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PAPER

Synthesis and properties of MIDA boronate containing aromatic amino acids: New peptide building blocks†

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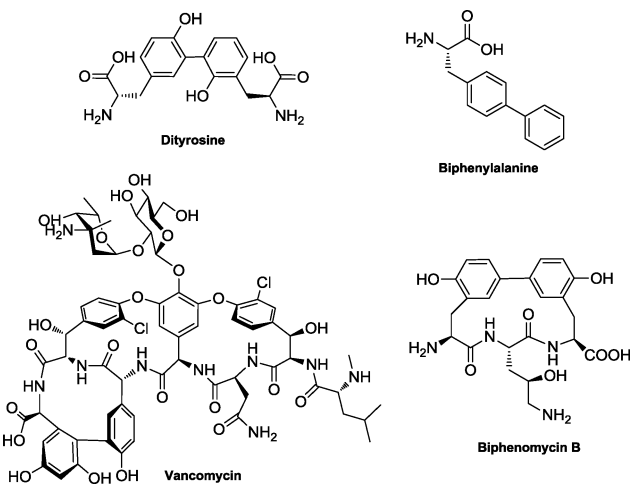
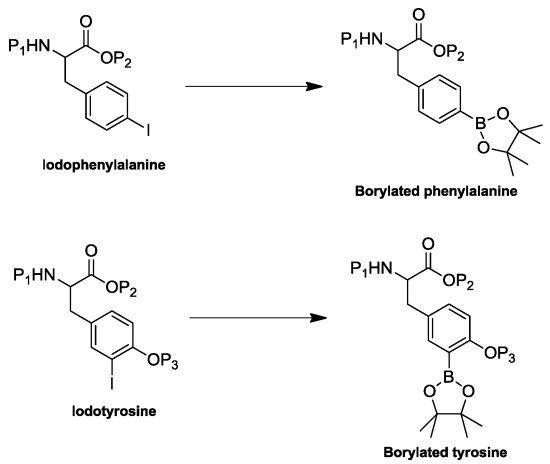
Herein, we report the synthesis of novel phenylalanine and tyrosine derivatives containing a *N*-methyliminodiacetic acid boronate group. These compounds can be prepared enantiomerically pure, they are stable to column chromatography and they can be stored in air for two months without degradation occurring. This new class of boronate containing aromatic amino acids has potential applications in both peptide chemistry and natural product synthesis.

Introduction

In recent years naturally occurring peptides have become increasingly investigated as drug candidates in a range of diseases.[1] However, the successful development of these peptide-based drugs relies on having synthetic access to both naturally occurring amino acids and also a diverse tool-box of novel non-proteinogenic amino acids. Within this area, amino acids that contain a biaryl structural motif such as the biphenylalanines[2] and dityrosine[3] have attracted considerable attention. This interest has largely been stimulated by the fact that similar biaryl motifs are found in a range of important naturally occurring cyclic peptides,[4] including the antibiotics Vancomycin and Biphenomycin B.



The most widely utilised approach to prepare biaryl amino acid motifs involves a Suzuki–Miyaura coupling strategy.[5] This approach requires the preparation of the boron containing aromatic amino acids. Such building blocks are typically obtained from the corresponding iodinated amino acids using Miyaura's palladium catalysed borylation (Scheme 1).[6,7]



Scheme 1 Miyaura borylation of iodinated aromatic amino acids.

However, issues regarding the compatibility of the reaction conditions required for Miyaura's borylation and amino acid chemistry have been reported. For example, racemisation of the α-carbon has been documented for both iodophenylalanine and iodotyrosine amino acid substrates.[8] Furthermore, some arylpinacolboronates (Bpin) including borylated tyrosine derivatives produced in this reaction have been shown to be difficult to purify and prone to degradation on silica gel.[7b,8a,9]

Herein, we report the synthesis of novel phenylalanine and tyrosine derivatives containing a *N*-methyliminodiacetic acid (MIDA) boronate group (Fig. 1). These compounds can be prepared enantiomerically pure, they are stable to column chromatography

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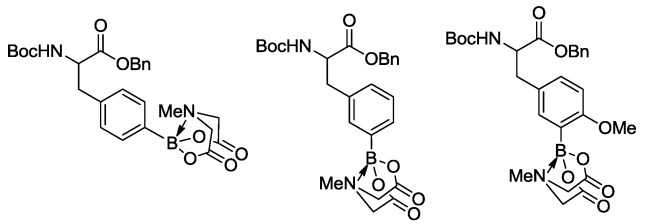
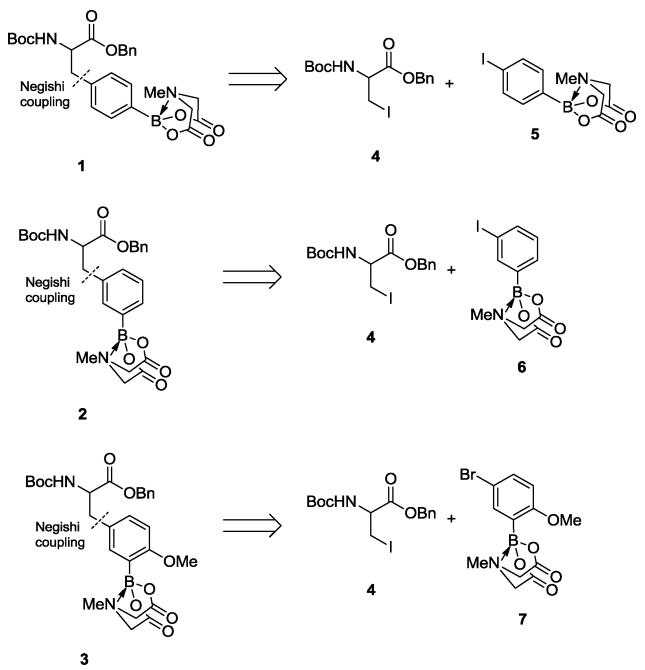


Fig. 1 Novel amino acid MIDA boronates prepared in this study.

and they can be stored in air for two months without degradation occurring.

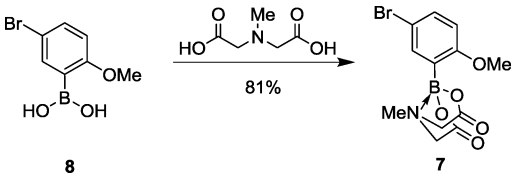
We envisaged that the boronates **1–3** could be accessed from the orthogonally protected iodoalanine[10] **4** using established palladium catalysed Negishi cross-coupling chemistry as shown in Scheme 2.[11] We postulated that the MIDA protecting group developed by Burke[12] would offer advantages over the Bpin protecting group that is currently utilised in the preparation of boronate containing aromatic amino acids. Although the MIDA protecting group has already been shown to be highly stable to a wide variety of synthetic reagents[12c] its application in the preparation of boronate containing amino acids has not been exploited until now.



Scheme 2 General synthetic strategy.

Results and Discussion

Two of the MIDA boronates required (**5** and **6**) were purchased commercially, however in theory these can also be easily prepared from the corresponding boronic acids using the MIDA protection conditions developed by Burke *et al.*[13] To illustrate this point, the MIDA boronate **7** which is not commercially available was readily synthesised in excellent yield from the available boronic acid **8** (Scheme 3). It is worth noting that a range of iodo/bromo

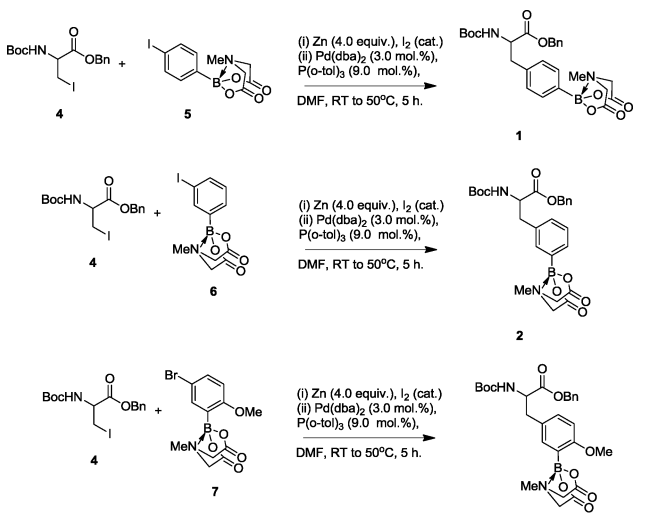


Scheme 3 Synthesis of MIDA boronate **7**. Reagents and conditions: Boronic acid (**8**) (1.0 equiv.), *N*-methyl aminodiacetic acid (1.2 equiv.), toluene: DMSO (15 : 1), Δ, 6 h, 81%. DMSO = dimethylsulfoxide.

aromatic and heteroaromatic boronic acids are commercially available meaning that one has ready access to a considerable variety of MIDA protected coupling partners for the Negishi cross-coupling outlined in Scheme 2.

The palladium catalysed Negishi cross-coupling of protected iodoalanines with aromatic halides has been investigated previously by Jackson.[11] This methodology was appealing to us as the reaction has been shown to proceed without racemisation of the α-carbon of the amino acid. After minor modification of Jackson's original cross-coupling conditions[14] we were able to obtain both stereoisomers of compounds **1–3** in good yields (Table 1). All of the products were purified on silica gel without witnessing any protodeborylation. It is noteworthy that **3a** and **3b** were found to be stable to column chromatography given the problems previously reported for the analagous Bpin boronates.[8a,9] In addition, under the anhydrous base-free conditions utilised the MIDA functionality remained intact. These results supported our initial hypothesis that the MIDA protecting group represents a

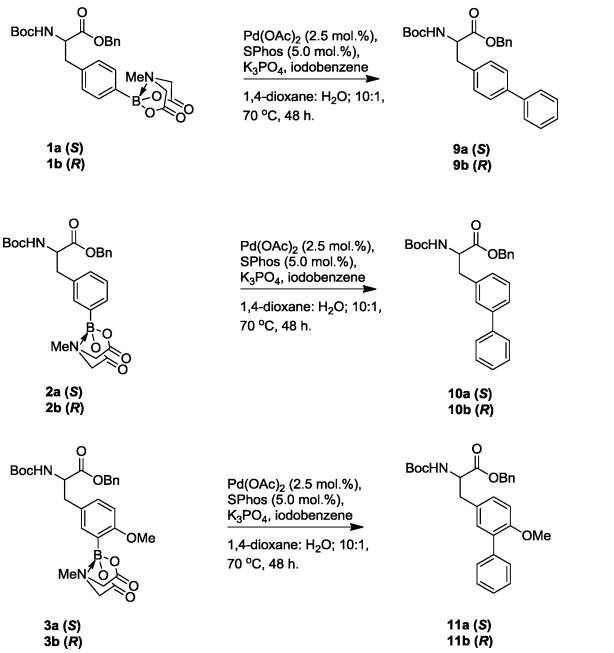
Table 1 Synthesis of amino acid MIDA boronates **1–3**



Entry	Iodoalanine (**4**) (stereochemistry)	Aromatic MIDA Boronate	Product (stereochemistry)	Yield (%)[a]
1	*S*	**5**	**1a** (*S*)	65
2	*R*	**5**	**1b** (*R*)	62
3	*S*	**6**	**2a** (*S*)	58
4	*R*	**6**	**2b** (*R*)	59
5	*S*	**7**	**3a** (*S*)	61
6	*R*	**7**	**3b** (*R*)	59

[a] Isolated yield given.

Table 2 Synthesis of biaryl amino acids **9–11**



Entry	Amino acid MIDA Boronate (Stereochem.)	Biaryl Amino acid	Yield (%)[a]	*ee* (%)[b]	Yield (%)[a,c]
1	**1a** (*S*)	**9a**	63	99.0	65
2	**1b** (*R*)	**9b**	65	97.4	67
3	**2a** (*S*)	**10a**	62	99.0	64
4	**2b** (*R*)	**10b**	57	99.0	59
5	**3a** (*S*)	**11a**	57	99.6	58
6	**3b** (*R*)	**11b**	58	99.6	62

[a] Isolated yield given. [b] Enantiomeric excess (*ee*) was determined by chiral HPLC. [c] Amino acid MIDA boronates used were stored at RT for 2 months.

good alternative to the Bpin group for the preparation of boronate containing amino acids.

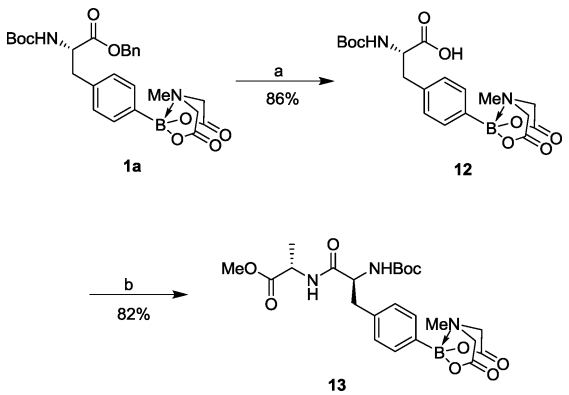
Compounds **1–3** can be used as synthetic building blocks to prepare various peptide biaryl motifs using Suzuki–Miyaura cross-coupling reactions. However, if **1–3** are used as coupling partners in this type of reaction the MIDA protecting group must be removed using a mild aqueous base prior to coupling. In theory, the use of a mild base in this hydrolysis step has the potential to cause racemisation of the α-carbon of the amino acid. Thus, in order to both confirm the enantiomeric purity of the amino acid MIDA boronates prepared (**1–3**) and to investigate their compatibility with Suzuki–Miyaura reaction conditions we decided to prepare the corresponding biaryl amino acids **9–11**.

The biaryl amino acids were prepared using the Suzuki–Miyaura conditions given by Knapp *et al.*[12a] in which the boronic acid is de-masked *in situ* by hydrolysis of the MIDA boronate. A trial hydrolysis reaction was first performed using the simple MIDA boronate **7**. Stirring at 50 °C for 2 h with 3.0 equiv. of K_3PO_4 afforded >90% of the desired free boronic acid **8** (as determined by ^{1}H NMR). We then proceeded to perform the Suzuki–Miyaura cross-coupling reactions with boronates **1–3** and iodobenzene (Table 2).

Both stereoisomers of the biaryl amino acids **9–11** were prepared in good yields using unoptimised reaction conditions.[15] Chiral HPLC analysis of the products confirmed that the initial stereochemistry of the iodoalanines **4a** and **4b** used had remained intact through both the Negishi coupling used to prepare the amino acid MIDA boronates **1–3** and the subsequent Suzuki–Miyaura cross-coupling.[16]

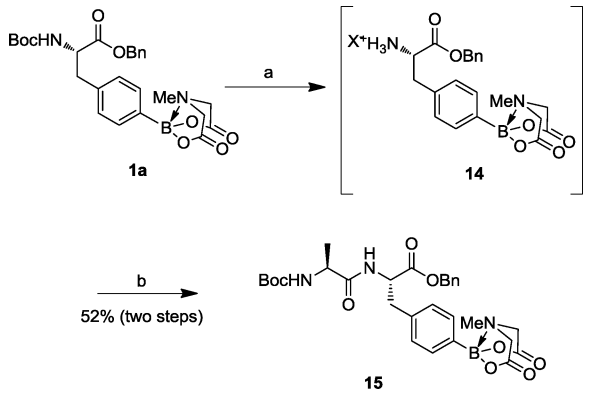
MIDA boronates have previously been reported to exhibit stability to long term benchtop storage.[12] This is one of the major advantages that the MIDA protecting group offers in terms of the preparation of useful synthetic building blocks. To confirm that the MIDA boronates prepared in this study display similar properties, **1–3** were left exposed to air at room temperature for a period of 2 months. ^{1}H NMR and TLC analysis after this period indicated that no detectable degradation of **1–3** had occurred. In addition we repeated the synthesis of the biaryl amino acids **9–11** using identical Suzuki–Miyaura coupling conditions to those given in Table 2. The isolated yields recorded for the biaryl amino acids this time were comparable to those previously obtained (see Table 2).

Having investigated the stability of the amino acid MIDA boronates we next turned our attention to confirming that; a) the orthogonal protecting groups could be selectivity cleaved and b) the MIDA group was stable to standard peptide coupling conditions.[17] Both of these properties are essential for new peptide building blocks to be of synthetic use. To investigate a) and b) we prepared two test dipeptides. Cleavage of the benzyl ester from **1a** was readily achieved through hydrogenolysis without affecting the MIDA ester functionality (Scheme 4). Amino acid **12** was then coupled to commercially available NH_2-Ala-OMe to give the dipeptide **13**. This conversion was achieved using PyBOP® mediated peptide coupling conditions. This synthetic step proceeded in excellent yield and the MIDA protecting group remained intact.



Scheme 4 Synthesis of MIDA boronate containing dipeptide **13**. Reagents and conditions: (a) 10% Pd/carbon, MeOH, RT, 2 h, 86% (b) NH_2-Ala-OMe, NMM, PyBOP®, RT, 15 h, 82%.

Having established that the benzyl ester could be selectively cleaved, a second dipeptide, accessed *via* the Boc protected nitrogen of **1a** was prepared. The Boc protecting group was removed using trifluoroacetic acid/dichloromethane to give the salt **14**. The TFA salt **14** was not isolated but reacted immediately with Boc-Ala-OH under PyBOP® amide coupling conditions to give dipeptide **15** in a 52% yield over two steps (Scheme 5). The



Scheme 5 Synthesis of MIDA boronate containing dipeptide **15**. Reagents and conditions: (a) TFA : DCM (1 : 1), RT, 5 h (b) Boc-Ala-OH, NMM, PyBOP®, RT, 15 h, 52% (two steps). TFA = trifluoroacetic acid.

MIDA protecting group was again found to be compatible with the reaction conditions used.

Conclusion

In summary, we have prepared three novel MIDA boronate containing aromatic amino acids **1–3** *via* a Negishi cross-coupling between an orthogonally protected iodoalanine and aromatic MIDA boronates. In the preparation of **1–3** no racemisation of the amino acid α-carbon was observed and column purification on silica gel was possible. Therefore, this methodology offers an alternative approach to access protected amino acid boronates in cases where the Bpin protecting group has been found to be unsuitable. Furthermore, we have shown that **1–3** are benchtop stable and that the MIDA functionality is compatible with reaction conditions of importance in peptide chemistry. We are currently in the process of investigating the further applications of **1–3** as building blocks in the preparation of biaryl containing peptide natural products.

Experimental Section

General

NMR spectra were collected using a Bruker Avance 400 MHz, Varian Inova 500 MHz and a Varian VNMRS 700 MHz. multiplicities; s = singlet, d = doublet, dd = doublet of doublets, m = multiplet, t = triplet, q = quartet, bd = broad doublet, bs = broad singlet). Chemical shifts are reported in δ units and are referenced to residual solvent peaks; $CHCl_3$ (^{1}H 7.26 ppm, ^{13}C 77.0 ppm), CH_3CN (^{1}H 1.94 ppm, ^{13}C 1.3 ppm) and DMSO (^{1}H 2.50 ppm, ^{13}C 39.5 ppm). All reactions were monitored by TLC using Merck precoated silica gel plates. Column chromatography was performed using silica gel (40–60 μM) using the solvent indicated. All reported yields refer to the isolated yield unless otherwise indicated and product purity was estimated to be > 95% by ^{1}H-NMR. (*R*) and (*S*)-iodoalanines were obtained as gifts from Onyx Scientific Ltd, Sunderland. PyBOP® was purchased from CEM Peptides. All other chemicals were purchased from Sigma Aldrich or Alfa Aesar and were used without further purification. 'NMM' refers to *N*-methylmorpholine. 'PyBOP®' refers to (Benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate. 'SPhos' refers to 2-dicyclohexylphosphino-2′,6′-dimethoxybiphenyl. Melting points were recorded on a Gallenkamp melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin Elmer Spectrum RX1 fitted with an ATR attachment. High resolution mass spectra were collected on a Waters Acquity LCT Premier XE. Enantiomeric excess (*ee*) was determined by HPLC and was performed by Onyx Scientific Ltd using an Agilent 1100 series. LC conditions: Chiralpak IA 5 μM 4.6 × 250 mm (220 nm); Mobile Phase: hexane:IPA (60 : 40); Flow rate: 1.0 mL min^{-1}; 5 μL injection. Optical rotations were measured with a Jasco P-1020 polarimeter.

2-(5-bromo-2-methoxyphenyl)-6-methyl-1,3,6,2-dioxazaborocane-4,8-dione 7

5-Bromo-2-methoxyphenyl boronic acid **8** (1.5 g, 6.5 mmol) and *N*-methyl iminodiacetic acid (1.2 g, 8.0 mmol) were dissolved in toluene (120 mL) and DMSO (8 mL) and heated at reflux (Dean–Stark apparatus) for 6 h. The solution was allowed to return to room temperature and the resulting precipitate filtered, washed with water (20 mL) followed by ether (40 mL) and oven dried to give the desired product **7** as a white solid* (1.8 g, 81%). m.p.: 276.2–275.4 °C; ν_{max}/cm^{-1} 3025, 2963, 2919, 2831, 1746, 1588, 1460, 1383, 1332, 1292, 1236, 1179, 1029, 1000, 902, 866, 800, 708, 653, 621; δ_H (400 MHz, CD_3CN) 2.63 (3 H, s, NCH_3), 3.75 (3 H, s, OCH_3), 3.95 (2 H, d, *J* 17.2 Hz, 2 × CH_a), 4.08 (2 H, d, *J* 17.2 Hz, 2 × CH_b), 6.89 (1 H, d, *J* 8.8 Hz, ArH), 7.51 (1 H, dd, *J* 8.8 and 2.4 Hz, ArH), 7.62 (1 H, br s, ArH); δ_C (100 MHz, CD_3CN) 46.7, 54.8, 63.2, 112.1, 112.6, 112.6, 132. 9, 136.5, 161.2, 168.2; δ_B (128 MHz, CD_3CN) 11.1; *m/z* (AP) 340.0093 (M^+ + Na. $C_{12}H_{13}BBrNO_5$ requires 340.0106). *This compound may be purified *via* column chromatography if required (SiO_2, 100% EtOAc).

General Procedure for the Synthesis of Amino Acid MIDA Boronates 1–3

Zinc dust (0.31 g, 4.8 mmol) was placed in a 2-necked round bottomed flask fitted with a thermometer and septum. The flask was evacuated under heating for 15 min. with vigorous stirring. After cooling to room temperature under argon, anhydrous DMF (1 mL) and I_2 (10 mg) were added and the light grey suspension stirred for 5 min. followed by the addition of (*S*)-iodoalanine **4a** or (*R*)-iodoalanine **4b** (0.50 g, 1.2 mmol) in DMF (1 mL) [exotherm]. Upon returning to room temperature $Pd(dba)_2$ (21 mg, 3 mol.%), P(*o*-tol)$_3$ (33 mg, 9 mol.%) and the relevant halogenated MIDA boronate **5**, **6** or **7** (1.14 mmol) were added as solids and the resulting black mixture stirred at 50 °C under argon for 6 h. After cooling to room temperature the reaction mixture was purified *via* column chromatography without work-up (SiO_2; 50/50 hexane/EtOAc → 100% EtOAc) to furnish the desired products as white or pale yellow solids.

(*S*)-benzyl 2-(tert-butoxycarbonylamino)-3-(4-(6-methyl-4,8-dioxo-1,3,6,2-dioxazaborocan-2-yl)phenyl)propanoate 1a

(0.375 g, 65%) from 0.409 g of 4-iodophenyl boronic acid MIDA ester **5**. m.p.: 105.2–106.6 °C; $[\alpha]_D^{24}$ = −10.7 (c 0.5 in MeOH); ν_{max}/cm^{-1} 2950, 2924, 2844, 1743, 1688, 1499, 1454, 1336, 1230, 1162, 1038, 990, 864, 752; δ_H (400 MHz, $CDCl_3$) 1.41 (9 H, s, ^{t}Bu),

2.48 (3 H, s, NCH_3), 3.02–3.14 (2 H, m, CH_2), 3.73 (2 H, dd, *J* 16.4 and 3.2 Hz, 2 × CH_a), 3.90 (2 H, br d, *J* 16.4 Hz, 2 × CH_b), 4.60–4.63 (1 H, m, CH), 5.01 (1 H, br d, *J* 8.4 Hz, NH), 5.08–5.16 (2 H, m, CH_2), 7.09 (2 H, d, *J* 7.6 Hz, ArH), 7.27–7.30 (2 H, m, ArH), 7.34–7.39 (5 H, m, ArH); δ_C (100 MHz, $CDCl_3$) 28.3, 38.3, 47.6, 54.6, 61.8, 67.2, 80.0, 128.4, 128.5, 128.6, 128.9, 129.4, 132.5, 135.2, 137.8, 155.1, 168.2, 171.7; δ_B (128 MHz, $CDCl_3$) 12.0; *m/z* (ESI) 532.2102 (M^+ + Na. $C_{26}H_{31}BN_2O_8$ requires 532.2107).

(*S*)-benzyl 2-(tert-butoxycarbonylamino)-3-(3-(6-methyl-4,8-dioxo-1,3,6,2-dioxazaborocan-2-yl)phenyl)propanoate 2a

(0.583 g, 58%) from 0.670 g of 3-iodophenyl boronic acid MIDA ester **6**. m.p.: 108.0–109.9 °C; $[\alpha]_D^{24}$ = −11.4 (c 0.4 in MeOH); ν_{max}/cm^{-1} 2963, 2913, 1750, 1742, 1704, 1499, 1455, 1337, 1252, 1166, 1037, 969, 864, 791, 753, 699; δ_H (400 MHz, $CDCl_3$) 1.37 (9 H, s, ^{t}Bu), 2.42 (3 H, s, NCH_3), 2.99 (1 H, dd, *J* 14.0 and 7.6 Hz, CH_a), 3.14 (1 H, dd, *J* 14.0 and 6.4 Hz, CH_b), 3.76 (2 H, dd, *J* 16.0 and 8.4 Hz, 2 × CH_a), 3.89 (2 H, br d, *J* 16.0 Hz, 2 × CH_b), 4.59–4.61 (1 H, m, CH), 4.96 (1 H, br d, *J* 6.4 Hz, NH), 5.09–5.19 (2 H, m, CH_2), 7.12 (1 H, d, *J* 6.8 Hz, ArH), 7.26–7.41 (8 H, m, ArH); δ_C (100 MHz, $CDCl_3$) 28.3, 38.4, 47.7, 54.8, 61.9, 67.1, 80.4, 128.4, 128.5, 128.6, 128.6, 130.8, 130.9, 133.2, 135.0, 135.3, 136.0, 155.1, 169.0, 172.0; δ_B (128 MHz, $CDCl_3$) 11.5; *m/z* (ESI) 532.2111 (M^+ + Na. $C_{26}H_{31}BN_2O_8$ requires 532.2107).

(*S*)-benzyl 2-(tert-butoxycarbonylamino)-3-(4-methoxy-3-(6-methyl-4,8-dioxo-1,3,6,2-dioxazaborocan-2-yl)phenyl)propanoate 3a

(0.190 g, 61%) from 0.198 g of 2-(5-bromo-2-methoxyphenyl)-6-methyl-1,3,6,2-dioxazaborocane-4,8-dione **7**. m.p.: 116.6–117.3 °C. $[\alpha]_D^{24}$ = −10.0 (c 0.5 in MeOH); ν_{max}/cm^{-1} 2956, 1750, 1746, 1700, 1489, 1454, 1338, 1290, 1237, 1167, 1029, 867, 820, 752, 700, 656. δ_H (400 MHz, $CDCl_3$) 1.40 (9 H, s, ^{t}Bu), 2.59 (3 H, s, NCH_3), 3.00–3.08 (2 H, m, CH_2), 3.77 (3 H, s, OCH_3), 3.91–3.96 (4 H, m, 2 × CH_2), 4.54–4.60 (1 H, m, CH), 4.96 (1 H, br d, *J* 7.6 Hz, NH), 5.10–5.17 (2 H, m, CH_2), 6.77 (1 H, d, *J* 8.4 Hz, ArH), 7.08 (1 H, dd, *J* 8.4 and 2.0 Hz, ArH), 7.33–7.38 (5 H, m, ArH), 7.43 (1 H, d, *J* 2.0 Hz, ArH); δ_C (100 MHz, $CDCl_3$) 28.3, 37.6, 47.5, 55.5, 63.7, 67.1, 79.9, 110.6, 128.4, 128.5, 128.6, 132.1, 133.9, 135.3, 135.8, 135.8, 137.4, 155.1, 161.3, 168.3, 171.9; δ_B (128 MHz, $CDCl_3$) 10.5; *m/z* (ESI) 562.2224 (M^+ + Na. $C_{27}H_{33}BN_2O_9$ requires 562.2213).

(*R*)-benzyl 2-(tert-butoxycarbonylamino)-3-(4-(6-methyl-4,8-dioxo-1,3,6,2-dioxazaborocan-2-yl)phenyl)propanoate 1b

(0.358 g, 62%) from 0.409 g of 4-iodophenyl boronic acid MIDA ester **5**. $[\alpha]_D^{24}$ = +10.0 (c 0.5 in MeOH); ν_{max}/cm^{-1} 2969, 1742, 1690, 1500, 1454, 1336, 1230, 1162, 1038, 991, 862, 753, 699. ^{1}H, ^{13}C and ^{11}B NMR data correspond to that of the (*S*)-enantiomer **1a**; *m/z* (ESI) 532.2117 (M^+ + Na. $C_{26}H_{31}BN_2O_8$ requires 532.2107).

(*R*)-benzyl 2-(tert-butoxycarbonylamino)-3-(3-(6-methyl-4,8-dioxo-1,3,6,2-dioxazaborocan-2-yl)phenyl)propanoate 2b

(0.562 g, 59%) from 0.671 g of 3-iodophenyl boronic acid MIDA ester **6**. $[\alpha]_D^{24}$ = +11.6 (c 0.5 in MeOH); ν_{max}/cm^{-1} 2879, 1756, 1742, 1704, 1499, 1454, 1336, 1251, 1166, 1038, 988, 891, 862, 788, 738, 699. ^{1}H, ^{13}C and ^{11}B NMR data correspond to that of the (*S*)-enantiomer **2a**; *m/z* (ESI) 532.2092 (M^+ + Na. $C_{26}H_{31}BN_2O_8$ requires 532.2107).

(*R*)-benzyl-2-(tert-butoxycarbonylamino)-3-(4-methoxy-3-(6-methyl-4,8-dioxo-1,3,6,2-dioxazaborocan-2-yl)phenyl)propanoate 3b

(0.360 g, 59%) from 0.390 g of 2-(5-bromo-2-methoxyphenyl)-6-methyl-1,3,6,2-dioxazaborocane-4,8-dione **7**. $[\alpha]_D^{24}$ = +9.9 (c 0.5 in MeOH); ν_{max}/cm^{-1} 2968, 1756, 1746, 1708, 1489, 1455, 1338, 1289, 1237, 1166, 1028, 868, 751, 700, 656. ^{1}H, ^{13}C and ^{11}B NMR data correspond to that of the (*S*)-enantiomer **3a**; *m/z* (ESI) 562.2210 (M^+ + Na. $C_{27}H_{33}BN_2O_9$ requires 562.2213).

General Procedure for the Synthesis of Biphenylalanines 9–11

The relevant boronic acid MIDA ester (0.3 mmol), $Pd(OAc)_2$ (1.7 mg, 2.5 mol.%), SPhos (6.2 mg, 5.0 mol.%), K_3PO_4 (0.22 g, 1.05 mmol) and iodobenzene (0.05 mL, 0.45 mmol) were dissolved in a degassed mixture of 1,4-dioxane/H_2O (1.8/0.18 mL) under argon. The resulting black solution was stirred at 70 °C for 48 h. Upon cooling the reaction mixture was purified *via* column chromatography without work-up (SiO_2, 100% hexane; 85% hexane/15% diethyl ether) to give the products as white or tan solids.

(*S*)-benzyl 3-(biphenyl-4-yl)-2-(tert-butoxycarbonylamino)-propanoate 9a

(82 mg, 63%) from 0.150 g of boronic acid MIDA ester **1a**. m.p.: 96.3 °C; $[\alpha]_D^{24}$ = −10.8 (c 0.5 in MeOH) (99.0% *ee*); ν_{max}/cm^{-1} 2988, 2913, 2838, 1738, 1686, 1519, 1490, 1298, 1248, 1151, 1022, 1006, 761, 738, 694; δ_H (400 MHz, $CDCl_3$) 1.42 (9 H, s, ^{t}Bu), 3.09–3.17 (2 H, m, CH_2), 4.64–4.69 (1 H, m, CH), 5.02 (1 H, br d, *J* 8.4 Hz, NH), 5.10–5.21 (2 H, m, CH_2), 7.11 (2 H, d, *J* 8.0 Hz, ArH), 7.28–7.30 (2 H, m, ArH), 7.32–7.36 (4 H, m, ArH), 7.42–7.45 (4 H, m, ArH), 7.54–7.57 (2 H, m, ArH); δ_C (100 MHz, $CDCl_3$) 28.3, 38.0, 54.5, 67.2, 80.0, 127.0, 127.0, 127.2, 128.5, 128.5, 128.6, 128.7, 129.8, 135.0, 135.2, 139.9, 140.8, 155.1, 171.7; *m/z* (ESI) 454.1999 (M^+ + Na. $C_{27}H_{29}NO_4$ requires 454.1994).

(*S*)-benzyl 3-(biphenyl-3-yl)-2-(tert-butoxycarbonylamino)-propanoate 10a

(81 mg, 62%) from 0.150 g of boronic acid MIDA ester **2a**. m.p.: 99.3 °C; $[\alpha]_D^{24}$ = −10.6 (c 0.5, MeOH) (99.0% *ee*); ν_{max}/cm^{-1} 2920, 2831, 1729, 1689, 1518, 1455, 1369, 1262, 1164, 1054, 1029, 978, 899, 754, 702; δ_H (400 MHz, $CDCl_3$) 1.41 (9 H, s, ^{t}Bu), 3.11–3.22 (2 H, m, CH_2), 4.66–4.71 (1 H, m, CH), 5.01–5.04 (1 H, br d, *J* 8.4 Hz, NH), 5.09–5.17 (2 H, m, CH_2), 7.02 (1 H, d, *J* 8.0 Hz, ArH), 7.24–7.37 (8 H, m, ArH), 7.41–7.47 (3 H, m, ArH), 7.52–7.55 (2 H, m, ArH); δ_C (100 MHz, $CDCl_3$) 28.3, 38.3, 54.5, 67.2, 80.0, 125.9, 127.2, 127.2, 127.3, 128.2, 128.3, 128.4, 128.6, 128.7, 128.9, 135.2, 136.4, 141.0, 141.5, 155.1, 171.7; *m/z* (ESI) 454.1980 (M^+ + Na. $C_{27}H_{29}NO_4$ requires 454.1994).

(*S*)-benzyl 2-(tert-butoxycarbonylamino)-3-(6-methoxybiphenyl-3-yl)propanoate 11a

(79 mg, 57%) from 0.162 g of boronic acid MIDA ester **3a**. m.p.: 130.6 - 130.8 °C; $[\alpha]_D^{24}$ = −9.8 (c 0.5 in MeOH) (99.6% *ee*);

ν_{max}/cm^{-1} 2950, 2924, 2851, 1725, 1702, 1504, 1489, 1444, 1366, 1240, 1208, 1154, 1030, 1012, 962, 865, 759, 730, 702; δ_H (400 MHz, $CDCl_3$) 1.41 (9 H, s, ^{t}Bu), 3.02–3.12 (2 H, m, CH_2), 3.78 (3 H, s, OMe), 4.60–4.65 (1 H, m, CH), 5.02 (1 H, br d, *J* 7.6 Hz, NH), 5.09–5.17 (2 H, m, CH_2), 6.83 (1 H, d, *J* 8.0 Hz, ArH), 6.98 (1 H, d, *J* 8.0 Hz, ArH), 7.04 (1 H, br s, ArH), 7.27–7.49 (10 H, m, ArH); δ_C (100 MHz, $CDCl_3$) 28.3, 37.4, 54.6, 55.6, 67.1, 80.0, 111.4, 127.0, 128.0, 128.0, 128.4, 128.6, 129.3, 129.5, 130.4, 132.0, 135.2, 135.2, 138.3, 155.1, 155.6, 171.8; *m/z* (ESI) 484.2093 (M^+ + Na. $C_{28}H_{31}NO_5$ requires 484.2100).

(*R*)-benzyl 3-(biphenyl-4-yl)-2-(tert-butoxycarbonylamino)-propanoate 9b

(85 mg, 65%) from 0.150 g of boronic acid MIDA ester **1b**. $[\alpha]_D^{24}$ = +11.7 (c 0.3 in MeOH) (97.4% *ee*); ν_{max}/cm^{-1} 2931, 2979, 1728, 1689, 1518, 1455, 1368, 1260, 1164, 1054, 1028, 978, 754, 698, 662.^{1}H and ^{13}C NMR data correspond to that of the (*S*)-enantiomer **9a**. *m/z* (ESI) 454.1977 (M^+ + Na. $C_{27}H_{29}NO_4$ requires 454.1994).

(*R*)-benzyl 3-(biphenyl-3-yl)-2-(tert-butoxy-carbonylamino)propanoate 10b

(74 mg, 57%) from 0.150 g of boronic acid MIDA ester **2b**. $[\alpha]_D^{24}$ = +10.6 (c 0.5 in MeOH) (99.0% *ee*); ν_{max}/cm^{-1} 2978, 2913, 1749, 1697, 1514, 1456, 1160, 1060, 898, 869, 758, 698.^{1}H and ^{13}C NMR data correspond to that of the (*S*)-enantiomer **10a**. *m/z* (ESI) 454.1996 (M^+ + Na. $C_{27}H_{29}NO_4$ requires 454.1994).

(*R*)-benzyl 2-(tert-butoxycarbonylamino)-3-(6-methoxybiphenyl-3-yl)propanoate 11b

(80 mg, 58%) from 0.162 g of boronic acid MIDA ester **3b**. $[\alpha]_D^{24}$ = +9.9 (c 0.3 in MeOH) (99.6% *ee*); ν_{max}/cm^{-1} 2927, 2831, 1729, 1689, 1518, 1454, 1369, 1261, 1164, 1054, 1028, 978, 801, 754, 702, 662. ^{1}H and ^{13}C NMR data correspond to that of the (*S*) enantiomer **11a**. *m/z* (ESI) 484.2091 (M^+ + Na. $C_{28}H_{31}NO_5$ 484.2100).

(*S*)-2-(tert-butoxycarbonylamino)-3-(4-(6-methyl-4,8-dioxo-1,3,6,2-dioxazaborocan-2-nyl)phenyl)propanoic acid 12

(*S*)-benzyl-2-(tert-butoxycarbonylamino)-3-(4-(6-methyl-4,8-dioxo-1,3,6,2-dioxazaborocan-2-yl)phenyl)propanoate **1a** (0.284 g, 0.56 mmol) was added to a suspension of 10% Pd/C (57 mg, 10% wt.) (50% wet) in MeOH (8 mL) at room temperature and the reaction mixture was stirred under an atmosphere of H_2 for 2 h. The reaction mixture was filtered though a plug of celite, washing with MeOH (5 mL) and the volatiles removed *in vacuo* to give to desired product **12** as a white solid (0.20 g, 86%) which was used without further purification (NMR indicated purity of greater than 90%). $[\alpha]_D^{24}$ = +24.8 (c 0.3 in MeOH); ν_{max}/cm^{-1} 2958, 2906, 1742, 1688, 1514, 1454, 1368, 1337, 1229, 1162, 1038, 992, 889, 863, 816, 710; δ_H (400 MHz, DMSO-d_6) 1.31 (9 H, s, ^{t}Bu), 2.47 (3 H, s, NCH_3), 2.82 (1 H, m, 1 × CH_a), 3.01 (1 H, dd, *J* 13.6 and 3.6 Hz, 1 × CH_b), 4.09–4.14 (3 H, m, CH and 2 × CH_a), 4.31 (2 H, d, *J* 17.2 Hz, 2 × CH_b), 7.09 (1 H, d, *J* 8.4 Hz, NH), 7.23 (2 H, d, *J* 7.6 Hz, ArH), 7.34 (2 H, d, *J* 7.6 Hz, ArH); δ_C (100 MHz, DMSO-d_6) 28.1, 36.4, 47.5, 55.0, 61.7, 78.0, 128.4, 132.2, 134.0, 138.7, 155.4, 169.4, 173.6; δ_B (128 MHz, DMSO-d_6) 10.6; *m/z* (ESI) 419.1640 (M–H. $C_{19}H_{25}BN_2O_8$ requires 419.1626).

(S)-methyl-2-((*S*)-2-(tert-butoxycarbonylamino)-3-(4-(6-methyl-4,8-dioxo-1,3,6,2 dioxazaborocan-2-yl)phenyl)-propanamido)propanoate 13

NMM (0.1 mL, 0.9 mmol) was added to a solution of NH_2-Ala-OMe. HCl (38 mg, 0.3 mmol) in DCM (2 mL) and the mixture stirred at room temperature for 5 min. followed by the addition of PyBOP® (155 mg, 0.3 mmol) and **12** (125 mg, 0.3 mmol) in DCM (1 mL). The resulting pale yellow solution was stirred at room temperature for 15 h. The volatiles were removed *in vacuo* to give a yellow oil which was purified *via* column chromatography (50/50 EtOAc/Hexane → 100% EtOAc) to afford the desired product **13** as a white solid (120 mg, 82%). m.p.: 130.5–131.9 °C. $[\alpha]_D^{24}$ = −10.1 (c 1.0 in CH_3CN); ν_{max}/cm^{-1} 2926, 1742, 1660, 1514, 1454, 1367, 1338, 1229, 1161, 1039, 991, 837; δ_H (500 MHz, CD_3CN) 1.32 (12 H, br s, ^{t}Bu), 2.48 (3 H, s, NCH_3), 2.81 (1 H, dd, *J* 13.5 and 9.5 Hz, 1 × CH_a), 3.11 (1 H, dd, *J* 13.5 and 4.0 Hz, 1 × CH_b), 3.66 (3 H, s, OCH_3), 3.88 (2 H, dd, *J* 17.0 and 4.0 Hz, 2 × CH_a), 4.06 (2 H, dd, *J* 17.0 and 2.0 Hz, 2 × CH_b), 4.27–4.32 (1 H, m, CH), 4.36–4.41 (1 H, m, CH), 5.56 (1 H, br d, *J* 8.0 Hz, NH), 7.04 (1 H, br d, *J* 6.5 Hz, NH), 7.25 (2 H, d, *J* 7.5 Hz, ArH), 7.42 (2 H, d, *J* 7.5 Hz, ArH); δ_C (125 MHz, CD_3CN) 18.5, 29.1, 39.4, 49.1, 49.6, 53.5, 57.1, 63.4, 80.6, 130.6, 134.1, 140.3, 157.0, 170.3, 173.0, 174.5; δ_B (128 MHz, CD_3CN) 11.0; *m/z* (ESI) 527.2156 (M^+ + Na. $C_{23}H_{32}BN_3O_9$ requires 527.2166).

(*S*)-methyl 2-((*S*)-2-(tert-butoxycarbonylamino)-3-(4-(6-methyl-4,8-dioxo-1,3,6,2-dioxazaborocan-2-yl)phenyl)propanamido)propanoate 15

TFA (2 mL) was added to a stirred solution of **1a** (65 mg, 0.13 mmol) in DCM (2 mL) at room temperature and the resulting pale yellow solution stirred for 5 h. The volatiles were removed under reduced pressure and residual TFA was removed by co-evaporation with ether (x 4). The crude material **14** was taken up in DCM (1 mL), NMM (0.04 mL, 0.38 mmol) was added and the solution stirred at room temperature for 5 min. followed by the addition of PyBOP® (66 mg, 0.13 mmol) and Boc-Ala-OH (24 mg, 0.13 mmol) in DCM (1 mL). After stirring at room temperature for 12 h the volatiles were removed under reduced pressure and purification *via* column chromatography (50/50 EtOAc/hexane → 100% EtOAc) afforded the title compound **15** as a white solid (38 mg, 52%). m.p.: 131.2–132.0 °C. $[\alpha]_D^{24}$ = −9.9 (c 1.0 in CH_3CN); ν_{max}/cm^{-1} 2938, 1742, 1680, 1518, 1455, 1369, 1343, 1252, 1191, 1042, 995, 833, 741, 700; δ_H (700 MHz, CD_3CN) 1.17 (3 H, d, *J* 7.0 Hz, CH_3), 1.39 (9 H, s, ^{t}Bu), 2.44 (3 H, s, NCH_3), 3.03 (1 H, dd, *J* 13.3 and 7.0 Hz, 1 × CH_a), 3.13 (1 H, dd, *J* 14.0 and 5.6 Hz, 1 × CH_b), 3.86 (2 H, dd, *J* 17.5 and 3.5 Hz, 2 × CH_a), 4.00 (1 H, br s, CH), 4.06 (2 H, d, *J* 17.5 Hz, 2 × CH_b), 4.68 (1 H, dd, *J* 13.3 and 7.0 Hz, CH), 5.07–5.11 (2 H, m, CH_2), 5.54–5.55 (1 H, m, NH), 6.93 (1 H, br s, NH), 7.18 (2 H, d, *J* 7.7 Hz, ArH), 7.30–7.32 (2 H, m, ArH), 7.33–7.39 (5 H, m, ArH); δ_C (175 MHz, CD_3CN): δ 18.4, 28.5, 38.1, 48.4, 50.9, 54.4, 62.7, 67.5, 79.9, 129.1, 129.1, 129.4, 129.9, 133.5, 136.7, 138.7, 156.3, 169.5, 172.1, 173.6; δ_B (128 MHz, CD_3CN) 11.3; *m/z* (ESI) 603.2468 (M^+ + Na. $C_{29}H_{36}BN_3O_9$ requires 603.2479).

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14 In our hands we found that Negishi coupling reactions utilising only 4.0 equiv. of zinc compared to the 6.0 equiv. reported by Jackson *et al.* (see ref. 10d) gave identical results. We also found that the less expensive catalyst $Pd(dba)_2$ could be used in place of $Pd_2(dba)_3$ but gave comparable yields in this reaction.

15 A $Pd(OAc)_2$ catalysis loading of 2.5 mol.% was utilised instead of 1.5 mol.% as this led to a slight increase in the reaction yields obtained. Increasing the catalysis loading to 5.0 mol.% has been reported to produced improve yields (see ref. 11a) but this was not investigated as in our study the primary focus was on confirming stereochemical integrity of the amino acids α-carbon.

16 We chose to use Buchwald coupling conditions (SPhos 5.0 mol.%) as such conditions had previously been documented to help suppress racemisation of the α-carbon on the amino acid (see ref. 8a).

17 The Bpin protecting group has previously been shown to be stable to standard peptide coupling conditions for example see ref. 5b.

