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## Diversity-oriented synthesis of peptide-boronic acids by a versatile building-block approach†

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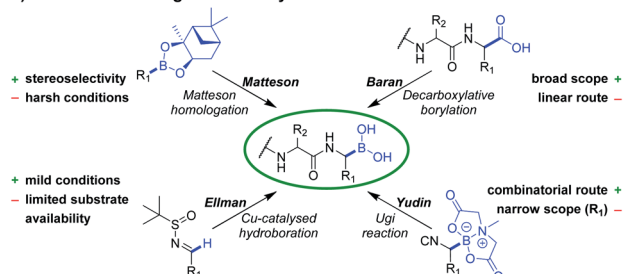
A new strategy for the synthesis of peptide-boronic acids (PBAs) is presented. 20 Fmoc-protected natural amino acids with orthogonal side-chain protection were straightforwardly converted into their corresponding boron analogues in three simple steps. Subsequent immobilisation on commercially available 1-glycerol polystyrene resin and on-resin transformations yielded a diversity of sequences in high purity. The strategy eliminates various synthetic obstacles such as multi-step routes, low yields, and inseparable impurities. The described method comprises great potential to be implemented in automated combinatorial approaches by markedly facilitating the access to a variety of PBAs. The coupling of amino acids or other building blocks with  $\alpha$ -aminoboronates allows the creation of hybrid molecules with significant potential in various scientific disciplines, such as medicinal chemistry, structural biology, and materials science.

### Introduction

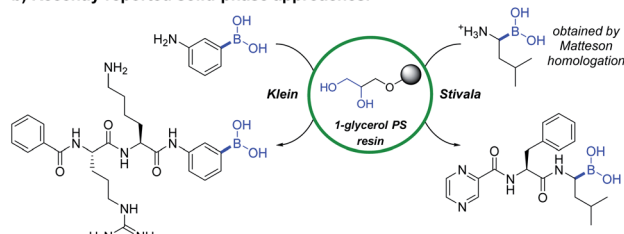
In the past years, boronic acids have gained importance within numerous research fields, with an unmet versatility as synthetic intermediates and various other applications.<sup>1,2</sup> Peptide-boronic acids (PBAs) in particular are used as protease inhibitors<sup>3–5</sup> and as covalent ligands in structural biology.<sup>4,6</sup> Bortezomib is the first FDA-approved PBA and concurrently the first-in-class proteasome inhibitor.<sup>7–9</sup> Numerous other investigational and approved PBA drugs followed, among these are ixazomib,<sup>10</sup> delanzomib,<sup>11</sup> vaborbactam<sup>12</sup> and taniborbactam.<sup>13</sup> However, synthesis and structure-activity relationship studies of PBAs remain tedious work, in which the construction of the  $\alpha$ -aminoboronate partial structure and deprotection of boronate esters constitute the crucial steps.

The established synthetic approaches towards PBAs and related compounds can be subdivided into late-stage borylations and building block approaches (Fig. 1). The most commonly used building block strategy remains the Matteson homologation, with chiral  $\alpha$ -chloroboronic esters as key intermediates.<sup>14,15</sup> While this transformation is highly stereocontrolled, the harsh reaction conditions restrict the substrate scope and necessitate various transformations after introduction of the boronic ester. An elegant substrate-controlled asymmetric borylation of imines was developed by Ellman and coworkers in 2008,<sup>16</sup> and optimised in 2014.<sup>17</sup> However, this

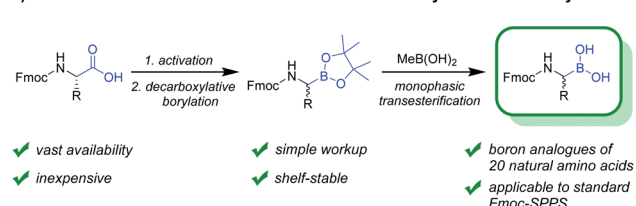
#### a) Established strategies in PBA synthesis and their limitations.



#### b) Recently reported solid-phase approaches.



#### c) This work: Fmoc- $\alpha$ -aminoboronates enable diversity-oriented PBA synthesis.



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† Electronic supplementary information (ESI) available: Experimental details, procedures and characterisation of all compounds, including <sup>1</sup>H and <sup>13</sup>C NMR spectra. See DOI: 10.1039/d0sc03999c

Fig. 1 Strategies for the synthesis of peptide-boronic acids. (a) Commonly used solution-phase approaches and their limitations. (b) Recently reported solid-phase approaches. (c) This work: facilitated access to a diversity of PBAs by introducing *N*-Fmoc- $\alpha$ -aminoboronic acids as versatile building blocks.



approach remains underexploited towards the synthesis of boron equivalents of proteinogenic amino acids, likely due to the scarcity of suitable aldehyde precursors.

Recently, Baran and coworkers reported the Ni-catalysed decarboxylative borylation of redox-active esters.<sup>18</sup> Along with its Cu-catalysed variant,<sup>19</sup> it constituted a milestone in boronic acid synthesis due to its broad scope. Although primary, secondary, tertiary and peptidic carboxylic acids were readily converted into their boron counterparts, *N*-Fmoc- $\alpha$ -amino-boronates have not been reported, probably due to their poor stability in presence of silica gel. The Yudin group recently reported the design of boron-based peptidomimetics in an elegant multicomponent approach using  $\alpha$ -boryl isocyanides (Fig. 1).<sup>5,20</sup> However, only derivatives of *boro*-Phe and *boro*-Leu have been reported. In 2020, Reyes *et al.* described the asymmetric Rh-catalysed synthesis of  $\alpha$ -aminoboronates using a chiral monophosphite ligand.<sup>21</sup> Although the concept is very promising, the reaction scope is restricted by the necessity of a hydrophobic interaction between aromatic moieties of substrate and chiral ligand. While late-stage borylations can be superior in linear synthesis routes, versatile building blocks are obviously indispensable for convergent and diversity-oriented reaction sequences.

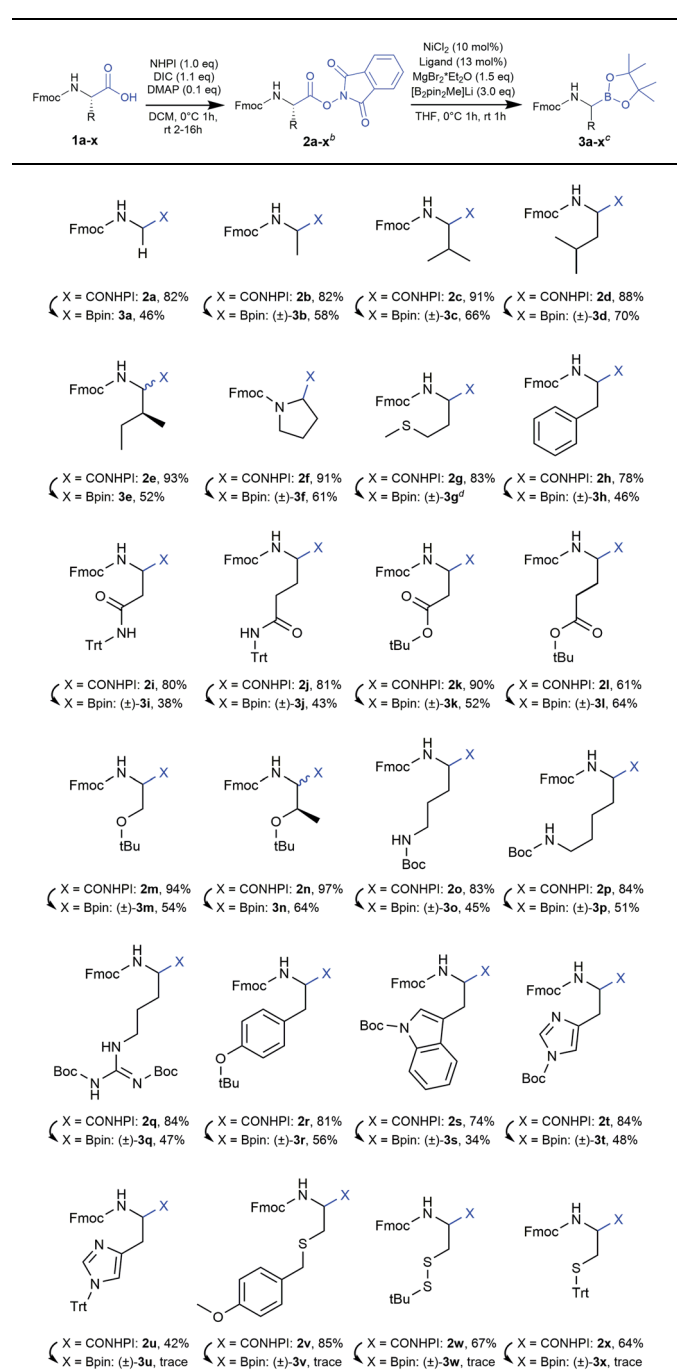
To date, several on-resin transformations of aromatic and aliphatic boronates have been described.<sup>22–26</sup> Our group recently reported commercially available 1-glycerol polystyrene resin to be compatible with Fmoc-based chemistry,<sup>27</sup> which has been applied to the solid-phase synthesis of bortezomib and ixazomib by Daniels and Stivala.<sup>28</sup> Obviously, a combinatorial approach consisting of routine and automatable steps would grant access to complex libraries, thereby allowing the exploration of novel chemical space and biomolecular interactions. However, no route has yet been described for the synthesis of Fmoc- $\alpha$ -aminoboronates. We hereby report a strategy to obtain these versatile building blocks, which can be readily employed in solid-phase synthesis to obtain a diversity of PBA sequences.

## Results and discussion

Considering the recent achievements in decarboxylative borylation reactions,<sup>18,19,29,30</sup> Fmoc- $\alpha$ -aminocarboxylic acids derived from natural amino acids appeared to be prime starting materials for an innovative building block strategy due to their diversity, wide availability and applicability to solid-phase synthesis.

We initially investigated the formation and stability of redox-active *N*-hydroxyphthalimide (NHPI) esters as substrates in decarboxylative borylations. Although only few examples of Fmoc-protected NHPI esters are described in the literature,<sup>31,32</sup> we found that transformations went smoothly in most cases and provided stable products in high yields (Table 1). Only some compounds showed instabilities and side reactions were observed, for example  $\delta$ -lactam formation<sup>33</sup> with all tested monoprotected (–Pbf, –Mtr, –Tos, –NO<sub>2</sub>) arginine derivatives. Fortunately, the NHPI ester of bis-Boc protected arginine (**2q**) could be easily obtained. Fmoc-His(Trt)-ONHPI (**2u**) was found

Table 1 Activation and borylation of Fmoc- $\alpha$ -aminocarboxylic acids<sup>a,b,c,d</sup>



<sup>a</sup> Isolated yields. <sup>b</sup> Reaction conditions: **1** (0.5–1.0 mmol scale, 1.0 equiv.), NHPI (1.0 equiv.), DIC (1.1 equiv.), DMAP (0.1 equiv.), DCM, 0 °C, 1 h; rt, 2–16 h. <sup>c</sup> Reaction conditions: NiCl<sub>2</sub>·6H<sub>2</sub>O (10 mol%), 4,4'-dimethoxy-2,2'-bipyridyl (13 mol%), MgBr<sub>2</sub>·OEt<sub>2</sub> (1.5 equiv.), [B<sub>2</sub>pin<sub>2</sub>Me]Li (3.0 equiv.), THF, 0 °C, 1 h; rt, 1 h; sIBX (6.0 equiv.), EtOAc, 40 °C, 2 h (see the ESI for details). <sup>d</sup> Without sIBX workup, therefore obtained as a crude material containing B<sub>2</sub>pin<sub>2</sub> impurities.

to be of limited stability towards silica gel, but decomposition could be minimised by using deactivated silica gel (SiO<sub>2</sub>/H<sub>2</sub>O 100 : 35, m/m) in the purification step.



The obtained redox-active esters were examined for their viability as substrates in the recently published Ni-catalysed decarboxylative borylation. To our delight, the vast majority of building blocks could be transformed into their corresponding pinacolyl boronates, however accompanied by the expected loss of stereoinformation at the  $\alpha$ -carbon due to the radical reaction mechanism.<sup>18</sup> For all tested cysteine derivatives (**3v**, **3w** and **3x**), only trace amounts could be identified, indicating that the presence of a sulfur atom in  $\beta$ -position is detrimental. No appreciable side reactions were observed during the borylation of Fmoc-Met-ONHPI (**2g**), where sulfur is located in  $\gamma$ -position. It should be noted that we were unable to obtain acceptable yields of Fmoc- $\alpha$ -aminoboronates by applying the operationally simpler Cu-catalysed decarboxylative borylation method.<sup>19</sup>

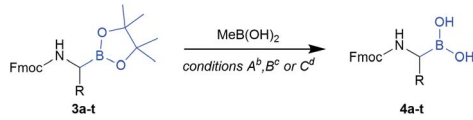
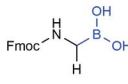
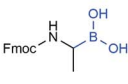
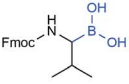
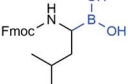
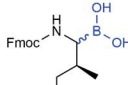
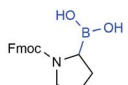
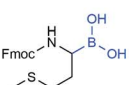
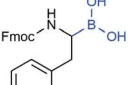
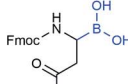
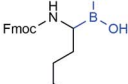
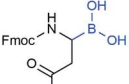
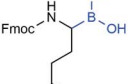
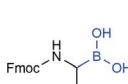
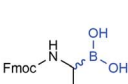
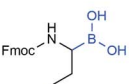
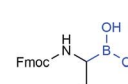
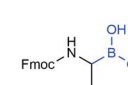
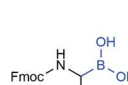
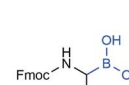
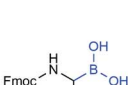
Workup of the crude borylation products proved demanding at first attempts.  $\alpha$ -Amino pinacolyl boronates are known to lack stability on silica gel or alumina columns, and it should be noted that the tested compounds even decomposed partially on deactivated silica gel and product fractions were often found to be contaminated with phthalimide and B<sub>2</sub>pin<sub>2</sub>. Therefore, chromatography did not seem feasible and the workup procedure was optimised to circumvent chromatographic purification: after filtration of the quenched reaction mixture, the crude residue was treated with stabilised 2-iodoxybenzoic acid (sIBX).<sup>34</sup> Delightfully, the addition of sIBX oxidatively destroyed the excess B<sub>2</sub>pin<sub>2</sub> while leaving the  $\alpha$ -amino pinacolyl boronates unaffected, thereby providing evidence of their relative stability towards mild oxidants. A short extraction procedure was appended to simultaneously remove phthalimide, B<sub>2</sub>pin<sub>2</sub> degradation products and IBX stabilisers (see the ESI† for details).

Applying the optimised workup procedure allowed us to obtain the desired *N*-Fmoc- $\alpha$ -pinacolyl boronates in good yields (Table 1). Most transformations went smoothly and without impairment of the respective side-chain functionalities, confirming the findings of Li *et al.*<sup>18</sup> and highlighting the broad scope of the Ni-catalysed decarboxylative borylation. Fmoc-Met-Bpin (**3g**) was found to be partially oxidised to its sulfoxide by IBX under the tested conditions as it is described for other thioethers.<sup>35</sup> Therefore, the IBX workup was bypassed in the case of **3g** to obtain the compound with B<sub>2</sub>pin<sub>2</sub> impurities, which could be removed in the subsequent step (*vide infra*).

Initial attempts to deprotect the pinacolyl boronates with established methods failed.<sup>36–38</sup> However, our recently published monophasic transesterification method<sup>39</sup> enabled the deprotection of pinacolyl building blocks in a straightforward fashion. The procedure was further optimised to allow a direct lyophilisation after complete conversion to avoid elevated temperatures. Reactants were transesterified with volatile methylboronic acid in mixtures of acetonitrile and dilute aqueous hydrochloric acid to give solutions that could be freeze-dried to obtain the desired compounds in very high yields (see the ESI† for details). While conditions A were expedient for acid-insensitive compounds and superior in terms of methylboronic acid equivalents, reducing the amount of dilute hydrochloric acid was essential to prevent premature side-chain deprotection of some acid-labile compounds (conditions B). Unexpectedly,

partial side-chain deprotection was observed for compounds **4n**, **4q** and **4t** even when binary water/acetonitrile mixtures were used as a solvent, presumably due to the acidity of methylboronic acid. Therefore, a buffer system using phosphate buffer pH 7.0 and a short extraction step were employed in the transesterification step (conditions C). With these three conditions in hand, all 20 investigated compounds could be obtained in

Table 2 Monophasic transesterification of  $\alpha$ -amino pinacolyl boronates<sup>a,b,c,d,e</sup>

|   |  |   |   |
|---|--|---|---|
| <br>(±)- <b>4a</b> boro-Gly <sup>b</sup><br>94%  | <br>(±)- <b>4b</b> boro-Ala <sup>b</sup><br>94% (53%, 2 steps) <sup>e</sup>   | <br>(±)- <b>4c</b> boro-Val <sup>b</sup><br>96%                                    | <br>(±)- <b>4d</b> boro-Leu <sup>b</sup><br>91%                                    |
| <br><b>4e</b> boro-Ile <sup>b</sup><br>93%   | <br>(±)- <b>4f</b> boro-Pro <sup>b</sup><br>97%                               | <br>(±)- <b>4g</b> boro-Met <sup>b</sup><br>(37%, 2 steps) <sup>e</sup>            | <br>(±)- <b>4h</b> boro-Phe <sup>b</sup><br>91%                                    |
| <br>(±)- <b>4i</b> boro-Asn(Trt) <sup>b</sup><br>84%                                 | <br>(±)- <b>4j</b> boro-Gln(Trt) <sup>b</sup><br>95%                        | <br>(±)- <b>4k</b> boro-Asp(tBu) <sup>c</sup><br>95%                             | <br>(±)- <b>4l</b> boro-Glu(tBu) <sup>c</sup><br>91%                             |
| <br>(±)- <b>4m</b> boro-Ser(tBu) <sup>f</sup><br>95%                                 | <br><b>4n</b> boro-Thr(tBu) <sup>d</sup><br>74% (55%, 2 steps) <sup>e</sup> | <br>(±)- <b>4o</b> boro-Orn(Boc) <sup>c</sup><br>93% (39%, 2 steps) <sup>e</sup> | <br>(±)- <b>4p</b> boro-Lys(Boc) <sup>c</sup><br>95% (36%, 2 steps) <sup>e</sup> |
| <br>(±)- <b>4q</b> boro-Arg(bis-Boc) <sup>d</sup><br>57% (23%, 2 steps) <sup>e</sup> | <br>(±)- <b>4r</b> boro-Tyr(tBu) <sup>c</sup><br>99%                        | <br>(±)- <b>4s</b> boro-Trp(Boc) <sup>c</sup><br>91%                             | <br>(±)- <b>4t</b> boro-His(Boc) <sup>d</sup><br>48% (30%, 2 steps) <sup>e</sup> |

<sup>a</sup> Isolated yields. <sup>b</sup> Reaction conditions (0.1–0.6 mmol scale): compound **3** (1.0 equiv.), MeB(OH)<sub>2</sub> (5.0 equiv.), MeCN/0.1 N HCl (1 : 1, v/v), rt, 16 h.

<sup>c</sup> Reaction conditions (0.1–0.6 mmol scale): compound **3** (1.0 equiv.), MeB(OH)<sub>2</sub> (10.0 equiv.), MeCN/0.1 N HCl (9 : 1, v/v), rt, 2 h. <sup>d</sup> Reaction conditions (0.1–0.6 mmol scale): compound **3** (1.0 equiv.), MeB(OH)<sub>2</sub> (10.0 equiv.), MeCN/phosphate buffer pH 7.0 (1 : 1, v/v), rt, 2 h.

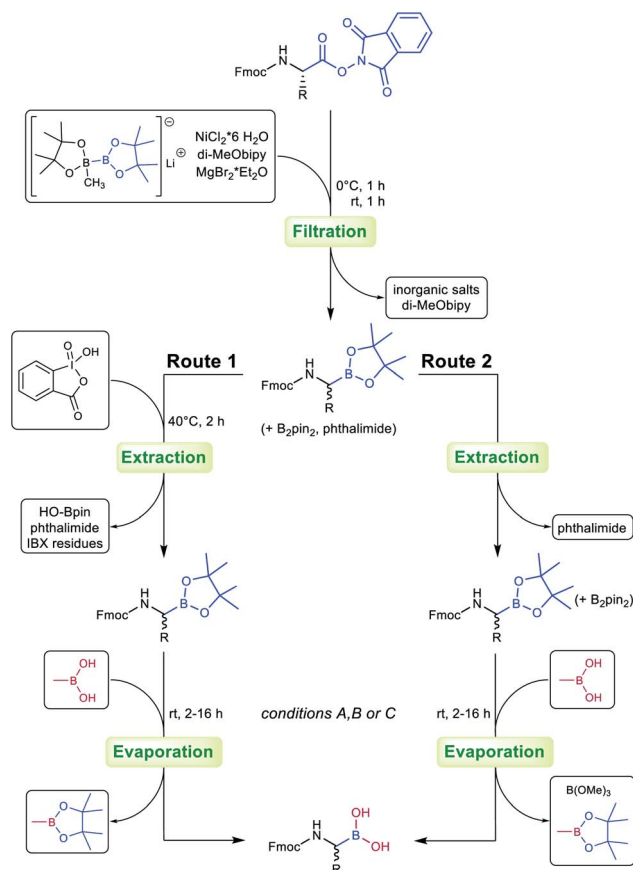
<sup>e</sup> Applying the same transesterification conditions to crude compound **3** according to route 2, Scheme 1.



high yields (Table 2). We emphasise that this is the first method to straightforwardly obtain a library of  $\alpha$ -aminoboronic acid building blocks that are readily employable in diversity-oriented synthesis approaches.

Our recent findings indicated that  $B_2pin_2$  could be converted into volatile or water-soluble degradation products by double transesterification with  $MeB(OH)_2$  under acidic aqueous conditions.<sup>39</sup> These results prompted us to circumvent IBX workup in the case of oxidation-sensitive derivative **3g**. Delightfully, the crude compound could be transesterified smoothly to give a product with boric acid contaminants that were easily removed by addition of methanol and evaporation of the formed trimethyl borate under reduced pressure (see the ESI† for details).

Inspired by these results, an optimised protocol with superior overall atom economy was established (Scheme 1, route 2) and tested for selected compounds (Table 2). While the oxidative destruction of excess  $B_2pin_2$  with IBX (route 1) allows yield determination and full characterisation of Fmoc- $\alpha$ -aminopinacolyl boronates, the simultaneous transesterification of pinacolyl boronates and  $B_2pin_2$  is considerably faster and less expensive. Additionally, IBX is a hazardous and potentially explosive reagent.<sup>40</sup> Route 2 is therefore preferable for large-scale syntheses and industrial applications.



**Scheme 1** Process optimisation for the preparation of Fmoc- $\alpha$ -aminoboronic acids. Route 1: oxidative removal of  $B_2pin_2$  contaminants with IBX. Route 2: simultaneous transesterification of pinacolyl boronates and  $B_2pin_2$  contaminants (see the ESI† for details).

The utility of the synthesised Fmoc- $\alpha$ -aminoboronic acids for solid-phase synthesis approaches was subsequently investigated. The compounds were readily soluble in methylene chloride, thereby enabling their straightforward immobilisation onto 1-glycerol polystyrene resin. No additives, *e.g.* bases, were necessary to efficiently immobilise the building blocks under these conditions. It should be noted that the use of tetrahydrofuran as in literature-known protocols<sup>27,28</sup> led to diminished yields, most likely due to its hygroscopy or its propensity to form peroxides that would be detrimental to boronic acids. Mild and efficient cleavage from solid support was achieved by treating the resin with DCM/MeOH/H<sub>2</sub>O (5 : 4 : 1, v/v/v). All 20 building blocks were tested regarding their loading efficiency and were shown to be readily immobilised and cleaved from solid support (Table 3).

As further proof of concept, a selection of building blocks was applied in standard Fmoc solid-phase synthesis protocols. Sequences could be obtained in high purity with full conservation of side-chain protecting groups. Due to the non-acidic cleavage conditions, the described method provides access to synthetic intermediates readily applicable to late-stage diversifications, *e.g.* petasis reactions<sup>41–43</sup> or cross-coupling reactions.<sup>44,45</sup>

Final compounds were obtained by side-chain deprotection using TFA-based cleavage solutions and subsequent HPLC purification. Syntheses were successful for building blocks with

**Table 3** Immobilisation experiments<sup>a</sup>

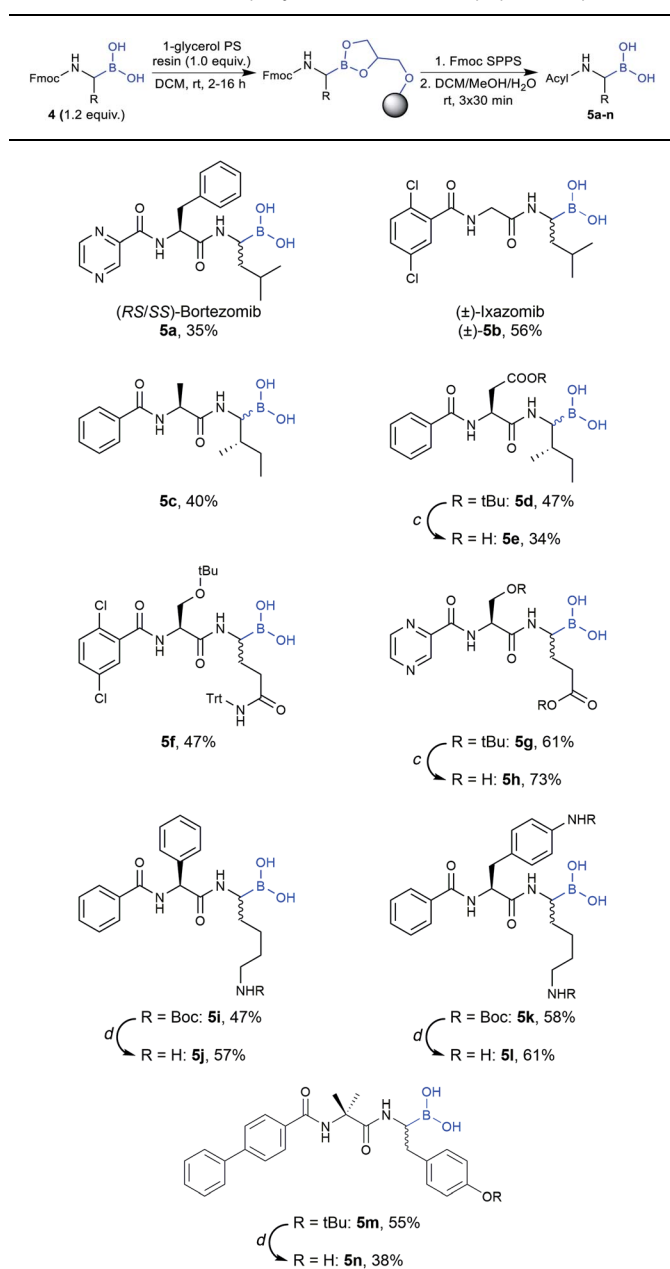
| Entry | 4              | Compound                       | Loading efficiency <sup>b</sup> |
|-------|----------------|--------------------------------|---------------------------------|
| 1     | (±)- <b>4a</b> | <i>boro</i> -Gly               | 66%                             |
| 2     | (±)- <b>4b</b> | <i>boro</i> -Ala               | 81%                             |
| 3     | (±)- <b>4c</b> | <i>boro</i> -Val               | 46%                             |
| 4     | (±)- <b>4d</b> | <i>boro</i> -Leu               | 60%                             |
| 5     | <b>4e</b>      | <i>boro</i> -Ile               | 64%                             |
| 6     | (±)- <b>4f</b> | <i>boro</i> -Pro               | 60%                             |
| 7     | (±)- <b>4g</b> | <i>boro</i> -Met               | 43%                             |
| 8     | (±)- <b>4h</b> | <i>boro</i> -Phe               | 46%                             |
| 9     | (±)- <b>4i</b> | <i>boro</i> -Asn(Trt)          | 44%                             |
| 10    | (±)- <b>4j</b> | <i>boro</i> -Gln(Trt)          | 62%                             |
| 11    | (±)- <b>4k</b> | <i>boro</i> -Asp( <i>t</i> Bu) | 71%                             |
| 12    | (±)- <b>4l</b> | <i>boro</i> -Glu( <i>t</i> Bu) | 84%                             |
| 13    | (±)- <b>4m</b> | <i>boro</i> -Ser( <i>t</i> Bu) | 67%                             |
| 14    | <b>4n</b>      | <i>boro</i> -Thr( <i>t</i> Bu) | 66%                             |
| 15    | (±)- <b>4o</b> | <i>boro</i> -Orn(Boc)          | 84%                             |
| 16    | (±)- <b>4p</b> | <i>boro</i> -Lys(Boc)          | 66%                             |
| 17    | (±)- <b>4q</b> | <i>boro</i> -Arg(bis-Boc)      | 54%                             |
| 18    | (±)- <b>4r</b> | <i>boro</i> -Tyr( <i>t</i> Bu) | 26%                             |
| 19    | (±)- <b>4s</b> | <i>boro</i> -Trp(Boc)          | 49%                             |
| 20    | (±)- <b>4t</b> | <i>boro</i> -His(Boc)          | 70%                             |

<sup>a</sup> Reaction conditions: 1-glycerol polystyrene resin (100.0 mg,  $B = 0.60 \text{ mmol g}^{-1}$ , 0.06 mmol, 1.0 equiv.), compound **4** (0.072 mmol, 1.2 equiv.), DCM (1.5 mL), rt, 2 h. Cleavage was performed with DCM/MeOH/H<sub>2</sub>O (5 : 4 : 1, v/v/v) for  $3 \times 30 \text{ min}$  (see the ESI† for details).

<sup>b</sup> Calculated by the molar ratio of cleaved compound **4** and the stated loading capacity of 1-glycerol polystyrene resin ( $B = 0.60 \text{ mmol g}^{-1}$ ).





Table 4 Proof-of-concept synthesis of selected peptide sequences<sup>a,b</sup>

<sup>a</sup> Isolated yields. <sup>b</sup> Loading step: compound 4 (1.2 equiv.), DCM, rt, 2–16 h. Peptide elongation was performed using standard Fmoc-SPPS protocols (see the ESI for details). Cleavage step: DCM/MeOH/H<sub>2</sub>O 5 : 4 : 1 (v/v/v), 3 × 30 min. <sup>c</sup> Reaction conditions: 40% TFA in methylene chloride, rt, 2 h. <sup>d</sup> Reaction conditions: MeCN/TFA/H<sub>2</sub>O (7 : 2 : 1, v/v/v), rt, 2 h.

nonpolar (5a–e), polar (5f–l) and aromatic (5m–n) side-chains, underlining the general versatility of the described approach (Table 4).

## Conclusions

We hereby present a straightforward method for the conversion of Fmoc- $\alpha$ -aminocarboxylic acids into their boron equivalents

in three simple steps. Additionally, the efficient deprotection of boronic esters under neutral, buffered conditions was established in the course of our investigations. Considering the utility of the intermediates for automated synthesis, the process was further optimised by establishing a fast protocol with enhanced atom economy. All building blocks were shown to be employable in standard Fmoc-based solid-phase synthesis protocols and yielded a diversity of peptide-boronic acids. The synthetic toolbox provided here will likely facilitate the diversity-oriented synthesis of PBAs with a multitude of potential applications in drug discovery, life sciences and materials research.

## Conflicts of interest

There are no conflicts to declare.

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