C−H Functionalization Hot Paper

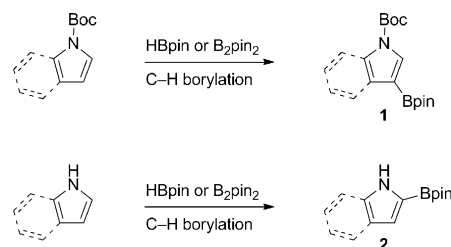# A Traceless Directing Group for C−H Borylation**

Sean M. Preshlock, Donald L. Plattner, Peter E. Maligres, Shane W. Krska,* Robert E. Maleczka Jr.,* and Milton R. Smith III*

In C−H functionalization, directing groups have played a pivotal role, even in some of the earliest examples that feature transition-metal catalysis.[1,2] Similarly, directing groups can alter regioselectivities in Ir-catalyzed C−H borylation.[3] Examples fall into two classes: 1) those where the directing group is already present in the substrate,[4] and 2) those where it must be installed.[5] An example of the latter class is the use of silylhydrides to facilitate the borylation of positions *ortho* to OH and NH substituents and to effect the functionalization at sp^2-hybridized positions in arylsilanes, which was described by Hartwig and co-workers.[5a,c] Likewise, Lassaletta et al. have shown that the conversion of aryl aldehydes into hydrazones facilitates borylation of the *ortho* position.[5e] Nevertheless, these methods require installation and removal of a directing group.

In contrast, traceless directing groups, the installation and removal of which do not require additional steps, would be attractive alternatives to more traditional approaches.[6] Herein, we demonstrate that the (pinacolato)boron (Bpin) group can function as a traceless directing group for C−H borylation reactions of nitrogen heterocycles and anilines.

We have previously demonstrated that the *tert*-butoxycarbonyl (Boc) group can be used as a directing group in Ir-catalyzed borylations of nitrogen-containing heterocycles, such as pyrroles, indoles, azaindoles, and pyrazoles.[5b] In the case of pyrrole and indole, the N-Boc-protected compounds are selectively borylated at the 3 position, whereas the parent heterocycles react selectively at the 2 position (Scheme 1).[7]

Although the Boc moiety is a widely used protecting group, its installation and removal are nevertheless required to produce the 3-borylated isomer of a parent heterocycle. Boc removal is particularly onerous for N-Boc-protected heterocycles because the Bpin group is not compatible with most deprotection methods, and the thermal conditions that generally proved to be the best failed for some substrates.[5b] Thus, it would be desirable to use a directing group that could

Scheme 1. Boc-directed borylation reactions of pyrroles and indoles.

be readily installed and removed without requiring isolation of intermediates.

In this vein, Bpin is potentially an attractive surrogate for Boc because B−N bonds readily hydrolyze.[8] Whereas sufficiently acidic N−H and O−H bonds will react with boron hydrides to evolve dihydrogen and to form B−N or B−O bonds, the N−H bonds of pyrrole and indole do not spontaneously react with HBpin to generate N−B bonds. This is clearly a kinetic issue as calculations (B3LYP//6-311++ G(2d,2p)) indicate that N−H borylation is thermodynamically preferred over C−H borylation by 10–12 kcalmol^{-1}. We reasoned that B−N bond formation could be facilitated by making the B−H bond in HBpin more hydridic. Inspired by the enhancement of hydride transfer with a Lewis base that was reported by Crudden and co-workers,[9] we examined the effect of adding tertiary amines to solutions of HBpin and indole or pyrrole. Gratifyingly, smooth conversion into the N-borylated heterocycles was observed under these conditions. The reaction with NEt$_3$ as the additive is significantly faster than that with NEt*i*Pr$_2$, which is consistent with the idea that heterolysis is promoted by coordination of the nitrogen lone pair of the tertiary amine to the boron center.

With the problem of N-borylation solved, we turned our attention to the Ir-catalyzed C−H borylation of N-borylated indole (**3**; Scheme 2), expecting that C−H borylation would occur selectively at the 3 position. The reaction was performed in solutions containing tertiary amines, which are compatible with C−H borylation.[10] Upon completion, the reaction was quenched with MeOH, and routine workup gave 3-borylated indole **5** in 57% yield. This demonstrates that Bpin can function as a traceless directing group, enabling a simple one-pot route to **5** from simple indole. This transformation is preferable to the stepwise Boc-directed route, as Boc installation and removal introduces two additional purification steps, reducing the overall yield to 42%, starting from indole.
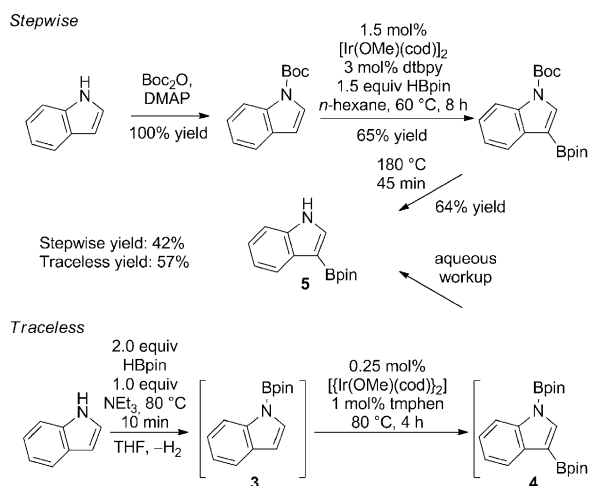
The selectivity that is observed under these conditions complements the selectivity that is typically found for Ir-catalyzed borylation. This expands the scope of the reaction as functionalization at either the 2 or 3 position can be

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Scheme 2. Comparison of the Boc-directed and the Bpin-directed synthesis of 3-Bpin-indole.

accomplished by carrying out the reaction in the absence or presence of a tertiary amine (Scheme 3). Borenium cations and electrophilic ruthenium catalysts will borylate the 3 position of *N*-methylindole; however, the route that employs the traceless directing group offers the advantage that unprotected indole can serve as a substrate.[11]
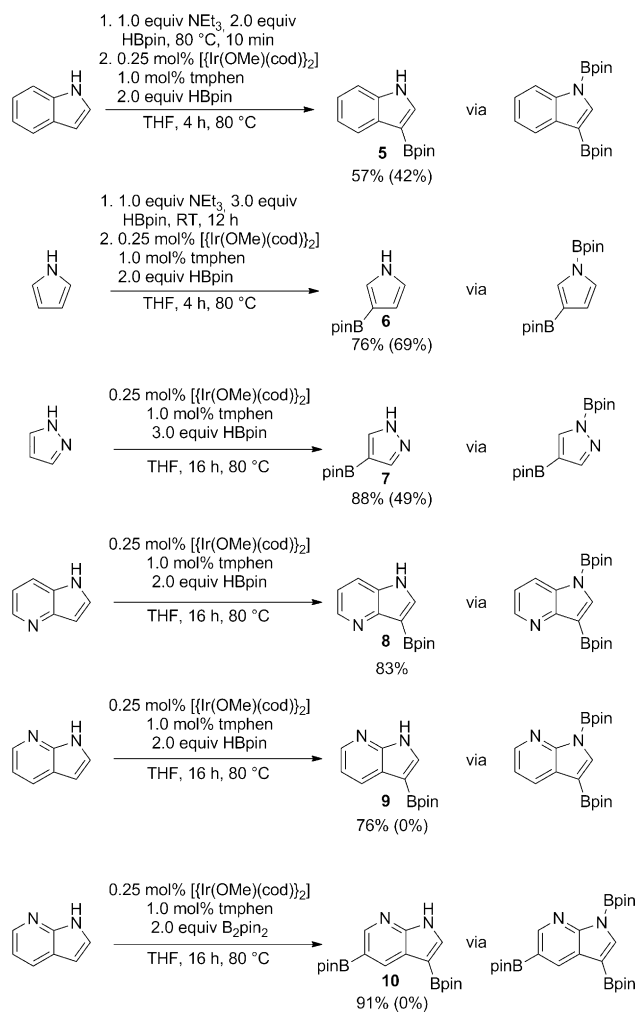
To examine the generality of this strategy, we subjected a number of other heterocycles that entail an NH moiety to

Scheme 3. Selective borylation of the 2 and 3 positions of indole.

the conditions developed for Bpin-directed functionalization (Scheme 4). For products **5** and **6**, amine-catalyzed N-borylation must be carried out prior to addition of the Ir catalyst for selective functionalization at the 3 position. For azaindoles and pyrazoles, which feature more acidic N—H bonds, N-borylation precedes C—H borylation, making the amine additive unnecessary. The parent heterocycles that are shown in Scheme 4 undergo borylation at the carbon atom that is in the β position of the NBpin group, and the N—Bpin bond hydrolyzes on workup with protic solvents. For pyrazole, dimeric pyrazabole intermediates may be present prior to workup.[12]

The yields for the syntheses of the borylated heterocycles using either Bpin or Boc as the directing group are compared in Scheme 4. It is clear that the approach that employs Bpin as a traceless directing group not only reduces the number of purification/isolation steps, but also leads to higher yields. For example, the yield of **7** is improved by more than 30% with our novel method. The case for azaindoles is even more striking, as the traceless-directing-group approach provides products **8–10** in good yield. Compounds **9** and **10** were inaccessible through the Boc-directed route because decomposition to unidentified products occurred during attempts at

Scheme 4. N—Bpin-directed borylation of selected N-heterocycles. Yields of isolated products are given. Yields in parentheses correspond to the Boc-directed route starting from the parent heterocycle, using yields reported for Boc protection.[15] The borylation of *N*-Boc-4-azaindole has not been reported.

thermal deprotection. Compound **10** was synthesized using B₂pin₂ (2 equiv). In the presence of Bpin (4 equiv), a second borylation occurs at the six-membered ring in analogous fashion to the borylation of *N*-Boc-7-azaindole with excess HBpin.[5b,13] Compound **10** can also be obtained with HBpin.

The regioselectivity for pyrroles and related heterocycles, which are typically borylated at the C—H bond next to nitrogen, has electronic origins.[14] Given the sensitivity of C—H borylation to steric bulk, the Bpin group of the N-borylated intermediates may function as a steric director, although electronic effects have yet to be discounted. The approach shown in Scheme 4 displays some generality for N-heterocycles. Nevertheless, imidazole did not give isolable products with either directing method. Traceless-directing-group borylation of tryptophan also failed.

We recently showed that N-Boc-protected anilines undergo *ortho* borylation.[5d] Theory and experiment support a mechanism where the selectivity is due to hydrogen bonding between the NH moiety of the aniline and an oxygen atom of the Bpin reagent in the transition state (transition state **A**;
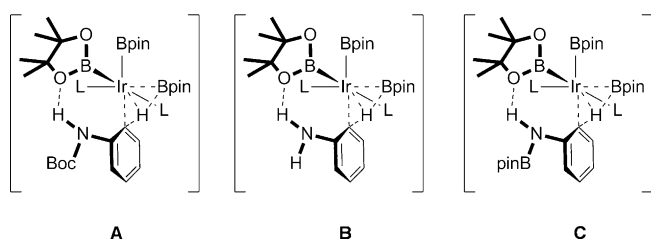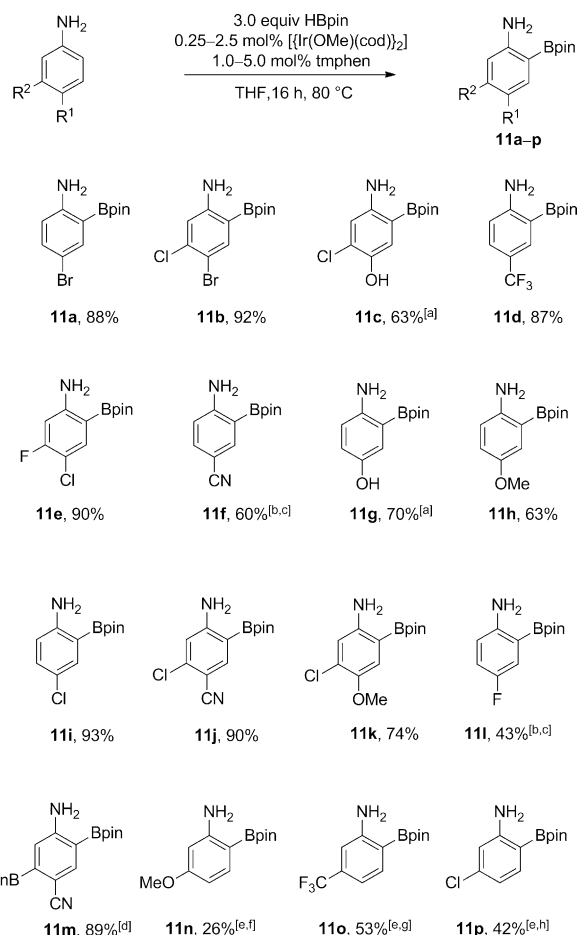
Figure 1. Calculated transition state for the *ortho* borylation of N-Boc-protected aniline (**A**) and putative transition state analogues for the *ortho* borylation of aniline (**B**) and N-Bpin-modified aniline (**C**).

Scheme 5. Traceless Bpin-directed borylation of anilines. Yields are for isolated materials. Unless otherwise noted, the borylation catalyst was generated from [{Ir(OMe)(COD)}$_2$] (0.25 mol%) and tmphen (1 mol%). See the Supporting Information for details. [a] HBpin (4 equiv). [b] HBpin (2 equiv). [c] 4,4′-bis(dimethylamino)-2,2′-dipyridyl (3 mol%) instead of tmphen; the reaction was run in hexanes with [{Ir(OMe)(COD)}$_2$] (1.5 mol%). [d] The substrate is 4-aminobenzonitrile. [e] tmphen (5 mol%) and [{Ir(OMe)(COD)}$_2$] (2.5 mol%). [f] Together with the 5-borylated product (47%). [g] Together with the 5-borylated product (21%). [h] Together with the 5-borylated product (17%).

Figure 1). In principle, unsubstituted anilines could engage in this reaction (**B**; Figure 1); however, conversions are poor when they are subjected to the reaction conditions that were effective for N-Boc-protected anilines. Nevertheless, the major products of the reactions of unprotected anilines are *ortho*-borylated, which suggests that practical *ortho*-selective borylation of anilines could be realized with a more reactive catalyst system.

Ultimately, conversions into *ortho*-borylated anilines were improved by changing the ligand from dtbpy to 3,4,7,8-tetramethyl-1,10-phenanthroline (tmphen) and using HBpin (2–3 equiv). Under these conditions, catalyst turnover numbers improved, making the synthesis of *ortho*-borylated anilines practical. The substrate scope of this reaction is shown in Scheme 5.

With the exception of compounds **11d**, **11h**, **11l**, and **11o**, all compounds shown in Scheme 5 have not been synthesized previously.[16] The yields of isolated products ranged from good to excellent, and in most cases, the yields obtained for the parent anilines exceeded those of their N-Boc-substituted counterparts. This is particularly noteworthy as the iridium catalyst loadings were generally eight times lower for the traceless reactions than for the N-Boc-directed analogues. As was the case for N-Boc-protected anilines, *para*-substituted anilines and *meta*, *para*-disubstituted anilines essentially gave only the *ortho*-borylated products, whereas *meta*-substituted anilines gave mixtures of isomers. In these cases, the *ortho*-borylated isomers could be isolated after purification by column chromatography. For *meta*-trifluoromethyl- and *meta*-chloro substituted anilines, **11o** and **11p** were formed as the major isomers. For 3-methoxyaniline, the *ortho*-borylated product **11n** was obtained as the minor regioisomer, along with the 5-borylated isomer as the major product. For aniline itself, 2 borylation is favored, but significant amount of 3 and 4 borylation are observed (*ortho*/*meta*/*para* = 2.3:1.5:1). This contrasts with what we previously found for PhNHCO$_2$Me, where the *ortho* selectivity was considerably higher (*ortho*/*meta*/*para* = 18:1:1).[5d] The preference for *ortho* borylation renders the iridium-catalyzed version complementary to the borenium-mediated electrophilic substitution developed by Ingleson and co-workers, who observed *para* substitution for *N,N*-dimethyl aniline.[11a] In contrast to the borenium chemistry, our borylation reaction tolerates trifluoromethyl groups (Scheme 5).

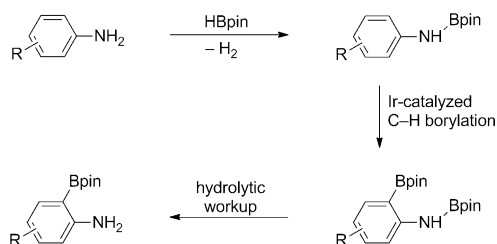The effects of solvent, ligand, and boron reagent on the regioselectivity for borylations of 3-substituted anilines were evaluated (see the Supporting Information for details). Solvent affects regioselectivity; less polar solvents enhance borylation at the 6 position (*ortho* to the nitrogen), whereas more polar solvents favor borylation at the 5 position (*meta* to the nitrogen). Ligand effects were also significant, with more electron-rich ligands favoring borylation at the 6 position. The choice of boron reagent also had an impact on the selectivities; relative to B$_2$pin$_2$, HBpin favored borylation at the 6 position.

To provide mechanistic insight, the borylation of 3-trifluormethylaniline with HBpin was monitored by ^{1}H and ^{11}B NMR spectroscopy. The spectra indicate that the mono-N-borylated intermediate, ArNHBpin, forms rapidly, but does not react further with HBpin to form ArNBpin$_2$. The N–B bond is maintained during the Ir-catalyzed C–H borylation. Once the reaction has reached completion, the
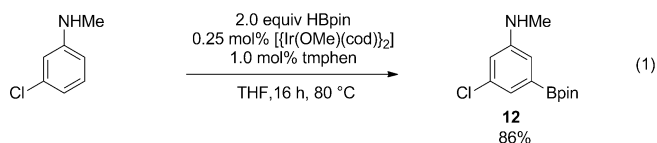
addition of MeOH leads to hydrolysis of the N−B bond to give the primary aniline product. These features are summarized in Scheme 6.
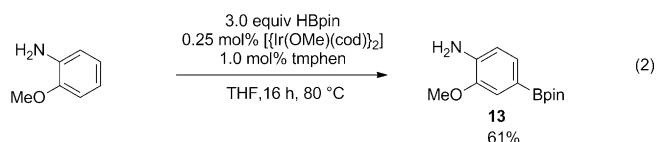

Scheme 6. Intermediates in the Bpin-directed aniline borylation.

In contrast to HBpin, B_2pin_2 does not borylate the nitrogen atom of anilines, even after heating at 80 °C for one hour. This observation, in combination with the reduced *ortho* selectivity with B_2pin_2, suggests that the aniline NH_2 does not direct *ortho* borylation as effectively as the NHBpin moiety.

Ortho-directed borylation is not observed for secondary aniline substrates. Although *ortho* selectivity is lost for *N*-methyl-3-chloroaniline, C−H borylation is nevertheless regioselective, affording compound **12** in high yield following workup [Eq. (1)].
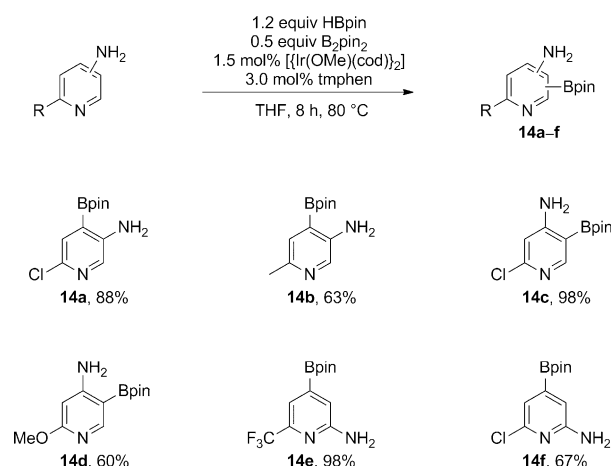

We noted that 2-substituted anilines do not give significant amounts of the *ortho*-borylated products with the Boc-directed approach or the Bpin-directed approach. This is likely due to unfavorable steric interactions between the Boc or Bpin group and the substituent at the 2 position in the transition states **A** or **C** (Figure 1). Whereas 2-methoxyaniline does not give the *ortho*-borylated product, it does undergo regioselective borylation at the 4 position [**13**; Eq. (2)], with

the 5-borylated isomer comprising less than 5% of the borylation products. This finding is surprising in light of the preference of *N,N*-dimethyl aniline for *meta* borylation (*meta/para* = 79:21, *meta/para* selectivity ca. 2:1).[17] The selectivity almost certainly has electronic origins, albeit non-obvious ones.

The traceless-directing-group approach is also effective for the borylation of certain aminopyridines (Scheme 7). A

Scheme 7. Bpin-directed borylation of aminopyridines. Yields of isolated materials are given. See the Supporting Information for details.

substituent in the *ortho* position of the pyridine nitrogen was critical to the success of these reactions, as 2- and 3-aminopyridine failed to give the borylated products. Substrates with an NH_2 moiety *meta* or *para* to the pyridine nitrogen gave reasonable to excellent yields of the corresponding products **14a–d**. For *meta*-aminopyridines, the borylation was selective for the *para* position (**14a,b**). For *para*-aminopyridines, borylation was observed at the less hindered *meta* position, yielding **14c** and **14d**. In the case of 2-aminopyridines, N-borylation was observed by ^1H and ^{11}B NMR spectroscopy. However, the reaction was not selective for the *ortho* position, and borylation occurred at the least hindered *para* position, affording compounds **14e** and **14f**.

In summary, we have shown that Bpin can function as a traceless directing group for C−H borylations of nitrogen heterocycles and anilines instead of the Boc moiety. For nitrogen heterocycles with less acidic NH groups, the addition of a tertiary amine is critical for successful borylation of the nitrogen atom. Traceless Bpin protection enables regioselective functionalization of C−H bonds of the parent compound without the need for separate installation and removal of the directing group. The resulting reactions are operationally simpler and generally higher yielding than their Boc-directed counterparts. For azaindoles, the use of Bpin as a traceless directing group gave products that are inaccessible with Boc-directed methods.

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