz) δ 172.9, 172.2, 170.6, 157.1, 136.9, 134.2, 133.8, 132.8, 128.9, 128.7, 128.5, 128.4, 128.0, 127.7, 126.5, 126.0, 80.6, 67.0, 55.3, 54.1, 52.6, 48.6, 40.1, 38.3, 31.3, 29.7, 28.5, 22.2, 18.3; HRMS (ESI^+) calcd for $C_{36}H_{47}N_4O_8$: 663.3394 $[M+H]^+$, found: 663.3359 $[M+H]^+$.

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