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

Saqib A. Iqbal, Jessica Cid, Richard J. Procter, Marina Uzelac, Kang Yuan, and Michael J. Ingleson*

Abstract: Indoles are privileged heterocycles found in many biologically active pharmaceuticals and natural products. However, the selective functionalization of the benzenoid moiety in indoles to the more reactive pyrrole 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 can proceed with C6 substituted indoles. The directing group can be readily removed in situ and the products isolated as the pinacol substituted indoles. The directing group can be readily functionalised and is highly selective. 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, indoles which are motifs found in many biologically active pharmaceuticals and natural products).

To date the selective natural products and pharmaceuticals (e.g. chloropeptin I, indoles which are motifs found in many biologically active pharmaceuticals and natural products). However, the selective functionalization of the benzenoid moiety in indoles to the more reactive pyrrole 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 substituted indoles. The directing group can be readily functionalised and is highly selective. 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.

(Scheme 1, middle left).[8] 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).[5,6c,9] 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,[5b,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 R₂N- or N-heterocycle groups with borylation generally forming six membered boracycles preferentially over other ring sizes.[13] 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 functionalisation often uses bulky phosphinyl directing groups installed at N1 which are challenging to remove (requiring refluxing with LiAlH₄).[5a,c,14] However, in limited cases N-acyl directing groups also have been used[5d,15] 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, acyl 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 acyl 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 thermodynamicallyfavoured 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 $S_{N}$Ar (see SI).

Based on these calculations the borylation of 1-benzoyl-indole, 1a, and 1-pivaloyl-indole, 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)BX₂]+ cations (e.g. BBr₃/ 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 BBr₂ 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 also has been observed in N-heterocycle directed borylation and the origin of this has been examined previously. The regioselectivity of borylation using BBr₃ was assessed by NMR spectroscopy in situ and post pinacol protection. This revealed that borylation of 1a led to C7 and C2 borylation products (with 3a and 4a formed in a 4:1 ratio). Borylation of 2a with BBr₃ led to more selective C7 borylation, with compound 5a-BBr₃, the major borylated product observed in situ (in ca. 85–90% conversion, see SI). 5a-BBr₃ and 6a-BBr₃ are more soluble (than benzoyl congeners) enabling in situ reaction monitoring. Notably, while minor amounts of 6a-BBBr₂ were observed in situ no 6a was observed after pinacol protection. To confirm regioselectivity ZnPh₂ was added to the reaction mixture from 2a/BBr₃ to form predominantly 7 (right, Scheme 4) which has a δ₁₁B of 8.6 ppm indicating a four-coordinate boron centre (in contrast 5a has a broad δ₁₁B at 26 ppm consistent with a weaker PinB-O pivaloyl interaction). 7 was isolated in 42% yield and subsequently crystallised with X-ray diffraction studies confirming the formulation as the C7-borylated regiosomer. The solid state structure of 7 revealed a B–O–D of 1.610(2) Å and a O–B–C angle of 104.3(1)° that deviates from that calculated for 5a-BBr₃ presumably due to the different steric demand of BPh₃ vs. BBr₃. The complete absence of C3-borylation is consistent with the requirement for boranes more electrophilic than BBr₃ (e.g. borenium salts) to effect intermolecular indole C3 borylation.

The substrate scope was explored next and notably C6 substituted N-pivaloyl-indoles were amenable to C–H borylation using BBr₃ 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

Scheme 2. Relative energy of C2 and C7 borylated isomers calculated at the M06-2X/6-311G(d,p) level with a polarizable continuum model of DCM.
with BBr$_3$ producing two C7-borylated products (5e and 5f) in varying amounts depending on the amount of BBr$_3$ 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–8l), 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-NO$_2$, and 4-CN substituted indoles did not furnish isolable C-BPin products, while attempts with para-tolyl N-pivaloyl indole, led to C2 borylation dominating (35:65 C7:C2). Compounds 8x–8l could be isolated (and structurally characterised by X-ray diffraction, Scheme 5).

Scheme 5. The directed borylation of N-benzoyl carbazole using BBr$_3$. Inset, the solid state structure of 10 and 11, ellipsoids at the 50% probability level.

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 BBr$_3$ (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 tBu group that presum-

Table 1: Substrate scope of pivaloyl-directed C7-borylation.

<table>
<thead>
<tr>
<th>Conditions</th>
<th>Products</th>
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<th>Conditions</th>
<th>Products</th>
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<tr>
<td>A = 1.2 equiv BBr$_3$ in DCM, 2. + pinacol/Et$_3$N, Conditions B = 2.2 equiv BBr$_3$ in DCM, 2. + pinacol/Et$_3$N 3. + MeOH, 60 °C. Yields are of isolated products post column chromatography.</td>
<td>8a</td>
<td>65%</td>
<td>8b</td>
<td>49%</td>
<td>8c</td>
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<tr>
<td>5a</td>
<td>65%</td>
<td>5b</td>
<td>74%</td>
<td>5c</td>
<td>73%</td>
</tr>
<tr>
<td>5f</td>
<td>33%</td>
<td>8x</td>
<td>71%</td>
<td>8y</td>
<td>75%</td>
</tr>
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Conditions A = 1.2 equiv BBr$_3$ in DCM. 2. + pinacol/Et$_3$N. Conditions B = 2.2 equiv BBr$_3$ in DCM, 2. + pinacol/Et$_3$N 3. + MeOH, 60 °C. Yields are of isolated products post column chromatography. [a] = using 1 equiv BBr$_3$. 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 BBr$_3$ products are stable to isomerisation in the presence of HBr this suggests that it is a C–(OR)Br or C–Br(OR)$_2$ species that is undergoing protodeborylation and leading to more selective C7–H borylation. While the species undergoing C2–C7 isomerisation on pinacol addition is unknown Lewis/Brsnsted acid initiated isomerisation of (RO)$_2$B-Aryl has been previously observed. 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 BBr$_3$ (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 tBu group that presumably results in large B-O-C-N dihedral angles in the pivaloyl analogue of 10. Benzoyl contains a smaller R group (phenyl relative to tBu), therefore N-benzoyl carbazole, 9, was combined with BBr$_3$. This did not lead to C–H borylation at room temperature, instead the Lewis adduct, 10, was formed which was poorly soluble in DCM facilitating isolation and characterisation (including by X-ray diffraction, Scheme 5). Heating combinations of 9/BBr$_3$ led to high yielding C–H borylation at the C1 position. The C–H borylated product, 11, could be isolated (and structurally characterised by X-ray diffraction studies) or protected at borin in situ to furnish the pinacol boronate ester 12 in excellent yield (96%). For 10 and 11, the C=O (1.284(3) and 1.296(7) Å) and O–B distances (1.485(3) and 1.504(8) Å) reveal minimal difference, while the O–B–C angle in 11 (109.9(5)°) is comparable to that calculated for 5a-BBr$_3$ and is close to ideal for four coordinate boron centres. Notably the B–O distance in 11 is significantly shorter than in 7 indicative of the greater Lewis acidity of the BBr$_3$ moiety relative to BPh$_3$.

We next explored the ortho borylation of anilines (Scheme 6). In previous work, borenium mediated electrophilic borylation of anilines proceeded at the para position. Ortho borylated anilines are accessible e.g., by directed lithiation of carbamate functionalised anilines, 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 BBr₃, 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 BBr₃ 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 B₂EG₂ (EG = ethylene glycolate). This report is notable, but while excellent for N/C0H systems it is low yielding with N-Me substituted anilines (<25%), in contrast to the high yielding formation of 13f using just commercially available DCM solutions of BBr₃.

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 SEAr in indoles) due to the preference for the formation of six membered bora-cycles over seven. Functionalisation of the C5/C0H indoles is important for accessing pharmaceuticals such as C4-amino-C5-functionalised indoles (e.g. Branebrutinib). 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). Directed ortho electrophilic borylation of N−H and N−Me anilines. Pivaloyl-directed C−H borylation proceeds at 20°C (over the course of 3–16 h), whereas as the benzoyl congener requires heating at 60°C for 16 h.

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 BBr₃. The process is complementary to borylation with [(amine)BBr₂]+ and to iridium-catalyzed directed borylation as C6-substituted indoles are tolerated using BBr₃, while it has complementary functional group tolerance to directed lithiation methods. Notably, in a number of cases pinacol induced isomerisation of the initial borylated regioisomer 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 BBr₃ will be applicable to many other systems.

**Acknowledgements**

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**Conflict of interest**

The authors declare no conflict of interest.
Keywords: boranes · borenium · borylation · directing groups · electrophilic aromatic substitution


[19] Attempts to use B-bromo-catecholborane, targeting selective C7-borylation, did not lead to any borylation, even of the activated indole 2b.


[23] Compounds 16 and 19 are both prone to C5 protodeborylation on prolonged exposure to silica.

[24] CCDC 1922250, 1922251 and 1922252 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.
Acyl-Directed ortho-Borylation of Anilines and C7 Borylation of Indoles using just BBr₃

**B-directed:** Acyl-directed electrophilic C–H borylation provides access to novel C₅ and C7 borylated indoles using just BBr₃ as the borylating agent via the formation of six-membered boracycles.