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Ni-catalyzed traceless, directed C3-selective C-H borylation of indoles

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ABSTRACT: A highly efficient and general protocol for traceless, directed C3-selective C-H borylation of indoles with [Ni(IMes)$_2$] as the catalyst is reported. Activation and borylation of N-H bonds by [Ni(IMes)$_2$] is essential to install a Bpin moiety at the N-position as a traceless directing group, which enables the C3-selective borylation of C-H bonds. The N-Bpin group which is formed is easily converted *in situ* back to an N-H group by the oxidiative addition product of [Ni(IMes)$_2$] and *in situ*-generated HBpin. The catalytic reactions are operationally simple, allowing borylation of a variety of substituted indoles with B$_2$pin$_2$ in excellent yields and with high selectivity. The C-H borylation can be followed by Suzuki-Miyaura cross-coupling of the C-borylated indoles in an overall two-step, one-pot process providing an efficient method for synthesizing C3-functionalized heteroarenes.

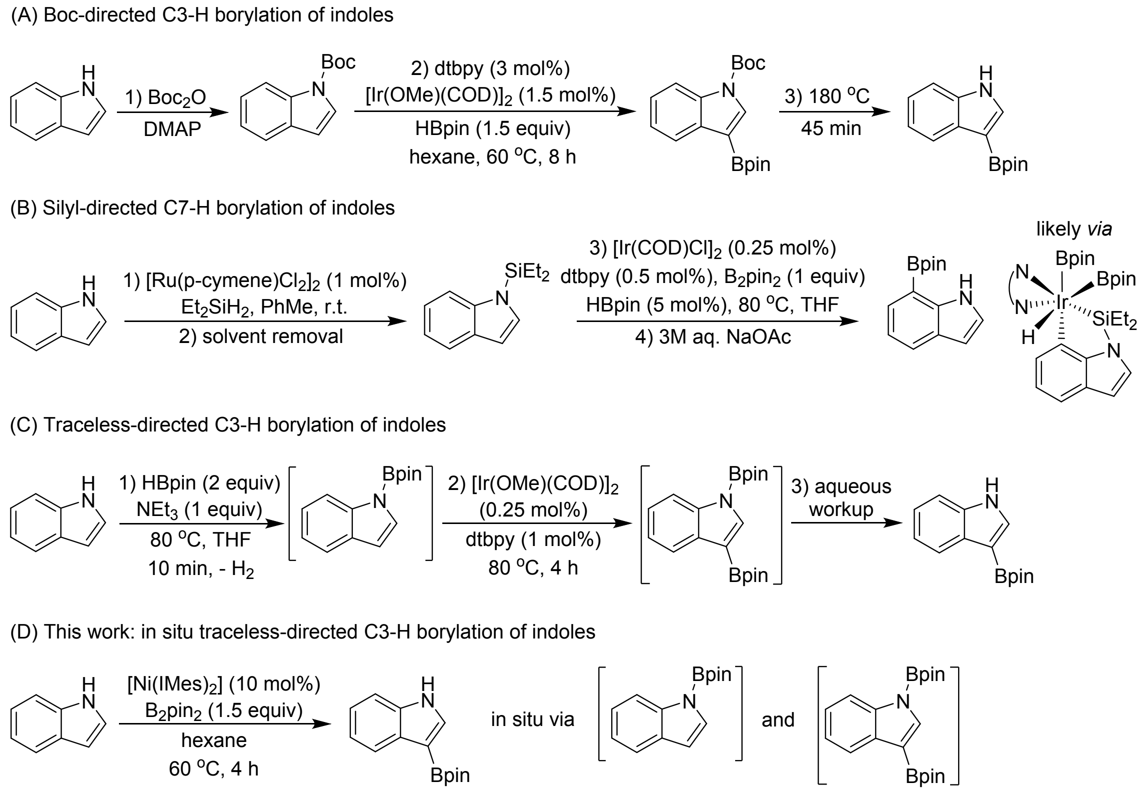
INTRODUCTION

Indoles have important biological functions, and construction of the ring from other substrates or direct functionalization of an existing indole are the usual approaches employed in synthesizing substituted derivatives.[1] Borylated indoles are of particular interest because they can serve as versatile building blocks for the construction of functional molecules.[2] Recently, transition metal-catalyzed direct C-H borylation has emerged as a powerful tool for the construction of C-B bonds due to its broad functional group tolerance and substrate scope allowing late-stage functionalization without the use of protecting groups.[2,3] The regioselectivity of the C-H functionalization of unprotected indoles, which have seven different sites, is typically driven by electronic effects. Therefore, C-H borylation reactions occur predominantly at the C2 position which contains the most acidic and reactive C-H bond.[4] However, the selectivity can be overridden by steric factors. Many groups including Ishiyama and Miyaura,[4] Hartwig,[5] Ito,[6] Marder,[7] Tobisu and Chatani,[8] Chattopadhyay,[9] Maleczka and Smith[10] *et al.* have reported the selective borylation of indoles using mainly Ir, but also Rh, Pt, Co, Ni and other catalysts.[11] Metal-free catalytic C-H borylation is also an attractive alternative as it offers a simple and cheap route to borylated indoles under mild conditions.[12]

Directing groups are usually employed to control regioselectivity in C-H functionalizations.[13] For example, Maleczka and Smith *et al.* used *tert*-butoxycarbonyl (Boc) as a directing group in the Ir-catalyzed C-H borylations of pyrroles, indoles, azaindoles, and pyrazoles ,and observed selective functionalization of the N-Boc-protected heterocycles at positions β to the N atoms (Scheme 1A).[10b] Hartwig and co-workers developed a one-pot protocol consisting of the Ru-catalyzed installation of a silyl group at the indole N-atom, Ir-catalyzed borylation of the silylindole, and subsequent hydrolysis of the N-silyl group to obtain C7-borylated indoles selectively (Scheme 1B).[5b] The groups of Ingleson, Houk and Shi employed a pivaloyl moiety as an effective directing group at the N-position to enable the C7 borylation of indoles and *ortho*-borylation of anilines simply by using BBr_3.[12j,l] The latter group also found that installation of pivaloyl groups at the C3 position of indoles enables borylation at the unfavorable C4 position.[12l]

Although site-selective C-H functionalization can be efficiently achieved with the assistance of directing groups, some difficult to remove or modify, thus limiting the practical application of this methodology. Therefore, employing traceless directing groups would be an attractive alternative to the traditional methods. Krska, Maleczka, Smith *et al.* demonstrated that the (pinacolato)boryl (Bpin) moiety can serve as a traceless directing group for selective Ir-catalyzed C-H borylation of indoles at the C3 position (Scheme 1C).[10d] The addition of a tertiary amine base ensures the borylation of the nitrogen atom. The N-Bpin moiety formed enables further Ir-catalyzed regioselective borylation of C3-H bonds, and an aqueous workup was subsequently required to remove the N-bound Bpin group to give the final 3-Bpin-indole product.

Scheme 1. Examples of directed C-H borylation of indoles

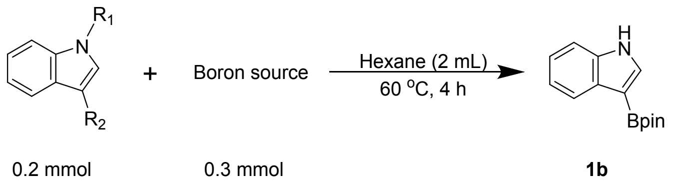


N-Heterocyclic carbene (NHC) transition metal complexes have proven to be efficient for homogeneous catalytic C-H activation.[8,14] Nakao, Hartwig *et al.* demonstrated an *anti*-Markovnikov addition of arenes and heteroarenes to alkenes catalyzed by a hindered Ni-NHC system.[14b,h] Tobisu, Chatani *et al.* developed [Ni(ICy)$_2$] (ICy = 1,3-dicyclohexylimidazolin-2-ylidene) which showed excellent activity for the borylation of arenes and N-substituted heteroarenes with B$_2$pin$_2$.[8a] Selective borylation of indoles was achieved at the reactive C2 position. Recently, Hahn *et al.* reported that unsubstituted 2-halogenoazoles undergo N-H oxidative addition with [Ni(PEt$_3$)$_2$] forming a Ni^{II}

hydride complex, rather than C-metalation of the C-Cl bond, at low temperature in THF.[15] In light of these findings and our long-standing interest in catalytic borylation reactions based on different NHC-metal complexes,[16] we report herein a highly selective traceless, directed C3-H borylation of indoles that employs [Ni(IMes)$_2$] (IMes = 1,3-dimesitylimidazoline-2-ylidene) as a catalyst without an additional base or hydrolysis to achieve: 1) *in situ* installation of Bpin as a traceless directing group at the indole N-position; 2) catalytic C3-H borylation; and 3) deprotection of the N-Bpin moiety back to an N-H group to provide C3-borylated indoles with excellent activity and selectivity (Scheme 1D).

■ RESULTS AND DISCUSSION

Table 1. Control experiments for the directed C3-H borylation of different indoles



Entry	Substrate	Boron source	[Ni(IMes)$_2$] (10 mol%)	Yield of 1b (%)[a]
1	R_1 = H, R_2 = H	B_2pin_2	√	89
2	R_1 = H, R_2 = H	B_2pin_2	⍰	-
3	R_1 = H, R_2 = H	HBpin	√	7
4	R_1 = H, R_2 = H	HBpin	⍰	-
5	R_1 = Bpin, R_2 = H	B_2pin_2	√	91
6	R_1 = Bpin, R_2 = H	B_2pin_2	⍰	-
7	R_1 = Bpin, R_2 = H	HBpin	√	trace[b]
8	R_1 = Bpin, R_2 = H	HBpin	⍰	-
9	R_1 = Bpin, R_2 = Bpin	B_2pin_2	√	trace
10	R_1 = Bpin, R_2 = Bpin	B_2pin_2	⍰	-
11	R_1 = Bpin, R_2 = Bpin	HBpin	√	94
12	R_1 = Bpin, R_2 = Bpin	HBpin	⍰	-

[a]Yields are based on indoles and were determined by GC-MS analysis *vs.* a calibrated internal standard and are averages of two runs. [b]The yield of indole was *ca.* 50% apart from **1b**.

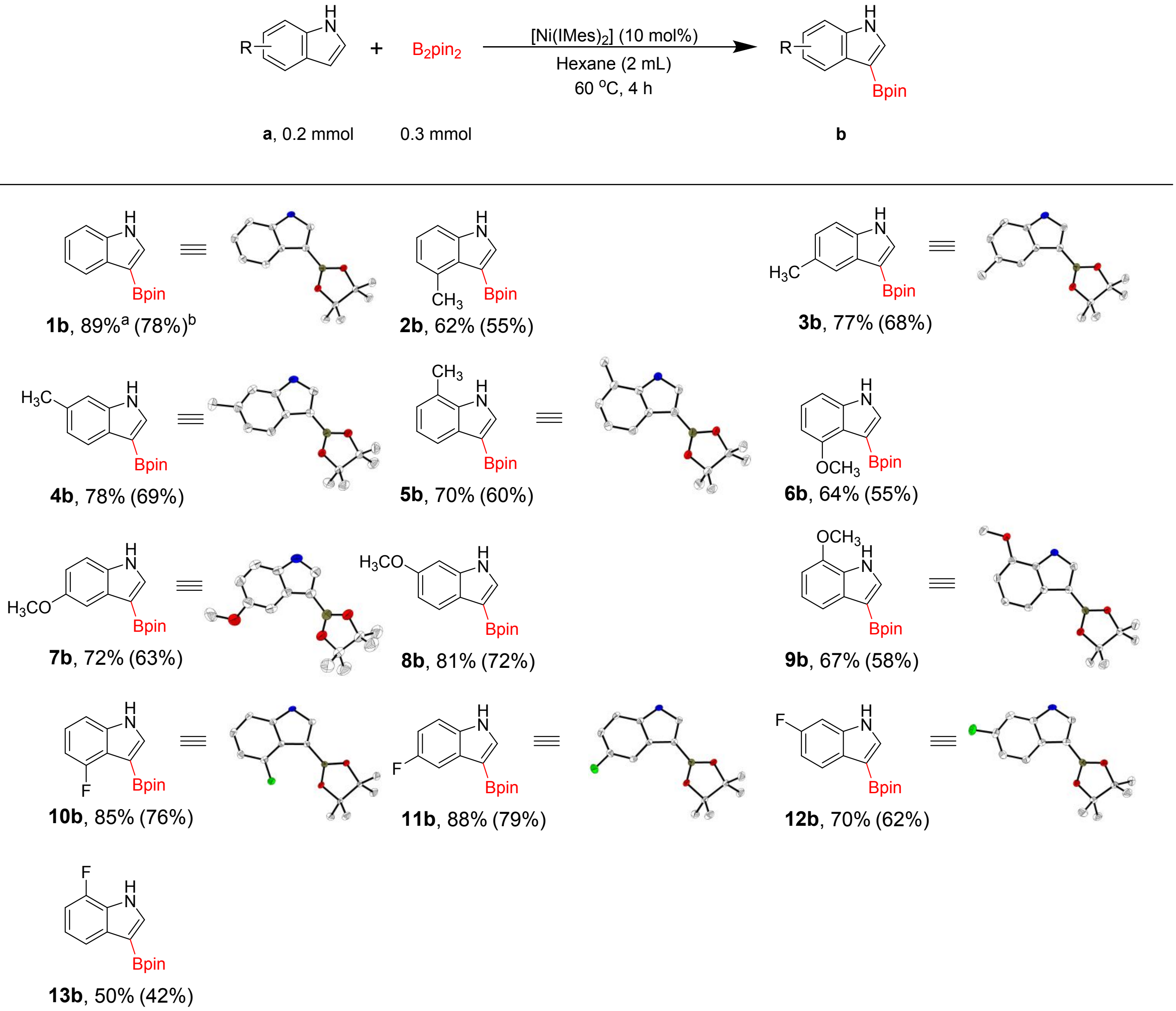
We first investigated the efficiency of the directed borylation reaction of indole (**1a**) with B_2pin_2 using 10 mol % [Ni(IMes)$_2$] as the catalyst and hexane as solvent at 60 ˚C. This initial result gave 3-Bpin-indole (**1b)** in an excellent yield of 89% with high selectivity for the C3 position after 4 h (Table 1, entry 1). A range of solvents was screened, with hexane proving to be optimal (Table S1). The non-polar solvent methylcyclohexane gave almost the same yield of **1b** as obtained in hexane, but the reactivity was low in polar solvents. Dichloromethane and acetonitrile, respectively, completely quench the reaction. The yield of **1b** is higher at a reaction temperature of 60 ˚C than that at 30-50 ˚C, but decreased significantly with decreasing number of equiv. of B_2pin_2 (Figure S1). When HBpin was employed as the boron source instead of B_2pin_2, only a 7% yield of **1b** was achieved (Table 1, entry 3). It is important to note that no reaction occurred in the absence of the [Ni(IMes)$_2$] catalyst (Table 1, entries 2 and 4).

We further examined the scope of indoles for the directed borylation with [Ni(IMes)$_2$] under the optimized conditions, and the results are summarized in Table 2. Indoles with either electron-donating (**2a-9a**) or electron-withdrawing (**10a-13a**) groups reacted smoothly to afford corresponding C3-borylated indoles in good to excellent yields, suggesting the excellent functional group tolerance of this method. The positions of Me and MeO substituents on the benzenoid unit of indole did not significantly affect the catalytic activity; placing them at the C5 or C6 positions resulted in slightly higher yields of products than when they were placed at the C4 or C7 positions (**2a-9a**). Because fluorinated organic compounds have exceptional properties that are being exploited in many applications,[17] it is important to note that fluoroindoles underwent C3-H borylation with fluoride moiety remaining intact under our conditions (**10a-13a**). Interestingly, 4-F-indole (**10a**) and 5-F-indole (**11a**) exhibited higher yields of products than 6-F-indole (**12a**) and 7-F-indole (**13a**) revealed the lowest activity with only a 50% yield of 3-Bpin-7-F-indole (**13b**). The C3 selectivity of the C-H borylation reported here was confirmed by the molecular structures of **1b**, **3b-5b**, **7b**, and **9b-12b** obtained by single-crystal X-ray diffraction.

Preliminary mechanistic studies were conducted to provide insight into the directed C3-H borylation process with the [Ni(IMes)$_2$] catalyst. First, we monitored the borylation of **1a** by GC–MS analysis. As shown in Table S2 (Supporting Information) and Figure 1, the yield of **1b** increased with longer reaction times. Importantly, the N-H monoborylation product 1-Bpin-indole (**1c**) and diborylation product 1,3-(Bpin)$_2$-indole (**1d**) were detected during the reaction. Compounds **1c** and

1d reached their maximum yields of 36% and 28% after 10 min and 30 min, respectively, and then the yields decreased to trace amounts at 1.5 and 4 h, respectively. The above results suggest that the N-borylated compound **1c** and the bis N/C3-borylated compound **1d** are important intermediates in the formation of **1b**.

Table 2. Substrate scope for the C3-H borylation of indoles with $[Ni(IMes)_2]$



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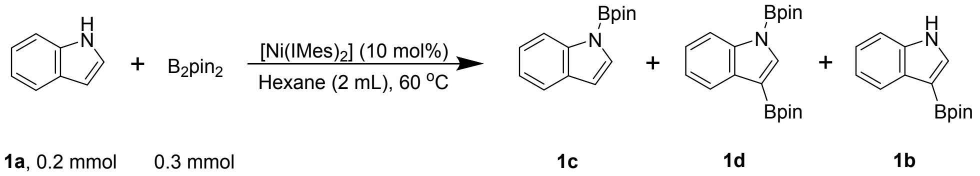
[a] The yields are based on indoles and were determined by GC-MS analysis vs. a calibrated internal standard and are averages of two runs. [b] Isolated yields based on 1 mmol indoles are given in parentheses.



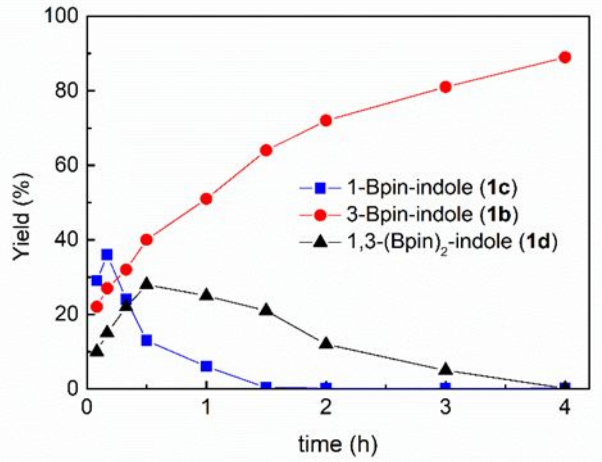


Figure 1. Yields of 1-Bpin-indole (**1c**), 1,3-(Bpin)$_2$-indole (**1d**) and 3-Bpin-indole (**1b**) as a function of time. The yields are based on indoles and were determined by GC-MS analysis.

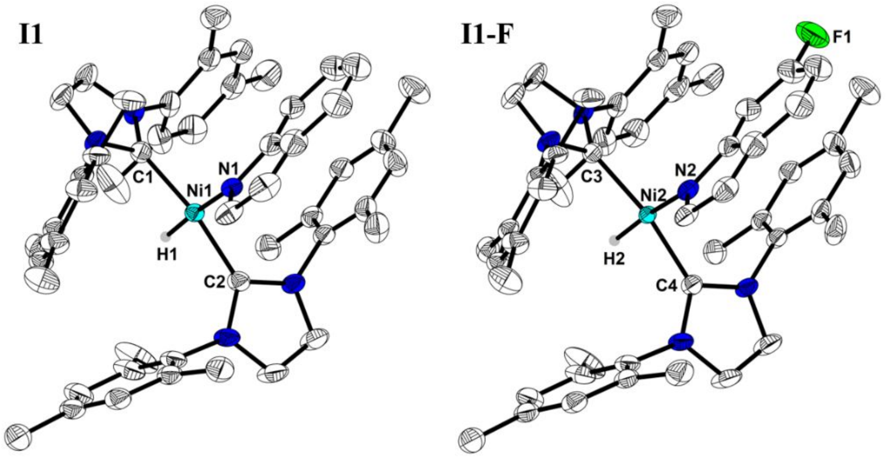


Figure 2. Molecular structures of [Ni(IMes)$_2$(H)(*N*-indolyl)] (**I1**) and [Ni(IMes)$_2$(H)(6F-*N*-indolyl)] (**I1-F**) from single-crystal X-ray diffraction data at 100 K. Atomic displacement ellipsoids are drawn at the 50% probability level, and some hydrogen atoms are omitted for clarity. Selected bond lengths (Å) and angles (deg) for **I1**: Ni(1)-C(1) 1.9047(18), Ni(1)-C(2) 1.9047(18), Ni(1)-N(1) 1.954(3), Ni(1)-H(1) 1.38(3); C(1)-Ni(1)-N(1) 100.3(2), C(1)-Ni(1)-H(1) 83.18(7), C(1)-Ni(1)-C(2) 166.3(1), C(2)-Ni(1)-N(1) 93.3(2), C(2)-Ni(1)-H(1) 83.18(7), N(1)-Ni(1)-H(1) 172.3(1). Selected bond lengths (Å) and angles (deg) for **I1-F**: Ni(2)-C(3) 1.906(3), Ni(2)-C(4) 1.906(3), Ni(2)-N(2) 1.951(5), Ni(2)-H(2) 1.43(7); C(3)-Ni(2)-N(2) 100.7(2), C(3)-Ni(2)-H(2) 83.2(1), C(3)-Ni(2)-C(4) 166.3(2), C(4)-Ni(2)-N(2) 92.8(2), C(4)-Ni(2)-H(2) 83.2(1), N(2)-Ni(2)-H(2) 170.7(1).

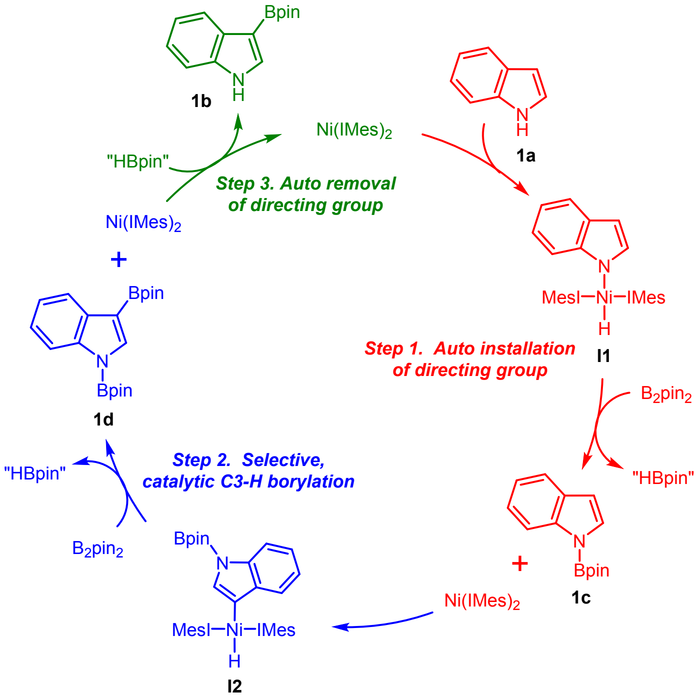
We also noted that the color of most [Ni(IMes)$_2$]-catalyzed indole borylations changes from dark purple to orange-yellow very quickly. *In situ* ^{1}H NMR spectra of the reaction 0.04 mmol of **1a** with 0.5 equiv of B_2pin_2 in the presence of 0.5 equiv of [Ni(IMes)$_2$] showed that the N-borylated compound **1c** was formed at the very beginning of the reaction (Figure S60). In addition, a resonance at δ -21.18 ppm suggested the formation of a Ni^{II} hydride complex (Figure S60). After heating at 60 ˚C for 30 min, **1a** was completely converted to **1c** and the Ni^{II} hydride complex (Figures S61). The reaction of 1 mmol of **1a** and 1 mmol of **12a**, respectively, with 1 equiv of [Ni(IMes)$_2$] in hexane (i.e., without B_2pin_2) was conducted at 60 ˚C for 4 h, yielding 76% and 75% of the corresponding Ni^{II} complexes [Ni(IMes)$_2$(H)(*N*-indolyl)] (**I1**) and [Ni(IMes)$_2$(H)(6F-*N*-indolyl)] (**I1-6F**). After isolation, the NMR spectra (Figure S52-S56) and X-ray diffraction analysis (Figure 2) confirmed the formation of Ni^{II} complexes **I1** and **I1-6F**, which result from an oxidative addition of the indole N-H bond to the Ni^0 complex [Ni(IMes)$_2$]. These results indicate that the facile activation of the N-H bond by [Ni(IMes)$_2$] generates intermediate **I1**, which then reacts with B_2pin_2 to give **1c**.

Reaction of **1c** with B_2pin_2 in the absence of [Ni(IMes)$_2$] was not detected (Table 1, entry 6). However, the reaction with 10 mol % [Ni(IMes)$_2$] gave **1b** in an excellent yield of 91% and a trace of **1d** at 60 ^{o}C for 4 h (Table 1, entry 5), indicating that **1c** requires the Ni-catalyst to form **1d**. *In situ* ^{1}H NMR spectra of the reaction of **1c** with [Ni(IMes)$_2$] clearly showed that the oxidative addition of the C3-H bond by the Ni^0 complex formed [Ni^{II}(IMes)$_2$(H$_{C3}$)(1-Bpin-indole)] (**I2**, Figure S62). Therefore, with [Ni(IMes)$_2$] and B_2pin_2, the conversion of **1c** to **1d** appears to occur *via* formation of intermediate **I2**. When HBpin was employed as the boron source instead of B_2pin_2 for the borylation of **1c**, there was no reaction without [Ni(IMes)$_2$] (Table 1, entry 8). When [Ni(IMes)$_2$] was present, HBpin as the boron source led to only trace amounts of **1d**; however, *ca*. half of **1c** was converted to **1a** (Table 1, entry 7)**.** This suggests that the conversion of N-Bpin to N-H is achieved by reaction with HBpin in the presence of [Ni(IMes)$_2$]. When **1d** was used as the substrate, it did not react with either B_2pin_2 or HBpin in the absence of [Ni(IMes)$_2$] (Table 1, entries 10 and 12). With [Ni(IMes)$_2$], B_2pin_2 as the boron source gave only a trace of **1b** (Table 1, entry 9), whereas reaction of HBpin with **1d** efficiently yielded 94% of **1b** (Table 1, entry 11).

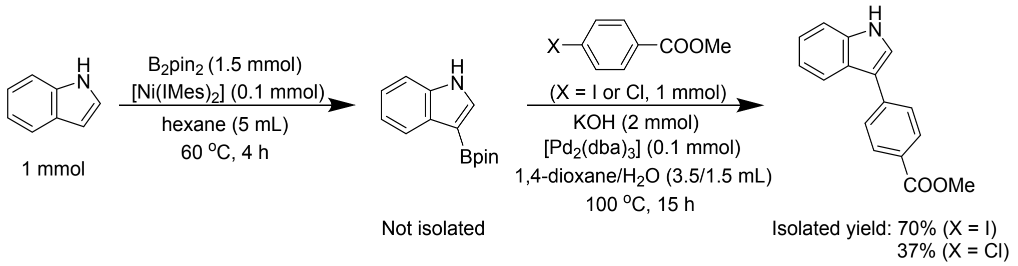
In light of these findings, a plausible mechanism for the C3-selective borylation of indoles with [Ni(IMes)$_2$] is shown in Scheme 2. First, the indoles undergo rapid N-H oxidative addition to [Ni(IMes)$_2$] to give the Ni^{II} hydride complex **I1**, which further reacts with B_2pin_2 *in situ* to install Bpin as a traceless directing group at the indole N-position to produce **1c** and release [Ni(IMes)$_2$].

Then, the regenerated [Ni(IMes)$_2$] catalyzes the C3-borylation of **1c**; [Ni(IMes)$_2$] thus inserts into the C3-H bond of **1c** to form the Ni^{II} hydride complex **I2**, which is converted with B$_2$pin$_2$ to the bis-N/C3-borylated indole **1d**, a step which also regenerates the Ni^0 complex [Ni(IMes)$_2$]. Finally, it appears that this, or another Ni-complex present in the reaction mixture, also catalyzes the removal of the directing group, i.e., that the conversion of N-Bpin to N-H to form the final C3-borylated indole **1b** is achieved by the [Ni(IMes)$_2$]-catalyzed reaction of **1d** with a source of hydrogen atoms, which we depict in Scheme 2 as *in situ* generated HBpin. While we do not observe HBpin by *in situ* GC-MS during the course of the reactions, and do not yet know the intimate details of this final step in the cycle, as the reaction proceed smoothly under an inert atmosphere and in carefully dried solvents, it would appear that the hydrogen atom source must be generated in the N-H or C-H activation steps.

Scheme 2. Plausible mechanism for the traceless-directed C3-selective C-H borylation of indoles with [Ni(IMes)$_2$]



Scheme 3. A one-pot C3-H borylation/Suzuki-Miyaura cross-coupling sequence for synthesis of C3-arylated indole



Arylindoles are key building blocks in many natural products and pharmaceuticals.[18] C3-Arylated indoles are particularly important because of their diverse biological activities such as antimicrobial, anti-inflammatory, and anticancer activities.[19] Thus, as a proof of principle, to demonstrate the synthetic utility of our protocol, a one-pot C3-H borylation / Suzuki-Miyaura cross-coupling sequence for the direct synthesis of C3-arylated indole was also investigated using the parent indole **1a** (Part VI in the Supporting Information). The *in situ* formed 3-borylated indole **1b** was directly employed in one-pot cross-coupling reactions with methyl 4-iodobenzoate and methyl 4-chlorobenzoate, using [$Pd_2(dba)_3$] (dba = dibenzylideneacetone) as the catalyst precursor (Scheme 3). The product 3-(methyl-4-benzoate)-indole was obtained in 70% and 37% isolated yield, respectively, demonstrating the potential for employing this C3-borylation methodology for the tandem synthesis of C3-arylated indoles. Finally, and in response to queries of the referees, we note that preliminary studies indicate that substrates such as pyrrole, a C2-substituted indole, and an indole containing an ester functionality can be borylated under these conditions, but the current corona virus situation and the resulting laboratory shut down has precluded more detailed studies of these and additional substrates at the moment.

■ CONCLUSIONS

We have developed an efficient, traceless, directed C3-selective C-H borylation of indoles with B_2pin_2 using [$Ni(IMes)_2$] as the catalyst. The reaction proceeds without any base and under mild conditions, displays broad scope and functional group tolerance, and furnishes borylated indoles in good to excellent yields with high selectivity. Bpin, as a traceless directing, group is installed at the N-position via activation of the N-H bond by [$Ni(IMes)_2$]. The N-borylated indole formed undergoes catalytic C3-selective C-H borylation with regenerated [$Ni(IMes)_2$] to form the bis-N/C3-borylated indole, which then generates the desired C3-borylated indole product by conversion of N-Bpin to

N-H with [Ni(IMes)$_2$] and *in situ*-generated HBpin. This protocol enables the *in situ* installation and removal of the directing group without additional operations, using a first-row transition metal catalyst, and can be followed, in the same pot, by a Suzuki-Miyaura cross-coupling with an aryl halide.

■ ASSOCIATED CONTENT

Details of synthetic methods, characterization (NMR and HRMS data) of products, and investigation of the reaction mechanism are included in the Supporting Information. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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