Divergent Elementoboration: The First 1,3-Haloboration of Alkynes

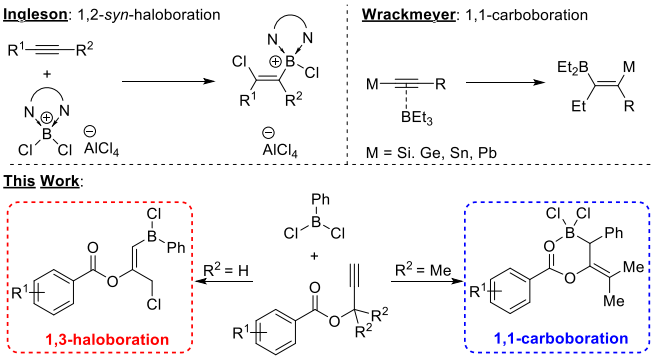
Lewis C. Wilkins,[‡[a]] Yashar Soltani,[‡[a]] James R. Lawson,[[a]] Ben Slater[[b]] and Rebecca L. Melen*[[a]]

Abstract: This work showcases the first 1,3-haloboration reaction of alkynes in which boron and chlorine add to propargyl systems in a proposed sequential oxazoliumborate formation with subsequent ring-opening and chloride migration. In addition, the functionalization of these propargyl esters with dimethyl groups in the propargylic position leads to stark differences in reactivity whereby a formal 1,1-carboboration prevails to give the 2,2-dichloro-3,4-dihydrodioxaborinine products as an intramolecular chelate. Significantly, this method represents a metal-free route to highly functionalized compounds in a single step to give structurally complex products.

The activation of carbon-carbon double and triple bonds by main group compounds has been a staple motif in the synthesis of a plethora of new element-carbon bonds such as C–C,[1] C–H,[2] C–N,[3] C–B[4] and C–O[5] bonds amongst many others.[6] Seminal work by Wrackmeyer *et al.* showcased a powerful methodology using trivalent boranes in conjunction with 'activated' alkynes i.e. M–C≡C–R where M = Si, Ge, Sn, Pb *inter alia*.[7] In these early cases, 1,1-carboboration reactions were observed whereby a 1,2-alkyl/aryl shift occurs between the distal and proximal carbons of the alkyne with the concomitant 1,2-shift of the R group from boron to carbon (Scheme 1, top). Further to this, Erker has demonstrated extensive use of the carboboration mechanism to affect a number of complex rearrangement processes such as benzannulations[8] and cyclizations,[9] amongst others.[10]

More recent work in such elementoboration reactions are seen through the synthetically useful haloboration reaction whereby a halogen, predominantly chlorine, is installed typically *via* a 1,1- or 1,2-haloboration to yield the corresponding chlorovinylboronic ester (Scheme 1, top). The formation of these species has been generated through the use of simple haloboranes such as BCl_3, or borocations developed by Ingleson *et al*. In the case of borocations, stereoselective control is observed to give predominantly the *syn*-addition product.[11] Interestingly, a similar study showcased a sequential alkyne addition to affect a formal 1,4-haloboration whereby phenylacetylene undergoes a 1,2-addition when exposed to $[LutBCl_2][AlCl_4]$ which, upon addition of various 1-trimethylsilylalkynes, undergoes a subsequent 1,2-carboboration to yield the diene product.[11d] All such haloboration reactions are convenient synthetic protocols to append functional groups to olefins, specifically in the formation of tri- and tetra-substituted alkenes through sequential cross-coupling reactions of the boronic ester.[12] Another aspect of the reaction outlined within is the installation of a pendant alkyl chloride (Scheme 1, bottom), which has countless uses within organic chemistry from reactions with acetylides, alkoxides, cyanates as well as Grignard chemistry.

Whilst a significant amount of research has focused on the sterically encumbered, strong Lewis acid, $B(C_6F_5)_3$, as well as others of a similar nature,[13] other commercially available boranes have seemingly been absent from recent studies. Hence this work aims to reinvigorate the use of such boranes in a range of synthetically imperative transformations.



Scheme 1. Background and overview to this work.

Herein we show how subtle adaptations to the alkyne starting material can dramatically alter the reactivity with the borane reagent to give the stereoselective *trans*-product of a formal 1,3-haloboration, or alternatively a complex 1,1-carboboration mechanism to yield a stable dichlorodihydrodioxaborinine heterocycle all in very good to excellent conversions. Importantly, these reagents are then well positioned to undergo further functionalization such as cross-couplings[14] or allylations.[15]

Initial investigations of the commercially available $PhBCl_2$ used the model substrate **1a** in a 1:1 stoichiometric ratio to yield a single product in near quantitative yields as observed *via in situ* multinuclear NMR spectroscopy. Detailed NMR spectroscopy (HSQC, HMBC) revealed the proposed structure of **3a**, which interestingly is the product of a formal 1,3-haloboration reaction, hitherto unreported in the literature. These encouraging initial results then led us to expand the substrate scope to a series of phenyl substituted propargyl esters (Figure 1, Scheme 2). It was observed that in most cases the target haloboration product could be clearly identified with conversions greater than 95% at ambient temperature with reaction times of 8 h (**3a**), 18 h (**3b**–**c**) and 48 h (**3d**).

[a] Dr. L.C. Wilkins, Mr. Y. Soltani, Dr. J.R. Lawson, Dr. R.L. Melen
School of Chemistry, Cardiff University,
Main Building, Park Place, Cardiff, CF10 3AT, Cymru/Wales, U.K.
E-mail: MelenR@cardiff.ac.uk
[b] Prof. B. Slater, Department of Chemistry, University College London,
20 Gordon Street, London WC1H 0AJ, U.K.
‡ These authors contributed equally to this work.

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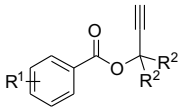
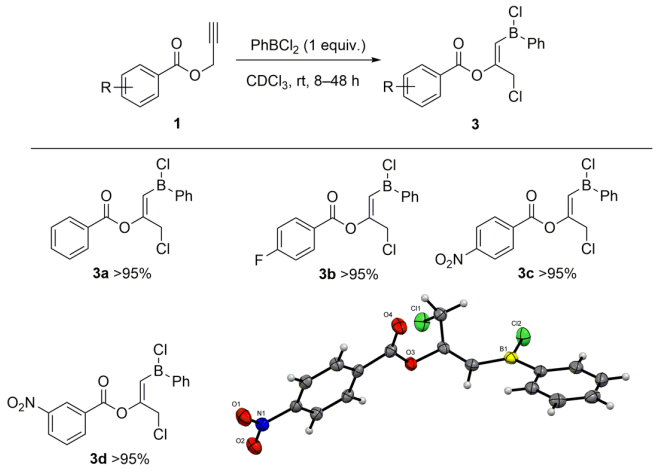


R^1	R^2		R^1	R^2	
H	H	**1a**	H	Me	**2a**
p-F	H	**1b**	*p*-Me	Me	**2b**
p-NO_2	H	**1c**	*p*-F	Me	**2c**
m-NO_2	H	**1d**			

Figure 1. Propargyl ester substrates used in this work.

Fortunately, the storage of a saturated CH_2Cl_2/hexane solution of **3c** at -40 °C produced a crop of crystals suitable for X-ray diffraction. The structure was unambiguously determined to be indeed the product of a formal 1,3-haloboration agreeing with spectroscopic analyses (Figure 2). Metrics of the solid-state structure are as expected with the stereochemical conformation being determined as the *trans* product. Earlier work by Erker showcased the ability of vinylboranes to undergo photoinduced interconversion between the *E*/*Z* conformers upon exposure to UV light[16] thus it was hoped similar reactivity could be observed here to yield the intramolecular chelate however, no such species could be detected in the ^{11}B NMR post-irradiation, leaving the spectra identical to that of the non-irradiated product **3**.

Conducting the reaction between $PhBCl_2$ and **1a** in a variation of solvents (d_6-benzene, d_8-toluene, CH_2Cl_2, C_6H_5Cl) appeared to make no difference in reactivity with all showing almost quantitative conversion within 9 hours. Additionally, trialling other boron reagents such as BCl_3 as well as the borocation [PhClB(2-DMAP)][$AlCl_4$][11a] were unsuccessful with a mixture of products prevailing as observed in the resultant multinuclear NMR spectra.



Scheme 2. Reaction between $PhBCl_2$ and **1** to give 1,3-haloboration products **3**. Values are given as *in situ* NMR conversions. Solid-state structure of compound **3c**, C: grey, H: white, N: blue, O: red, B: yellow-green, Cl: green. Thermal ellipsoids shown at 50% probability (inset).

To gain some insight into the proposed mechanism, isotopic labelling studies were performed. The terminal position of the alkyne was deuterated selectively using an amine appended resin (WA50) in accordance with the literature.[17] Tracking the reaction progress using both ^1H and ^2H NMR spectroscopy whilst comparing the *in situ* data of the protic *vs.* deuterated compounds shed light on the fate of the terminal alkynyl hydrogen atom and hence the reaction mechanism (see below, Scheme 4). A ^1H resonance at δ = 6.6 ppm is observed in **3a** for the proton on the carbon adjacent to boron which is evidently absent in **3a^D** (Figure 2). Additionally, following the ^2H NMR spectra of the reactions using **1a** and **1a^D** clearly shows the alkyne resonance at δ = 2.5 ppm diminishing in intensity with the commensurate appearance of the previously identified new resonance at δ = 6.6 ppm.

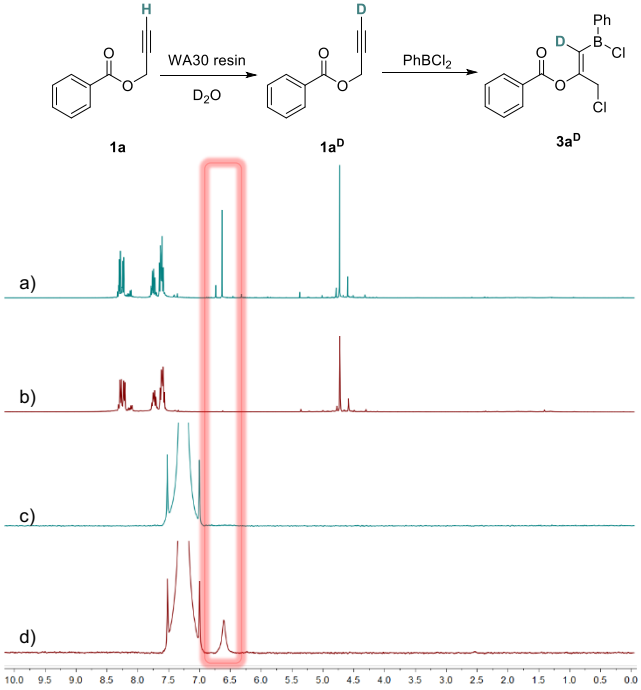
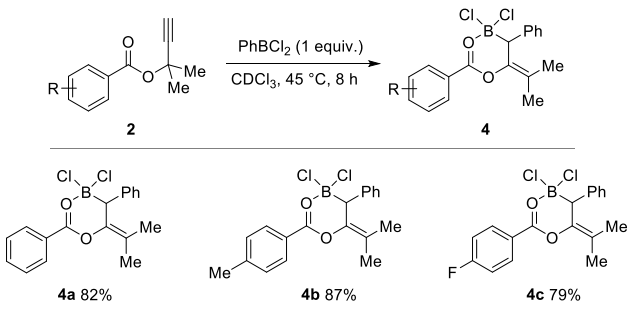


Figure 2. Stacked *in situ* spectra for the reaction between propargyl ester **1a** or **1a^D** $PhBCl_2$ to yield a) **3a** (^1H); b) **3a^D** (^1H); c) **3a** (^2H); d) **3a^D** (^2H).

Further derivatization of the starting materials to include methyl groups in the propargylic position was undertaken to yield compounds **2a**–**2c** (Figure 1). Upon exposure of **2** to a stoichiometric amount of $PhBCl_2$, new resonances in the ^1H and ^{11}B NMR spectra were noted after 8 h at 45 °C which, interestingly, were not consistent with the 1,3-haloboration products **3** from reagents **1**. Indeed, a broad singlet resonance was observed in the ^1H NMR spectrum at *ca.* δ = 3.8 ppm alongside a sharp singlet resonance in the ^{11}B NMR spectrum at *ca.* δ = 8 ppm indicating the formation of a chelating dioxaborinine type structure as seen in Scheme 3. This was further expounded *via* the ^{13}C NMR spectra with the presence of a new sp^3 carbon adjacent to boron presenting a resonance at *ca.* δ = 40 ppm *vs.* 120 ppm for the adjacent sp^2 carbon in **3**. Storing **4a**–**c** as a saturated CH_2Cl_2/hexane solution produced a number of colorless crystals suitable for X-ray diffraction, which indeed determined the molecular structure to be the product of a formal 1,1-carboboration reaction (Figure 3). Of particular note is the regioselectivity of this reaction with the product predominating as the selective transfer of the aryl group over the chloride fragment.[18] This migration pattern could be confirmed once again through detailed 2D NMR spectroscopy to affirm the molecular

connectivity revealed in the solid-state structure (see supporting information).



Scheme 3. Reaction between $PhBCl_2$ and **2** to give 1,1-carboboration products **4**. Yields are given as isolated yields.

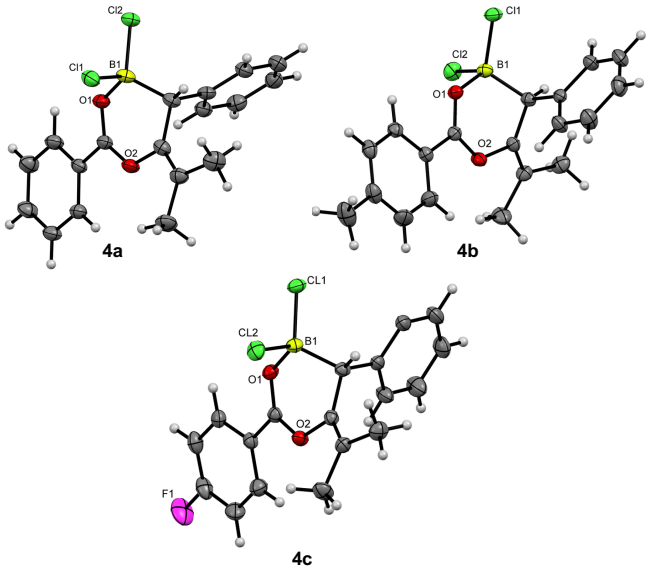
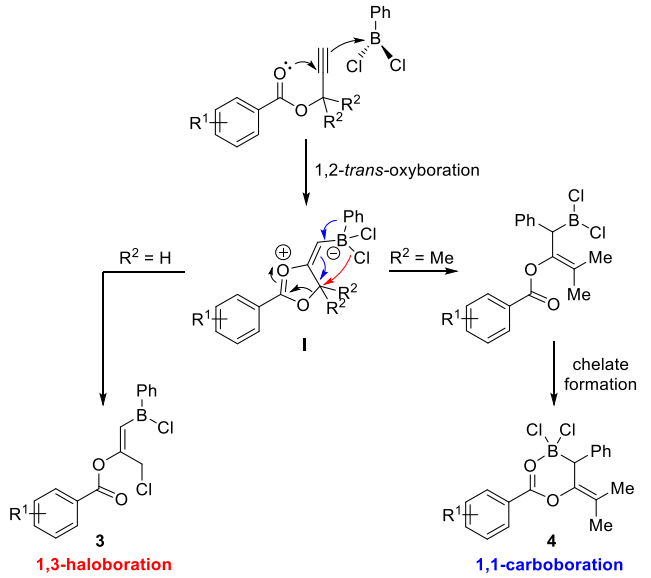


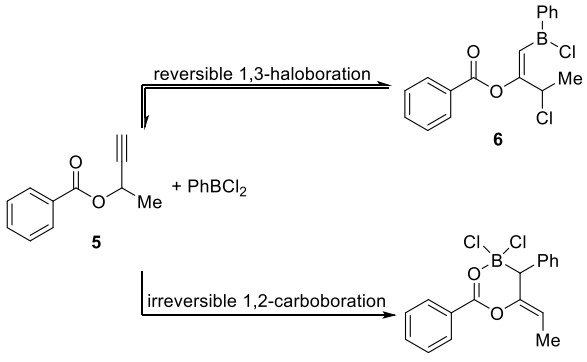
Figure 3. Solid-state structure of compounds **4a**–**c**, C: grey, H: white, O: red, B: yellow-green, Cl: green, F: pink. Thermal ellipsoids shown at 50% probability.

When comparing the divergent elementoboration observed here, it is proposed that the inclusion of non-H groups in the propargylic position must play a critical role in which pathway is undertaken in this reaction. Mechanistically we propose that an initial 1,2-*trans*-oxyboration step occurs to yield the zwitterionic dioxolium borate.[19] During the formation of this 5-membered dioxolium intermediate (**I**, Scheme 4), when simple hydrogen atoms occupy the R^2 position, the formation of **3** is more stable and thus favourable compared to when methyl groups are included in the R^2 position. Conversely, if more bulky methyl groups are included, then the chloride migration pathway is less favoured over 1,2-aryl group migration resulting in the generation the intramolecular chelate **4**. These experimental findings are supported through *in silico* studies (see later and supporting information).



Scheme 4. Proposed mechanism for the divergent elementoboration of **1** and **2** using $PhBCl_2$.

Additionally, when using compound **5** which features a combination of H and Me in the propargyl position, a more complex transformation is observed when monitoring the reaction coordinate over time. Analysing the *in situ* ^{1}H and ^{11}B NMR spectra suggests that after initial combination of $PhBCl_2$ with **5**, the haloboration product **6** prevails as observed by the characteristic broad singlet at δ = 6.35 ppm alongside the formation of a resonance at *ca*. δ = 5.2 ppm for the proposed vinyl and methylene protons respectively (see supporting information). Over time, these resonances reduce in intensity giving way to a new broad singlet at δ = 3.36 ppm, consistent with the generation of the proton in the adjacent to the borane in the chelating structure **7**. In addition, new resonances appear for the newly formed vinyl proton quartet at δ = 5.45 ppm, and the methyl doublet at δ = 1.90 ppm. This assertion is bolstered when observing the *in situ* ^{11}B NMR spectra over time whereby the expected singlet at *ca*. δ = 55.1 ppm forms after 1 h at ambient temperature which reduces in intensity over time yielding another singlet resonance at *ca*. δ = 9.1 ppm, again indicating the reversible formation of **6** *en route* to **7** (Scheme 5).



Scheme 5. Conversion of **5** to **6** and **7** *via* a proposed reversible 1,3-haloboration or 1,2-carboboration mechanism. Conducted at ambient temperature in $CDCl_3$.

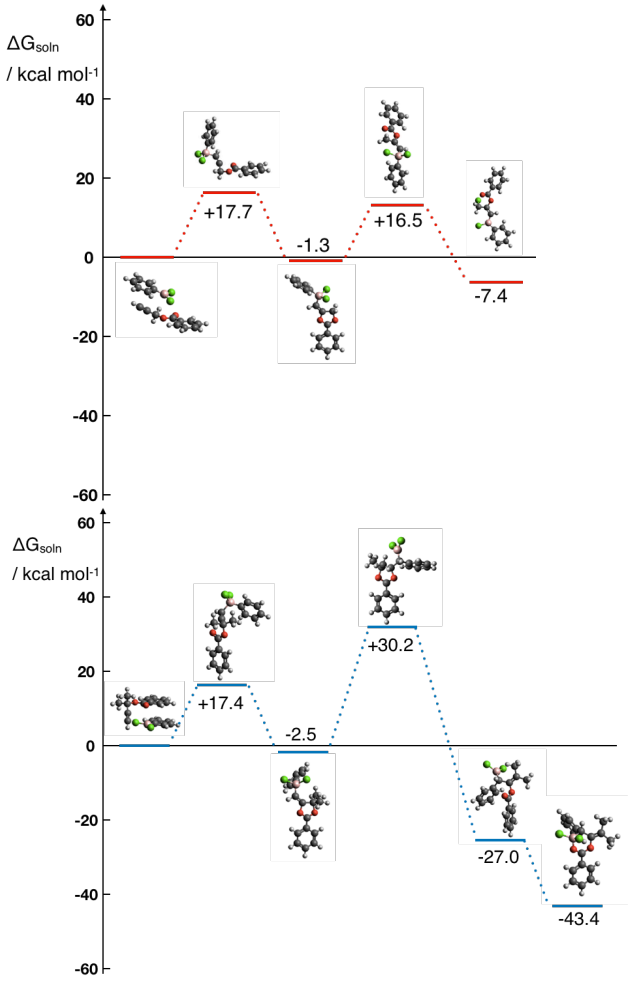


Figure 4. Free energy diagram comparing the mechanism and energetics of the haloboration (red) and carboboration (blue) reactions yielding products **3** and **4** respectively.

To shed light on the divergent reactivity realised in this work, density functional theory calculations (see supporting information 3.1) were performed to probe the reaction pathways, summarised in Figure 4. Formation of products **3** and **4** proceeds in line with Scheme 5 *via* the key dioxolium intermediate; chloride migration is the transition state for haloboration and phenyl migration is the rate determining transition state for carboboration. As is clear from the comparison of pathways, carboboration is thermodynamically preferred over haloboration and the hypothetical carboboration product (see supporting information, Table S1) for R^2 = H is > 30 kcal mol^{-1} more stable than the haloboration product, raising the question of why carboboration does not occur for R^2 = H. It is shown that after 1,2-trans-oxyboration, formation of the analogue of **4**, R^2 = H is hindered due to a high reverse barrier (+28.9 kcal mol^{-1}) from the product and a prohibitively large barrier for phenyl migration (+37.20 kcal mol^{-1}) required for the 1,1-carboboration mechanism (see supporting information 3.2.3 and 3.2.4). Conversely, the analogue of **3**, R^2 = Me has a comparatively low reverse barrier from the product (+23.3 kcal mol^{-1}) and a low barrier for phenyl migration (+28.2 kcal mol^{-1}) in comparison to R^2 = H, hence migration of phenyl is competitive and once migration occurs, there is a strong free energy incentive to form the chelate **4**. Intriguingly, in line with the observed reversible behaviour of the mono-methlyate **5** to form haloboration product **6** and then the carboboration product **7**, calculations show an intermediate reverse barrier from the product of +25.8 kcal mol^{-1} and an intermediate barrier for phenyl migration of +29.2 kcal mol^{-1}. These findings show that **3** and **6** are more kinetically stable than the R^2 = Me analogue of **3**, explaining why both **3** and **6** are observed. The relatively low barriers for phenyl migration to form **4** and **7** with the strong thermodynamic driving force explain why the carboboration products occur for R^2=Me and R^2=Me, H. Overall, these calculations reveal a subtle interplay of kinetic and thermodynamic factors that are acutely sensitive to the R^2 groups, which cause profoundly different reaction products.

In summary, this work has shown both the formal 1,1-carboboration as well as the first instance of a formal 1,3-haloboration of alkynes can occur through simple tuning of the alkyne starting material being used. All of these multi-step reactions proceed cleanly with high conversions and yields being noted in a one-pot, atom efficient manner, garnering synthetically useful and functionally diverse compounds for further reactivity. In depth computational studies have helped elucidate the proposed mechanism that differentiates this divergent elementoboration.

Conflict of interest: The authors declare no conflict of interest.

Keywords: Haloboration • Boron • Alkyne • Mechanism • Lewis acid

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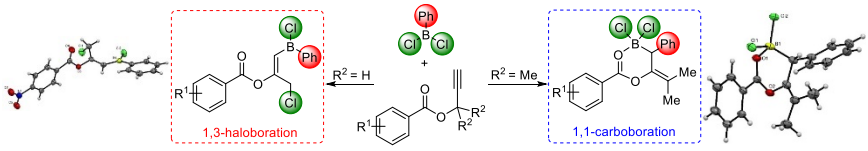

Lewis C. Wilkins,[‡] Yashar Soltani[‡] James R. Lawson, Ben Slater and Rebecca L. Melen[a]*

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