Acyl-Directed ortho-Borylation of Anilines and C7 Borylation of Indoles using just BBr₃

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Abstract: Indoles are privileged heterocycles found in many biologically active pharmaceuticals and natural products. However, the selective functionalization of the benzenoid moiety in indoles in preference to the more reactive pyrrolic unit is a significant challenge. Herein we report that N-acyl directing groups enable the C7-selective C–H borylation of indoles using just BBr₃. This transformation shows some functional-group tolerance and notably proceeds with C6 substituted indoles. The directing group can be readily removed in situ and the products isolated as the pinacol boronate esters. Acyl-directed electrophilic borylation can be extended to carbazoles and anilines with excellent ortho selectivity. 4-amino-indoles are amenable to this process, with acyl group installation and directed electrophilic C–H borylation enabling selective formation of C5-BPin-indoles.

C–H borylation is a powerful methodology to form synthetically versatile C–B bonds.[1] Numerous methods have been developed, with iridium-catalysed C–H borylation one of the most notable.[1] This method functionalises the pharmaceutically important heteroarene indole at the C2-position.[2] Alternative indole C–H borylation methods include electrophilic borylation (dominated by electronic effects)[3] and C–H lithiation/borylation (controlled by C–H acidity).[4] However, these also functionalise the pyrrole unit (at C3 and C2, respectively, Scheme 1 top left). Indole C–H borylation that occurs selectively on the less reactive benzenoid unit is desirable, including for accessing C5 and C7-functionalised indoles which are motifs found in many biologically active natural products and pharmaceuticals (e.g. chloropeptin I, teleocidins, hippadine, tiplaxtinin).[5] To date the selective C5–H/C7–H borylation of indoles in the presence of C2–H/C3–H requires prefunctionalised indoles (e.g. halide at C5/C7) or functionalisation of the more reactive C2–H/C3–H site prior to C5–H/C7–H borylation and then unmasking of the C2–H/C3–H.[6] To the best of our knowledge, one example of directed iridium-catalysed C–H borylation[7] provides the only exception to these requirements (Scheme 1, middle left). This process while notable uses ruthenium and iridium catalysts and substrates containing C6 substituents are not viable (6,7-disubstituted indoles are also bioactive motifs for example, indole isosteres of combrestatins).[5–8] Therefore a simple, precious metal free route for the C–H borylation of indoles that is selective for: (i) C7 (over C2), including for C6 substituted indoles, and (ii) C5 (over C3), would be highly notable particularly if using a readily removed directing group.

C–H borylation using BX₃ (X = Cl or Br) is an attractive method to form organoboranes,[9,10,11] and directed borylation using BX₃ has proved to be a powerful route to form B–C bonds for organic materials applications.[12] Directed electrophilic C–H borylation is dominated by directing R,N- or N-heterocycle groups with borylation generally forming six membered boracycles preferentially over other ring sizes.[12] The extension of C–H borylation using BX₃ to the C5/C7 positions of indoles would be highly attractive. However, this requires conditions that disfavour electrophilic C3–H borylation (which is relatively facile) and a directing group that: (i) is compatible with BX₃; (ii) enables selective borylation at the desired position; (iii) is readily deprotected post C–H borylation. Transition metal-catalysed C7–H indole function-
alisation often uses bulky phosphinyl directing groups installed at N1 which are challenging to remove (requiring refluxing with LiAlH4), however, in limited cases N-acyl directing groups have also been used and these are more readily removed. Herein we demonstrate that N-acyl directing groups are compatible with BBr3 and lead to C7–H borylation of indoles generating useful C7-BPin products on work up (Scheme 1, bottom). Notably, borylation is compatible with C6 substituted indoles in contrast to the iridium-catalysed process. Furthermore, acryl directing groups also enable ortho C–H borylation of anilines using BBr3, including of 4-amino indoles which affords C5-BPin indoles.

To guide our selection of appropriate acryl directing groups initially we probed the thermodynamic outcome from indole borylation at C2 and C7 computationally. Notably, the C7 borylated isomer is calculated to be thermodynamically favoured over the C2 (Scheme 2) isomer in all cases, this is attributed to (i) the differing degrees of steric clash between R and the C7–H and C2–H hydrogens (as previously noted), (ii) the differing bond angles in 5 and 6-membered boracycles, with the former leading to compressed O-B-C angles relative to the latter (which approaches the ideal for tetrahedral boron, Scheme 2). C7-borylation is also calculated to be the kinetic outcome (for R = Bu) based on borylation proceeding via acyl—BBr3 formation, [acyl—BBr3]+ formation and then S=Ar (see SI).

Based on these calculations the borylation of 1-benzoylindole, 1a, and 1-pivaloylindole, 2a, was targeted. To disfavour borenium cation formation and indole C3 borylation conditions were required avoiding coordinating exogenous base. For example, using reagents which lead to [(amine)BX]+ cations (e.g. BBr2/2,6-lutidine) led to the borylation of 2a at C3 selectively (see SI) with no C2 or C7 borylation observed (Scheme 3). Therefore, BCl3 and BBr3 in the absence of base were utilised.

While BCl3 resulted in no borylation of 1a and 2a, with BBr3, C–B bond formation proceeded with both these indoles, forming products with δ11B ≈ 0 ppm (distinct to amide-BBr3 adducts for which δ11B is ca. –10 ppm). Subsequent addition of pinacol/ Et3N led to formation of the pinacol boronate esters 3a–5a (Scheme 4). The disparity between BCl3/ BBr3

![Scheme 2](image-url)

 ![Scheme 3](image-url)

 ![Scheme 4](image-url)
The substrate scope was explored next and notably C6 substituted N-pivaloyl-indoles were more reactive to C–H borylation using BBBr3 in moderate to good yields (e.g., 5c and 5d) (Table 1). The 6-methoxy derivative 2e was also a viable substrate, however, it underwent competitive ether cleavage with BBBr3 producing two C7-borylated products (5e and 5f) in varying amounts depending on the amount of BBBr3 used. Conditions for one-pot C–H borylation, pinacol protection and pivaloyl deprotection simply required the addition of methanol after BPin formation and heating to 60°C. The removal of the pivaloyl group occurs without any observable C–B cleavage. This enables three steps to be achieved in one-pot with no solvent switches with 8a formed in 71% isolated yield. These conditions were applicable to indoles substituted at C2, C3, C4, C5 and C6 (8g–8i), and containing electron withdrawing and donating groups. The reaction was performed on a 3 mmol scale to provide 0.82 g of 8g in 86% yield. However, 5-SMe, 5-NO2 and 4-CN substituted indoles did not furnish isolable C-BPin products, while attempts with a bulkier group at C6, 6-(p-tolyl)-N-pivaloyl-indole, led to C2 borylation dominating (35:65 C7:C2). Compounds 8x are useful in Suzuki-Miyaura cross couplings, allylations and halogenations,[8] and we note that 8a readily undergoes oxidation with H2O2/NaOH to form 7-hydroxy-indole.

During substrate screening minor C2–BBBr3 borylation (forming 6x-BBBr3) often was observed. Attempts to form the C7–BBBr3 products (5x-BBBr3) selectively by heating (in sealed tubes so BBBr3 does not leave the system) failed to change the C2:C7 ratio suggesting that C–H borylation of these indoles is irreversible under these conditions. However, it was observed that the ratio of C2–C7 BBBr3 products was different to that of the C2–C7 BPin products (with C7–BPin increasing). Furthermore, in a number of cases the amount of 5x:8x isolated was greater than that possible based on the observed 5x-BBBr3:6x-BBBr3 ratio (precluding C2-selective protodeborylation during pinacol addition as the only origin of ratio changes). For example, substrate 2k borylates to form a 5k-BBBr3:6k-BBBr3 ratio of ca. 55:45 (by 1H NMR spectroscopy), however, post work up 8k was isolated in 75% yield. This indicates that addition of pinacol enables C2–B protodeborylation and C7–H borylation. As the BBBr3 products are stable to isomerisation in the presence of HBr this suggests that it is a C–B(OR)Br or C–B(OR)2 species that is undergoing protodeborylation and leading to more selective C7–H borylation.[9] While the species undergoing C2→C7 isomerisation on pinacol addition is unknown Lewis/Broensted acid initiated isomerisation of (RO)2B-Aryl has been previously observed.[17]

To expand the utility of acyl-directed electrophilic borylation other N-heterocyclic frameworks were explored. However, N-pivaloyl-carbazole did not undergo C–H borylation using BBBr3 (even on heating). This is attributed to steric crowding between the two proximal C–H units (at C1 and C8, Scheme 5, top left) and the pivaloyl 'Bu group that isomerisation in the presence of HBr is unknown Lewis/Broensted acid initiated isomerisation of (RO)2B-Aryl has been previously observed.[17]

![Scheme 5](image)

**Scheme 5.** The directed borylation of N-benzoyl carbazole using BBBr3. Inset, the solid state structure of 10 and 11, ellipsoids at the 50% probability level.[24]

| Table 1 | Substrate scope of pivaloyl-directed C7-borylation. |
|---------|---------------------------------------------------|
| ![Diagram](image) | ![Diagram](image) |

Conditions A = 1. 2.2 equiv BBBr3 in DCM, 2. + pinacol/Et3N. Conditions B = 2.2 equiv BBBr3 in DCM, 2. + pinacol/Et3N 3. + MeOH, 60°C. Yields are of isolated products post chromatography. [a] = using 1 equiv BBBr3.
We next explored the ortho borylation of anilines (Scheme 6). In previous work, borenium mediated electrophilic borylation of anilines proceeded at the para position.\textsuperscript{[17]} Ortho borylated anilines are accessible e.g., by directed lithiation of carbamate functionalised anilines,\textsuperscript{[20]} however, this approach has functional group limitations (e.g., C–Br). Both N-pivaloyl and N-benzoyl anilines were found to undergo selective ortho borylation using BBr$_3$, with no para-borylation observed.

This methodology was applicable to o-, m- and p-substituted anilines, forming 13c–e in good yield, including for a bromo containing derivative (13d). Directed borylation with BBr$_3$ also can be applied to tertiary amides with the N-Me derivative, 13f, formed in good yield (83%). Smith, Chattopadhyay and co-workers have recently developed directed iridium-catalysed ortho-borylation of anilines using B$_2$Eg$_2$ (Eg = ethylene glycolate).\textsuperscript{[21]} This report is notable, but while excellent for N-H systems it is low yielding with N-Me substituted anilines (< 25%),\textsuperscript{[21]} in contrast to the high yielding formation of 13f using just commercially available DCM solutions of BBr$_3$.

N-Bn-indol-4-yl-2,2-dimethylpropanamide, 14, next was investigated with it hypothesised that borylation would occur at C5 instead of C3 (the preferred site for $S_E^2$Ar in indoles) due to the preference for the formation of six membered bora-cycles over seven.\textsuperscript{[13c]} Functionalisation of the C5–H of indoles is important for accessing pharmaceuticals such as C4-amino-C5-functionalised indoles (e.g. Branebrutinib).\textsuperscript{[5,22]} The thermodynamics of C5 vs. C3 borylation again was probed by DFT calculations which showed the C5 isomers 15A to be more stable than the C3 isomers 15B (inset, Scheme 7) for both halide and pinacol substituents. C5 borylation of 14 was achieved in high selectivity with the pinacol boronate ester 16 formed in moderate yield (77 % in situ and 40% post purification). Attempts to monitor the borylation of 14 at the BBr$_3$ stage were prevented by this intermediate being poorly soluble. Finally, the ability to perform a C5/C7 double C–H borylation using BBr$_3$ was demonstrated using 17 (made in one step from 4-amino-indole). This formed 18 selectively post pinacol protection. Notably, in situ NMR spectra prior to pinacol addition show that the C3, C7 diborylated compound, 19, was formed as the major product and this does not isomerise on standing. However, addition of pinacol induces isomerisation of the C3–B moiety to form the thermodynamically favoured C5-BPin unit and yield the desired C5/C7 product in good conversion (72 %).

In summary, N-pivaloyl is an effective and readily removed directing group enabling C7 borylation of indoles and ortho borylation of anilines simply using commercial solutions of BBr$_3$. The process is complementary to borylation with [(amine)BBr$_2$]$^+$ and to iridium-catalyzed directed borylation as C6-substituted indoles are tolerated using BBr$_3$, while it has complementary functional group tolerance to directed lithiation methods. Notably, in a number of cases pinacol induced isomerisation of the initial borylated regio-isomer is essential to access the desired products containing C5–B and C7–B units. Due to the simplicity of this process and the many heterocycles containing N–H groups we believe acyl-directed borylation with BBr$_3$ will be applicable to many other systems.
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Conflict of interest

The authors declare no conflict of interest.

Keywords: boranes · borenium · borylation · directing groups · electrophilic aromatic substitution

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