Complex Boron-Containing Molecules through a 1,2-Metalate Rearrangement/*anti*-S$_N$2′ Elimination/Cycloaddition Reaction Sequence

Chloe Tillin
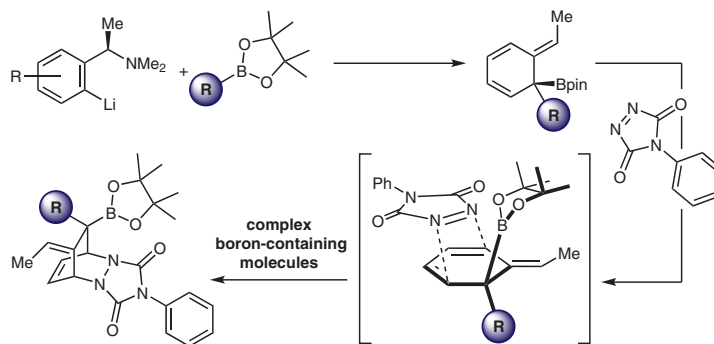Raphael Bigler
Renata Calo-Lapido
Beatrice S. L. Collins
Adam Noble
Varinder K. Aggarwal* [ORCID]

School of Chemistry, University of Bristol, Cantock's Close, Bristol
BS8 1TS, UK
v.aggarwal@bristol.ac.uk

Abstract The three-component coupling of benzylamines, boronic esters, and 4-phenyl-3*H*-1,2,4-triazole-3,5(4*H*)-dione (PTAD) is reported. The boronate complex formed from an *ortho*-lithiated benzylamine and a boronic ester undergoes a stereospecific 1,2-metalate rearrangement/*anti*-S$_N$2′ elimination in the presence of an N-activator to provide a dearomatized tertiary boronic ester. Interception of this dearomatized intermediate with a dienophile leads to stereopredictable cycloaddition reactions to generate highly complex three-dimensional boron-containing molecular structures. When enantioenriched α-methyl-substituted benzylamines are employed, the corresponding cycloaddition adducts are formed with excellent enantiospecificities.

Key words cycloaddition, 1,2-metalate rearrangement, phenyltriazoledione, benzylamines, boronic esters, multicomponent reaction

Boronic esters are highly versatile molecules in organic synthesis due to the wealth of stereospecific transformations that they have been shown to undergo. Transformation into alcohols, amines, halogens, or unsaturated carbon moieties (alkenes or alkynes) can occur through stereoretentive or stereoinvertive pathways, whereas homologation reactions can be used to build up complex carbon skeletons.[1,2] Furthermore, α-amino boronic acids have been shown to act as potent inhibitors of serine protease, leading to the development of, for example, bortezomib, a treatment for relapsed and refractory multiple myeloma.[3] Thus, the development of novel methods for the synthesis of alkyl boronic esters with high enantiopurity is of utmost importance. Although recent years have seen a huge growth in the development of such methods,[4] access to structurally complex alkyl boronic esters possessing an array of useful functionalities remains a challenge. We were interested in the development of a method for the synthesis of densely

functionalized organoboron molecules, rich in orthogonal functionality that could be used for subsequent synthetic elaboration. Here, we detail a simple one-pot procedure that generates complex three-dimensional boron-containing architectures that bear multiple sites of orthogonal reactivity.

We recently reported a method for the enantiospecific synthesis of *ortho*-substituted benzylic boronic esters by a 1,2-metalate rearrangement/*anti*-S$_N$2′ elimination/1,3-borotropic shift reaction sequence starting from enantioenriched α-substituted benzylamines [Scheme 1(A)].[5] This reaction sequence passes through a key dearomatized tertiary boronic ester intermediate **Int-I**, with the subsequent 1,3-borotropic shift driven by the favorable rearomatization. We have also shown that this key enantioenriched dearomatized intermediate can participate in allylboration and allylic Suzuki–Miyaura cross-coupling reactions to provide complex enantioenriched products [Scheme 1(B)].[5,6] Importantly, all of these transformations use rearomatization as a driving forcing. We were, however, interested in diverting reactivity along an alternative pathway, avoiding rearomatization and thereby retaining valuable functionality. In this way, we postulated that we might be able to intercept the dearomatized intermediate **Int-I** through a Diels–Alder cycloaddition reaction with an appropriate dienophile. As depicted in Scheme 1(C), this should give rise to complex three-dimensional architectures that possess not only a tertiary boronic ester moiety, but also two electronically differentiated alkene moieties (an allyl boronic ester and an isolated alkene), along with the functionalities associated with the boronic ester component and the dienophile. Interception of dearomatized intermediates has a significant history in organic synthesis, and it has been used in total syntheses[7] and, more recently, as a powerful method in transition metal-catalyzed transformations.[8] A number of issues were expected to arise in the realization of this pro-
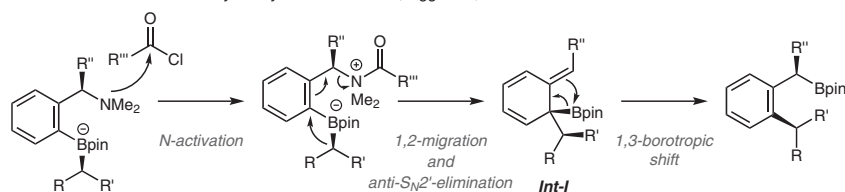
450

Synlett   C. Tillin et al.   THIEME OPEN ACCESS   **Letter**
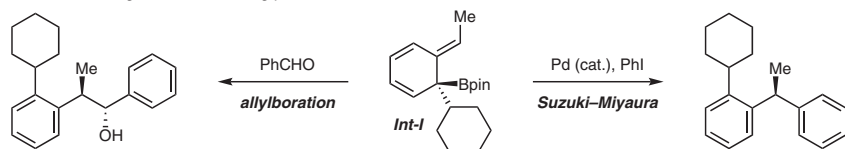
**Scheme 1** Rearomatizing transformations of **Int-I** and proposed cycloaddition pathway

cess, including (i) the well-known limited reactivity of cyclohexadienes, further compounded by the presence of a sterically demanding tertiary boronic ester; (ii) the facial selectivity in the Diels–Alder cycloaddition, which should give rise to diastereomeric mixtures; and (iii) the potential for matched/mismatched reactivities when both chiral benzylamines and boronic esters are used.

We began our studies by preparing the key dearomatized intermediate through treatment of lithiated benzylamine **Li-1a** with 2-cyclohexyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (CyBpin; **2a**), followed by activation of the amine moiety with $ClCO_2CMe_2CCl_3$ ($Me_2Troc–Cl$), in line with our previous reports (Scheme 2). To our delight, the addition of 4-phenyl-3*H*-1,2,4-triazole-3,5(4*H*)-dione (PTAD; 1.1 equivalents) to the reaction mixture at room temperature, followed by stirring for one hour, provided cycloaddition product **3aa** in 51% isolated yield and a remarkable dr of 17:1 (determined by ^{1}H NMR analysis of both the crude and purified product); the product was obtained as the *syn*-isomer (here, *syn* designates the relationship between the Bpin moiety and the triazolidine group). We chose PTAD as the dienophile on the basis of reports in the literature that addressed the poor reactivity of cyclohexadienes towards cycloaddition reactions due to the high distortion energies associated with accessing the transition-state geometry.[9] Studies by Houk and co-workers investigated the superior reactivity of PTAD as a dienophile for such systems.[10] Indeed, other dienophiles tested (e.g., maleic anhydride, diethyl acetylenedicarboxylate, and diethyl fumarate) were all unreactive.[11]
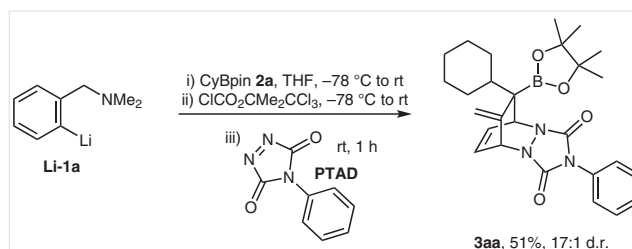
Scheme 2 Cycloaddition of **Int-I** with PTAD

We then went on to assess the scope of the boronic ester component by using the lithiated benzylamine **Li-1a** (Scheme 3). The Boc-protected piperidine boronic ester **2b** provided the cycloaddition product **3ab** in 67% yield and an excellent dr (>20:1), as did the 1-adamantyl boronic ester **2c** (**3ac**; 42% yield, >20:1 dr). Interestingly, when the phenylboronic ester **2d** was used, the *syn*-isomer was still favored, but diastereoselectivity was poor (1.5:1). Furthermore, where less sterically bulky boronic esters, such as the cyclopropyl boronic ester **2e** or the primary boronic esters **2f–j** were used, the diastereoselectivity was inverted to favor the *anti*-isomer. The entries shown in Scheme 3 also highlight the range of functionalities tolerated by the reaction, including protected alcohols (**3ah**) or aldehydes (**3aj**), along with azides (**3ai**) or carbamates (**3ab**).

We rationalize the selectivities observed in Scheme 3 as follows [Scheme 4(A)]. When the R group on the boronic ester is large (e.g., **3aa–ac** in Scheme 3), the dienophile approaches the diene of **Int-I** past the smaller Bpin moiety, leading to the *syn*-isomer with high diastereoselectivity.

451

Synlett   C. Tillin et al.   THIEME OPEN ACCESS   Letter
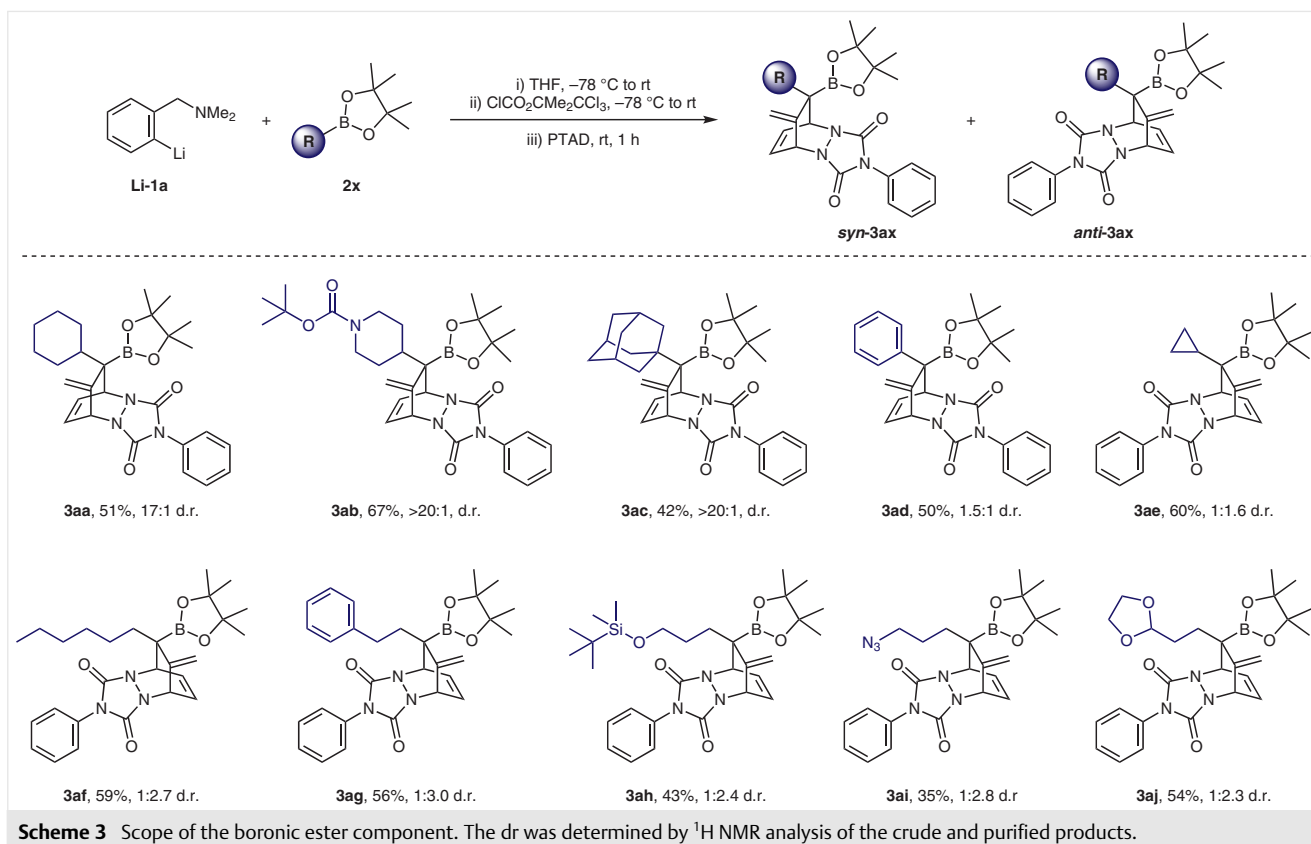
Scheme 3 Scope of the boronic ester component. The dr was determined by ^{1}H NMR analysis of the crude and purified products.

The remarkable diastereoselectivities observed in these cases indicate that the Bpin group, which is widely regarded as bulky, is considerably less sterically demanding than simple α-branched alkyl groups.[12] When R is small, for example a cyclopropyl or primary alkyl group, the dienophile approaches past this group, avoiding the Bpin moiety, thereby providing the *anti*-isomer. In these cases, the steric difference between the smaller R group and the relatively small Bpin moiety is less, and the diastereoselectivity is correspondingly reduced. For the phenylboronic ester **2d**, approach past the Bpin moiety is still favored, but with much lower selectivity.
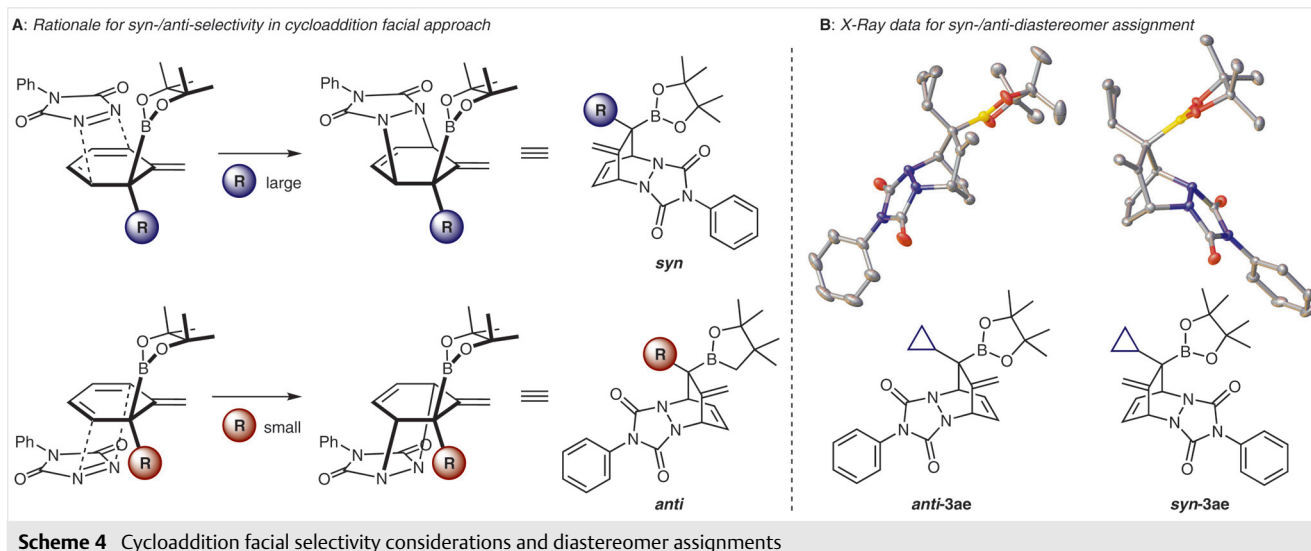
Scheme 4 Cycloaddition facial selectivity considerations and diastereomer assignments

The cycloaddition products were usually isolated as mixtures of diastereoisomers, and their relative configurations were assigned through analysis of the ^{13}C NMR chemical shifts. For the *anti*-isomers, diagnostic downfield shifts are observed for one of the alkene signals, due to donation of electron density from the alkene into the proximal empty p-orbital on boron. These ^{13}C NMR assignments were further supported by the separation of the *syn-* and *anti*-isomers for the cyclopropyl product **3ae**; single-crystal X-ray diffraction analyses of the two isomers confirmed our assignments [Scheme 4(B)].

We then assessed the scope of the benzylamine component (Scheme 5). Methyl substituents were accommodated in both the *meta-* and *ortho*-positions (**3ba** and **3ca**), and fluorine substituents were also tolerated (**3da** and **3ea**). Interestingly, whereas putative cycloaddition adducts could be identified in the crude ^{1}H NMR spectra for electron-rich benzylamines, such as those bearing methoxy substituents, attempts to isolate these products by chromatography were frustrating, as despite extensive assessment of the chromatographic medium, no product could be isolated. We postulate that the enol ether present in such cycloadducts might be activated by the silica during chromatography, facilitating a series of deleterious side reactions.
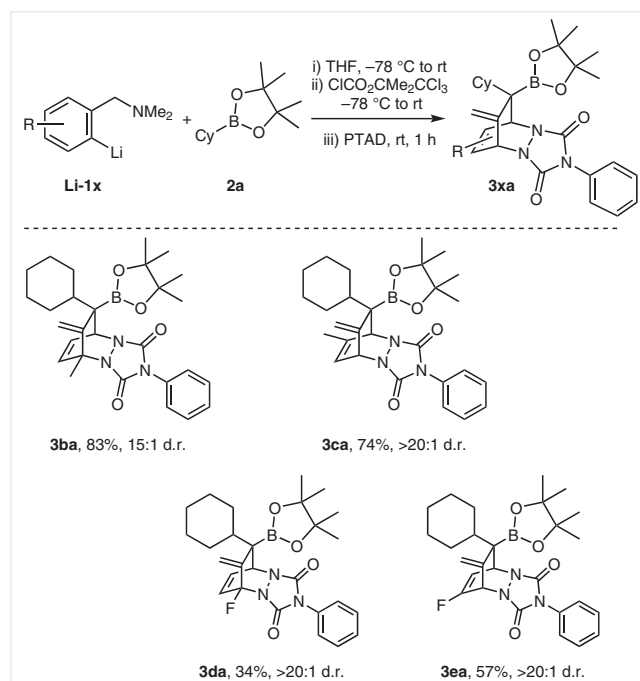
Scheme 5 Scope of the benzylamine component. The dr was determined by ^{1}H NMR analysis of the crude and purified products.

We then addressed enantioenriched α-methyl-substituted benzylamines. We have previously reported that the 1,2-metalate rearrangement/*anti*-S$_N$2′ elimination sequence

proceeds with excellent enantiospecificity for secondary boronic esters due to a selective N-acylation of a low-energy conformation of the boronate complex, in which the hydrogen atom of the benzylic position lies in the plane of the aromatic ring towards the boronate.[5] This leads to the generation of the tertiary boronic ester dearomatized intermediate **Int-I** in excellent levels of enantiospecificity. We expected this enantioenrichment to be transferred directly through the cycloaddition process, and this was borne out by the generation of cycloadduct **3fa** from the α-methyl-substituted benzylamine **1f** (97:3 er) in 69% yield, 95:5 er, and >20:1 dr (Scheme 6). Primary alkyl boronic ester **2g** provided cycloadduct **3fg** in 30% yield, 91:9 er, and 1:2.2 dr in favor of the *anti*-isomer (the er refers to the major *anti*-diastereoisomer, but this is expected to be the same for the minor *syn*-diastereoisomer). When we used both enantioenriched chiral amine **1f** and enantioenriched boronic ester **2k** (95:5 er), cycloadduct **3fk** was formed in 9:1 dr with respect to all other isomers. The use of the opposite enantiomer of the benzylamine **1g** (1:99 er) provided cycloadduct **3gk** in similar yield and diastereoselectivity, indicating no matched/mismatched behavior. Such behavior was also observed when the menthol-derived boronic ester **2l** reacted with the two enantiomers of the α-methyl-substituted benzylamine to provide **3fl** (17:1 dr) and **3gl** (>20:1 dr).

In summary, we have developed an enantiospecific, one-pot, 1,2-metalate rearrangement/*anti*-S$_N$2′ elimination/cycloaddition reaction sequence that generates complex three-dimensional structures with exquisite enantioselectivity and predictable diastereoselectivities. The convergent three-component nature of this process leads to structures bearing diverse orthogonal functionalities. Studies are ongoing to exploit this functionality in subsequent transformations, so as to permit access to valuable, densely functionalized, chiral building blocks.

Acknowledgment

We thank Dr. Hazel A. Sparkes for assistance with X-ray crystallography. We thank Stefan Aichhorn for useful discussions and Belén Rubial for assistance with HPLC analysis.

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1610389.

453

Synlett   C. Tillin et al.   THIEME OPEN ACCESS   Letter
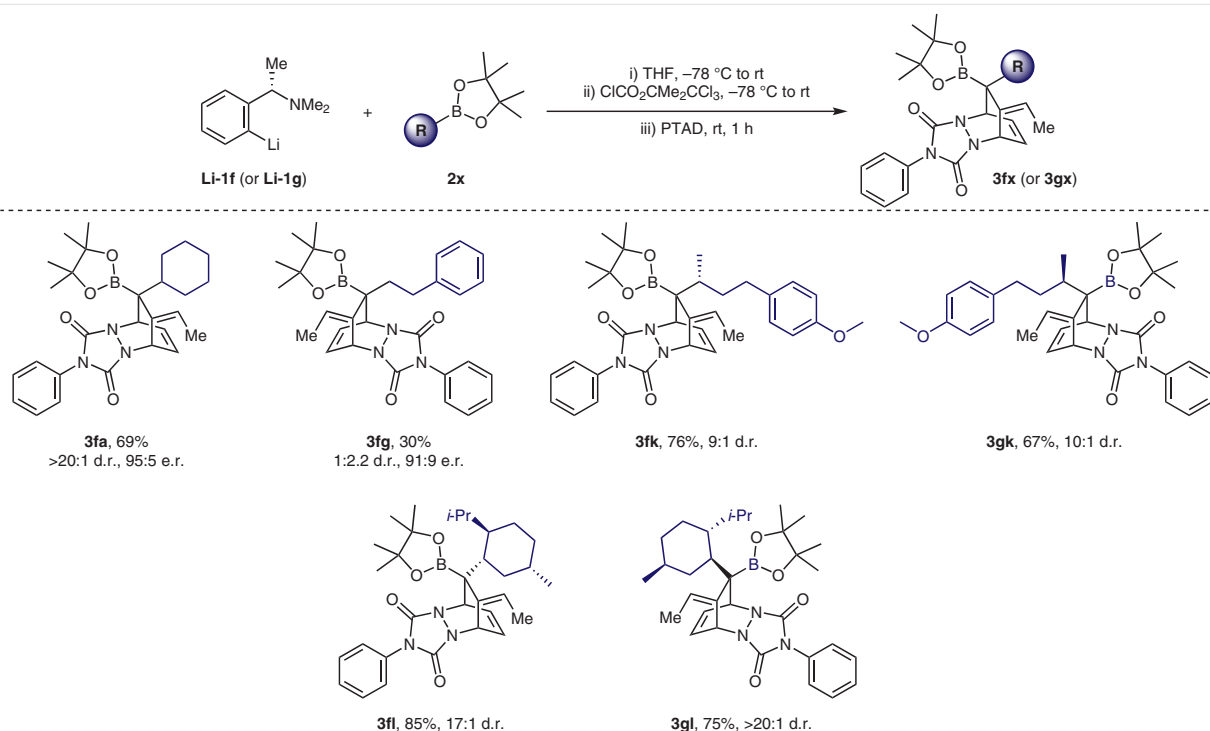
Scheme 6 Reactivity of enantioenriched α-methyl benzylamines. The dr was determined by ^{1}H NMR analysis of the crude and purified products.

References and Notes

(1) Sandford, C.; Aggarwal, V. K. *Chem. Commun.* **2017**, *53*, 5481.

(2) Leonori, D.; Aggarwal, V. K. *Acc. Chem. Res.* **2014**, *47*, 3174.

(3) (a) Matteson, D. S. *Med. Res. Rev.* **2008**, *28*, 233. (b) Smoum, R.; Rubinstein, A.; Dembitsky, V. M.; Srebnik, M. *Chem. Rev.* **2012**, *112*, 4156.

(4) Collins, B. S. L.; Wilson, C. M.; Myers, E. L.; Aggarwal, V. K. *Angew. Chem. Int. Ed.* **2017**, *56*, 11700.

(5) Aichhorn, S.; Bigler, R.; Bigler, E. L.; Aggarwal, V. K. *J. Am. Chem. Soc.* **2017**, *139*, 9519.

(6) Rubial, B.; Collins, B. S. L.; Bigler, R.; Aichhorn, S.; Noble, A.; Aggarwal, V. K. *Angew. Chem. Int. Ed.* **2018**, DOI: 10.1002/anie.201811343.

(7) Roche, S. P.; Porco, J. A. Jr *Angew. Chem. Int. Ed.* **2011**, *50*, 4068.

(8) (a) Okumura, M.; Shved, A. S.; Sarlah, D. *J. Am. Chem. Soc.* **2017**, *139*, 17787. (b) Okumura, M.; Sarlah, D. *Synlett* **2018**, *29*, 845. (c) Hernandez, L. W.; Klöckner, U.; Pospech, J.; Hauss, L.; Sarlah, D. *J. Am. Chem. Soc.* **2018**, *140*, 4503.

(9) Paton, R. S.; Kim, S.; Ross, A. G.; Danishefsky, S. J.; Houk, K. N. *Angew. Chem. Int. Ed.* **2011**, *50*, 10366.

(10) (a) Chen, J. S.; Houk, K. N.; Foote, C. S. *J. Am. Chem. Soc.* **1998**, *120*, 12303. (b) Levandowski, B. J.; Houk, K. N. *J. Org. Chem.* **2015**, *80*, 3530.

(11) See Supporting Information for details.

(12) Huang, Q.; Zard, S. Z. *Org. Lett.* **2018**, *20*, 5304.

(13) (±)-(5*S*,8*R*,11*S*)-11-Cyclohexyl-10-methylene-2-phenyl-11-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5,8-dihydro-1*H*-5,8-ethano[1,2,4]triazolo[1,2-*a*]pyridazine-1,3(2*H*)-dione (3aa)

Typical Procedure

Boronic ester **2a** (500 μmol) was added to the *ortho*-lithiated benzylamine **Li–1a** (525 μmol, 1.05 equiv; prepared from **1a**) in THF (2 mL) at –78 °C, and the solution was stirred at –78 °C for 15 min, after which the cooling bath was removed, and the mixture was stirred for a further 15 min. ClCO$_2$CMe$_2$CCl$_3$ (132.0 mg, 550 μmol, 1.10 equiv) was added at –78 °C, and the solution was stirred for 15 min at –78 °C, after which the cooling bath was removed and the mixture was stirred for a further 5 min. PTAD (96.3 mg, 550 μmol, 1.10 equiv) was added, and the solution was stirred for 1 h at r.t. CHCl$_3$ (50 mL) was added and the solution was washed with H$_2$O (25 mL) and sat. aq NaCl (25 mL), then dried (MgSO$_4$), filtered, and concentrated under reduced pressure. Purification by flash column chromatography [silica gel. EtOAc–pentane (15:85)] gave a white solid; yield: 121 mg (50%), dr = 17:1; mp 86 °C, R_f = 0.47 (EtOAc–pentane, 15:85).IR (liquid film): 2927, 1771, 1710, 1397, 1138, 908, 727, 644 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.48–7.36 (m, 4 H, Ar-*H*), 7.34–7.28 (m, 1 H, Ar-*H*), 6.50 (ddd, $^3J_{H,H'}$ = 7.7, 5.5 Hz, $^4J_{H,H'}$ = 1.8 Hz, 1 H, =C*H*), 6.43 (ddd, $^3J_{H,H'}$ = 7.7, 5.4 Hz, $^4J_{H,H'}$ = 1.7 Hz, 1 H, =C*H*), 5.39 (s, 1 H, =C*H*H), 5.26–5.21 [m, 2 H, =CH*H* (1 H) + C*H*N (1 H)], 5.11 (dd, $^3J_{H,H'}$ = 5.5 Hz, $^4J_{H,H'}$ = 1.7 Hz, 1 H, C*H*N), 2.08–2.00 (m, 1 H, C*H*H), 1.79–1.61 (m, 4 H, C*H*H), 1.26 [s, 6 H, C*H*$_3$ (pin)], 1.24 [s, 6 H, C*H*$_3$ (pin)], 1.23–1.02 [m, 6 H, C*H* (1 H) + C*H*H (5 H)]. ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$): δ = 155.8 (CO), 155.3 (CO), 142.9 (=C), 131.8 (arom.), 129.9 (=CH), 129.0 (2 C, arom.), 128.6 (=CH), 128.0 (arom.), 125.4 (2C, arom.), 113.9 (=CH$_2$), 84.2 [2 C, O*C*(CH$_3$)$_2$], 59.0 (*C*HN), 57.0 (*C*HN), 44.4 (*C*H), 31.0 (*C*H$_2$), 29.8 (*C*H$_2$), 27.3 (*C*H$_2$), 27.1 (*C*H$_2$), 26.4 (*C*H$_2$), 25.1 [2 C, *C*H3 (pin)], 24.4 [2 C, *C*H3 (pin)]. Carbons attached to boron were not observed due to quadrupolar relaxation. ^{11}B{^{1}H} NMR (128 MHz, CDCl$_3$): δ = 33.5 (br s). HRMS (ESI): *m/z* [M + Na]$^+$ calcd for C$_{27}$H$_{34}$BN$_3$NaO$_4$: 498.2535; found: 498.2554.