

EDGE ARTICLE

Cite this: *Chem. Sci.*, 2023, 14, 963

All publication charges for this article have been paid for by the Royal Society of Chemistry

Received 3rd November 2022
Accepted 20th December 2022

DOI: 10.1039/d2sc06088d

rsc.li/chemical-science

Synthesis of 3-borylated cyclobutanols from epihalohydrins or epoxy alcohol derivatives†

Tyler R. McDonald and Sophie A. L. Rousseaux *

There is an increasing interest in cyclobutanes within the medicinal chemistry community. Therefore, methods to prepare cyclobutanes that contain synthetic handles for further elaboration are of interest. Herein, we report a new approach for the synthesis of 3-borylated cyclobutanols *via* a formal [3 + 1]-cycloaddition using readily accessible 1,1-diborylalkanes and epihalohydrins or epoxy alcohol derivatives. 1-Substituted epibromohydrin starting materials provide access to borylated cyclobutanols containing substituents at three of the four positions on the cyclobutane core, and enantioenriched epibromohydrins lead to enantioenriched cyclobutanols with high levels of enantiospecificity (>98%). Finally, derivatization studies demonstrate the synthetic utility of both the OH and Bpin handles.

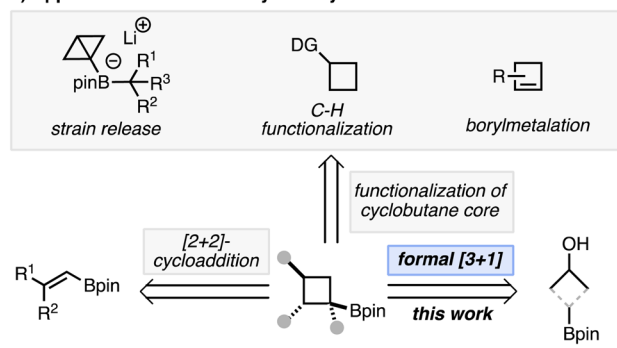
Cyclobutanes are featured in a wide range of structurally interesting and biologically relevant natural products.¹ Within the pharmaceutical industry, cyclobutanes have been gathering attention as they provide a rigid, sp³ rich, well-defined 3-dimensional backbone that enables them to act as bioisosteres for aromatic rings,^{2a,b} while also allowing researchers to “escape flatland”.²

As interest in incorporating cyclobutanes into target molecules increases, so does the need to develop efficient methods for their synthesis. The preparation of borylated cyclobutanes is particularly desirable, as the boron moiety acts as a convenient synthetic handle for further elaboration *via* a range of C–C,³ C–N,⁴ C–O,⁵ or carbon–halogen⁶ bond forming processes. Current strategies to synthesize borylated cyclobutanes typically fall into four broad categories: (a) [2 + 2]-cycloadditions,⁷ (b) strain release/increase reactions,⁸ (c) C–H functionalizations,⁹ and (d) borylmetalation of alkenes¹⁰ (Scheme 1a).¹¹ While significant work has gone towards the development of these methods, they often require starting materials that are not readily available and/or already contain the cyclobutane core. As such, finding new methods to rapidly access cyclobutanes is desirable.

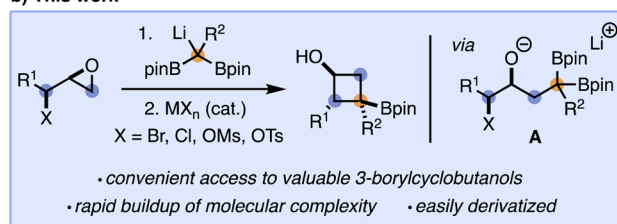
We hypothesized that a formal [3 + 1]-cycloaddition using 1,1-diborylalkanes and epoxy alcohol derivatives as stable and readily accessible starting materials could provide a convenient approach to borylated cyclobutanols while addressing some of the limitations with current methodologies (*e.g.* starting material synthesis). It has been known since the 1960s that, compared to boronic esters, 1,1-diborylalkanes are effective nucleophiles upon activation with a Lewis base.^{11a} This behavior

has been attributed to the second boronic ester being able to stabilize, through resonance, the negative charge resulting from Lewis base coordination and deborylation.^{11a} Based on important contributions from the groups of Meek and Morken,^{11e,12} we anticipated that adding lithiated 1,1-diborylalkanes to epihalohydrins or epoxy alcohol derivatives would result in a ring opening reaction to generate an alkoxide (**A**, Scheme 1b), which could then act as a Lewis base and trigger the cyclization reaction to form the desired product (Scheme 1b).^{13–15}

a) Approaches to access borylated cyclobutanones



b) This work



Scheme 1 (a) Conventional methods to access borylated cyclobutanes. (b) This work.

Department of Chemistry, University of Toronto, 80 St. George Street, Toronto, ON, Canada. E-mail: sophie.rousseau@utoronto.ca

† Electronic supplementary information (ESI) available. See DOI: <https://doi.org/10.1039/d2sc06088d>



Herein, we report the realization of this strategy and demonstrate that the resulting cyclobutanes, which contain two complementary heteroatom handles (OH and Bpin), can be readily derivatized to form a range of cyclobutane products.^{3k} The reaction works well with substituted 1,1-diborylalkanes and alkyl C₃-biselectrophiles and is, to the best of our knowledge, the only method to directly access 3-borylated cyclobutanols.

Cyclobutanes are notoriously difficult to form *via* cyclization reactions: not only are they highly strained, with strain energies comparable to cyclopropanes (~27 kcal mol⁻¹),¹⁶ but substitutions to form cyclobutanes have high entropic and stereo-electronic barriers when compared to cyclopropane formation.¹⁷ With these challenges in mind, we began our studies by evaluating the reaction of **1a** with epibromohydrin (**2a**) in the presence of various metal salts, solvents, and ligands (Table 1).

We initially screened a range of Zn salts with the idea that the boronate complex formed from **A** would undergo transmetalation prior to cyclization. Transmetalations of this type have been reported before,¹² however initial control reactions revealed that the reaction proceeds in the absence of a metal additive. Empirically, we found that the addition of Zn(II) salts was beneficial for yield and reproducibility. These Zn(II) salts may play a role in sequestering reactive organolithium species (*e.g.* excess LDA or lithiated 1,1-diborylalkane) before heating – thereby limiting detrimental side reactions. The notable success of Zn(CN)₂ leads us to suspect that cyanide may also

play a role as a Lewis base to trigger deborylation and subsequent cyclization. Throughout optimization, side products resulting from direct substitution of the C–X bond (**4a**, Table 1), epoxide formation from intermediate **A** (**4a**), and semipinacol rearrangement from intermediate **A** (**5a** and **6a**) were observed in yields ranging from approx. 5–30% depending on the reaction conditions employed. Using 20 mol% ZnCl₂, **3a** was obtained in 67% yield with a 4 : 1 diastereoselectivity. Various ligands were also investigated, with bpy giving similar results to the reaction free of exogenous ligand, and TMEDA giving a modest improvement in yield. Moving to Zn(OTf)₂ resulted in an improved 77% yield, however we found Zn(CN)₂ to be particularly effective for this transformation, with **3a** being obtained in 96% yield and a 6 : 1 d.r. Switching to a non-polar, non-coordinating solvent such as toluene resulted in a complete shutdown of reactivity, however the addition of HMPA – which is known to facilitate substitution reactions in non-polar solvents¹⁸ – led to product formation, albeit in lower yield than when THF was used.

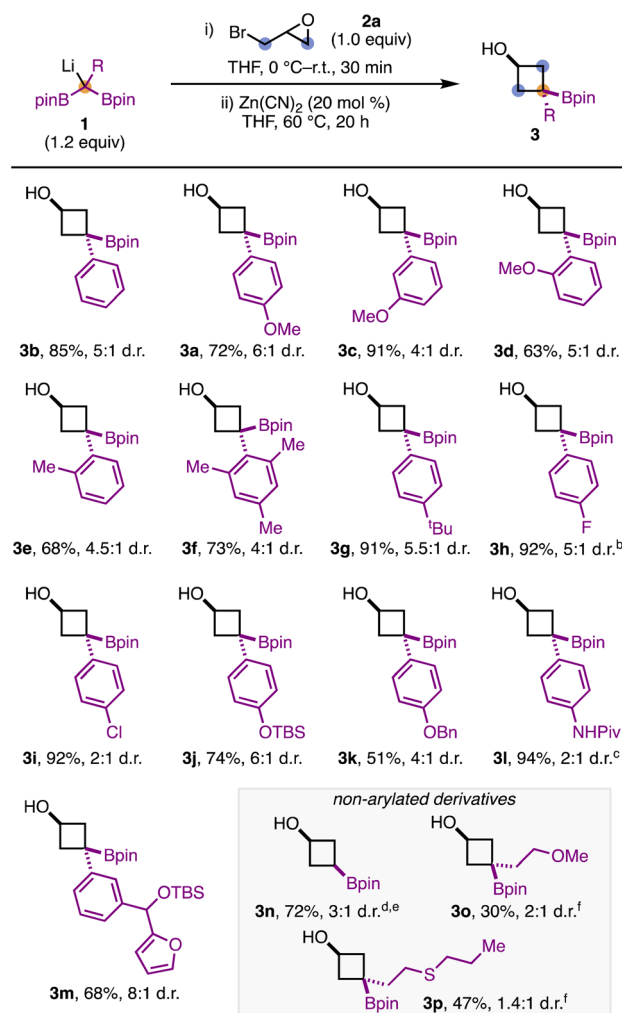
We next explored the scope of the reaction (Scheme 2). Overall, 1-aryl-1,1-diborylalkanes led to borylated cyclobutanols in good to excellent yields. Phenyl-substituted 1,1-diborylmethane give **3b** in 85% yield and 5 : 1 d.r. 4-, 3-, and 2-anisyl derivatives were all competent in this reaction, leading to products **3a**, **3c**, and **3d** respectively, in good to excellent yields. The reaction was tolerant of substitution at the *ortho* position(s) of the aromatic ring, as demonstrated with products **3d**, **3e**, and **3f**. 1,1-Diborylalkanes bearing halogenated arenes are compatible with this chemistry, as seen with **3h** and **3i**. For **3h**, ZnCl₂ was found to be a more effective additive (*cf.* 44% yield with Zn(CN)₂).¹⁹ Silyl and benzyl ether-protected phenol derivatives were compatible with the reaction conditions, leading to **3j** and **3k** in 74% and 51% yield, respectively. Additionally, amides (**3l**) and O-heterocycles (**3m**) are also tolerated. Notably, for **3l** the reaction was performed with the magnesiated 1,1-diborylalkane, generated from magnesium diisopropylamide. Using 1,1-diborylmethane as a starting material resulted in the non-substituted borylated cyclobutanol **3n** in 72% yield and 3 : 1 d.r.; it should be noted that CuCl was required for this substrate. Currently, 1,1-diborylalkane starting materials bearing simple alkyl substituents (*e.g.* R = benzyl) do not efficiently undergo the transformation.²⁰ The inclusion of directing groups such as ethers or thioethers can partially remedy this challenge, resulting in the formation of **3o** and **3p** in 30% and 47% yield, respectively, when 1.0 equivalent of CuCl is used. 1,1-Diborylalkanes bearing heterocycles (*e.g.* pyrimidine) were unable to be tested in the reaction, as they underwent rapid protodeborylation during preparation. This decomposition is consistent with reports detailing similar systems.²¹

With respect to the 1,3-biselectrophile reaction partner, a range of different leaving groups were compatible with this chemistry (Scheme 3a). Along with epibromohydrins, epichlorohydrins were also efficient in this reaction, leading to product **3h** in 87% yield and 5 : 1 d.r. Epoxy mesylates and tosylates were also competent, although the epoxy mesylate starting material benefited from the addition of one equivalent of LiBr. Substituted epibromohydrins were tolerated in this reaction,

Table 1 Reaction optimization with (Bpin)₂CH(4-OMePh)^a

Entry	MX _n	Solvent	Ligand	% 3a	d.r.
1	—	THF	—	58	6 : 1
2	ZnCl ₂	THF	—	67	4 : 1
3	ZnCl ₂	THF	bpy	60	5 : 1
4	ZnCl ₂	THF	TMEDA	78	5 : 1
5	CuCl	THF	—	75	2 : 1
6	Zn(OTf) ₂	THF	—	77	4 : 1
7	Zn(CN) ₂	THF	—	96	6 : 1
8	Zn(CN) ₂	Toluene	—	<1	—
9	Zn(CN) ₂	Toluene/HMPA ^b	—	55	4 : 1

^a Yields and diastereomeric ratios determined by ¹H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard. ^b Toluene/HMPA ratio of 15/1 (v/v); HMPA (0.10 mL) was added to the reaction 10 minutes after adding the metal. For full details, see ESI (Table S1).

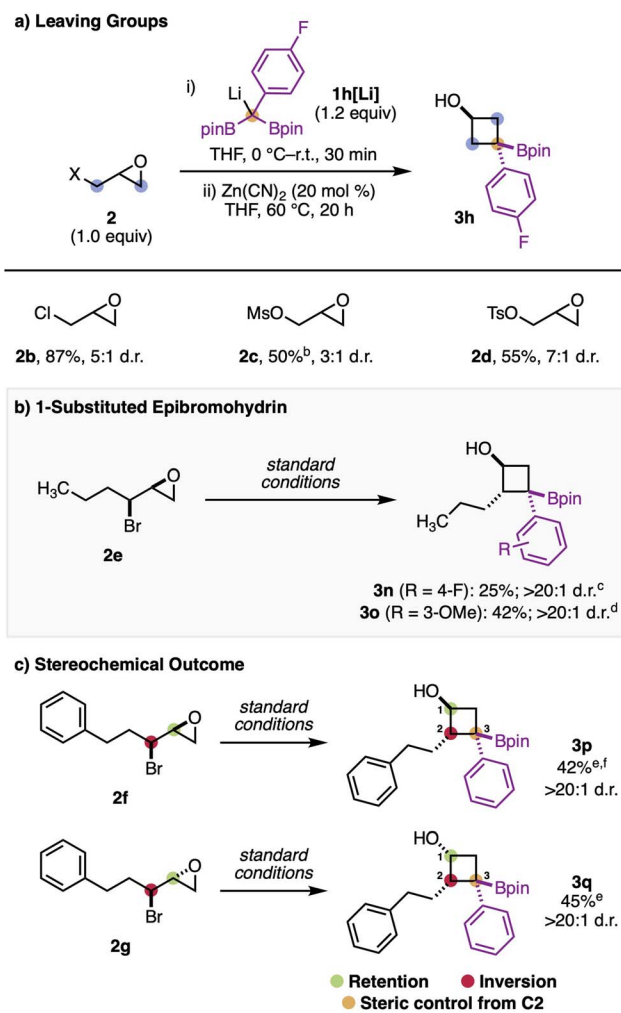


^aReported yields are the combined isolated yields of both diastereomers, the major isomer is shown; d.r.'s were determined by ¹H, ¹⁹F NMR or GC-MS analysis of the crude reaction mixtures. Reactions performed on 0.20 mmol scale. ^bZnCl₂ used in place of Zn(CN)₂. ^cMagnesiated starting material used in place of lithiated starting material, see SI for further details. ^dCuCl used in place of Zn(CN)₂. ^eReaction performed on 0.80 mmol scale. ^fCuCl (1.0 equiv.) used in place of Zn(CN)₂.

Scheme 2 Scope of 1,1-diborylalkanes.^a

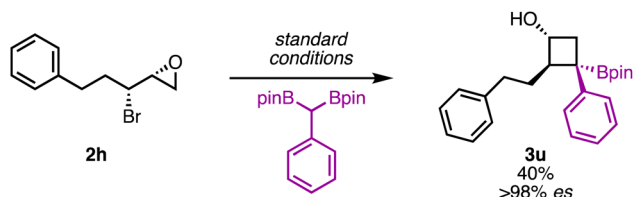
resulting in products (**3q**, **3r**, **3s**, and **3t**) with at least one substituent at three of the four positions on the cyclobutane core (Scheme 3b and c). Notably, in all cases where substituted epibromohydrins were used, only a single diastereomer was isolated.

The stereochemical relationship between the alcohol and the substituent at the 2-position of the cyclobutane core is determined by the stereochemical relationship of the starting epibromohydrin: *syn*-epibromohydrins result in *trans* products (**3q**, **3r**, **3s**), and *anti*-epibromohydrins result in *cis* products (**3t**) (Scheme 3c). Since α -boryl anions are able to planarize, we questioned whether the C3 stereocenter was controlled by steric effects from the substituent at the 2-position or by the alcohol at the 1-position (through coordination). When diastereomers **2f** and **2g** were tested, we found that the relative stereochemistry at C3 was primarily controlled by the substituent at C2, presumably through steric effects (Scheme 3c). This may explain why

Scheme 3 Scope of electrophiles.^a

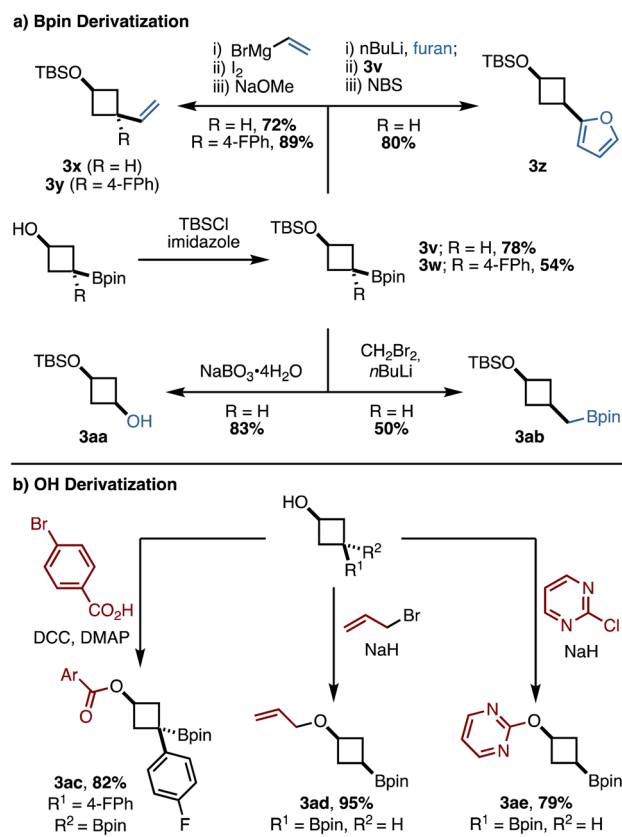
substituted epibromohydrins result in a single diastereomer of product and non-substituted epibromohydrins or epoxy alcohol derivatives do not – when there is a substituent, the steric interactions become greater and therefore selectivity is improved.

To further verify that the stereochemical information in the starting material was translated to the product, enantio-enriched 1-substituted epibromohydrin **2h** was used as a substrate. The reaction was found to proceed with high enantiospecificity (>98% es, Scheme 4). This is significant because enantioenriched epibromohydrins can be readily accessed *via* the corresponding allylic alcohols, thereby providing a synthetically convenient approach to enantioenriched, polysubstituted borylated cyclobutanols. These examples further highlight how this method enables rapid buildup of complexity from readily accessible, stereochemically defined starting materials.



Scheme 4 Stereospecificity using an enantioenriched epibromohydrin.

The products of these reactions contain both an alcohol and a boronic ester as synthetic handles, priming them for derivatization. We focused our efforts on derivatizations that may be of particular interest to medicinal chemists. For the Bpin handle (Scheme 5a), initial TBS protection of the alcohol followed by Zweifel olefination efficiently yielded alkenylated products **3x** and **3y**, with **3y** bearing a newly formed all-carbon quaternary stereocenter. The incorporation of heterocycles, such as furan, was possible using conditions reported by Aggarwal and coworkers, generating **3z** in 80% yield.^{3e} Oxidation of the boronic ester using sodium perborate tetrahydrate cleanly yielded cyclobutanol **3aa** in 83% yield, and the presence of both a protected and an unprotected alcohol in this product should enable selective, orthogonal functionalization. Finally,



^aSee supplementary information for full experimental details. Reported yields are isolated yields.

Scheme 5 Product derivatization studies.^a

a Matteson homologation resulted in the homologated product **3ab** in 50% yield.

Functionalization of the alcohol handle was also explored (Scheme 5b). We found that esterification *via* DCC coupling efficiently produced **3ac** in 82% yield. Etherification and S_NAr reactions proceeded smoothly and led to products **3ad** and **3ae**, respectively, in good to excellent yields. These transformations suggest that the alkoxide can act as an effective nucleophile despite its potential sequestration as a boronate complex. Furthermore, the incorporation of heteroareamics (**3z**, **3ae**) *via* derivatization partially addresses the aforementioned difficulties in accessing heteroarene-substituted 1,1-diborylalkanes.

Throughout our studies, we noticed different reactivity patterns depending on the 1,1-diborylalkane that was being used. These differences manifested in three main observations: (i) both Zn and Cu salts effectively convert aryl substituted 1,1-diborylalkanes $[(Bpin)_2CHAR]$ to the desired cyclobutanols, whereas only Cu salts were effective with alkyl- and non-substituted starting materials; (ii) the use of Cu salts led to a diminished d.r., and (iii) aryl substituted 1,1-diborylalkanes lead to product in the absence of a metal additive, which was not the case for alkyl- and non-substituted 1,1-diborylalkanes. The observation that the reaction proceeds without the addition of a metal additive is noteworthy as it suggests that lithium-based Lewis bases can trigger boryl migration. In contrast, previous work has shown that in similar systems, Li alkoxides are rarely able to effectively promote C-to-O boryl-migrations in the absence of a transition metal.^{11e,15e} Indeed, in their report detailing ring opening reactions with $LiCH(Bpin)_2$ and subsequent substitutions with allylic electrophiles, Meek and coworkers found that CuCl was required, suggesting that Lewis base coordination alone was insufficient for the reaction to proceed.¹² In our case, the additional stabilization provided by an aryl substituent may allow the transfer to occur, suggesting that this reaction may proceed through Lewis base activation and does not require transmetalation. With this in mind, the observation that CuCl is required for unsubstituted and alkyl-substituted 1,1-diborylalkane starting materials suggests that there may be a change in mechanism for these substrates, and that transmetalation is necessary for product formation (Fig. S16 and S17[†]). Further mechanistic studies are currently ongoing in our laboratory to better understand the unique interplay between the substrate structure and reaction mechanism.

In summary, we have developed a formal [3 + 1]-cycloaddition to generate 3-borylated cyclobutanols. This reaction takes advantage of epihalohydrins and epoxy alcohol derivatives as C_3 -biselectrophiles and lithiated 1,1-diborylalkanes as C_1 -bisnucleophiles. 1-Substituted epibromohydrins resulted in the formation of highly substituted borylated cyclobutanols, allowing for rapid buildup of molecular complexity within a single transformation. When 1-substituted epibromohydrins are used, a single diastereomer is obtained, with the stereochemistry at the C3 position being controlled by the substituent at C2. The reaction proceeded with high levels of stereospecificity, and when enantioenriched 1-substituted epibromohydrins were used, enantioenriched products were

obtained. Finally, both the alcohol and the boronic ester were demonstrated to be orthogonal synthetic handles, allowing for convenient derivatization and elaboration of the products. We anticipate that these synthetic handles may alleviate some of the challenges regarding incorporation of cyclobutanes into more complex molecular scaffolds and are continuing to explore their potential in our laboratory.

Data availability

The synthetic procedures, characterization, and spectral data supporting this article have been uploaded as part of the ESI.†

Author contributions

T. R. M. and S. A. L. R. contributed to project conception, experiment design and analysis, and the writing of this manuscript.

Conflicts of interest

The authors declare no conflicts of interest.

Acknowledgements

We thank NSERC (Discovery Grants and Canada Research Chair programs), the Canada Foundation for Innovation (Project No. 35261), the Ontario Research Fund, the Alfred P. Sloan Foundation, and the University of Toronto for generous financial support of this work. We also acknowledge the Canada Foundation for Innovation (Project No. 19119) and the Ontario Research Fund for funding the Centre for Spectroscopic Investigation of Complex Organic Molecules and Polymers. T. R. M. thanks NSERC for a graduate scholarship (CGS D). We would like to thank John J. Monteith for verifying reaction reproducibility.

References

- (a) J. Li, K. Gao, M. Bian and H. Ding, *Org. Chem. Front.*, 2020, **7**, 136–154; (b) M. Wang and P. Lu, *Org. Chem. Front.*, 2018, **5**, 254–259; (c) Y.-Y. Fan, X.-H. Gao and J.-M. Yue, *Sci. China: Chem.*, 2016, **59**, 1126–1141; (d) A. Sergeiko, V. V. Poroikov, L. O. Hanuš and V. M. Dembitsky, *Open Med. Chem. J.*, 2008, **2**, 26–37.
- (a) K. C. Nicolaou, D. Vourloumis, S. Totokotsopoulos, A. Papakyriakou, H. Karsunky, H. Fernando, J. Gavrilyuk, D. Webb and A. F. Stepan, *ChemMedChem*, 2016, **11**, 31–37; (b) A. F. Stepan, C. Subramanyam, I. V. Efremov, J. K. Dutra, T. J. O'Sullivan, K. J. DiRico, W. S. McDonald, A. Won, P. H. Dorff, C. E. Nolan, S. L. Becker, L. R. Pustilnik, D. R. Riddell, G. W. Kauffman, B. L. Kormos, L. Zhang, Y. Lu, S. H. Capetta, M. E. Green, K. Karki, E. Sibley, K. P. Atchison, A. J. Hallgren, C. E. Oborski, A. E. Robshaw, B. Sneed and C. J. O'Donnell, *J. Med. Chem.*, 2012, **55**, 3414–3424; (c) K. C. Nicolaou, *Angew. Chem., Int. Ed.*, 2014, **53**, 9128–9140; (d) F. Lovering, J. Bikker and C. Humblet, *J. Med. Chem.*, 2009, **52**, 6752–6756; (e) D. Blanco-Ania, S. A. Gawade, L. J. L. Zwinkels, L. Maartense, M. G. Bolster, J. C. J. Benningshof and F. P. J. T. Rutjes, *Org. Process Res. Dev.*, 2016, **20**, 409–413; (f) P. Arya, R. Joseph, Z. Gan and B. Rakic, *Chem. Biol.*, 2005, **12**, 163–180; (g) S. L. Schreiber, *Science*, 2000, **287**, 1964–1969; (h) R. Breinbauer, I. R. Vetter and H. Waldmann, *Angew. Chem., Int. Ed.*, 2002, **41**, 2878–2890; (i) E. Lee-Ruff and G. Mladenova, *Chem. Rev.*, 2003, **103**, 1449–1484; (j) J. C. Namyslo and D. E. Kaufmann, *Chem. Rev.*, 2003, **103**, 1485–1538.
- (a) G. Zweifel, H. Arzoumanian and C. C. Whitney, *J. Am. Chem. Soc.*, 1967, **89**, 3652–3653; (b) D. A. Evans, T. C. Crawford, R. C. Thomas and J. A. Walker, *J. Org. Chem.*, 1976, **41**, 3947–3953; (c) R. J. Armstrong, C. García-Ruiz, E. L. Myers and V. K. Aggarwal, *Angew. Chem., Int. Ed.*, 2017, **56**, 786–790; (d) Y. Wang, A. Noble, E. L. Myers and V. K. Aggarwal, *Angew. Chem., Int. Ed.*, 2016, **55**, 4270–4274. For heteroaryl cross-couplings, see: (e) A. Bonet, M. Odachowski, D. Leonori, S. Essafi and V. K. Aggarwal, *Nat. Chem.*, 2014, **6**, 584–589; (f) M. Odachowski, A. Bonet, S. Essafi, P. Conti-Ramsden, J. N. Harvey, D. Leonori and V. K. Aggarwal, *J. Am. Chem. Soc.*, 2016, **138**, 9521–9532; (g) J. Llaveria, D. Leonori and V. K. Aggarwal, *J. Am. Chem. Soc.*, 2015, **137**, 10958–10961. For reviews on cross-couplings and functionalizations of boronic esters, see: (h) N. Miyaura and A. Suzuki, *Chem. Rev.*, 1995, **95**, 2457–2483; (i) A. Suzuki, *Organomet. Chem.*, 1999, **576**, 147–168; (j) A. Suzuki, *Angew. Chem., Int. Ed.*, 2011, **50**, 6722–6737; (k) C. Sandford and V. K. Aggarwal, *Chem. Commun.*, 2017, **53**, 5481–5494; (l) J. W. B. Fyfe and A. J. B. Watson, *Chem*, 2017, **3**, 31–55.
- (a) S. N. Mlynarski, A. S. Karns and J. P. Morken, *J. Am. Chem. Soc.*, 2012, **134**, 16449–16451; (b) A. P. Pulis, D. J. Blair, E. Torres and V. K. Aggarwal, *J. Am. Chem. Soc.*, 2013, **135**, 16054–16057.
- (a) H. C. Brown and G. Zweifel, *J. Am. Chem. Soc.*, 1961, **83**, 2544; (b) A. G. Davies and B. P. Roberts, *J. Chem. Soc. B*, 1967, **17**; (c) J. L. Stymiest, V. Bagutski, R. M. French and V. K. Aggarwal, *Nature*, 2008, **456**, 778; (d) V. Bagutski, R. M. French and V. K. Aggarwal, *Angew. Chem., Int. Ed.*, 2010, **49**, 5142; (e) G. W. Kabalka, T. M. Shoup and N. M. Goudgaon, *Tetrahedron Lett.*, 1989, **30**, 1483; (f) S. Radomkit and A. H. Hoveyda, *Angew. Chem., Int. Ed.*, 2014, **53**, 3387.
- (a) H. C. Brown and C. F. Lane, *J. Chem. Soc. D*, 1971, **521**, 2544–2551; (b) H. C. Brown, N. R. De Lue, G. W. Kabalka and H. C. Hedgcock Jr, *J. Am. Chem. Soc.*, 1976, **98**, 1290–1291; (c) H. C. Brown and C. F. Lane, *Tetrahedron*, 1988, **44**, 2763–2772; (d) C. Sandford, R. Rasappan and V. K. Aggarwal, *J. Am. Chem. Soc.*, 2015, **137**, 10100–10103; (e) R. Larouche-Gauthier, T. G. Elford and V. K. Aggarwal, *J. Am. Chem. Soc.*, 2011, **133**, 16794–16797.
- (a) R. H. Fish, *J. Org. Chem.*, 1969, **34**, 1127–1128; (b) W. G. Hollis Jr, W. C. Lappenbusch, K. A. Everberg and C. M. Woleben, *Tetrahedron Lett.*, 1993, **34**, 7517–7520; (c) S. C. Coote and T. Bach, *J. Am. Chem. Soc.*, 2013, **135**,

- 14948–14951; (d) S. C. Coote, A. Pöthig and T. Bach, *Chem.–Eur. J.*, 2015, **21**, 6906–6912; (e) R. A. Kleinnijenhuis, B. J. J. Timmer, G. Lutteke, J. M. M. Smits, R. de Gelder, J. H. van Maarseveen and H. Hiemstra, *Chem.–Eur. J.*, 2016, **22**, 1266–1269; (f) M. M. Parsutkar, V. V. Pagar and T. V. RajanBabu, *J. Am. Chem. Soc.*, 2019, **141**, 15367–15377; (g) O. P. Demchuck, O. V. Hryshchuk, B. V. Vashchenko, A. V. Kozyt'skiy, A. V. Tymtsunik, I. V. Komarov and O. O. Grygorenko, *J. Org. Chem.*, 2020, **85**, 5927–5940; (h) S. O. Scholz, J. B. Kidd, L. Capaldo, N. E. Flikweert, R. M. Littlefield and T. P. Yoon, *Org. Lett.*, 2021, **23**, 3496–3501; (i) Y. Liu, D. Ni, B. G. Stevenson, V. Tripathy, S. E. Braley, K. Raghavachari, J. R. Swierk and M. K. Brown, *Angew. Chem., Int. Ed.*, 2022, **61**, e202200725; (j) Y. Liu, D. Ni and M. K. Brown, *J. Am. Chem. Soc.*, 2022, **144**, 18790–18796.
- 8 (a) Z. X. Giustra, X. Yang, M. Chen, H. F. Bettinger and S.-Y. Liu, *Angew. Chem., Int. Ed.*, 2019, **58**, 18918–18922; (b) M. Silvi and V. K. Aggarwal, *J. Am. Chem. Soc.*, 2019, **141**, 9511–9515; (c) A. Fawcett, T. Biberger and V. K. Aggarwal, *Nat. Chem.*, 2019, **11**, 117–122; (d) R. Davenport, M. Silvi, A. Noble, Z. Hosni, N. Fey and V. K. Aggarwal, *Angew. Chem., Int. Ed.*, 2020, **59**, 6525–6528; (e) S. H. Bennett, A. Fawcett, E. H. Denton, T. Biberger, V. Fasano, N. Winter and V. K. Aggarwal, *J. Am. Chem. Soc.*, 2020, **142**, 16766–16775; (f) D. P. Hari, J. C. Abell, V. Fasano and V. K. Aggarwal, *J. Am. Chem. Soc.*, 2020, **142**, 5515–5520; (g) L. Guo, A. Noble and V. K. Aggarwal, *Angew. Chem., Int. Ed.*, 2021, **60**, 212–216.
- 9 (a) R. Murakami, K. Tsunoda, T. Iwai and M. Sawamura, *Chem.–Eur. J.*, 2014, **20**, 13127–13131; (b) J. He, Q. Shao, Q. Wu and J.-Q. Yu, *J. Am. Chem. Soc.*, 2017, **139**, 3344–3347; (c) X. Chen, L. Chen, H. Zhao, Q. Gao, Z. Shen and S. Xu, *Chin. J. Chem.*, 2020, **38**, 1533–1537; (d) R. Oeschger, B. Su, I. Yu, C. Ehinger, E. Romero, S. He and J. Hartwig, *Science*, 2020, **368**, 736–741.
- 10 (a) H. Ito, T. Toyoda and M. Sawamura, *J. Am. Chem. Soc.*, 2010, **132**, 5990–5992; (b) M. Guisán-Ceinos, A. Parra, V. Martín-Heras and M. Tortosa, *Angew. Chem., Int. Ed.*, 2016, **55**, 6969–6972; (c) J. A. M. Mercer, C. M. Cohen, S. R. Shuken, A. M. Wagner, M. W. Smith, F. R. Moss III, M. D. Smith, R. Vahala, A. Gonzalez-Martinez, S. G. Boxer and N. Z. Burns, *J. Am. Chem. Soc.*, 2016, **138**, 15845–15848; (d) K. M. Logan and M. K. Brown, *Angew. Chem., Int. Ed.*, 2017, **56**, 851–855; (e) H. A. Clement, M. Boghi, R. M. McDonald, L. Bernier, J. W. Coe, W. Farrell, C. J. Helal, M. R. Reese, N. W. Sach, J. C. Lee and D. G. Hall, *Angew. Chem., Int. Ed.*, 2019, **58**, 18405–18409; (f) E. N. Hancock, E. L. Kuker, D. J. Tantillo and M. K. Brown, *Angew. Chem., Int. Ed.*, 2020, **59**, 436–441; (g) L. Nóvoa, L. Trulli, A. Parra and M. Tortosa, *Angew. Chem., Int. Ed.*, 2021, **60**, 11763–11768; (h) A. K. Simlandy, M.-Y. Lyu and M. K. Brown, *ACS Catal.*, 2021, **11**, 12815–12820; (i) K. Nguyen, H. A. Clement, L. Bernier, J. W. Coe, W. Farrell, C. J. Helal, M. R. Reese, N. W. Sach, J. C. Lee and D. G. Hall, *ACS Catal.*, 2021, **11**, 404–413; (j) L. Nóvoa, L. Trulli, I. Fernández, A. Parra and M. Tortosa, *Org. Lett.*, 2021, **23**, 7434–7438.
- 11 For other miscellaneous methods, see: (a) S. P. Rhodes and H. C. Brown, *J. Am. Chem. Soc.*, 1969, **91**, 4306–4307; (b) I. D. Gridnev and A. Meller, *J. Org. Chem.*, 1998, **63**, 3599–3606; (c) H.-W. Man, W. C. Hiscox and D. S. Matteson, *Org. Lett.*, 1999, **1**, 379–381; (d) T. C. Atack, R. M. Lecker and S. P. Cook, *J. Am. Chem. Soc.*, 2014, **136**, 9521–9523; (e) K. Hong, X. Liu and J. P. Morken, *J. Am. Chem. Soc.*, 2014, **136**, 10581–10584; (f) X.-F. Zhou, Y.-D. Wu, J.-J. Dai, Y.-J. Li, Y. Huang and H.-J. Xu, *RSC Adv.*, 2015, **5**, 46672–46676; (g) D. Hu, L. Wang and P. Li, *Org. Lett.*, 2017, **19**, 2770–2773; (h) C. Shu, A. Noble and V. K. Aggarwal, *Angew. Chem., Int. Ed.*, 2019, **58**, 3870–3874; (i) J. C. Beck, C. R. Lacker, L. M. Chapman and S. E. Reisman, *Chem. Sci.*, 2019, **10**, 2315–2319; (j) D. Wang, C. Mück-Lichtenfeld and A. Studer, *J. Am. Chem. Soc.*, 2019, **141**, 14126–14130; (k) J. Michalland, N. Casaretto and S. Z. Zard, *Angew. Chem., Int. Ed.*, 2022, **61**, e202113333.
- 12 S. A. Murray, M. Z. Liang and S. J. Meek, *J. Am. Chem. Soc.*, 2017, **139**, 14061–14064.
- 13 (a) J. J. Eisch, S. K. Dua and M. Behrooz, *J. Org. Chem.*, 1985, **50**, 3674–3676; (b) J. E. Jeffery, F. Kerrigan, T. K. Miller, G. J. Smith and G. B. Tometzki, *J. Chem. Soc., Perkin Trans. 1*, 1996, 2583–2589; (c) W.-C. Cheng, C. Halm, J. B. Evarts, M. M. Olmstead and M. J. Kurth, *J. Org. Chem.*, 1999, **64**, 8557–8562; (d) J. Vogelgesang, A. Frick, G. Huttner and P. Kircher, *Eur. J. Inorg. Chem.*, 2001, 949–971; (e) P. Grongsaard, P. G. Bulger, D. J. Wallace, L. Tan, Q. Chen, S. J. Dolman, J. Nyrop, R. S. Hoerrner, M. Weisel, J. Arredondo, T. Itoh, C. Xie, X. Wen, D. Zhao, D. J. Muzzio, E. M. Bassan and C. S. Shultz, *Org. Process Res. Dev.*, 2012, **16**, 1069–1081; (f) M. Jung and V. N. G. Lindsay, *J. Am. Chem. Soc.*, 2022, **144**, 4764–4769.
- 14 For reviews on the synthesis and reactivity of 1,1-diborylalkanes, see: (a) D. S. Matteson, *Synthesis*, 1975, **3**, 147–157; (b) N. Miralles, R. J. Maza and E. Fernández, *Adv. Synth. Catal.*, 2018, **360**, 1306–1327; (c) R. Nallagonda, K. Padala and A. Masarwa, *Org. Biomol. Chem.*, 2018, **16**, 1050–1064; (d) Y. Lee, S. Han and S. H. Cho, *Acc. Chem. Res.*, 2021, **54**, 3917–3929; (e) C. Zhang, W. Hu and J. P. Morken, *ACS Catal.*, 2021, **11**, 10660–10680; (f) A. B. Cuenca and E. Fernández, *Chem. Soc. Rev.*, 2021, **50**, 72–86.
- 15 For miscellaneous examples of reactions using 1,1-diborylalkanes, see: (a) W. Jo, J. Kim, S. Choi and S. H. Cho, *Angew. Chem., Int. Ed.*, 2016, **128**, 9842–9846; (b) A. Ebrahim-Alkhalil, Z.-Q. Zhang, T.-J. Gong, W. Su, X.-Y. Lu, B. Xiao and Y. Fu, *Chem. Commun.*, 2016, **52**, 4891–4893; (c) R. Gava and E. Fernández, *Chem.–Eur. J.*, 2019, **25**, 8013–8017; (d) O. Salvado, R. Gava and E. Fernández, *Org. Lett.*, 2019, **21**, 9247–9250; (e) B. Lee and P. J. Chirik, *J. Am. Chem. Soc.*, 2020, **142**, 2429–2437.
- 16 J. Li, K. Gao, M. Bian and H. Ding, *Org. Chem. Front.*, 2020, **7**, 136–154.

- 17 P. Deslongchamps, *Stereoelectronic Effects in Organic Chemistry*, Elsevier Science Limited, University of Michigan, 1983.
- 18 R. R. Dykstra, *Hexamethylphosphoric Triamide in Encyclopedia of Reagents for Organic Synthesis*, John Wiley & Sons, 2001.
- 19 When $\text{Zn}(\text{CN})_2$ is used for this substrate the major side product is protodemetalated starting material. We suspected that this may have been due to the Lewis basicity of the cyanide anion, which prompted us to attempt the reaction using less Lewis basic ZnCl_2 .
- 20 This is in agreement with previous observations made by Meek and coworkers. See ref ¹². Instead, the product resulting from semi-pinacol rearrangement of intermediate A is obtained as the major side-product.
- 21 X. Ma and Y. Jiang, *ChemRxiv*, 2022, preprint, DOI: [10.26434/chemrxiv-2022-96vc8](https://doi.org/10.26434/chemrxiv-2022-96vc8). This content is a preprint and has not been peer-reviewed.