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Catalytic Electrophilic C-H Borylation using NHC-Boranes and Iodine Forms C2-, not C3-, Borylated Indoles.**

John S. McGough^[a], Jessica Cid^[a] and Michael J. Ingleson^{*[a]}

Abstract: Activation of *N*-heterocyclic carbene boranes (NHC·BH₃) by I₂ enables the metal free catalytic C-H borylation of heteroarenes with formation of H₂ as the by-product in a process that uses only bench stable precursors. The borylation of indoles using NHC·BH₃/I₂ produces C2-borylated indoles exclusively in contrast to other catalytic electrophilic C-H borylation methods. Mechanistic studies indicate that this is due to C3 to C2 boron migration facilitated by the absence of exogenous Brønsted bases. Thus this C-H borylation methodology proceeds under sufficiently Brønsted acidic conditions to enable the thermodynamic C2-borylated indole isomer to be formed instead of the C3 borylated-isomer. This demonstrates that electrophilic C-H borylation can be used to access a wider range of borylated regioisomers than reported to date.

Due to the considerable utility of organo-boronic acid derivatives in modern synthesis¹ the development of new methods to construct C-B bonds, in particular directly from C-H precursors, is a field of significant topical interest.^{1b, 2} Transition metal catalysis has achieved considerable advances in this area,³ most notably using iridium catalysis which now represents a powerful synthetic tool.^{1b, 2} One alternative to iridium catalysed C-H borylation is transition metal free electrophilic C-H borylation,⁴ with early methods using stoichiometric main group Lewis acid activators to generate the requisite strong boron electrophile, thus producing stoichiometric by-products (e.g. [amineH][Anion]).⁵ Recent advances have utilised main group catalysts (Figure 1, top) to enable the intermolecular electrophilic C-H borylation of (hetero)arenes with H₂ the only by-product.⁶ Whilst notable, to date all these electrophilic C-H borylation procedures functionalise heteroarenes under electronic control and exclusively produce C3 borylated indoles.⁴⁻⁶ The inability of catalytic electrophilic C-H borylation to access other borylated heteroarene regioisomers, e.g. C2-borylated indoles, is a current limitation of this approach.

In contrast to the electrophilic C-H borylation of indoles, the electrophilic C-H palladation of indoles gives either C2 or C3 functionalised indoles depending on whether the reaction operates in the presence of a base (for C3-regioisomers) or the presence of a moderate/strong Brønsted acid (for C2-regioisomers).⁷ In the presence of a suitable Brønsted acid a

Figure 1: Top, previous main group catalysed electrophilic borylation, middle stoichiometric C2 borylation in the absence of base, bottom this work C2 borylation using NHC-boranes and sub-stoichiometric I₂ as catalyst.

mechanism involving initial palladation at the indole C3 position is still proposed to proceed, but deprotonation of the arenium cation is relatively slow or reversible. This enables migration of Pd from C3 to C2 prior to irreversible deprotonation.⁷ In contrast, in the catalytic electrophilic C-H borylation of indoles moderate Brønsted bases are present (or are evolved during borylation by amine dissociation from borenium cations, or by indole reduction producing indolines). This generally results in (i) rapid deprotonation of C3-borylated arenium cations, and/or (ii) rapid quenching of any other strong Brønsted acids.⁴⁻⁶ Therefore, only functionalization at the indole C3 position has been observed in all the catalytic electrophilic borylation processes reported to date. One route to developing a C2 selective electrophilic C-H borylation of indoles requires slow (relative to C3 to C2 boron migration) or reversible deprotonation of the C3-borylated arenium cation, a process facilitated by the absence of an exogenous base and / or the presence of a strong Brønsted acid.⁸ Precedence for this hypothesis is provided by the reaction of B(C₆F₅)₃ with *N*-Me-indole which over 10 days affords the C2-borylated arenium species (Figure 1 middle),⁹ indicating that migration of boron from C3 to C2 can occur in indoles in the absence of an effective exogenous Brønsted base.

Building on the seminal studies by Vedejs, Curran and Lacôte,¹⁰ we recently reported that NHC-boranes (NHC = *N*-heterocyclic carbene) activated with sub-stoichiometric iodine effect alkyne C-H borylation in the absence of exogenous base.¹¹ The turnover enabling step was proposed to involve the expected by-product from C-H borylation, HI, reacting with another equivalent of NHC·BR₂(H) to regenerate the active boron electrophile, NHC·BR₂(I), and H₂. Therefore this C-H borylation system operates under strongly Brønsted acidic conditions, thus potentially enabling formation of C2 borylated indoles. In addition, the C-H borylation of heteroarenes with NHC·BH₃/I₂ represents an attractive and relatively simple route

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to access (heteraryl)BH₂(NHC) compounds,¹² as iodine is an inexpensive activator, and NHC-boranes are readily synthesized (and commercially available)¹³ with both being bench stable. Furthermore, the products from C-H borylation using I₂/NHC-BH₃ are NHC-BH₂(Aryl), which are bench stable boranes useful in Suzuki-Miyaura coupling reactions,¹⁴ and as masked boronic acids.¹⁴ Herein we report the development of, and mechanistic studies into, a catalytic in I₂ C-H borylation methodology to form NHC-BH₂(indole) exclusively as the C2-borylated isomers in contrast to other catalytic electrophilic C-H borylation reactions.

1,2-dimethyl imidazolylidene borohydride (Ime₂-BH₃, **1**) was synthesized on multigram scale from NaBH₄ and the imidazolium iodide using the route of Curran and co-workers.¹² Consistent with previous reports, the addition of 0.5 equivalents of I₂ to **1** in *ortho*-dichlorobenzene (o-DCB) results in evolution of H₂ and formation of Ime₂-BH₂, **2**, as indicated by a triplet in the ¹¹B NMR spectrum at -31.7 ppm (¹J_{BH} = 112 Hz).¹⁵ To determine if **2** is an effective electrophile for S_EAr compound **1** was combined with 5 mol% I₂ and *N*-Me-indole (2 equiv.) was added. No borylation was observed at ambient temperature or at 60 °C but heating at 130 °C led to the production of one major new product at -30.8 ppm in the ¹¹B NMR spectrum (triplet, ¹J_{BH} = 84 Hz); a number of minor resonances also were observed including a doublet at -23.9 ppm. The identity of the major product was shown to be the C2-borylated *N*-Me-indole by multinuclear NMR spectroscopy and X-ray crystallography. Therefore borylation under these base free conditions yields the C2 isomer, *N*-Me-2-(BH₂(Ime₂))-indole, **3a** (Figure 2, inset), and not the C3 isomer. With its identity in hand the *in-situ* conversion to **3a** was determined to be 47 % (based on **1**).

Figure 2. Top, C2-borylation of *N*-Me-indole, inset top right, solid state structure of **3a** (ellipsoids at 50% probability, hydrogens omitted except on boron). Bottom, effect of catalyst and reagent ratio of conversion to **3a** / **4**.

Attempts using higher loadings of I₂, did lead to a greater conversion, but there was also an increase in the by-product corresponding to the -23.9 ppm doublet in the ¹¹B NMR spectrum. Surmising that this was due to double S_EAr by a single boron centre as observed in the catalytic sila-Friedel Crafts reaction of indoles,¹⁶ the amount of *N*-Me-indole was increased to 7 equivalents. This led to the formation of a 3:2 mixture of **3a** and compound **4** (Figure 2, bottom) which could be separated by chromatography. Multinuclear NMR and mass spectroscopy confirmed that this by-product was indeed the

double indole S_EAr product **4**. Upon optimisation, 1.25 eq. of indole : **1** proved to be the best ratio for maximising conversion to **3a** while minimising formation of **4**. Using 1.25 eq. of a substituted indole and 5 mol% of I₂ revealed that a range of indoles underwent borylation at C2 (Figure 3) indicating this is a general method for achieving C2-borylation under electrophilic conditions. Under these conditions, no indoline was observed during C-H borylation. Notably the borylated indoles **3a-d** are stable to column chromatography and even to boiling water (used to remove unreacted **1**) highlighting their suitability as stabilised masked boronic acids. This protocol was also viable for the borylation of 2-methylthiophene. However, the yields of all the borylated products were moderate at best, with the major mass balance being **1**, with minor amounts of (heteroaryl)₂B(H)(Ime₂) species analogous to **4** also observed.

Figure 3. C-H borylation using **1** / 5 mol% I₂. Conversions are *in-situ* by ¹H NMR spectroscopy relative to mesitylene as an internal standard.

Attempts to improve the conversion using other NHC-BH₃ activators were performed. The addition of Brønsted acids containing more coordinating (relative to I⁻) anions, including HOTs, HCl and CF₃COOH, formed the desired NHC-BH₂X compound as previously reported.¹⁵ However, these species did not result in any borylation of *N*-Me-indole at 130 °C in o-DCB. Activators that contain/form less nucleophilic anions (than I⁻), such as HNTf₂, B(C₆F₅)₃ and Ph₃C[B(C₆F₅)₄] were also explored. The use of sub-stoichiometric quantities of these three activators with **1** led to the hydride bridged diborane {[Ime₂-BH₂]₂(μ-H)}⁺, termed **[6]**⁺ (Scheme 1),^{10, 17} as expected (and also confirmed crystallographically). Notably, on heating mixtures of **1** / **[6]**⁺ in the presence of heteroarenes led to the boronium cation, **[7]**⁺ (δ_{11B} = -33.1, t ¹J_{BH} = 89 Hz), being formed, with no significant borylation of *N*-Me-indole or 2-Me-thiophene (< 10% conversion in all cases) observed over a range of catalyst loadings. The identity of **[7]**⁺ was confirmed by independent synthesis, NMR and mass spectroscopy.

Scheme 1. Activation of **1** leading to the boronium cation **[7]**⁺ on heating.

The addition of weak exogenous bases 2,6-dichloropyridine (Cl₂-py) and NPh₃, whose conjugate acids are strongly Brønsted

acidic, also was explored to facilitate borylation. However, with **1** / *N*-Me-indole (or 2-Me-thiophene) and I_2 or $B(C_6F_5)_3$ no C-H borylation occurred in the presence of these two bases. Furthermore, with Cl_2 -py boronium salts $[IMe_2\text{-}BH_2(Cl_2\text{-}py)][\text{Anion}]$ were observed. Combined the above results indicate that iodide is essential in $NHC\text{-}BH_2X$ presumably as it provides an optimal nucleophilicity (more than $NHC\text{-}BH_3$ thus preventing formation of $[6]^+$ and thus $[7]^+$, but low enough to be displaced by a heteroarene), low Brønsted basicity (thus deprotonation is relatively slow or reversible under these conditions) and the generated acid (HI or a protonated indole) is able to react with further equivalents of **1** to regenerate **2** enabling turnover.

As modifying the activator / reaction conditions (i.e. temperature or duration) failed to improve C-H borylation yields variation in the NHC was explored next. It was hypothesized that increasing the NHC steric bulk would help prevent deactivation reactions and the formation of double borylation products (such as **4**). Therefore $IPr_2\text{-}BH_3$ (**8**, IPr_2 = *N,N'*-diisopropyl imidazolyldiene), $IPr_2Me_2\text{-}BH_3$ (**9**, IPr_2Me_2 = *N,N'*-diisopropyl-3,4-dimethyl imidazolyldiene) and $IMes\text{-}BH_3$ (**10**, $IMes$ = *N,N'*-bis(2,4,6-trimethylphenyl) imidazolyldiene) were synthesised using established routes, and utilised in the borylation of *N*-Me-indole using the conditions optimised with **1** (Figure 4).

Figure 4. Borylation of *N*-Me-indole with NHC-boranes containing NHCs of varying steric demand. Inset solid state structure of **11c2** (hydrogens omitted for clarity and thermal ellipsoids at 50 % probability).

C-H borylation is effective with **8** and **9** with an increase in yield using these two NHC-boranes. The *in-situ* NMR spectra for borylation using **9** revealed no doubly borylated product analogous to **4** and significantly fewer minor products in the ^{11}B NMR spectrum, and again there was no evidence for indoline formation (by 1H NMR spectroscopy). The much lower yield using **10** is notable as based on percentage buried volume ($\%V_{bur}$)¹⁸ values derived from transition metal NHC complexes the four NHCs used herein appear to have comparable steric demand. To determine the NHC steric impact in $NHCBH_3$ complexes the previously reported solid structures of **1**, **8**, **9** and **10** were used to calculate modified $\%V_{bur}$ values, termed $\%V_{bur}(B-C)$ values using a B-C distance of 1.59 Å.^{12, 19} The $\%V_{bur}(B-C)$ is now significantly greater for IMes relative to those for transition metal complexes, and also greater for IMes in **10** than that for the NHCs in **1**, **8** and **9** (Figure 4, bottom). Thus the slower C-H borylation reaction with **10** is attributed to the considerably larger steric demand of IMes increasing kinetic barriers during the borylation reaction.

Scheme 2. The synthesis of **11c3** via stoichiometric electrophilic borylation.

As the regioisomer (C2 or C3) produced by C-H borylation can be sensitive to steric effects it was important to confirm which borylated regioisomer is formed with the bulkier NHC-boranes. Multinuclear NMR spectroscopy was consistent with indole C2 borylation and for the product derived from **9**, **11c2**, an X-ray diffraction study also confirmed C2-borylation (inset Figure 4). Furthermore, the C3-borylated isomer, **11c3**, was synthesized for comparison using an ambient temperature stoichiometric (in activator) electrophilic C-H borylation route commencing from $[IPr_2Me_2BCl_2][AlCl_4]^{20}$ and using tri-*t*-Bu-pyridine (TBP) as exogenous base (Scheme 2). The dichloroborane initial product was converted to the dihydroborane **11c3** by treatment with excess $LiAlH_4$. While the δ_{11B} for **11c3** and **11c2** are comparable, the 1H NMR spectra are diagnostic as the indole C2-*H* resonance for **11c3** is observed at 6.39 ppm, whereas **11c2** has a C3-*H* resonance at 5.56 ppm (a comparable δ_{1H} to that observed in **3a**). It is particularly noteworthy that borylation using $[IPr_2Me_2BCl_2][AlCl_4]$ in the presence of a base at 20 °C leads to C3 borylation exclusively whilst that using $NHC\text{-}BH_3/I_2$ at higher temperatures and in the absence of base leads to the C2 isomer

Figure 5. Reaction conditions: **9**, 10 mol% I_2 , 1.25 equivalents arene, 170 °C, 24 hours. *In-situ* yields versus Me_4Si as an internal standard. Isolated yields are given in parentheses. ^ 0.5 equivalents of heteroarene.

A range of indoles were amenable to catalytic borylation using $9/I_2$ and the products were readily isolated in moderate yields. The use of the benzyl protecting group was viable with **9** with only C2 regioisomers again observed. Notably, stabilising and destabilising (towards the C2-borylated arenium cation that is formally cationic at the three coordinate C3 position) F and Cl substituents (σ_p^+ values -0.07 and +0.11) at the C6 position both led to C2 borylated products (Figure 5). The forcing conditions and reactive boron electrophiles present in this methodology do however result in functional group incompatibilities (i.e. with CF_3 , NO_2 and OMe). In contrast, other activated heteroarenes including pyrroles and thiophenes were compatible, as were C3 substituted indoles.

The mechanism leading to (indole)BH₂(NHC) could proceed via (i) electrophile addition at C3, C3 to C2 migration and then deprotonation, or (ii) direct insertion of the boron electrophile at C2-H (with concomitant H₂ evolution) followed by hydride transfer from NHC·BH₃ to (indole)BH(I)(NHC). The latter mechanism is observed for intramolecular C-H borylations with [(amine)BH₂]⁺ species.²¹ With NHC·BH₃/I₂ we disfavoured mechanism (ii) based on the absence of a KIE during *N*-Me-indole borylation using **1** or IMe₂·BD₃ (**1b₃**) activated with I₂. The transition state for the C-H insertion mechanism involves considerable B-H elongation, thus the absence of a KIE using **1** (**1b₃**)/I₂ disfavors an analogous mechanism. Furthermore, the borylation of *N*-Me-indole and its isotopomer deuterated at C2 with **1** / I₂ resulted in a KIE of 2.2. For S_EAr proceeding in the presence of a strong Brønsted acid a KIE > 1 has been observed previously as deprotonation of the arenium cation becomes rate limiting (instead of formation of the σ complex being rate limiting which is more common in S_EAr reactions).²² The KIE value using **1** is also consistent with those for electrophilic palladations in the presence of Brønsted acids.⁷ Furthermore, in indole borylation C3 to C2 migration leads to the thermodynamic product based on the relative electronic energies of the two isomers (calculated at the M06-2X/6-311G(d,p) level, with PCM DCM) showing that **3a** is lower in energy than the C3-isomer by 3.9 kcal mol⁻¹.

With the above observations supporting a S_EAr mechanism it is notable that 1,2-dimethylindole and 2-phenyl-*N*-methyl-indole result in no C3 borylated product using **1** or **9** / I₂. C3-borylated indoles are more prone to protodeboration than the C2 regioisomers under acidic conditions,²³ thus it is feasible that C3 borylated isomers are formed reversibly under these conditions but only the C2-isomer is sufficiently robust towards protodeboration to accumulate. To test this **11c₃** was heated for 24 h at 130 °C which resulted in minimal consumption of **11c₃**. However, adding **11c₃** to a mixture of **9** / I₂ / *N*-Me-Indole and heating to 130 °C for 24 h (conditions that generate HI or another Brønsted acid as the by-product from S_EAr) led to the complete consumption of **11c₃** (and formation of **11c₂**). This confirms the presence of a strong Brønsted acid during catalytic indole C-H borylation and that protodeboration (or protonation and migration of boron to C2) of **11c₃** does occur. A mechanism consistent with these observations is provided in Scheme 3.

Scheme 3. Proposed cycle for C2 indole borylation. The Brønsted acid is shown as HI, it is also feasible to be a protonated indole. Furthermore, deprotonation could be of other indole arenium tautomers after H migration.²⁴

In conclusion, herein we demonstrate that catalytic electrophilic C-H borylation using NHCBH₃/I₂ represents a simple route to form (heteroaryl)BH₂(NHC) complexes that previously have been shown to be useful synthetic intermediates. Furthermore, this method furnishes C2-borylated indoles instead of the C3 regioisomers normally formed via S_EAr borylation. The key to accessing C2-regioisomer products is the use of NHC·BH₃/I₂ which enables C-H borylation to be performed in the absence of an effective Brønsted base, and instead borylation is operating in the presence of a competent Brønsted acid. These conditions therefore are distinct to other catalytic electrophilic C-H borylation methodologies and indicate that it is possible to access a wider range of borylated products via boron-Freidel-Crafts approaches than has been reported to date.

Keywords: boranes • C-H activation • borylation • electrophilic substitution • Lewis acids

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Entry for the Table of Contents

COMMUNICATION

John S. McGough, Jessica Cid and
Michael J. Ingleson*

**Catalytic Electrophilic C-H Borylation
using NHC-Boranes and Iodine Forms
C2-, not C3-, Borylated Indoles.****

Borylated indoles: I'll C2 it. Activation of *N*-Heterocyclic carbene boranes by I_2 enables the metal free catalytic C-H borylation of heteroarenes with formation of H_2 as the by-product in a process that requires only bench stable precursors. The C-H borylation of indoles using $NHC-BH_3/I_2$ produces C2-borylated indoles exclusively in contrast to other catalytic electrophilic C-H borylation methods.