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Haloboration of *o*-Alkynyl Phenols Generates Halogenated Bicyclic-Boronates**

*Kang Yuan and Michael J. Ingleson**

Abstract: Benzoxaborinines are intermediates en-route to bicyclic boronates that are important active pharmaceutical ingredients (APIs). Herein, the haloboration of *o*-alkynyl-phenols using BX_3 (X = Cl or Br) is disclosed as a route to form C4-X-benzoxaborinines with good functional group tolerance. Computational studies indicated that there are two similar in barrier mechanisms: (i) double alkyne haloboration followed by *retro*-haloboration; (ii) concerted *trans*-haloboration involving an exogenous chloride source. The C4-halide in these benzoxaborinines is useful, with a one-pot haloboration-Negishi cross coupling protocol effective to form benzoxaborinines with an alkyl or an aryl at C4. Therefore this method is a useful addition to the toolbox for synthesising bicyclic-boronates that are attracting increasing attention as APIs.

The past twenty years have witnessed the growing utilisation of boron as a function providing element in pharmaceuticals.[1–3] The majority of approved boron containing drugs are B–O containing boracycle derivatives,[4] with one important application being as β-lactamase inhibitors (BLIs).[5,6] While Vaborbactam (Figure 1, left) was the pioneer boronate BLI,[7] recent work has led to bicyclic boronate BLIs.[5,6] Notably, three in advanced clinical trials have the same core structure (Figure 1 inset, red). While the importance of bicyclic boronates is growing,[1,4] synthetic approaches remain limited.[8,9] This is particularly the case for all sp^2 B,O boracycles e.g. oxaborinines,[10–12] thus current routes to cyclic boronate BLIs generally use well-established yet inefficient approaches.[13,14] The development of new routes to bicyclic boronates relevant to bioactives would facilitate exploration in this area, particularly if the method concomitantly incorporates an additional modifiable functional group (e.g. a halide).

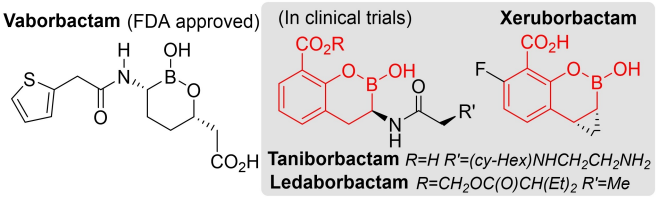

Figure 1. (Bi)cyclic boronate based β-lactamase inhibitors.

Recently, a novel approach to form the BLI Xeruborbactam was reported.[15] This method proceeds via benzoxaborinine **A** (Figure 2, top) which was accessed by a nickel catalysed boron insertion into benzofuran **B**. While notable, this approach has functional group limitations and it does not tolerate substituents at the C3 position of the benzofuran.[16] Therefore developing a new route to benzoxaborinines that: (i) has complementary functional group tolerance to the nickel chemistry; (ii) is compatible with esters at C8 (due to their importance in BLIs), and (iii) contains a functionalisable handle at the C4 position (the position derived from the C3 of benzofurans on boron insertion) is highly desirable.

The haloboration of an oxo-functionalised aryl-alkyne is an attractive route to form C4-halogenated analogues of **A** as it forms the vinyl-B unit concomitantly with a vinyl halide.[17] However, an appropriate group on oxygen is

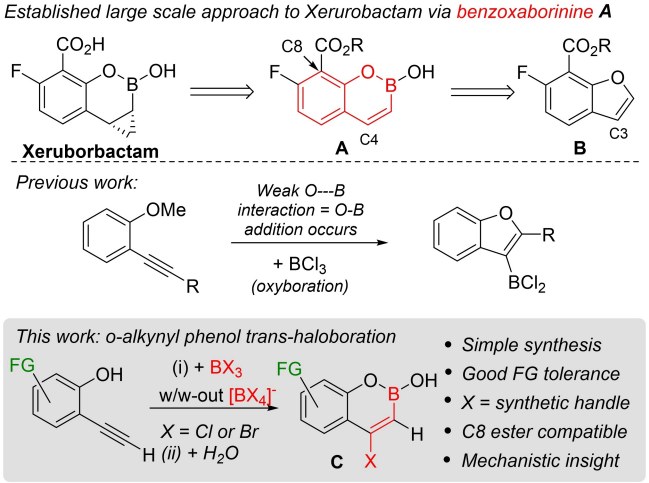

Figure 2. Top, large-scale route to Xeruborbactam via **A** and **B**. Middle, previous work leading to oxyboration. Bottom, this approach leading to *trans*-haloboration.

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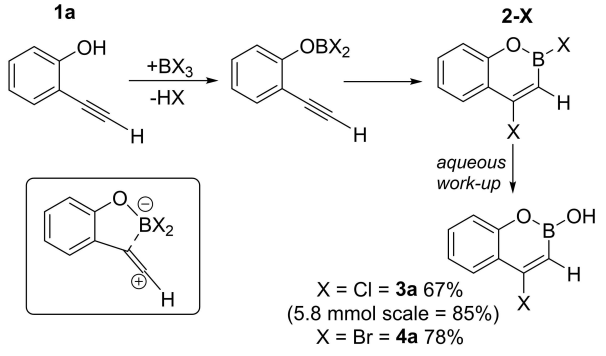
required. For example, *o*-alkynyl anisoles react with BCl_3 by oxyboration and not haloboration (Figure 2, middle).[18] This is attributed to the Ar(Me)O→BCl_3 interaction being weak and BCl_3 dissociation leading to activation of the alkyne and thus oxyboration.[19] We hypothesised that moving from *o*-alkynyl anisoles to *o*-alkynyl phenols will preclude the formation of benzofurans as BX_3 will react rapidly with the phenolic OH to form $ArylOBX_2$ and HX. This step lowers the nucleophilicity of the oxygen center (disfavoring alkyne oxyboration with free BX_3), while incorporating a boron Lewis acid for intramolecular activation of the alkyne. Haloboration would then enable incorporation of boron within an all sp^2 boracycle (e.g. **C**, Figure 2 bottom).[20] Herein we report that *o*-alkynyl-phenol haloboration is a simple method to form C4-halogenated benzoxaborinines that are useful intermediates for accessing an increasingly important class of bioactives.[21]

The terminal alkyne **1a** was utilised in initial studies as it disfavored five membered boracycle formation (the interaction of the boron center in $ArylOBX_2$ with the internal carbon of the alkyne would lead to a high in energy vinyl cation intermediate, inset Scheme 1). Initial reactions combined **1a**, BCl_3 and a hindered base to sequester the HCl byproduct from the formation of $ArylOBCl_2$ (see below). This led to rapid (<1 h at ambient temperature) formation of a compound that was consistent with **2-Cl** (Figures S1–S4, the δ_{11B} = 35.1 for **2-Cl** is closely comparable to that of (Ar)B(Cl)(OR)).[22]

An optimisation study (Table S1) revealed that controlling the order of addition and performing the reaction in an open system under N_2 enabled formation of **2-Cl** in good conversion without a base and using commercial 1 M BCl_3 solutions. The reaction proceeded in a range of robust (to BCl_3) solvents such as, chlorobenzene, heptane (note **2-Cl** precipitated during synthesis in heptane) and trifluorotoluene, but for ease of in situ analysis and work-up dichloromethane was the only solvent used hereon. Post formation of **2-Cl** an aqueous work-up led to isolation of the boronate **3a** in good yield. Under identical conditions combinations of **1a** and BBr_3 led to a comparable outcome and formation of **4a** in good isolated yield (78 %). As BCl_3 has improved functional group tolerance relative to BBr_3,[23] only BCl_3 was utilised hereon. It should be noted that **3a** can be isolated on 5.8 mmol scale in 85 % yield without column chromatography, highlighting the simplicity of this procedure to form benzoxaborinines.

With optimised conditions in hand a substrate scope study was performed (Figure 3). Substituents at all four positions on the benzene unit were tolerated (**3b–3e**), with **3e** demonstrating that di-substituted precursors were also viable substrates. Alongside fluoro (**3b**), this process tolerated chloro (**3c**), bromo (**3d**) and phenoxy (**3g**), all groups not reported in the nickel catalysed route to benzoxaborinines.[16] **1b** and **1c** have an electron withdrawing group *meta* to the alkyne (σ_{meta} = +0.34 and +0.37, respectively), thus have a less nucleophilic alkyne (than **1a**), nevertheless both undergo *trans*-haloboration in good yield.

The advantage of using BCl_3 is demonstrated by the ability to generate benzoxaborinines containing functional groups that would undergo side-reactions with BBr_3, this includes MeO- (**3h**), an enolisable ketone (**3i**), CF_3 (**3j**) and



Scheme 1. The synthesis of C4-halogenated benzoxaborinines by *trans*-haloboration. Inset, the putative vinyl cation from reaction at the internal carbon of the alkyne.

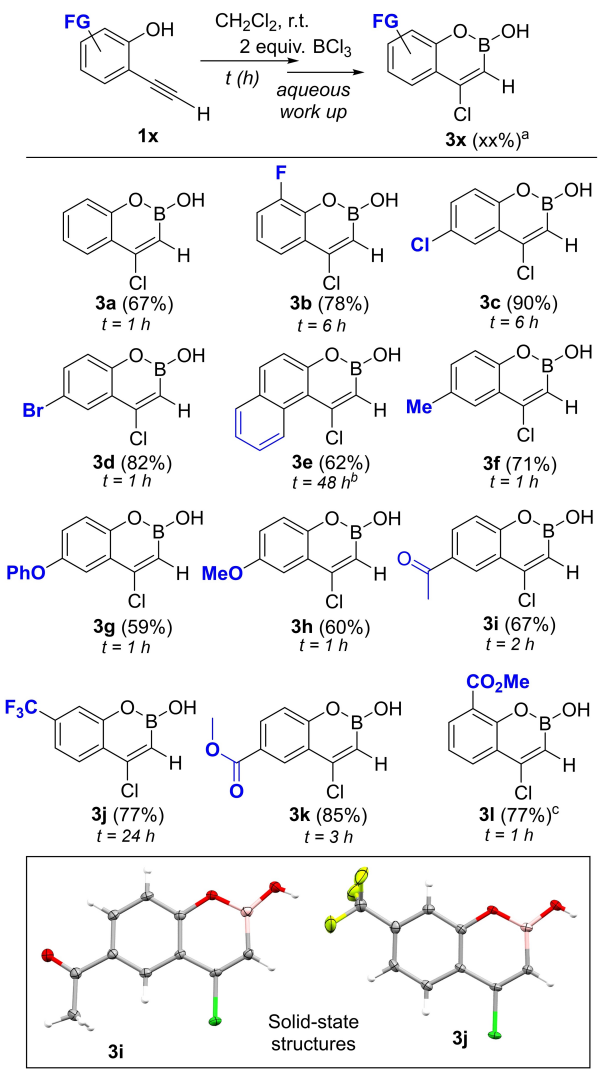


Figure 3. Scope of *o*-alkynyl-phenol *trans*-haloboration. *a* = isolated yield. *b* = at 60 °C. *c* = with 1 equiv $[Bu_4N][Cl]$ and 3 equiv BCl_3.

an ester (**3k**). It should be noted that **1j**, with CF_3 *para* to the alkyne, was much less reactive than **1a** under these conditions taking *ca.* 12 h at room temperature to reach high in situ conversions (Figure S23), an observation consistent with the σ_{para} of CF_3 (+0.53). The *trans*-haloboration of the important (for accessing BLIs) precursor to the C8 ester substituted benzoxaborinine (**3l**) required further optimisation. Under the standard conditions from Figure 3, **1l** was converted to **5** (Figure 4) in <50 % conversion. In situ NMR spectroscopy revealed that one other major product is formed which contained two boron centers, one three and one four coordinate (Figures S31 and S32). We assign this as compound **D**, with the *cis*-haloborated alkene isomer assigned based on NOE experiments, with no other haloboration isomers observed.[24,25]

Previously, we demonstrated that the addition of a boron Lewis acid and an anionic borate (e.g. $B(C_6F_5)_3$/$[HB(C_6F_5)_3]^-$) to an alkyne led to *trans*-elementoboration, in this case alkyne *trans*-hydroboration.[26] Here, the anionic borate presumably converts a vinyl cation (from reaction of an alkyne and $B(C_6F_5)_3$) to an alkene by transferring hydride

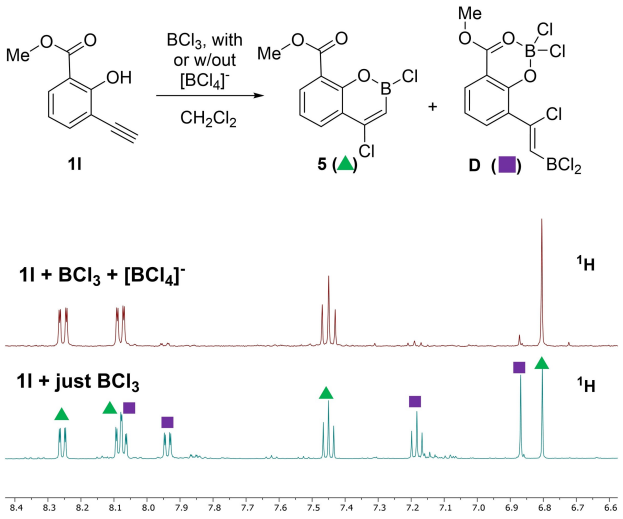


Figure 4. The effect of exogenous $[BCl_4]^-$ on the haloboration of **1l**.

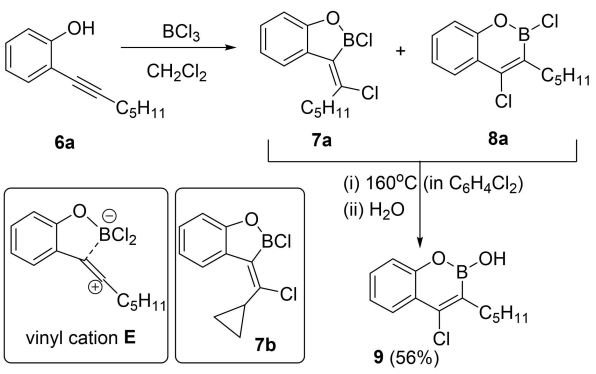


Figure 5. The haloboration of **6a**. Inset bottom left, the proposed vinyl cation **E** leading to **7a** and inset bottom middle **7b**; right formation of five membered boracyclic compound **9**.

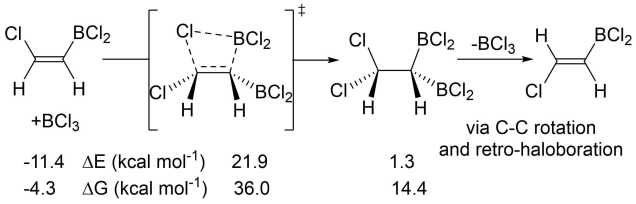
to the face opposite the borane. This approach was extended to *trans*-haloboration by using excess BCl_3 and one equivalent of $[^nBu_4N]Cl$ (this combination forms $[BCl_4]^-$ in situ by ^{11}B NMR spectroscopy) which led to the formation of **5** as the major product (>95 % by in situ NMR spectroscopy, Figure 4). This modified procedure enabled **3l** to be accessed in good isolated yield (77 %). Therefore O-directed alkyne *trans*-haloboration can be used to access a C4-chlorinated analogue of the key intermediate for forming bicyclic boronate BLIs (e.g. **A**).

The *trans*-haloboration of an internal alkyne, **6a** (Figure 5), was explored next. In this case, using BCl_3 the five membered boracycle **7a** was the major product with the desired benzoxaborinine (**8a**) only a minor product. Presumably, the pentyl group affords sufficient stabilisation to the vinyl cation (**E**, Figure 5) to enable a lower energy pathway to the five membered boracycle. While compound **7a** proved challenging to isolate, a congener where pentyl is replaced with cyclopropyl led to the formation of the analogous compound, **7b** (Figure 5), as effectively the only product (Figure S39 and S40) enabling full characterisation of **7b**. Compounds **7a** and **7b** have comparable NMR data (excluding the alkyl resonances), supporting the formulation of **7a** as the five membered boracyclic isomer. Returning to synthesising **8a**, in directed electrophilic borylation five membered boracycles are often the kinetic product while six membered are invariably the thermodynamic product for boracycles containing all sp^2 centres.[20] This was confirmed in this case using calculations based on the model alkyne **6-Me** (where pentyl is replaced with Me), with **7-Me** being 14 kcal mol^{-1} higher in energy than the six membered isomer **8-Me** (at the M06-2x/6-311+G(d,p) level with PCM (CH_2Cl_2)). Therefore the reaction of **6a** and BCl_3 was repeated and heating the reaction mixture in *o*-dichlorobenzene to ≥140 °C led to the isomerisation of **7a** and formation of **8a** as the major product (Figure S37). This enabled **9** (Figure 5) to be isolated in 56 % yield post work up. Therefore O-directed alkyne *trans*-haloboration is also viable for accessing C3, C4 disubstituted benzoxaborinines.

We next attempted to gain insight into how the *trans*-alkene stereochemistry is realised as this precludes *syn*-addition of B–Cl to the alkyne. Firstly, the intermediacy of *o*-alkynyl-arylOBCl_2 species was supported by monitoring reactions in situ—which revealed it is formed extremely rapidly (<5 min). In some cases, such as those starting with **1j** or **6a**, this species is present for hours at room temperature before conversion to the haloboration product(s) is complete (e.g. Figure S8 and S24). Note, the use of excess BCl_3 in these reactions minimises substituent scrambling (e.g. to form $(RO)_2BCl$ species). In the reactions using just BCl_3 no $[BCl_4]^-$ is observed by ^{11}B NMR spectroscopy (e.g. Figure S8). However, this does not preclude some $[BCl_4]^-$ being present that could catalyse *trans*-haloboration as BCl_3 and $[BCl_4]^-$ undergo fast halide exchange, thus only an average δ_{11B} is observed even at low temperature for mixtures of BX_3 and $[BX_4]^-$.[27] Notably, in the *trans*-haloboration of **1j** (which at room temperature using just BCl_3 requires 12 h for high conversion to **3j**), the addition of exogenous $[BCl_4]^-$ led to much more rapid formation of **3j**

(formation complete in <1 h), suggesting the involvement of an exogenous halide donor in some cases. As attempts to observe intermediates by in situ NMR spectroscopy did not reveal any species (in addition to ArylOBCl$_2$ and the haloboration product (e.g. **2-Cl**)) mechanisms using just BCl_3 and using a combination of BCl_3 and $[BCl_4]^-$ were explored at the M06-2x/6-311+G(d,p) level with a PCM (CH_2Cl_2).[28] Note, a mechanism where the *o*-alkynyl-arylOBCl$_2$ intermediate undergoes *trans*-haloboration with just BCl_3 and then condensation (of the vinylBCl$_2$ and O-BCl$_2$) to form **2-Cl** and release BCl_3 is precluded. This is based on the absence of any *trans*-haloboration of alkyne **11** (no *trans* isomer of **D** is observed), an observation fully consistent with previous reports where BCl_3 only results in the *cis* chloroboration of terminal alkynes at room temperature.[17]

The first route explored computationally uses just BCl_3, and is related to work from Uchiyama and co-workers (Scheme 2)[29] who found that the double *syn*-haloboration



Scheme 2. Previously calculated pathway for intermolecular *trans*-haloboration of alkynes. Free alkyne (ethyne) and BCl_3 are set as zero energy in this work.[29]

of ethyne followed by retro-haloboration (BX_3 elimination) is a possible mechanism to form *trans*-haloborated alkene products from alkynes when using BBr_3. With BCl_3, this process has a high barrier ($\Delta G^{\ddagger}=36$ kcal mol^{-1}, Scheme 2) partly due to the entropic penalty, as indicated by the smaller $\Delta E^{\ddagger}$ of 21.9 kcal mol^{-1} for this step. In the formation of **PD1A** (Figure 6) via double haloboration—retro haloboration, one of the haloboration steps starting from *o*-alkynyl-PhOBCl$_2$ and BCl_3, will be intramolecular. Thus, the entropic penalty will be lower in this case potentially leading to barriers that would be consistent with an ambient temperature reaction.

Starting from **SM1A**, BCl_3 addition to the alkyne proceeds via a vinyl cation intermediate (**I1A**) which contains a near linear CCC unit (C–C–C=173.5°). Halide transfer from boron to carbon then affords the BCl$_2$ substituted vinyl halide **I2A** as the *cis* isomer via **TS2A** ($\Delta G^{\ddagger}=+22$ kcal mol^{-1}) in a slightly exergonic step (relative to **SM1A**). The second haloboration is intramolecular, proceeding via interaction of the ArylOBCl$_2$ unit with the vinylic unit to produce a benzyl cation type intermediate (**I3A**). Halide transfer from boron to the benzyl cation then occurs in a separate step to form **I4A**. Note the double haloboration product **I4A** is only 5 kcal mol^{-1} higher in free energy than the starting alkyne **SM1A**+BCl_3, in contrast to the fully intermolecular process which is much more endergonic (Scheme 2). The final step is retro-haloboration to form the benzoxaborinine product **2-Cl** and BCl_3 which proceeds via a low barrier (**TS5A**) and results in an overall transformation that is significantly exergonic

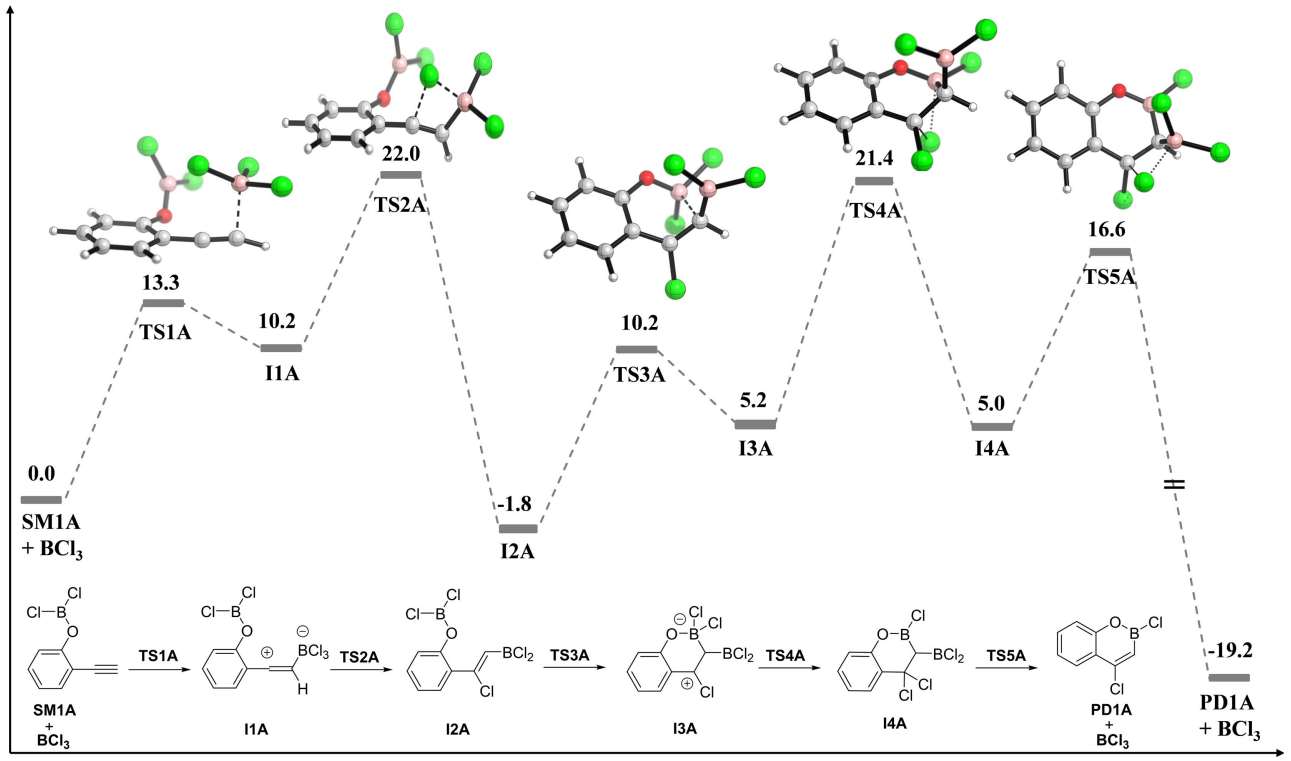


Figure 6. Formation of **2-Cl** (**PD1A**) by double haloboration and *retro*-haloboration using BCl_3 (ΔG, kcal mol^{-1}).

(−19.2 kcal mol^{-1}). The highest barrier in the process (ΔG = 23.2 kcal mol^{-1}), is consistent with the formation of **2-Cl** occurring at room temperature, suggesting this is a feasible mechanism.

The same sequence of steps also was investigated for the CF_3 analogue derived from **1j** (Figure S136). Most notably for this derivative, the equivalent states to **I1A**, **I3A TS2A** and **TS4A** are all higher in energy (by between 2–4 kcal mol^{-1}), consistent with a build-up of positive charge at carbon in these intermediate/transition states, hence the electron withdrawing CF_3 *para* to the alkyne retards the haloboration reaction. The highest barrier to form the CF_3 analogue of **2-Cl** starting from the CF_3-substituted *o*-alkynyl-ArOBCl$_2$ is 25.0 kcal mol^{-1}. This is consistent with **1j** requiring significantly longer at room temperature (≥ 12 h) for high conversions when using just BCl_3 relative to **1a** (which undergoes complete haloboration with just BCl_3 in < 1 h).

Given the faster formation of *trans*-haloboration products observed for some substrates by the addition of exogenous $[BCl_4]^-$, an alternative $[BCl_4]^-$ mediated mechanism was calculated for the **1a** (Figure 7) and **1j** (Figure S137) derived systems. This mechanism proceeds by intramolecular activation of the alkyne by the ArOBCl$_2$ Lewis acid and concomitant transfer of chloride from $[BCl_4]^-$ to the opposite face of the alkyne (**TS6A**). For both substrates studied, this concerted *anti*-haloboration process proceeds with a barrier of ca. 25 kcal mol^{-1}. This step forms the anionic borate intermediate **I5A** and BCl_3, which then react by transfer of chloride from **I5A** to BCl_3 via a low energy transition state to form the products (e.g. **PD1A**) and regenerate the $[BCl_4]^-$ anion. With a difference in the highest barrier between the two calculated mechanisms of < 2 kcal mol^{-1} for the two substrates explored both mechanisms can be operating in solution to form the *trans*-haloboration products. Note, with accuracies generally limited to ca. 2 kcal mol^{-1} for DFT calculations,[30] the actual barrier for the $[BCl_4]^-$ mediated process is presumably slightly lower than that for the double haloboration—retro haloboration process for the CF_3 derivative, hence the faster conversion observed on addition of exogenous $[BCl_4]^-$ for this substrate.

Finally, the feasibility of functionalising the benzoxaborinines was explored. While a range of Suzuki–Miyaura coupling conditions led to decomposition of **3x**, viable Negishi coupling conditions were identified. These were applicable to a one-pot haloboration-cross coupling process that did not require isolation of the benzoxaborinine (**3x**). Instead the primary (i.e. **2-Cl**) crude product from haloboration was made and used in situ. Starting from **1g**, a sequence of haloboration, cross coupling and work-up led to the formation of **10** in a 53 % yield based on the starting alkyne (Scheme 3). Note, this is a good yield considering it is for a multi-step sequence involving making O–B, C–B and C–Cl bonds and converting the C–Cl into a C–C bond. An identical procedure using $ZnPh_2$ led to formation of **11** in 39 % yield based on the starting alkyne. In this case the B-chloro-benzoxaborinine had undergone sp^{2}C–Csp^2 coupling and arylation at boron. Analysis of intermediates reveal that B–C bond formation also is occurring using $ZnEt_2$, but in this case the B–Et bond is transformed during work-up to B-OH. Conversion of the B-Aryl unit to B-OH can be achieved using reported conditions to form B-OH containing cyclic boronates from B-Aryl derivatives (Figure S44).[31]

Next, an arylzinc nucleophile was generated in situ from 4-bromoanisole (by lithium/halogen exchange and trapping with $ZnCl_2$, Scheme 4). The crude arylzinc nucleophile then was combined with the crude product from the reaction of

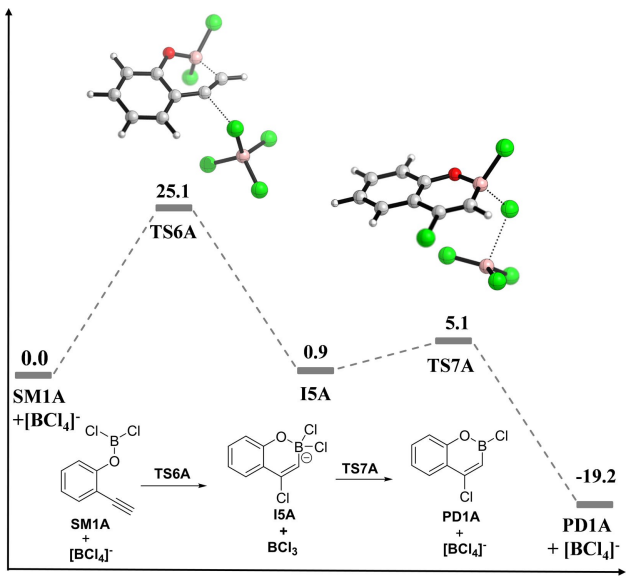
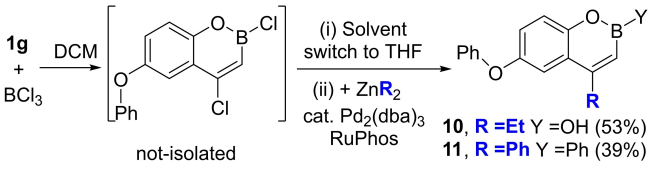
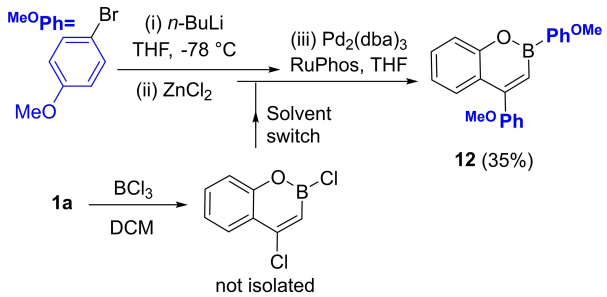


Figure 7. The formation of **2-Cl** (**PD1A**) by haloboration mediated by $[BCl_4]^-$ (ΔG, kcal mol^{-1}).



Scheme 3. Negishi cross-coupling using crude benzoxaborinine and commercial diorganozinc reagents. (xx%) values are overall yields based on **1g**.



Scheme 4. Formation of **12** from the *o*-alkynyl phenol via a haloboration—Negishi cross coupling sequence. (xx%) values are overall yields based on **1a**.

1a with BCl_3 and under the same conditions that produced **10** and **11** this mixture formed the C–C coupled (and B-arylated) product **12** in a 35% yield (yield based on starting alkyne).

In conclusion, o-alkynyl phenol haloboration using BX_3 represents a simple route to make benzoxaborinines while concomitantly installing a functionalisable group (a halide) at the C4-position. This approach has good functional group tolerance for an electrophilic borylation reaction, which is complementary to that of the Ni catalysed method.[16] This haloboration methodology also was able to generate important (for accessing BLIs) C8-ester functionalised benzoxaborinines in good yield by using BCl_3 alongside an exogenous chloride donor ($[BCl_4]^-$). A computational study identified two viable mechanisms to furnish *trans*-haloboration products: (i) a double haloboration/retro-haloboration process and (ii) a concerted *anti*-haloboration process. Finally, the combined *trans*-haloboration—Negishi coupling sequence represents a useful addition to the synthetic chemists toolbox for accessing bicyclic-boronates that are increasingly utilised as active pharmaceutical ingredients.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the Supporting Information of this article.

Keywords: Benzoxaborinines · Boron · Cyclic-Boronates · Electrophilic Addition · Haloboration

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Communications

Boron Chemistry

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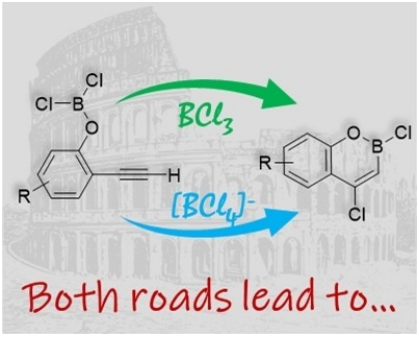
Haloboration of *o*-Alkynyl Phenols Generates Halogenated Bicyclic-Boronates



O-directed alkyne *trans*-haloboration using BX_3 (X = Cl or Br) leads to C4-halogenated benzoxaborinines that are useful intermediates for accessing the core structure found in bicyclic boronate based β-lactamase inhibitors. A computational study identified two viable mechanisms to furnish the *trans*-haloboration products.