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## Convergent synthesis of bicyclic boronates *via* a cascade regioselective Suzuki–Miyaura/cyclisation protocol†

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Bicyclic boronates have recently emerged as promising candidates to invoke targeted biomolecular interactions, given their selectivity for specific functionalities. Despite this, the general stability of the C–B bond *in vivo*, for such heterocycles, remains an intractable challenge that can often preclude their utility in drug discovery. To address this challenge, *de novo* strategies that allow expedient access to strategically substituted boronates, that enable modulation of the C–B bond are urgently required. Herein we disclose an operationally simple, regioselective cross-coupling/cyclisation reaction of easily accessible *vicinal* boronic esters with 2-halophenols to rapidly forge 3-substituted bicyclic boronates. The utility of the platform was demonstrated *via* expedient access to Xeruborbactam derivatives, chemoselective manipulation of formed products and the convergent approach to bicyclic boronates with a pendent biomolecular probe.

Boron heterocycles are privileged scaffolds with applications that transcend the chemical sciences, including chemical sensing and their use as conducting materials.<sup>1–3</sup> Their unique properties have, more recently, been translated to drug discovery,<sup>4–6</sup> where bicyclic systems such as benzoxaborines (BOBs) and benzazaborines (BABs) among others, are frequently leveraged to tune stability of the boron handle and elicit a desired target inhibition (Fig. 1A).<sup>7–11</sup> The versatility of these motifs is exemplified with reactivity against neurological, oncological and bacterial targets,<sup>5</sup> with Xeruborbactam, a potent beta-lactamase inhibitor, currently in phase III clinical trials.<sup>11</sup> Their utility stems from the dexterity of boron to form various covalent and non-covalent interactions with biomolecules (Fig. 1B), enabling the practitioner to design therapeutics with site-specific interactions in mind. For example, benzoxaborines

offer the ability to selectively bind serine amino acids, form chelation with sugar targets and elicit  $\pi$ -stacking interactions, underpinning their potential as a powerful pharmacophore.<sup>12</sup> However, the unpredictable metabolic stability of heterocyclic C–B bonds remains an intractable challenge in the design of state-of-the-art therapeutics,<sup>13,14</sup> and as such, novel platforms that allow expedient access to boron heterocycles to assess their biological activity and stability are urgently required.

Whilst the wide spread utility of boron heterocycles has culminated in a plenum of strategies for their chemical synthesis,<sup>15–18</sup> the construction of BOB scaffolds is predominantly achieved *via* two main synthetic strategies (Fig. 1C); nickel catalysed boron insertion,<sup>19,20</sup> or the activation of unsaturated bonds using electrophilic boron reagents.<sup>21</sup> The former was elegantly achieved by the Yorimitsu group using benzofuran precursors to provide expedient access to BOB scaffolds in a single step,<sup>19</sup> while the latter is typically achieved using *ortho*-substituted, styrenes or phenyl acetylenes, in the presence of a highly electrophilic boron reagent, such as BBr<sub>3</sub> that compromise functional group compatibility. Despite these notable advances, strategies that enable the strategic incorporation of substituents in either the 3-, or 4-position remain a persistent challenge. The Ingleson group recently made prominent strides in addressing this deficiency through the advent of a halo-borylation protocol that facilitates the incorporation of a chloride handle on the 4-position.<sup>22</sup> However, a general strategy to achieve 3-substitution is conspicuously underdeveloped, yet desirable given its spatial proximity and potential ability to modulate steric and electronic properties of the adjacent boron motif.

Given the vast array of approaches to construct unsaturated *vicinal* boron systems,<sup>23–25</sup> in combination with Miyaura's venerable, sterically driven regioselective activation of the terminal boron,<sup>26,27</sup> we envisaged a simple disconnection that would facilitate a convergent approach to 3-substituted benzoxaborines *via* a cascade annulation with easily accessible 2-halophenols (Fig. 1D).<sup>28–30</sup> Here, the terminal boron serves as a traceless handle for Suzuki–Miyaura cross-coupling, while the latter is

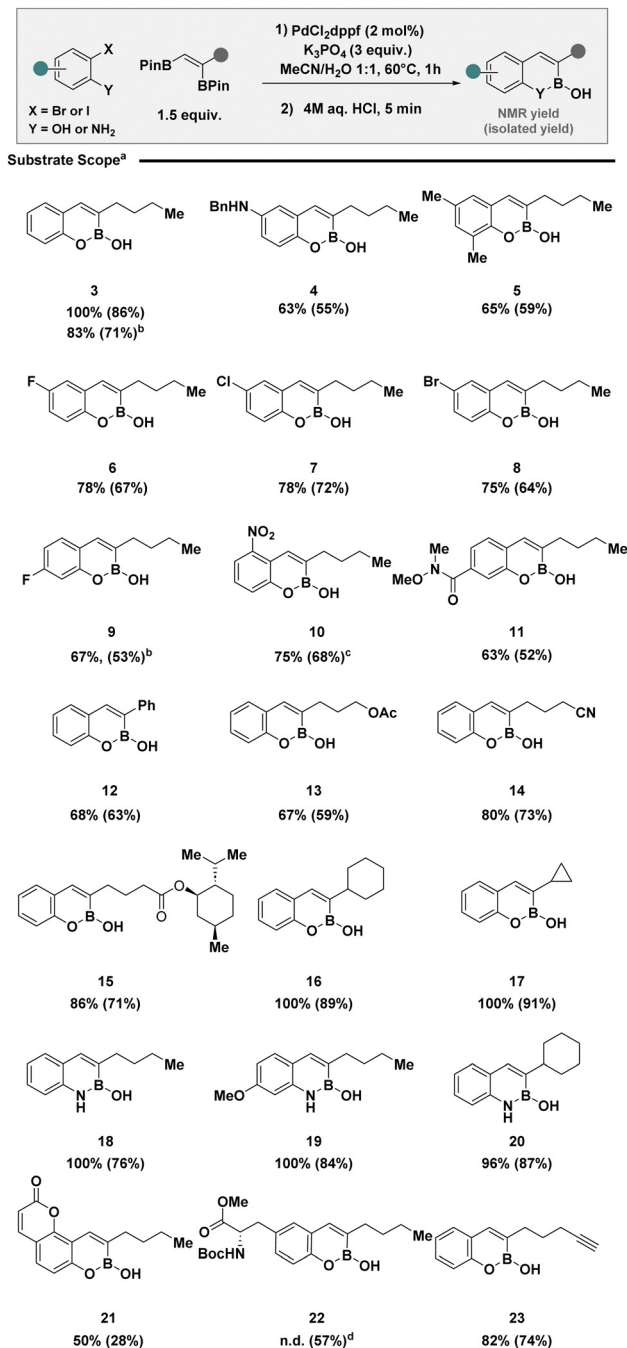
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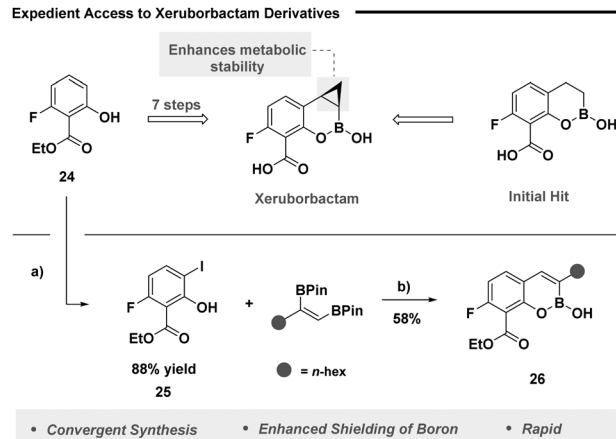
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Inspired by the proposed aromatic character of bicyclic boronates and given their ability to be effectively retained during developed reaction conditions, we anticipated that substrate **8** could be leveraged in chemoselective cross-coupling enabling exploration of chemical space with the retention of the core heterocycle scaffold (Fig. 3, top). Selective Suzuki–Miyaura cross-coupling of thiophene boronic acid was

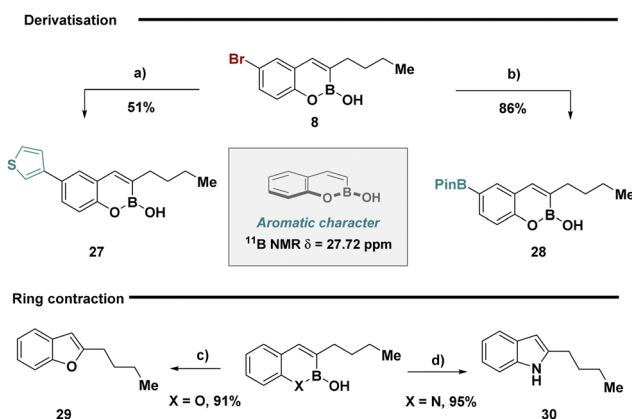


**Fig. 2** Expedient access to xeruborbactam derivatives. (a) **24** (1 equiv.), TIOAc (1 equiv.), DCM, rt. (b) **25** (1 equiv.), **2** (1.5 equiv.), PdCl<sub>2</sub>dppf-DCM (2 mol%), K<sub>3</sub>PO<sub>4</sub> (3 equiv.), MeCN/H<sub>2</sub>O (1:1), 60 °C.

achieved to forge **27**, while a Miyaura borylation enabled the inversion of reactivity generating the nucleophilic boronic ester **28**. Motivated by recent advances in skeletal editing deletion sequences,<sup>33</sup> substrates **3** and **18** could be easily transformed to the benzofuran and indole respectively in high yields (Fig. 3, bottom).

Given their unique ability to selectively bind serine amino acid residues,<sup>12</sup> bicyclic boronates have been frequently employed as chemical probes for target identification in order to unravel the intricacies of biomolecular mechanisms.<sup>5</sup> To further demonstrate the utility of our convergent approach we utilized substrate **23** in copper catalysed “click” reactions to efficiently connect biomolecular probes (Fig. 4). The reaction was efficient in incorporating biotin (**31**), an efficient tool for targeted delivery,<sup>34</sup> and warhead **32**, a potent ubiquitin recruiter.<sup>35</sup>

In summary, we have developed an operationally simple convergent synthesis of 3-substituted bicyclic boronates *via* a cascade regioselective cross-coupling/annulation protocol



**Fig. 3** Product derivatisation. (a) **8** (1 equiv.), boronic acid (5 equiv.), PdCl<sub>2</sub>dppf-DCM (2 mol%), K<sub>3</sub>PO<sub>4</sub> (3 equiv.), THF, 50 °C. (b) **8** (1 equiv.), B<sub>2</sub>Pin<sub>2</sub> (1.5 equiv.), KOAc (3 equiv.), 1,4-dioxane, 80 °C. (c) **3** (1 equiv.), NaOH, H<sub>2</sub>O<sub>2</sub>, THF/EtOH, 0 °C → rt; then 4 Å mol sieves, DCM/TFA. (d) **18** (1 equiv.), NaOH, H<sub>2</sub>O<sub>2</sub>, THF/EtOH, 0 °C → rt.



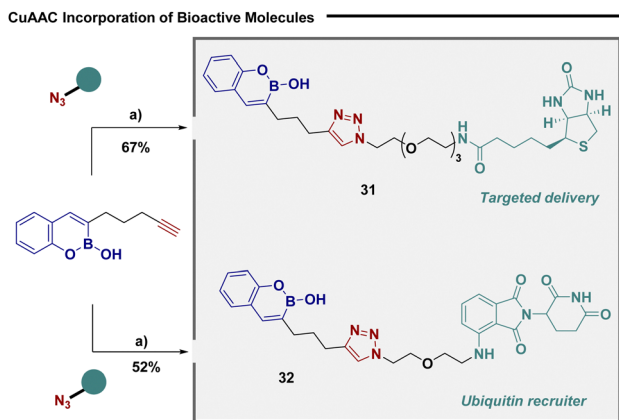


Fig. 4 Click enabled synthesis of biochemical probes. (a) **23** (1 equiv.), azide (1 equiv.), Cu(MeCN)<sub>4</sub>BF<sub>4</sub> (30 mol%), DCM, rt.

using easily accessible *vicinal* boronic esters and 2-halophenols. The transformation demonstrates high functional group tolerance enabling late stage functionalisation of targets and expedient access to Xeruborbactam derivatives. The stability of the bicyclic boronates under aqueous basic media inspired chemoselective cross-coupling strategies, while a convergent approach could be strategically aligned with copper-based “click” strategies to attach pendent biochemical probes. It is envisaged the enclosed platform will enable users to efficiently access a prominent set of boron containing heterocycles finding future applications in the chemical sciences, most notably medicinal chemistry.

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## Data availability

The data supporting this article have been included as part of the ESI.†

## Conflicts of interest

There are no conflicts to declare.

## Notes and references

- 1 A. Pal, M. Bérubé and D. G. Hall, *Angew. Chem., Int. Ed.*, 2010, **49**, 1492–1495.
- 2 C. R. Wade, A. E. J. Broomsgrove, S. Aldridge and F. P. Gabbaï, *Chem. Rev.*, 2010, **110**, 3958–3984.
- 3 C. D. Entwistle and T. B. Marder, *Angew. Chem., Int. Ed.*, 2002, **41**, 2927–2931.

- 4 S. Chatterjee, N. M. Tripathi and A. Bandyopadhyay, *Chem. Commun.*, 2021, **57**, 13629–13640.
- 5 R. J. Grams, W. L. Santos, I. R. Scorei, A. Abad-García, C. A. Rosenblum, A. Bitá, H. Cerecetto, C. Viñas and M. A. Soriano-Ursúa, *Chem. Rev.*, 2024, **124**, 2441–2511.
- 6 M. Z. H. Kazmi, O. M. Schneider and D. G. Hall, *J. Med. Chem.*, 2023, **66**, 13768–13787.
- 7 C.-J. Lu, J. Hu, Z. Wang, S. Xie, T. Pan, L. Huang and X. Li, *MedChemComm*, 2018, **9**, 1862–1870.
- 8 A. Vlasceanu, M. Jessing and J. P. Kilburn, *Bioorg. Med. Chem.*, 2015, **23**, 4453–4461.
- 9 F. J. R. Rombouts, F. Tovar, N. Austin, G. Tresadern and A. A. Trabanco, *J. Med. Chem.*, 2015, **58**, 9287–9295.
- 10 A. Krajnc, J. Brem, P. Hinchliffe, K. Calvopiña, T. D. Panduwawala, P. A. Lang, J. J. A. G. Kamps, J. M. Tyrrell, E. Widlake, B. G. Saward, T. R. Walsh, J. Spencer and C. J. Schofield, *J. Med. Chem.*, 2019, **62**, 8544–8556.
- 11 S. J. Hecker, K. R. Reddy, O. Lomovskaya, D. C. Griffith, D. Rubio-Aparicio, K. Nelson, R. Tsivkovski, D. Sun, M. Sabet, Z. Tarazi, J. Parkinson, M. Totrov, S. H. Boyer, T. W. Glinka, O. A. Pemberton, Y. Chen and M. N. Dudley, *J. Med. Chem.*, 2020, **63**, 7491–7507.
- 12 D. B. Diaz and A. K. Yudin, *Nat. Chem.*, 2017, **9**, 731–742.
- 13 B. J. Graham, I. W. Windsor, B. Gold and R. T. Raines, *Proc. Natl. Acad. Sci. U. S. A.*, 2021, **118**, e2013691118.
- 14 B. J. Graham, I. W. Windsor and R. T. Raines, *ACS Med. Chem. Lett.*, 2023, **14**, 171–175.
- 15 C. Körner, P. Starkov and T. D. Sheppard, *J. Am. Chem. Soc.*, 2010, **132**, 5968–5969.
- 16 J. M. Halford-McGuff, M. Varga, D. B. Cordes, A. P. McKay and A. J. B. Watson, *ACS Catal.*, 2024, **14**, 1846–1854.
- 17 J. J. Blackner, O. M. Schneider, W. O. Wong and D. G. Hall, *J. Am. Chem. Soc.*, 2024, **146**, 19499–19508.
- 18 Y. Sumida, R. Harada, T. Kato-Sumida, K. Johmoto, H. Uekusa and T. Hosoya, *Org. Lett.*, 2014, **16**, 6240–6243.
- 19 H. Saito, S. Otsuka, K. Nogi and H. Yorimitsu, *J. Am. Chem. Soc.*, 2016, **138**, 15315–15318.
- 20 H. Lyu, I. Kevlishvili, X. Yu, P. Liu and G. Dong, *Science*, 2021, **372**, 175–182.
- 21 P.-Y. Peng, G.-S. Zhang, M.-L. Gong, J.-W. Zhang, X.-L. Liu, D. Gao, G.-Q. Lin, Q.-H. Li and P. Tian, *Commun. Chem.*, 2023, **6**, 176.
- 22 K. Yuan and M. J. Ingleson, *Angew. Chem., Int. Ed.*, 2023, **62**, e202301463.
- 23 T. Ishiyama, N. Matsuda, N. Miyaura and A. Suzuki, *J. Am. Chem. Soc.*, 1993, **115**, 11018–11019.
- 24 R. L. Thomas, F. E. S. Souza and T. B. Marder, *J. Chem. Soc., Dalton Trans.*, 2001, 1650–1656.
- 25 J. B. Morgan and J. P. Morken, *J. Am. Chem. Soc.*, 2004, **126**, 15338–15339.
- 26 T. Ishiyama, M. Yamamoto and N. Miyaura, *Chem. Lett.*, 1996, 1117–1118.
- 27 S. N. Mlynarski, C. H. Schuster and J. P. Morken, *Nature*, 2014, **505**, 386–390.
- 28 M. Wienhold, J. J. Molloy, C. G. Daniliuc and R. Gilmour, *Angew. Chem., Int. Ed.*, 2021, **60**, 685–689.
- 29 F. H. Vaillancourt, E. Yeh, D. A. Vosburg, S. Garneau-Tsodikova and C. T. Walsh, *Chem. Rev.*, 2006, **106**, 3364–3378.
- 30 T. P. Pathak and S. J. Miller, *J. Am. Chem. Soc.*, 2012, **134**, 6120–6123.
- 31 S. H. Boyer, A. Gonzalez-de-Castro, J. A. H. Dielemans, L. Lefort, Z. Zhu, M. Gnahn, J. Schörghuber, S. Steinhof, A. H. M. de Vries and S. J. Hecker, *Org. Process Res. Dev.*, 2022, **26**, 925–935.
- 32 R. C. Cambie, P. S. Rutledge, T. Smith-Palmer and P. D. Woodgate, *J. Chem. Soc. Perkin Trans. 1*, 1976, 1161–1164.
- 33 S. H. Kennedy, B. D. Dherange, K. J. Berger and M. D. Levin, *Nature*, 2021, **593**, 223–227.
- 34 J. B. Geri, J. V. Oakley, T. Reyes-Robles, T. Wang, S. J. McCarver, C. H. White, F. P. Rodriguez-Rivera, D. L. Parker, E. C. Hett, O. O. Fadeyi, R. C. Oslund and D. W. C. MacMillan, *Science*, 2020, **367**, 1091–1097.
- 35 G. Lu, R. E. Middleton, H. Sun, M. Naniang, C. J. Ott, C. S. Mitsiadis, K.-K. Wong, J. E. Bradner and W. G. Kaelin, *Science*, 2014, **343**, 305–309.

