Formation of C(sp$^2$)–Boronate Esters by Borylative Cyclization of Alkynes Using BCl$_3$

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Abstract: BCl$_3$ is an inexpensive electrophile which induces the borylative cyclization of a wide range of substituted alkynes to regioselectively form polycycles containing synthetically versatile C(sp$^2$)–boronate esters. It proceeds rapidly, with good yields and is compatible with a range of functional groups and substitution patterns. Intermolecular 1,2-carboboration of alkynes is also achieved using BCl$_3$ to generate trisubstituted vinyl boronate esters.

C(sp$^2$)–boronic acid and ester derivatives are ubiquitous in modern synthetic chemistry because of their good ambient stability, low toxicity, utility in C–C bond formations, and facile transformation into other important functional groups.$[^1]$ Classic synthetic approaches to forming C(sp$^2$)–B bonds require Grignard or organolithium reagents, and thus have issues with functional-group compatibility, and often require C(sp$^2$)–halide precursors and cryogenic temperatures.$[^{10}]$ Simple methods which are functional-group tolerant for forming C(sp$^2$)–B bonds are highly desirable, particularly reactions that proceed directly from hydrocarbon precursors. The most notable recent breakthrough in this area is iridium-catalyzed direct C–H borylation.$[^2]$ Whilst this reaction has developed into a truly powerful transformation, the discovery of new routes, particularly transition-metal-free methods, to efficiently generate C(sp$^2$)–boronate esters, which are challenging to access by iridium catalysis, remains desirable. Recent advances in transition-metal-free borylation include benzannulations,$[^3]$ radical mediated borylation,$[^4]$ electrophilic borylation,$[^5]$ and carbanion-mediated borylation.$[^6]$

One underexplored approach to metal-free C(sp$^2$)–B bond formation proceeding from simple hydrocarbon precursors is the borylative cyclization of alkynes, wherein a boron electrophile activates an alkyne for intramolecular electrophilic cyclization with a second π-system. This approach represents a step-economical reaction which would simultaneously create new C(sp$^2$)–B and C–C bonds to generate new polycyclic frameworks such as borylated dihydroquinolines, dihydroanthalenes, and phenanthenes, which are prevalent in (or are key precursors to) biologically active molecules, pharmaceuticals (e.g. Nafoxidine; Scheme 1) and/or organic materials.$[^7]$ Alkyne cyclization with concomitant functional-group installation has been principally limited to chalcogen and halogen electrophiles,$[^8]$ and to the best of our knowledge, to date, the borylative cyclization of alkynes to form polycyclic structures containing C(sp$^2$)–boronate esters requires transition-metal catalysis.$[^9]$ Metal-free borylative cyclization to form polycyclic C(sp$^2$)–B(OR)$_2$ species is not documented. Furthermore, metal-free borylative cyclization is distinct from the reactivity of transition metals and heavier group 13 electrophiles (e.g., GaCl$_3$), which catalyze the cyclosimerization of alkynes without concomitant functional-group installation (Scheme 1).$[^{10}]$

Given the ubiquity of alkyne functionalization using boron electrophiles (e.g., hydroboration) the cyclization of unactivated$[^{11}]$ alkynes induced by any boron electrophile is relatively scarce. Noteworthy exceptions use B(C$_3$F$_5$)$_3$ to initiate cyclization, thus generating a variety of borylated polycyclic structures.$[^{12}]$ Whilst notable, these reactions use the expensive (relative to BCl$_3$) electrophile B(C$_3$F$_5$)$_3$, which can concomitantly install a C,F$_3$ group, and more significantly, precludes formation of the desirable boronic acid derivatives.$[^{13}]$ Herein, we report borylative cyclization, using BCl$_3$, as a method which is functional-group tolerant and rapidly generates polycyclic structures containing C(sp$^2$)–boronate esters. The reaction features concomitant C–C and C–B bond formation under mild reaction conditions from simple starting materials.

Our studies into borylative cyclization started with 1,4-diphenylbut-1-ynes (e.g., 1a; Scheme 2), thus targeting borylated dihydroanthalenes because of their importance in pharmaceuticals.$[^{14}]$ BCl$_3$ was utilized as it is inexpensive and more electrophilic than BF$_3$, with Et$_3$O-BF$_3$ previously shown

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not to cyclize aryl-substituted alkynes. The addition of BCl to 1a at 20 °C in CH₂Cl₂ led to complete consumption of 1a within 10 minutes (Scheme 2). In the ¹H NMR spectrum there was the appearance of a characteristic doublet at δ = 6.79 ppm, which is attributed to the aromatic proton ortho to the newly formed carbon–carbon bond. The appearance of a broad resonance at δ = 54 ppm in the ¹³B NMR spectrum was also consistent with a vinylBCl moiety. In situ formation of the pinacol boronate ester was facile, and 2a was isolated as the desired cyclized product in 91% yield. Formation of the borylated dihydronaphthalene presumably proceeds by activation of the alkyne by BCl, with the potentially competing haloboration reaction disfavored for internal alkynes and BCl. The BCl-activated alkyne (as a vinyl cation or a π complex) is sufficiently electrophilic at the carbon center to undergo an intramolecular S₈Ar reaction by a 6-endo-dig cyclization; no 5-exo-dig cyclized products were observed throughout this work. Loss of H⁺ as HCl then leads to rearomatization, with no competing protodeboronation of the newly formed vinylBCl moiety, which is subsequently pinacol protected. The borylative cyclization of 1a with BCl is distinct to the reactivity of transition metals and heavier group 13 Lewis acids (e.g., GaCl₃ and InCl₃) which catalyze the cycloisomerization of similar alkynes (Scheme 1, top). The disparity observed between BCl and the heavier group 13 analogues presumably arises from the less polar and stronger B–C bond (relative to Ga–C), which makes the borylated compounds more resistant to protodemetalation and thus enables isolation of the desired C(sp²)–boronate esters. Notably, protodeboronation products are observed as a minor component for a number of substrates (these may also form by HCl initiated cyclization), but performing the reaction with the hindered base 2,4,6-tri-tert-butylpyridine (TBP) enables cleaner borylative cyclization (this requires 2 equiv of BCl, with 1 equiv consumed by formation of [(TBP)H][BCl₄]).

The functional-group tolerance of the BCl borylative cyclization proved to be broad (Scheme 2). Substrates containing halide substituents (1b–d) at the ortho- and para-positions of the aryl alkyne, and the pentfluoro aryl alkyne were all rapidly cyclized (reactions complete within 10 min) and the corresponding pinacol boronate esters were isolated in yields of greater than 70%. The alkyne 1b was successfully cyclized open to air and using unpurified CH₂Cl₂, albeit using excess BCl (due to H₂O present in unpurified CH₂Cl₂). Only a 7% decrease in the yield of the isolated product was noted compared to the reaction under rigorously anhydrous conditions, thus highlighting the robustness of this reaction. Trifluoromethyl groups often undergo C–F activation with strong boron electrophiles, but in this case the CF₃-containing alkyne 1e was successfully cyclized and isolated in 97% yield. 2e was also produced on a gram scale, and isolated in a 96% yield (1.74 g). The alkyne 1f, containing a Lewis basic nitrile functionality, reacted rapidly with BCl, initially resulting in the formation of two compounds. One compound was consistent with a vinylBCl species and the other with a R–
CN—BCl adduct (determined by 1B NMR spectroscopy). After twelve hours the desired cyclized product was the only species observed in the 1B NMR spectrum, with reversible coordination between the nitrile group and BCl3 only slowing the cyclization and not leading to any observable side products. The structure of 2f was also confirmed by X-ray crystallography (Scheme 2). Other alkynes possessing oxo-containing functional groups, including a tosyl-protected amine linker (1g), nitro (1h), and ester (1i), were all cyclized and isolated as the pinacol boronate ester in greater than or equal to 70% yields. 1i required two equivalents of BCl3 for complete cyclization with one equivalent of BCl3 coordinating to the ester moiety and the second inducing the cyclization. The ester—BCl3 adduct was subsequently cleaved on addition of NEt3 during the esterification step to yield 2i. The ether-containing substrates 1j and 1k were also amenable to cyclization with BCl3, with minimal ether cleavage observed, presumably because of the rapid nature of the BCl3-induced cyclization. The cyclization of 1g and 1k confirms that this methodology is not limited to forming dihydronaphthalenes, but is also applicable to dihydroquinoline and chromene formation. Toly-substituted alkynes (11-o) reacted with BCl3 to give a mixture of cyclized products attributable to Brønsted acid initiated methyl group migration. This migration was avoided simply by repeating the cyclization in the presence of TBP, which effectively sequesters the HCl by-product, and the alkynes 11-o all cleanly cyclized to give the desired product.

Previous work on electrocyclic cyclization using iodonium salts only succeeded when the alkyne substituent was capable of electronically stabilizing the vinyl cation intermediate (e.g., p-MeOC6H4-phenylfunctionalized alkynes). Attempts at borylative cyclization of the terminal alkyne 4-phenyl-1-butyne failed because of preferential haloboration with BCl3. In contrast, upon addition of BCl3, the bromo-terminated alkyne 1p was converted into two products. Post esterification the major product was the dihydronaphthalene, 2p (Scheme 2), and the minor component was that derived from haloboration of 1p (by GC-MS). Cyclization of an alkyl terminated alkyne, 1q, was achieved with BCl3, but in addition to the borylated dihydronaphthalene product (2q) a naphthalene and tetralin were produced, consistent with transfer hydrogenation proceeding under these reaction conditions. When cyclization was repeated with BCl3 and TBP, 2q was isolated in a 67% yield, thus confirming that aryl groups for the stabilization of vinyl cations are not essential for BCl3-induced cyclization. TBP/BCl3 also enabled the cyclization of alkynes substituted with naphthyl and vinyl groups to form 2r and 2s, respectively. In the absence of TBP lower yields were observed.

In contrast to the borylative cyclization of 1i and 1k with BCl3, it was observed that for other ether-containing substrates (e.g., 1t and 1u), BCl3 with and without TBP, gave extremely low yields of the isolated desired products (Scheme 2). In situ NMR analysis showed that 1t reacted rapidly with BCl3 to initially produce the cyclized product and ether-cleavage products (ArylOBCl3 and chloromethane). Previously, we reported that the borocation, [Cl3B(2-DMAP)][AlCl4] (3), which can be readily produced and handled in air for short periods, is reasonably tolerant of methoxy groups during borylation reactions and it does not haloborate internal alkynes. Using 3 led to more selective borylative cyclization reactions, thus enabling isolation of 2t and 2u in moderate yields (36 and 57%). The selectivity disparity between BCl3 and 3 is attributed to the lower nucleophilicity of [AlCl4]- versus Cl- (produced during cyclization with BCl3), thus suppressing ether cleavage by attack of the anion on the Me+- of Ar(Me)O—BCl3 adducts. The more electrophilic (relative to BCl3) borocation 3 was also essential for cyclizing substrates containing deactivated internal aromatic nucleophiles. For example, the alkyne 1v did not react when combined with BCl3 (at 20°C or at raised temperatures), but using 3 and heating at 60°C for 2.5 hours led to full cyclization. It is noteworthy that 1v (and 1o and 1u) cyclized to produce only one regioisomer, thus borylative cyclization is also highly regioselective. To the best of our knowledge 4-R-1,2-dihydronaphthalenes borylated at the C3-position are currently unknown and represent useful intermediates because of the importance of this structure in pharmaceuticals (e.g., Nafoxidine).

To demonstrate the utility of the borylated products 2e was coupled with 4-bromotoluene to produce 4 in 75% yield (Scheme 3). This proof-of-principle synthesis of a nafoxidine analogue proceeds in an overall 63% yield over three steps starting from the commercially available terminal alkyne and haloarene precursors. The cross-coupled product 4 can be readily oxidized using [Ph2C][BF4] to produce the 1,2-disubstituted naphthalene in good yield upon isolation (75% from 4; see the Supporting Information). Alternatively, this oxidation procedure was adapted to allow dehydrogenation of 2e, thus generating the borylated naphthalene 5 in 93% yield (Scheme 3). Regioselectively functionalized naphthalenes are useful in their own right or as precursors to higher acenes. To date the selective formation of 1-substituted-2-borylated-naphthalenes by iridium catalysis requires installation of directing groups at C1, whereas borylative cyclization/oxidation offers more versatility in the nature of the C1 substituent.

With the functional-group tolerance and utility of the products from 4-aryl-1-alkyne borylative cyclization confirmed, our attention turned to identifying other systems amenable to BCl3-induced cyclization guided by previously reported metal-catalyzed cycloisomerization reactions. The borylative cyclization of a 2-alkynyl-1,1'-biphenyl was selected as it undergoes cycloisomerization and represents a more rigid analogue of 4-aryl-1-alkynes. 2-(p-tolylethynyl)-1,1'-biphenyl underwent borylative cyclization using BCl3/THF. Whilst the reaction is slower than dihydronaphthalene
Electrophilic borylative cyclization of diynes.

The reactivity observed by combining B(CF$_3$)$_3$, phenylacetylene, and N-tBu-pyrrole.[23] 1-Phenyl-1-propyne shows no reactivity with 2-methylthiophene or BCl$_3$ alone, yet when all three were combined in the presence of TBP, the product (12) from a trans-1,2-carboboration was isolated after esterification in a 41% yield (Scheme 6). Thus BCl$_3$-induced alkyne carboboration is not limited to intramolecular π-nucleophiles.

In conclusion, BCl$_3$ is an inexpensive and functional-group-tolerant electrophile for the transition-metal-free borylative cyclization of alkenes. It provides rapid, high-yielding access to hitherto unknown C(sp$^3$)–boronate esters which are versatile synthetic intermediates. This methodology has been exemplified by forming a range of important polycyclic structures. The π-nucleophile is not limited to internal π-systems, as intermolecular nucleophiles are also amenable. These features, combined with the multitude of alkenes which are reported to undergo metal-catalyzed cycloisomerizations, indicates that borylative cyclization is a powerful, transition-metal-free route for accessing polycyclic structures containing C(sp$^3$)–boronate esters.

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