Alkynyl Moiety for Triggering 1,2-Metallate Shifts: Enantiospecific sp²–sp³ Coupling of Boronic Esters with p-Arylacetylenes

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Abstract: The enantiospecific coupling of secondary and tertiary boronic esters to aromatics has been investigated. Using p-lithiated phenylacetylenes and a range of boronic esters coupling has been achieved by the addition of N-bromosuccinimide (NBS). The alkyne functionality of the intermediate boronate complex reacts with NBS triggering the 1,2-migration of the group on boron to carbon giving a deaeromatized bromoallene intermediate. At this point elimination and rearomatization occurs with neopentyl boronic esters, giving the coupled products. However, using pinacol boronic esters, the boron moiety migrates to the adjacent carbon resulting in formation of ortho boron-incorporated coupled products. The synthetic utility of the boron incorporated product has been demonstrated by orthogonal transformation of both the alkyne and boronic ester functionalities.

For over half a century, cross-coupling reactions, particularly the Suzuki–Miyaura reaction, have been widely used in synthesis with applications spanning pharmaceuticals, agrichemicals and materials. However, although extraordinarily useful for sp²–sp² coupling, this reaction shows rather limited scope for aliphatic boron reagents. Primary organoboron reagents work well, but apart from a few specific examples (chiral) secondary and tertiary boronic esters do not. Recently, we reported a unique approach to the stereospecific sp²–sp³ coupling of boronic esters by exploiting the reaction of boronate complexes with electrophiles (Scheme 1a).[3] The coupling reaction worked well with electron rich heteroaromatics and aromatics bearing donor groups in the meta-position. However, without such features no coupling occurred and bromination at the sp³ center occurred instead (Scheme 1a).[4]

In order to broaden the substrate scope to an even greater range of aromatics, we envisaged the introduction of a functional group exo to the aromatic ring that would be more reactive than the sp³ center, and still trigger the 1,2-metallate shift. We considered the use of alkynes because they should react with electrophiles in the desired way and because of the ease with which they can be transformed into a variety of other functional groups.[5] Furthermore, alkynes are an important substituent in their own right owing to their prominence in natural products and as a site for rapid and site-selective conjugation, through a variety of Click reactions.[6] We hypothesized that treatment of the TMS-phenylacetylene derived boronate complex (C) with NBS should result in bromination of the alkyne[7] which would trigger 1,2-metallate shift[8] leading to a deaeromatized bromoallene intermediate (D) (Scheme 1b).[8] Upon reaction with a nucleophile, elimination and rearomatization would result.[3]
Here, we describe the realization of this hypothesis. To test our idea, we chose cyclohexyl pinacol boronic ester (CyBpin, 1a) and TMS-p-bromophenylacetylene (2a) as standard substrates. Treatment of bromoalkyne 2a with n-BuLi in THF at −78 °C followed by CyBpin gave boronate complex 3a. Subsequent addition of NBS in MeOH afforded a mixture of products comprising the desired coupled product 4a (40%), a product with boron incorporation in the ortho-position 4b (52%) as well as a small amount of 5 (6%) along with Cy–Br formed through the direct bromination at the sp³ carbon (Scheme 2, entry 1). At this point, we decided to optimize the reaction conditions to maximize the formation of either 4a or 4b, initially focusing on the maximally functionalized boron-incorporated product 4b. We had previously observed such products when coupling electron-rich aromatics with boronic esters and found that tPrOH/MeCN gave the best ratio.[8] We therefore carried out a brief solvent study (entries 2–5) and again found that tPrOH/MeCN was optimal here too, giving the highest ratio, leading to a 76% yield of 4b (entry 4). In THF/MeCN the reaction predominantly favored the undesired sp³ bromination pathway, showing the need for an alcohol co-solvent (entry 3).

In order to promote the formation of the de-borinated coupled product 4a, we needed to promote nucleophilic attack at the boron atom and so decided to tune the steric environment around the boron center with a variety of diol ligands. Of the diols tested, the least hindered neopentyl glycol gave the highest selectivity for the coupled product 4a (82%) with minimal amounts of 4b and 5 (entry 8). With increasing steric hindrance around boron, an increasing proportion of the boron incorporation product 4b was observed. Additional solvent screening showed that in TFE/THF, the sp³ bromination pathway could be eliminated (entry 9).

Using the optimized conditions for creating boron-free products we explored the substrate scope of the aromatic component, employing a range of arylalkynes with a standard secondary boronic ester 6a obtained in 96:4 er using our lithiation–borylation methodology (Table 1).[9] With simple p-bromophenylalkyne 2a, the reaction furnished the expected coupled product 7a in 92% yield and with 100% enantioselectivity. With alkyl substituents in the ortho- (2b) and meta-positions (2c) the desired product 7b and 7c were obtained in 85% and 86% yield, respectively. Similarly, the naphthylalkyne 2d also afforded the expected coupled product 7d in good yield (89%) (minor amounts (~5%) of boron incorporation was observed in all cases). Electron-donating substituents on the aromatic ring (2e and 2f) smoothly afforded the coupled products 7e and 7f in excellent yields (82 and 90% respectively). However, the introduction of electron-withdrawing groups such as fluoro (2g) or trifluoromethoxy (2h) on the aromatic ring favored the direct sp³ bromination pathway (~9:1) with neopentyl boronic esters, so the corresponding pinacol boronic esters were tested.

In comparison to pinacol, it is known that neopentyl boronic esters promote undesired S₂2 reaction at the sp³ carbon.[10] Pleasingly, with 2g, and the pinacol boronic ester 9a the coupled product 7g was obtained in 71% yield. With trifluoromethoxy 2h, the desired product 7h was obtained in

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**Table 1**: Scope of NBS-mediated coupling of phenylacetylenes with secondary boronic ester.[9]

| Entry | Solvent | B/Or2 | Solvent | Entry | B/Or2 | Solvent |
|-------|---------|-------|---------|-------|-------|---------|
| 1     | tPrOH/THF, 0.3 m | 52:6 | 6      | B(pin) 1 | tPrOH/THF, 0.3 m | 52:6 |
| 2     | TFE/THF | 59:9 | 7      | B(pin) 1 | TFE/THF | 50:15:35 |
| 3     | tPrOH/MeCN | 25:58 | 8      | B(pin) 1 | tPrOH/MeCN | 82:7:8 |
| 4     | tPrOH/MeCN | 6:76:14 | 9     | B(pin) 1 | tPrOH/MeCN | 71:12:3 |
| 5     | HFP/MeCN | 26:47:2 | 10    | B(pin) 1 | HFP/MeCN | 46:26:30 |

[a] Reaction conditions: p-bromophenylacetylene 2a (1.1 equiv), n-BuLi (1.1 equiv) in THF (0.3 m) at −78 °C for 1 h, then 1a–c (1.0 equiv) in THF (0.3 m) at −78 °C, then at 0 °C addition of NBS (1.5 equiv) in specified solvent (0.3 m). Yields were determined by ³H-NMR spectroscopy. [b] Solvent exchange. cpg: cis-1,2-cyclopentyl glycol.
a modest yield of 32% together with undesired direct bromination at the sp² carbon (in 2:3 ratio) and minor amounts of boron incorporated products (≈10%). With other strongly electron withdrawing groups for example, CF₃, CN, CO₂Bu bromination of the sp² carbon dominated over the attack on the deactivated aromatic ring. A dimethyacetel functionality 2i (representing a masked aldehyde) reacted efficiently with the corresponding neopentyl boronic ester to provide the coupled product 7i in 66% yield. In all cases the reactions occurred with complete enantiopurity.

We then turned our attention to the scope of secondary and tertiary neopentyl boronic esters in our coupling chemistry (Table 2). Secondary boronic esters bearing alkyl, alkenyl, cyclopropyl and silyl ether functionalities 6a–d and natural product-derived boronic ester 6e smoothly converted to the corresponding coupled product 7a, 8b–e in good yields and 100% es. Other commonly occurring functional groups were tolerated in the boronic ester including azide (6f) and carbamate (6g). With tertiary neopentyl boronic esters 6h and 6i, the reaction proceeded smoothly to furnish the coupled products 8h and 8i in 43% and 79% yield, respectively.

We then turned to exploring the scope for the boron incorporation using pinacol boronic esters using the identified conditions (Scheme 2, entry 4). Reaction of boronic ester 9a with 2a gave the expected boron-incorporated product 10a in 78% yield with 100% es (Table 3). On a gram-scale under standard reaction conditions, 10a was obtained in 66% yield. Similarly, with other electron-rich phenylacetylenes 2b,c and 2f, the reaction proceeded smoothly to provide the corresponding products 10ab, 10ac and 10af in good yields. In the case of 2c and 2f, a regiosomeric mixture of products (10ac1–c2 and 10af1–f2) were observed. With other electron-withdrawing groups (e.g. CF₃, CN, CO₂Bu, F and OCF₃) on the aromatic ring, in MeCN/PrOH solvent, bromination at the sp² carbon was favored (>95%) over bromination of the deactivated phenylacetylene.

The scope of secondary pinacol boronic esters was also investigated (Table 3). An array of aromatic, secondary and tertiary boronic esters bearing phenyl, alkyl, alkenyl, cyclopropyl, ester, azido, silyl ether, nitrile and amide functional groups 9b–j all worked well furnishing the products 10b–j in good yield (52–81%) and 100% es. Natural product-derived boronic esters 9k and 9l were transformed exclusively to the boron incorporated product 10k and 10l in 88% and 76% yields, respectively with complete diastereoselectivity.

The mechanism that accounts for the generation of the boron-free and boron-incorporated products is shown in Scheme 3. Following the formation of boronate complex I, the reaction with NBS leads to the bromoallene intermediate II.

If the boronic ester is unhindered, subsequent attack by MeOH at boron promotes elimination leading to product Va (Path a). In contrast, if the boronic ester is hindered, nucleophilic attack is less favored, especially with tPrOH as solvent, and migration of the boron to the adjacent carbon occurs instead, relieving steric encumbrance and eliminating bromide. This leads to carbocation intermediate IV, which then eliminates to the product Vb (Path b).

The boron incorporated products provide a rich source of functionality which can be chemoselectively converted into a range of diverse products (Scheme 4). Using K₂CO₃/MeOH the orthogonal deprotection of the TMS group was achieved providing the terminal alkyne 11a in 87% yield.¹⁄₂ Hydration of 10a with 20 mol% triflic acid in TFE furnished ketone 11b in 76% yield.¹⁄₂ Under standard CuAAC conditions,¹⁄₂ 11a was transformed to the corresponding triazole product 11c in 85% yield. Oxidation of the boronic ester with H₂O₂/NaOH
and hydroxylamine sulfonic acid (HSA)\textsuperscript{[15]} gave the desired phenol 11\textit{d} and aniline 11\textit{e} in 90 and 62\% respectively.

Under standard Sonagashira conditions with iodobenzene, 11\textit{a} smoothly converted to the functionalized alkyne 11\textit{f} in 90\% yield.

In summary, we have successfully developed an efficient enantiospecific sp\textsuperscript{2}–sp\textsuperscript{3} coupling of a range of aromatic alkynes with a broad range of enantioenriched boronic esters. The alkyne acts as a reactive handle for reaction with NBS which triggers the coupling process. Importantly, conditions were found which either lead to the coupled product or to the coupled product bearing an \textit{ortho} boronic ester. The maximally functionalized product is highly versatile as each functional group can be transformed chemoselectively making it an ideal intermediate in synthesis.

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**Table 3:** Scope of NBS-mediated coupling of boronic esters with phenylacetylenes providing boron-incorporated products.

| Reaction conditions: | p-bromophenylacetylene 2a–c,f (1.1 equiv), n-BuLi (1.1 equiv) in THF (0.3 \text{m}) at –78 °C for 1 h, then 9a–l (1.0 equiv) in THF (0.3 \text{m}) at –78 °C, then solvent exchange to \text{PrOH} followed by addition of NBS (1.5 equiv) in MeCN (0.3 \text{m}). | [b] Isolated as phenol after oxidation with H\textsubscript{2}O\textsubscript{2}/NaOH. |

| Product | Yield | Functional Groups | Remarks |
|---------|-------|------------------|---------|
| 10a | 78\% es 100\% | TMS, Br | |
| 10ab | 80\% es 100\% | TMS, pinB | |
| 10acf | 44\%, es 99\% | TMS, Me | |
| 10ac2 | 35\%, es 99\% | TMS, ind | |
| 10af1 | 32\%, es 100\% | TMS, BPin | |
| 10af2 | 28\%, es 99\% | TMS, BPin | |
| 10b | 53\% | TMS, Ph, Bpin | |
| 10c | 62\% es 99\% | TMS, Ph, Bpin | |
| 10d | 73\% es 100\% | TMS, Ph, CO\textsubscript{2}Bu | |
| 10e | 81\% es 100\% | TMS, Ph, CO\textsubscript{2}Bu, N\textsubscript{3} | |
| 10f | 73\% es 100\% | TMS, Ph, CO\textsubscript{2}Bu, OTBS | |
| 10g | 70\% es 100\% | TMS, Ph, CO\textsubscript{2}Bu, DTBS | |
| 10h | 66\% es 100\% | TMS, Ph, CN | |
| 10i | 52\% es 100\% | TMS, Ph, CO\textsubscript{2}Bu, N\textsubscript{3} | |
| 10j | 68\% es 100\% | TMS, Ph, CO\textsubscript{2}Bu, TBSO | |

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**Scheme 4.** Synthetic transformations of product 10\textit{a}.

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Conflict of interest

The authors declare no conflict of interest.

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