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Novel Aryl Boronate Ester Protected Amino Acids as Orthogonal Building Blocks for Fmoc Solid-Phase Peptide Synthesis

Chao Liu,[†a] Yan Zou,[†a] Hui Song,[c] Yuan-Ye Jiang*[b] and Hong-Gang Hu*[a]

Dedication ((optional))

Abstract: Three novel aryl boronate ester protected amino acids and their on-resin deprotection methods were developed. These useful building blocks were found to exhibit favourable chemical properties that are fully compatible with Fmoc strategy solid-phase peptide synthesis. Furthermore, the side over-oxidation product of methionine was minimized by using *N*-methyl-*N*-phenylaniline *N*-oxide as oxidizing reagent. Effective applications of the three new amino acids for synthesis of different types of peptidomimetics have been demonstrated by high-quality preparation of lipidated peptide MP-196 C-C_8, on-resin head-to-tail cyclization of desotamide B and lactam bridging of hPTHrP-(11-19) through a facile and metal-free procedure by standard Fmoc solid-phase peptide synthesis.

Introduction

With the development of peptide chemistry, cyclization or side chain modification of peptides allows for the generation of many interesting peptidomimetics with excellent pharmacological properties. Due to their improved selectivity and stability, these modified peptides have received tremendous attention for the development of novel pharmaceuticals.[1]

Classical methods usually prepare these analogues in solution phase after cleavage of the on-resin linear precursors. Tedious operations and repeated purifications are inevitable for this synthetic strategy and therefore, resulting in some cases a considerable loss of products.[2] Thus, the total solid phase synthesis (SPPS) method is considered as an attractive alternative in which the final cyclization or modification step is achieved while the peptide still remains anchored to the resin. The latter strategy requires the introduction of orthogonally protected amino acid building blocks which are compatible with tert-butyloxycarbonyl (Boc), tert-butyl (tBu), 2,2,4,6,7-pentamethyl-dihydrobenzo-furane-5-sulfonyl (Pbf) and trityl (Trt) groups in Fmoc SPPS. To date, the most frequently used building blocks are Fmoc-Lys(Alloc)-OH (Alloc, allyloxycarbonyl), Fmoc-Asp(OAllyl)-OH and Fmoc-Asp-OAllyl. They have so far been widely adopted during cyclic, branched, and chimeric peptides synthesis and successfully applied in protein modifications.[3] However, on-resin removal of Alloc/Allyl groups requires the use of Pd $(PPh_3)_4$ which may cause palladium contamination problem detrimental to the preparation of peptides for pharmaceutical use. Furthermore, the use of inert atmosphere and the time-consuming process hinder the convenient operation demanded by SPPS.[4] Thus, the development of innovative building blocks as more appropriate alternatives still remains a necessity.

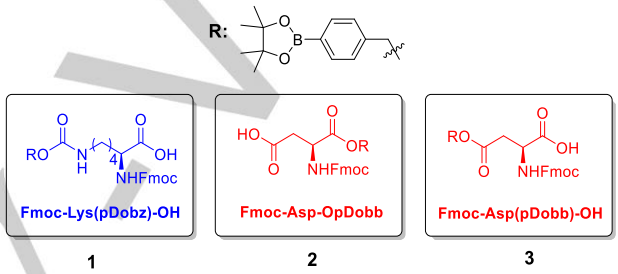

Figure 1. Structures of aryl boronate ester based building blocks.

Aryl boronic acids or aryl boronate esters are widely used in organic chemistry, but their applications were majorly focused on synthetic intermediates and fluorescence probes.[5] Intriguingly, *p*-dihydroxyborylbenzyloxycarbonyl (Dobz) group was employed as an effective *N*-α-protecting group in the synthesis of small peptides (up to a pentamer) through solution phase coupling by Roberts in 1975.[6] In 2014, pDobz-Cys(Trt)-OH (pDobz, *p*-dihydroxyborylbenzyl- oxycarbonyl pinacol ester) was employed in the total synthesis of modified histones. After cleavage from the solid support, the corresponding Dobz group was successfully removed by a rapid aryl boronate oxidation reaction mediated by H_2O_2.[7] This less time-consuming and metal-free deprotection process may render pDobz or pDobb (dihydroxyborylbenzyl pinacol ester) a superior capping group for development of orthogonal amino acid building blocks such as Fmoc-Lys(pDobz)-OH (**1**), Fmoc-Asp-OpDobb (**2**) and Fmoc-Asp(pDobb)-OH (**3**) (**Figure 1**). Furthermore, the acid-stable chemical property[7] makes these building blocks orthogonal to various acid-liable protecting groups frequently employed in SPPS such as *p*-methoxybenzyloxycarbonyl (Moz)[8], *p*-nitrobenzyloxycarbonyl (pNZ)/*p*-nitrobenzyl (pNB)[9] and 4-methyltriphenyl (Mtt)[10], *etc*. Nevertheless, the aqueous-phase based deprotection condition and the lack of oxidation selectivity of H_2O_2 (especially for methionine) restrict their applications in SPPS.[11] Therefore, to develop pDobz/pDobb based amino acids building blocks suitable for SPPS, the critical issue is to establish a general on-resin deprotection method at the very beginning.

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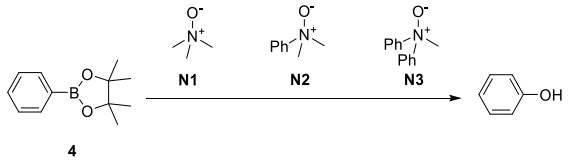
Table 1. The theoretical calculation results.



Entry	*N*-oxide	ΔG‡ (kcal/mol)
1	N1	26.7
2	N2	24.6
3	N3	20.2

Recently, we are interested in a mild and rapid transformation from aryl boric acid to phenol mediated by trimethylamine *N*-oxide (N1, TMAO) through a metal-free condition reported by Köster and Morita in 1967[12]. This reaction was accelerated by turning to *N*,*N*,*N*-dialkylaryl *N*-oxides reported by Falck in 2012[13]. The *N*-oxide together with sorts of phenylboronic acids or aryl boronate pinacol esters gave the corresponding phenols with high chemical yields. Subsequently, this reaction was well studied by Bertozzi and co-workers, which was applied as a novel bond-cleaving bioorthogonal reaction inside mammalian cells. They found that the reaction between *N*,*N*,*N*-dialkylaryl *N*-oxide and bis(pinacolato)-diboron (B_2pin_2) showcased a second-order rate constant as high as 2.3×10^3 M^{-1} S^{-1}.[14] Taking these explorations into account, we speculate *N*-oxide may solve the deprotection issue of pDobz/pDobb group on solid phase for the following reasons. 1) This reaction was found to explicit a quite higher reaction rate in DCM, the most frequently used solvent in SPPS, than in water. 2) Some oxidation-sensitive substrates (sulfide and aldehydes) were intact under this condition, which may solve the methionine over-oxidation problem as aforementioned.[13] 3) This reaction could carry on at ambient temperature, without base and in the presence of oxygen and water, offering a simple and convenient operation required by SPPS.

Results and Discussion

At the beginning of our study, theoretical calculations were employed to compare several economical and easy-to-prepare *N*-oxide candidates (**Table 1**). The concerted N-O bond cleavage and O-C bond formation was proposed to be the rate-limiting step for the oxidation reaction by Bertozzi and co-workers.[14] Therefore, the free energy barriers of this step referring to separate reactants were calculated at the level of theory of M06/6-11+G(d,p)//M06/6-31G(d) in solution-phase with SMD solvation model (solvent=water) (see the Supporting Information).The calculation results showed that two phenyl-substituted *N*-oxide (N3) is superior to the ones bearing one (N2) or no phenyl group (N1).

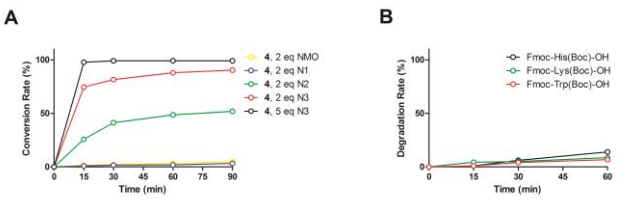
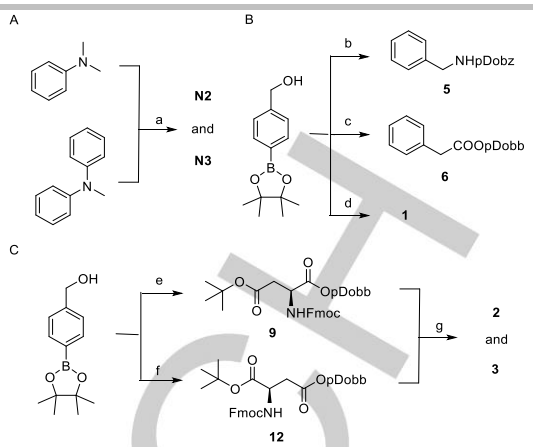


Figure 2. A) The conversion rates of **4** (0.2 mmol, DCM, rt) with 2.0 eq or 5.0 eq *N*-oxides. B) The degradation rates of Fmoc-His(Boc)-OH, Fmoc-Lys(Boc)-OH, Fmoc-Trp(Boc)-OH (0.2 mmol, rt) with 5.0% TFA/DCM containing 20.0% *m*-cresol.



Scheme 1. Synthesis route of small molecules. Reagents and conditions: a) MCPBA, DCM, rt, 1 h, 79.8% for N2 and 73.7% for N3; b) i) BTC, THF, rt, 12 h; ii) NaN_3, 1,4-dioxane/water, rt, 2 h; iii) Benzylamine, Et_3N, DMF, rt, 12 h, 81.4% in 3 steps; c) 2-phenylacetic acid, DCC, DMAP,DCM, rt, 4 h, 79.3%; d) i) BTC, THF, rt, 12 h; ii) NaN_3, 1,4-dioxane/water, rt, 2 h; iii) Fmoc-Lys-OH, Et_3N, DMF, rt, 12 h, 71.8% in 3 steps; e) Fmoc-Asp(OtBu)-OH, DCC, DMAP, DCM, rt, 4 h, 85.9%; f) Fmoc-Asp-OtBu, DCC, DMAP, DCM, rt, 4 h, 83.4%; g) TFA/DCM (3:1, v/v), rt, 2 h, 95.0% for 2 and 95.3% for 3;

To confirm this result, we obtained N2 and N3 from *N,N*-dimethylaniline and *N*-methyl-*N*-phenylaniline *via* the oxidation of 3-chloroperbenzoic acid (MCPBA) respectively (**Scheme 1A**). Then, phenyl boronic acid pinacol ester (**4**) were subjected to 2.0 equivalent of NMO (*N*-Methyl morpholine-*N*-oxide), N1, N2 and N3 in DCM (0.2 M). It was found that the introduction of aromatic groups into *N*-oxide has expectedly accelerated the oxidation rate. Hence, we finally selected the N3 as the oxidizing agent. Although the oxidation of the substrate was observed, the reaction was unable to be completely realized even after 90 minutes treatment. Considering the facile removing of excess reactants during SPPS reactions, we choose to adjust the equivalent of N3 to accelerate this conversion. It was demonstrated that 5.0 equivalents of N3 could convert more than 97.0% substrates in 15 minutes which was an acceptable reaction time for SPPS (**Figure 2A**, **Table S1**, see the Supporting Information). Meanwhile, the stability of Fmoc-Met-OH was investigated under this condition. As results, more than 96.0% of methionine remained intact after treatment with 5.0 equivalents of N3 in 15 minutes. Besides, there was only less than 10.0% oxidation by-products generating even after 90 minutes exposure **(Table S2**, see the Supporting Information). Hence, 5.0 equivalents of N3 for 15 minutes oxidation was selected as the suitable condition.

In a previous report, the pDobz group was deprotected from amine in a basic condition (pH= 9.5) after oxidation through quinomethide form as an intermediate in the aqueous phase.[6] However, we noticed that the carbobenzoxy form could also be

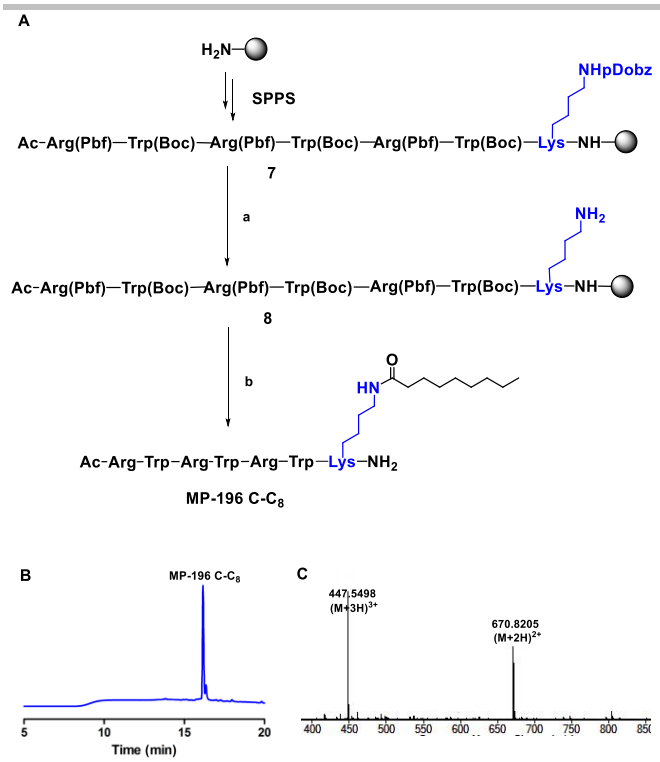


Figure 3. A) Synthesis route of MP-196 C-C_8, Reagents and conditions: a) i) 5.0 eq N3, DCM, rt, 15 min; ii) TFA/*m*-cresol/DCM (5:20:75, *v/v/v*), rt, 15 min; b) i) HATU, HOAt, DIPEA, DMF, rt, 15 min; ii) Octanoic acid/DMF, rt, 2 h; iii) TFA/TIPs/EDT/Water (95:2:2:1, *v/v/v/v*), rt, 2 h, 47.3% yield. B) HPLC profile of the crude MP-196 C-C_8. C) HR-MS of MP-196 C-C_8.

cleaved through acidic medium with different rates based on the substituted groups.[6][15] Therefore, we were interested in the method of acidic removing of Moz group, which was very close to the pDobz/pDobb group after oxidation.[8] It was pointed out that Moz group could be removed in high yield with 5.0% TFA for 30 minutes, accompanied by 20.0% degradation of Boc, which could be accelerated by 20.0% *m*-cresol addition.[16] To investigate this condition, we built pDobz protected benzylamine and pDobb protected 2-phenylacetic acid (**5** and **6 Scheme 1B**). After treatment with 5 equivalents of N3 for 15 minutes, they were subjected to different acidic conditions (1.0-5.0% TFA with or without 20.0% *m*-cresol) and monitored at 15, 30 and 60 minutes by HPLC. We found that both of the intermediates completely convert to benzylamine and phenylacetic acid in 15 minutes in the presence of 5% TFA/DCM solution containing 20.0% *m*-cresol (**Table S3** and **S4**, see the Supporting Information). Subsequently, protecting groups frequently used during Fmoc SPPS such as Boc, tBu, Pbf and Trt were tested under this condition. Trace degradation (< 5.0%) was only observed for the Boc protecting group (**Figure 2B, Table S5**, see the Supporting Information).

Having the deprotection condition available, our next plan was to explore the application of **1** in side chain modified peptide total synthesis. First of all, **1** was synthesized as follows (**Scheme 1B**). The commercially available (4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-phenyl) methanol was converted to carbonchloridate form through triphosgene (BTC) in THF. Then, 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-benzyl carbon-azidate (pDobz-N_3) was obtained after addition of NaN_3 in 1,4-dioxane/water which was better than carbonochloridate form for storage and use because of its chemical stability and solid-state property. The reaction of pDobz-N_3 with Fmoc-Lys-OH in the presence of Et_3N provided Fmoc-Lys(pDobz)-OH (**1**) with a yield of 71.8%. We chose the cationic antimicrobial peptides MP-196 C-C_8, a side chain lipidated MP-196 derivative, as our first target.[17] It contains multiple repeated arginine and tryptophan sequences and is currently considered to be one of the typical antimicrobial peptides. Among all the lipidated MP-196 derivatives, those with lipid chains of eight carbon atoms turned out to be the most promising candidate for antibacterials development.[18] Building block **1** was successfully incorporated into linear peptide on resin (**7**) through SPPS. Then, it was subjected to the general deprotection condition (5 equivalent of N3 in DCM for 15 minutes, then 5% TFA/ DCM solution containing 20.0% *m*-cresol for 15 minutes) to achieve the linear peptide with a free amino group at Lys side chain (**8**). Coupling with *n*-octanoic acid using O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexaflu orophosphate (HATU), 1-hydroxy-7-azabenzotriazole (HOAt) and *N,N*-Diisopropylethylamine (DIEA) in DMF for 2 hours and the following global deprotection and cleavage by trifluoroacetic acid (TFA), triisopropylsilane (TIPs), 1,2-Ethanedithiol (EDT) and water (95:2:2:1, *v/v/v/v*) successfully provided the crude MP-196 C-C_8 in a purity of 85.2% and a yield of 47.3% after purification by RP-HPLC (**Figure 3**).

To investigate the applicability of building block **2**, we synthesized Desotamide B, a 6-residue head-to-tail cyclopeptide with growth inhibitory activity against Gram-positive bacteria.[19] In the previous studies, these kinds of cyclopeptide containing Asp and/or Asn residue were synthesized *via* on-resin head-to-tail cyclization strategy with Allyl based building blocks.[20] Herein, we first prepared **2** as follows (**Scheme 1C**). The esterification reaction between Fmoc-Asp(OtBu)-OH and (4-(4,4,5,5-tetra-

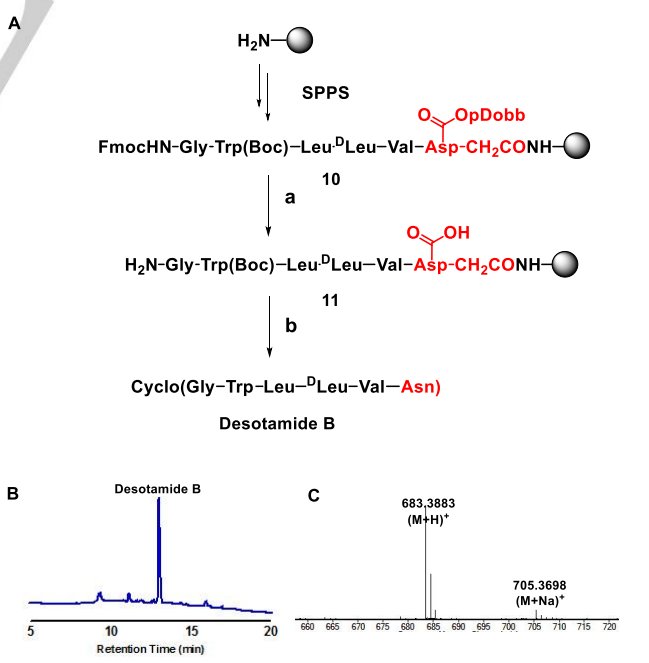


Figure 4. A) Synthesis route of Desotamide B, Reagents and conditions:a) i) 5.0 eq N3 in DCM, rt, 15 min; ii) 20.0% piperidine/DMF, rt, 10 min; iii) TFA/*m*-cresol/DCM (5:20:75, *v/v/v*), rt, 15 min; b) i) PyAOP, HOAt, NMM, NMP, rt, 12 h; ii) TFA/TIPs/EDT/Water (95:2:2:1, *v/v/v/v*), rt, 2 h, 43.8% yield. B) HPLC profile of the crude Desotamide B. C) HR-MS of Desotamide B.

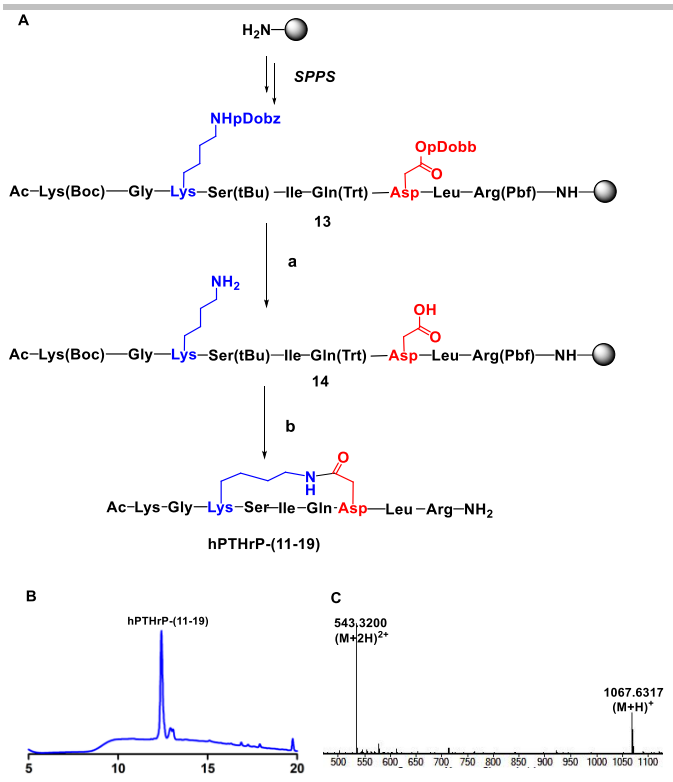


Figure 5. A) Synthesis route of hPTHrP-(11-19), Reagents and conditions: A) i) 5.0 eq N3 in DCM, rt, 15 min; ii) TFA/*m*-cresol/DCM (5:20:75, *v/v/v*), rt, 15 min; b) i) PyAOP, HOAt, NMM, NMP, rt, 12 h, ii) TFA/TIPs/EDT/ Water (95:2:2:1, *v/v/v/v*), rt, 2 h, 38.1% yield. B) HPLC profile of the crude hPTHrP-(11-19).C) HR-MS of hPTHrP-(11-19).

methyl-1,3,2-dioxaborolan-2-yl)phenyl) methanol promoted by dicyclohexylcarbodiimide (DCC) and 4-dimethylaminopyridine (DMAP) afforded Fmoc-Asp(OtBu)-OpDobb (9) in 85.9% yield. Then, Fmoc-Asp-OpDobb (**2**) was obtained after deprotection of tBu group by TFA/DCM (3:1, v/v) with a yield of 95.0%. After introduction of **2** into the linear peptide (**10**) *via* SPPS, pDobb was deprotected on-resin successfully with the general deprotection condition. Then, the Fmoc group was deprotected with 20.0% piperidine/DMF, followed by the on-resin cyclization in the presence of (7-azabenzotriazol-1-yloxy) tripyrrolidino phosphonium hexafluoro phosphate (PyAOP), HOAt and 4-methyl- morpholine (NMM) for 12 hours. However, after cleavage from the resin by TFA/TIPs/EDT/water (95:2:2:1, v/v/v/v), we were unable to obtain the desired product. However, considering the trace cleavage linear peptide (**11**) was correct (**Figure S2**, see the Supporting Information), we suspected that the free C-terminal might be interfered by piperidine during the Fmoc deprotection step by some means and could be rectified in acidic conditions. To support this notion, we reversed the treatment order of TFA/*m*-cresol/DCM and piperidine/DMF. Gratifying, crude Desotamide B was successfully obtained in 81.6% purity and a yield of 43.8% after purification by RP-HPLC (**Figure 4**).

Finally, building block **3** was employed to synthesize a lactam-bridge mimetic cyclopeptide, hPTHrP-(11-19) ([Ac-Lys-Gly-Lys-Ser-Ile-Gln-Asp-Leu-Arg-NH_2]), a fragment of the potent parathyroid hormone receptor 1 (PTHR1) antagonist containing an extended and stabilized α-helical conformation.[21] Its non-biogenic cyclization *via* lactam formation between side chains of Lys and Asp used to be realized through Fmoc/tBu strategy with Allyl/Alloc based building blocks.[22] First of all, Fmoc-Asp(pDobb)-OH (**3**) was obtained through the similar method from **12** (**Scheme 1C**). Fully protected linear peptide could be easily obtained by coupling Fmoc-Lys(pDobz)-OH (**1**) and **3** into the peptide backbone (**13**) *via* SPPS. The following simultaneous deprotection of pDobz/pDobb provided the on-resin cyclization precursor (**14**). Treatment with PyAOP/HOAt/NMM on solid support and the following cleavage and global deprotection provided the hPTHrP-(11-19) with a high purity of 79.3% and a yield of 38.1% after purification by RP-HPLC (**Figure 5**).

Conclusions

In summary, it is the first time to describe the employment of aryl boronate ester protected amino acids as building blocks for facile and efficient preparation of various peptidomimetics. We successfully solved their deprotection issue on solid support and the methionine over-oxidation problem reported in the previous study was minimized by using theoretical calculation optimized N3 as oxidizing reagent. These novel building blocks were found to exhibit favourable chemical properties that are fully compatible with the Fmoc strategy SPPS and orthogonal to Boc, tBu, pbf and Trt groups as demonstrated by high-quality synthesis of MP-196 C-C_8, Desotamide B and hPTHrP-(11-19). They may provide superior alternatives in the synthesis of peptidomimetics for pharmaceutical use because of their less-time-consuming and metal-free handling properties. More importantly, owing to their acid-stable chemical properties, these building blocks are orthogonal to various acid-liable protecting groups such as Moz, pNZ/pNB and Mtt which can be employed to prepare more complex peptidomimetics and proteins. Further applications of these building blocks are being explored in our team.

Experimental Section

Supporting Information (see footnote on the first page of this article): Experimental procedures, characterization data, and ^{1}H and ^{13}C NMR spectra of the products.

Acknowledgements

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Keywords: Aryl boronate ester • Orthogonal building blocks • Peptide synthesis

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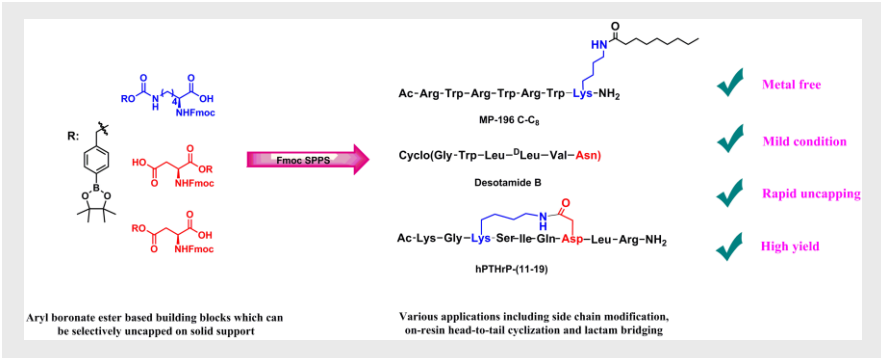

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