



Cite this: *Chem. Commun.*, 2024, 60, 13223

Received 10th September 2024,
Accepted 17th October 2024

DOI: 10.1039/d4cc04653f

rsc.li/chemcomm

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

Alessandro Marotta,^{ab} Hannah M. Kortman,^{ab} Chiara Interdonato,^a Peter H. Seeberger^{ID ab} and John J. Molloy^{ID *a}

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 Xeruborbastam 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.^{1–3} Their unique properties have, more recently, been translated to drug discovery,^{4–6} 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).^{7–11} The versatility of these motifs is exemplified with reactivity against neurological, oncological and bacterial targets,⁵ with Xeruborbastam, a potent beta-lactamase inhibitor, currently in phase III clinical trials.¹¹ 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 π -stacking interactions, underpinning their potential as a powerful pharmacophore.¹² However, the unpredictable metabolic stability of heterocyclic C–B bonds remains an intractable challenge in the design of state-of-the-art therapeutics,^{13,14} 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,^{15–18} the construction of BOB scaffolds is predominantly achieved *via* two main synthetic strategies (Fig. 1C); nickel catalysed boron insertion,^{19,20} or the activation of unsaturated bonds using electrophilic boron reagents.²¹ The former was elegantly achieved by the Yorimitsu group using benzofuran precursors to provide expedient access to BOB scaffolds in a single step,¹⁹ 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_3 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.²² 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,^{23–25} in combination with Miyaura's venerable, sterically driven regioselective activation of the terminal boron,^{26,27} 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).^{28–30} Here, the terminal boron serves as a traceless handle for Suzuki–Miyaura cross-coupling, while the latter is

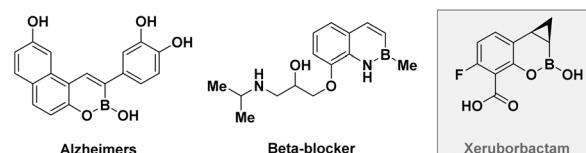
^a Department of Biomolecular Systems, Max-Planck-Institute of Colloids and Interfaces, 14476 Potsdam, Germany. E-mail: john.molloy@mpikg.mpg.de

^b Department of Chemistry and Biochemistry, Freie Universität Berlin, 14195 Berlin, Germany

† Electronic supplementary information (ESI) available. See DOI: <https://doi.org/10.1039/d4cc04653f>

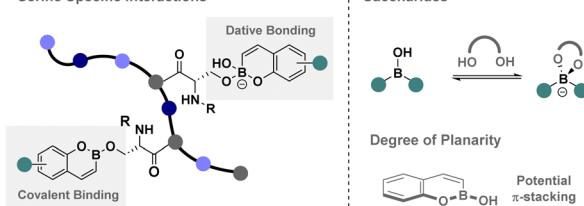


A. Selected Biologically Active Bicyclic Boron Heterocycles



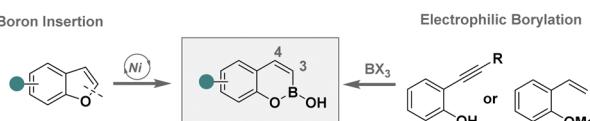
B. Interactions with Biomolecules

Serine Specific Interactions



C. Synthetic Strategies Towards Benzoaxaborines

Boron Insertion



D. This Work: Convergent Synthesis of Boron Heterocycles

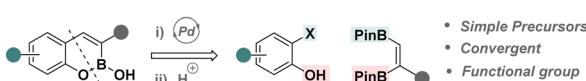
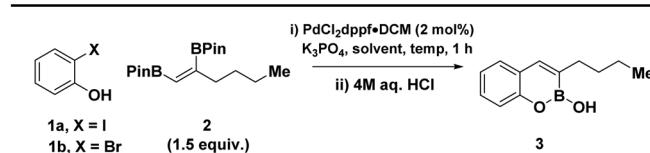


Fig. 1 (A) Biologically active boron heterocycles; (B) interactions with biomolecules; (C) synthetic strategies towards benzoxaborines; (D) convergent synthesis of boron heterocycles via palladium catalysed annulation

trapped under basic media with the pendent phenolate. Subsequent removal of the pinacol ligand *via* a switch to acidic media would grant direct access to 3-substituted boron heterocycles. Herein we describe the convergent synthesis of highly coveted 3-substituted boron heterocycles *via* palladium-catalysed annulation of *ortho*-halo phenols with *vicinal* BPins. The strategy demonstrates high functional group tolerance and is leveraged to, provide expedient access to Xeruborbactam derivatives, facilitate subsequent chemoselective activation of boron heterocycles, and provide a construct for the chemical synthesis of BOB containing biomolecular probes.

We initiated our reaction optimisation probing the efficiency of 2-iodophenol **1a** and *vicinal* BPin **2** to undergo a cascade cross-coupling/cyclization protocol (Table 1). Utilizing $PdCl_2(dppf) \cdot DCM$ as a catalyst, at $60\ ^\circ C$, provided our initial hit forming the target cyclised BOB **3**, as a single regioisomer in low yields after acidic work up (entry 1). Regulating reaction media was critical, as biphasic mixtures with increasing water content proved to be more effective for cross-coupling for both THF and acetonitrile (entries 2 to 4). Increasing reaction concentration afforded the target BOB in quantitative yield (entry 5), while the use of less equivalents of *vicinal* BPin was detrimental to the reaction (entry 6). Translation of optimal conditions to 2-bromophenol was ineffective (entry 7). Although increasing temperature to $80\ ^\circ C$ and reaction time to 16 hours with acetonitrile only

Table 1 Optimization of reaction conditions^a



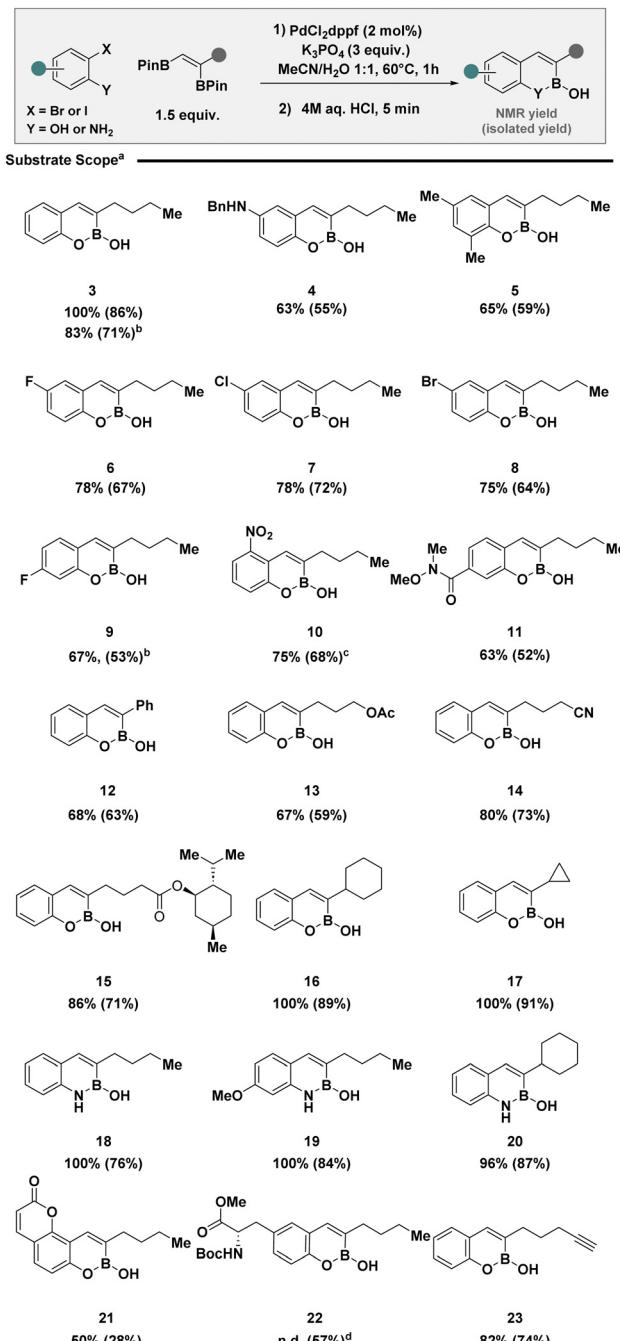
Entry	X	Solvent (ratio)	Temp. (°C)	Yield ^b (%)
1	I	THF/H ₂ O (50:1)	60	16
2	I	THF/H ₂ O (4:1)	60	68
3	I	THF/H ₂ O (1:1)	60	91
4	I	MeCN/H ₂ O (1:1)	60	92
5 ^c	I	MeCN/H ₂ O (1:1)	60	Quant.
6 ^{cd}	I	MeCN/H ₂ O (1:1)	60	74
7 ^c	Br	MeCN/H ₂ O (1:1)	60	Trace
8 ^{ce}	Br	MeCN/H ₂ O (1:1)	80	27
9 ^{ce}	Br	THF/H ₂ O (1:1)	80	73
10 ^{ce}	Br	THF/H ₂ O (1:1)	100	83

^a Standard conditions: 1 (0.1 mmol), 2 (1.5 equiv.), K₃PO₄ (3 equiv.), solvent (0.1 M), temp., 1 h. ^b Determined by ¹H NMR spectroscopy against a known internal standard (1,3,5-trimethoxybenzene). ^c 0.2 M reaction concentration used. ^d 1.1 equiv. of 2 used. ^e Reactions were run for 16 h.

resulted in a moderate increase in yield (entry 8), a concomitant solvent switch enabled a substantial increase to 73% yield (entry 9). Finally increasing the temperature to 100 °C afforded the target BOB in 83% yield.

Having developed a set of general reaction conditions for both 2-iodo- and 2-bromophenols, the scope and limitations were established (Scheme 1). Pleasingly, the protocol was amenable to a range of 2-halophenols with varying substitution patterns including electron neutral (3) and electron rich examples (4 and 5). Electron poor systems, often problematic for activation with electrophilic reagents,²¹ were compatible (6 to 11). It is pertinent to note, chemoselective activation of 2-iodophenols in the presence of competing halides was well tolerated, providing a synthetic handle for subsequent transformations (7 and 8), which would be otherwise challenging using nickel catalysis technologies.¹⁹ Modifications of the *vicinal* boronic ester was also effective including styrenes (12), long chain aliphatics containing modifiable functionalities (13–15), and adjacent alicyclic rings (16 and 17). The use of 2-idoanilines, enabled translation to benzazaborines (18 to 20). The exploration of substrate scope culminated in the synthesis of coumarin derivative (21), tyrosine analogue (22) and BOB (23) with a strategically placed alkyne motif for application in click chemistry to access biomolecular probes.

Cognizant of the therapeutic effects of Xeruborbactam, we next set out to probe our designed method on a similar framework (Fig. 2). Xeruborbactam is readily accessed from intermediate **24** in a seven-step large-scale process (Fig. 2, top).³¹ It was envisaged the strategic pairing of a site selective iodination strategy with our developed method would grant expedient access to analogues of this nature. Selective iodination was readily achieved using an established platform (Fig. 2, bottom),³² while our annulation process enabled the synthesis of analogue **26**, underpinning the ability of the developed protocol to access biologically relevant heterocyclic frameworks.



Scheme 1 Substrate scope. ^aReactions were performed in MeCN/H₂O (1:1) on a 0.1 mmol scale using iodophenol (1 equiv.), vicinal BPin (1.5 equiv.), PdCl₂dppf-DCM (2 mol%) and K₃PO₄ (3 equiv.) at 60 °C for 1 h. All reactions afforded a single regioisomer. ^bReactions were performed using bromophenol in THF/H₂O (1:1) at 100 °C for 16 h. ^cReactions were run for 16 h. ^dReaction used 1 M aq. HCl.

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

Expedient Access to Xeruborbactam Derivatives

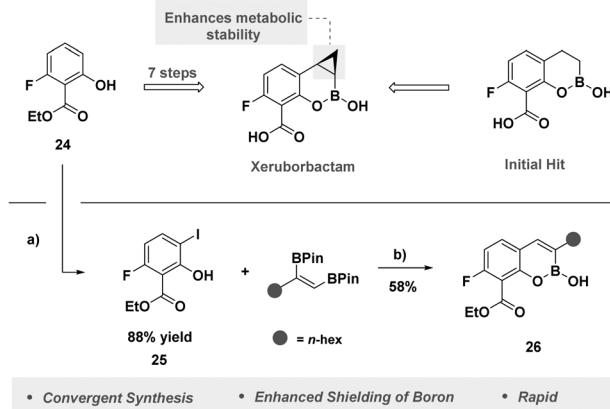


Fig. 2 Expedient access to xeruborbactam derivatives. (a) **24** (1 equiv.), I₂ (1 equiv.), TlOAc (1 equiv.), DCM, rt. (b) **25** (1 equiv.), **2** (1.5 equiv.), PdCl₂dppf-DCM (2 mol%), K₃PO₄ (3 equiv.), MeCN/H₂O (1:1), 60 °C.

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,³³ 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,¹² bicyclic boronates have been frequently employed as chemical probes for target identification in order to unravel the intricacies of biomolecular mechanisms.⁵ 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,³⁴ and warhead 32, a potent ubiquitin recruiter.³⁵

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

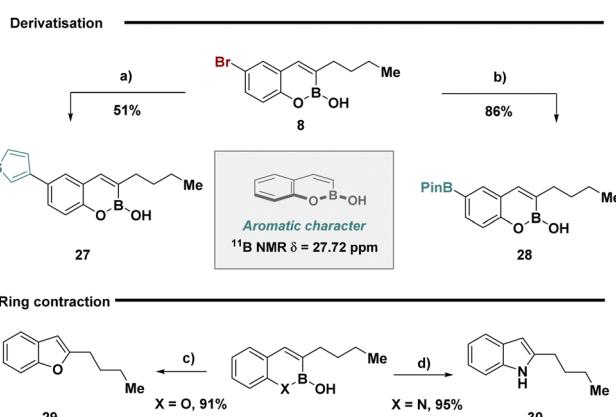


Fig. 3 Product derivatisation. (a) **8** (1 equiv.), boronic acid (5 equiv.), PdCl₂dppf-DCM (2 mol%), K₃PO₄ (3 equiv.), THF, 50 °C. (b) **8** (1 equiv.), B₂Pin₂ (1.5 equiv.), KOAc (3 equiv.), 1,4-dioxane, 80 °C. (c) **3** (1 equiv.), NaOH, H₂O₂, THF/EtOH, 0 °C → rt; then 4 Å mol sieves, DCM/TFA. (d) **18** (1 equiv.), NaOH, H₂O₂, THF/EtOH, 0 °C → rt.

CuAAC Incorporation of Bioactive Molecules

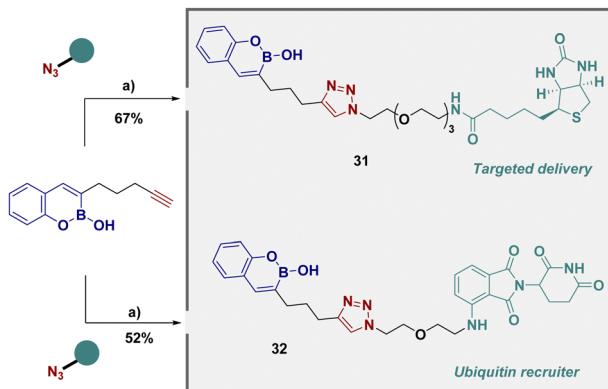


Fig. 4 Click enabled synthesis of biochemical probes. (a) **23** (1 equiv.), azide (1 equiv.), $\text{Cu}(\text{MeCN})_4\text{BF}_4$ (30 mol%), DCM, rt.

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.

We gratefully acknowledge financial support from the Max-Planck Society. A. M. and J. J. M. thank the Fonds der Chemischen Industrie, FCI for funding. We thank the Mass Spec facility in the Organic Chemistry Department of Freie Universität Berlin. We thank Kane Bastick for preliminary experiments. Open Access funding provided by the Max Planck Society.

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. Bita, 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. Vlaescanu, 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. Calvopiná, 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. Dieleman, L. Lefort, Z. Zhu, M. Gnahn, J. Schörghuber, S. Steinhofer, 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. Naniong, C. J. Ott, C. S. Mitsiades, K.-K. Wong, J. E. Bradner and W. G. Kaelin, *Science*, 2014, **343**, 305–309.

