HHS Public Access

Author manuscript

Angew Chem Int Ed Engl. Author manuscript; available in PMC 2016 September 22.

Published in final edited form as:

Angew Chem Int Ed Engl. 2013 December 2; 52(49): 12915–12919. doi:10.1002/anie.201306511.

A Traceless Directing Group for C–H Borylation

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Abstract

N-borylation of nitrogen heterocycles and anilines provides a traceless directing group for subsequent catalytic C–H borylations. Selectivities that previous required Boc protection can be realized with the advantages that the NBpin directing group can be installed and removed in situ and product yields improve substantially.

Keywords

C–H activation; catalysis; borylation; anilines; N-heterocycles

In C–H functionalization, directing groups have played a pivotal role, even in some of the earliest transition metal catalyzed examples.[1],[2] Similarly, it has been shown that directing groups can alter regioselectivities in Ir-catalyzed C–H borylations.[3] Examples fall into two classes: (i) those where the directing group is already present in the substrate,[4] and (ii)

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those where it must be installed.[5] An example of the latter class is Hartwig's use of silylhydrides to facilitate the borylation ortho to OH and NH functionality and effect the functionalization at sp^2 positions in arylsilanes.[5a, 5c] Likewise, Lassaletta has shown that conversion of aryl aldehydes to hydrazones facilitates *ortho*-boyrlations.[5e] Nevertheless, these methods require installation and removal of the directing group.

In contrast, traceless directing groups, where installation and removal 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 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 pyrrole, indole, azaindoles, and pyrazole.[5b] In the case of pyrrole and indole, the *N*-Boc protected compounds borylate selectively at the 3-position, in contrast to the parent heterocycles, which react selectively at the 2-position (Scheme 1).[7]

While Boc is a widely used protecting group, installation and removal is nevertheless required to produce the 3-borylated isomers of the parent heterocycles. Boc removal for *N*-Boc heterocycles is particularly onerous because the Bpin group is not compatible with most deprotection protocols, and the thermal conditions that proved to be the best failed for some substrates.[5b] Thus, it would be desirable to use a directing group that could be installed and removed readily without requiring isolation of intermediates.

In this vein, Bpin is potentially an attractive surrogate for Boc since B–N bonds hydrolyze readily.[8] While E–H (E = N, O) bonds that are sufficiently acidic will react with boron hydrides to evolve dihydrogen forming B–E bonds, the NH bonds of pyrrole and indole do not react spontaneously with HBpin to generate N–B bonds. This is clearly a kinetic issue since calculations (B3LYP//6-311++G(2d,2p)) indicate that N–H borylation is thermodynamically preferred over C–H borylation by 10–12 kcal·mol^{-1}. We reasoned that B–N bond formation could be facilitated by making the B–H in HBpin more hydridic. Inspired by Lewis base enhancement of hydride transfer 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 to *N*-borylated heterocycles was observed under these conditions. The reaction with NEt_3 as additive is significantly faster than that with NEt^iPr_2, consistent with heterolysis being promoted by coordination of the N lone pair of the tertiary amine to B.

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 borylations.[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 indole. This is preferable to the stepwise Boc-directed route where Boc

installation and removal introduces two additional purification steps reducing the yield from indole to 42%.

The selectivity under traceless conditions complements that typically found for Ir catalyzed borylation. This expands the scope of the reaction as functionalization at either the 2 or 3-position can be accomplished by carrying the reaction out in the absence or presence of a tertiary amine (Scheme 3). We note that borenium cations and electrophilic Ru catalysts will borylate the 3-posiition of N-methylindole; however, the traceless route offers the advantage that unprotected indole can serve as substrate.[11]

In order to examine the generality of this strategy, we subjected a number of other NH containing heterocycles to the traceless conditions. The results are shown in 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 pyrazole, where the N–H bonds are more acidic, *N*-borylation precedes C–H borylation, making the amine additive unnecessary. The parent heterocycles in Scheme 4 undergo borylation at the C that is β to the NBpin group, and the N-Bpin bond hydrolyzes on workup with protic solvents. For pyrazole, dimeric pyrazabole structures may be present prior to workup.[12]

Scheme 4 compares yields of borylated heterocycles prepared through *N*-Boc direction and traceless Bpin direction. It is clear that traceless Bpin direction not only minimizes purification/isolation steps but also improves isolated yields. For example, the yield of **7** is improved by more than 30% when the traceless route is employed. The case for azaindoles is even more striking, as the traceless direction provides products **8**–**10** in good yield. Compounds **9** and **10** were inaccessible via the Boc-directed route because decomposition to unidentified products occurred during attempted thermal deprotection. Compound **10** was synthesized using 2 equiv B_2pin_2. With 4 Bpin equiv present, a second borylation occurs at the 6-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 sterics, the Bpin group in the *N*-borylated intermediates may function as a steric director, although electronic effects have yet to be discounted. The approach in Scheme 4 has some generality for *N*-heterocycles. Nevertheless, imidazole did not give isolable products with either directing method. Traceless borylation of tryptophan, also failed.

We recently showed that *N*-Boc anilines undergo ortho-borylation.[5d] Theory and experiment support a mechanism where the selectivity is due from hydrogen bonding between the aniline NH and a Bpin oxygen in the transition state (Figure 1A). In principle, unsubstituted anilines could engage in this reaction (Figure 1B); however, conversions are poor when catalysts and conditions effective for *N*-Boc anilines are employed. Nevertheless, the major products of unprotected anilines are predominately ortho-borylated, suggesting that practical ortho selective borylation of aniline could be realized if catalysis could be enhanced.

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

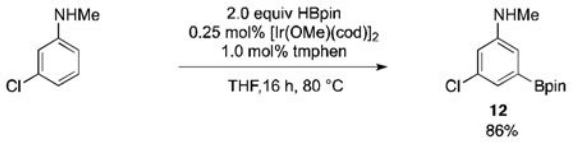
With the exception of compounds **11d** and **11o** all compounds in Table 1 are new.[16] The yields of isolated products ranged from good to excellent, and in most cases the yields for the parent anilines exceeded those obtained for their *N*-Boc counterparts. This is particularly noteworthy since most of the Ir catalyst loadings for traceless reactions were 8 times lower than for the *N*-Boc directed analogs. As was the case for *N*-Boc anilines, para-substituted anilines and meta, para-disubstituted anilines gave essentially only ortho-borylated products, while meta substituted anilines gave isomer mixtures. In these cases the ortho-borylated isomers could be isolated after purification by column chromatography. For *m*-CF_3 and -Cl anilines, compounds **11o** and **11p** are the major isomers in the reaction mixture. For 3-methoxyaniline the ortho-borylated product **11n** is the minor regioisomer with the 5-borylated isomer being the major product. For aniline itself, 2-borylation is favored, but significant 3 and 4-borylation is observed (*o:m:p* = 2.3:1.5:1). This contrasts with what we previously found for $PhNHCO_2Me$, where ortho selectivity was considerably higher (*o:m:p* = 18:1:1).[5d] The preference for ortho borylation makes the Ir catalyzed chemistry complementary to the borenium mediated electrophilic substitutions developed by Ingleson, where *para*-substitution occurs for *N*,*N*-dimethyl aniline.[11a] In contrast to the borenium chemistry, the borylation reaction in Table 2 tolerates CF_3 groups.

The effects of solvent, ligand, and boron reagent on the regioselectivity for borylations of 3-substituted anilines were evaluated (see Supporting Information for details). Solvent affects regioselectivity with less polar solvents enhancing borylation at the 6-postion (ortho to N), while more polar solvents favor borylation at the 5-position (meta to N). Ligand effects were also significant, with more electron rich ligands favoring borylation at the 6-position. The choice of boron reagent also impacted selectivities with HBpin favoring borylation at the 6-position relative to B_2pin_2.

To provide mechanistic insight, the borylation of 3-trifluormethylaniline with HBpin was monitored by ^1H and ^{11}B NMR. 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 Ir catalyzed C–H borylation. Once the reaction is complete, addition of MeOH hydrolyzes the N–B bond to give the primary aniline product. These features are summarized in Scheme 5.

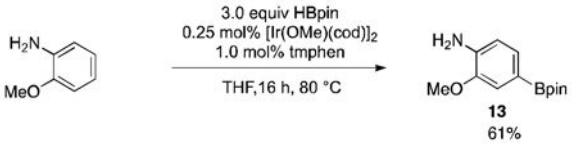
In contrast to HBpin, B_2pin_2 does not *N*-borylate anilines, even after heating at 80 °C for 1 h. This, coupled with the reduced ortho selectivity with B_2pin_2, suggests that the aniline NH_2 does not direct *ortho*-borylation as effectively as the NHBpin moiety.

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).



(1)

We note that 2-substituted anilines do not give significant amounts of *ortho*-borylated products for Boc or traceless directed approaches. This is likely due to unfavorable steric interactions between Boc and Bpin groups and substituents at the 2-position for the transition states in Figs. 1A and 1C. While 2-methoxyaniline does not give an 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 *N*,*N*-dimethyl aniline's preference for meta borylation (meta:para = 79:21, meta:para selectivity ~ 2:1).[17] The selectivity almost certainly has electronic origins —albeit non-obvious ones.



(2)

Traceless direction is also effective for borylating certain aminopyridines (Table 2). Substitution ortho to the pyridine nitrogen was critical to the success of these reactions as 2 and 3-aminopyridine failed to give borylated products. Substrates with NH_2 meta or para to the pyridine N gave reasonable to excellent yields of products **14a**–**d**. For *meta*-aminopyridines, the borylation is selective for the para position **14a**,**b**. For the *para*-aminopyridines, the borylation is seen at the less hindered meta position yielding **14c**,**d**. In the case of 2-aminopyridine substrates, ^{1}H and ^{11}B NMR spectra show that *N*-borylation occurs. However, the ortho direction is lost and borylation occurs at the least hindered para position, affording compounds **14e**,**f**.

In summary, we have shown that Bpin can function in lieu of Boc as a traceless directing group for C–H borylations of nitrogen heterocycles and anilines. For nitrogen heterocycles with less acidic NH groups the addition of a tertiary amine is critical to the *N*-borylation step. Traceless Bpin protection enables regioselection functionalization of the C–H bonds of the parent compounds without the need for separate installation and removal of the directing group. The resulting procedures are operationally simpler and generally higher yielding than Boc directed reactions. In the case of azaindoles traceless Bpin direction gives products that are inaccessible via Boc-directed protocols.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We thank the NSF (GOALI-1012883), the NIH (GM63188), and the ACS Green Chemistry Institute Pharmaceutical Roundtable for generous financial support.

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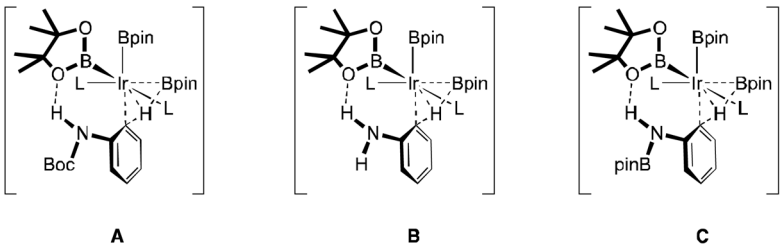
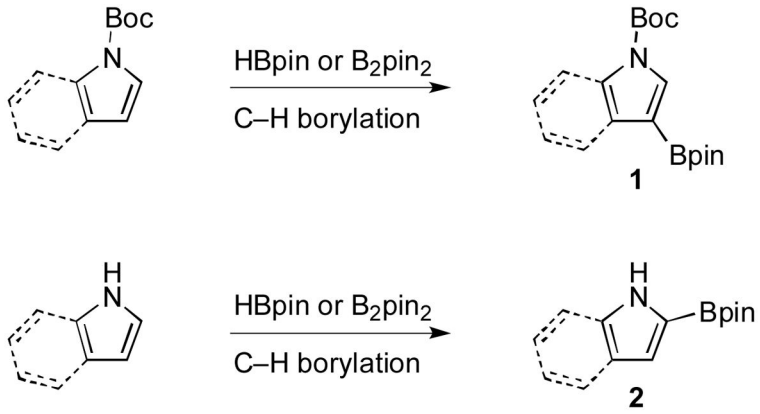
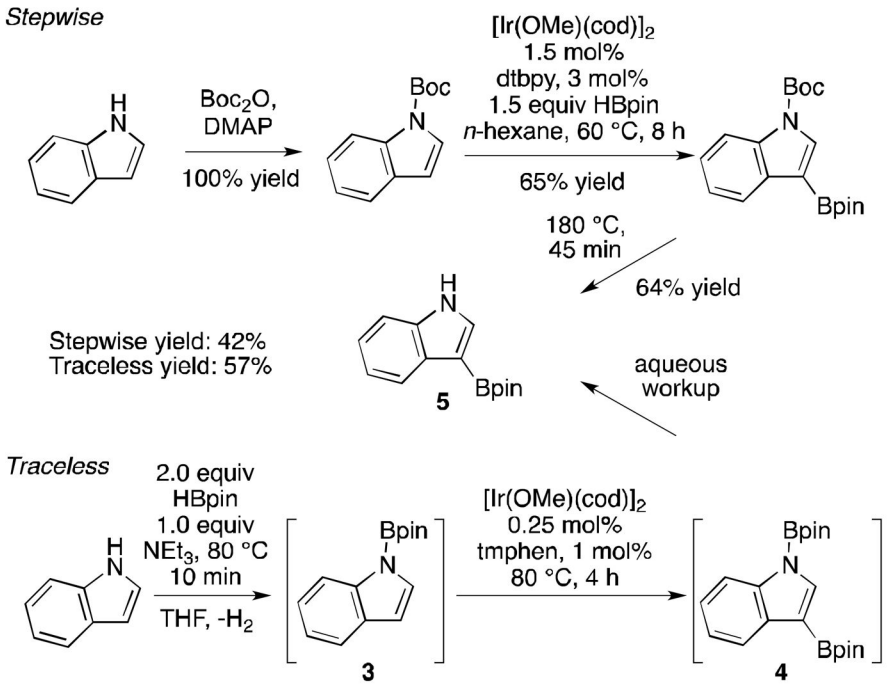


Figure 1.

Representation of the calculated transition state for ortho-borylation of N-Boc aniline (**A**) and putative transition state analogs for ortho-borylation of aniline (**B**) and N-Bpin aniline (**C**).

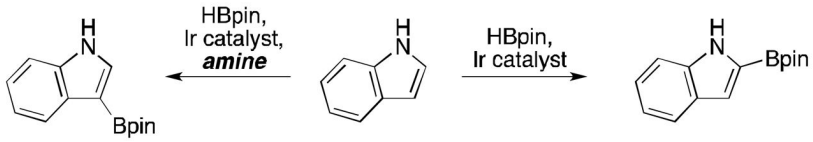


Scheme 1.
Boc-directed borylations of pyrroles and indoles.

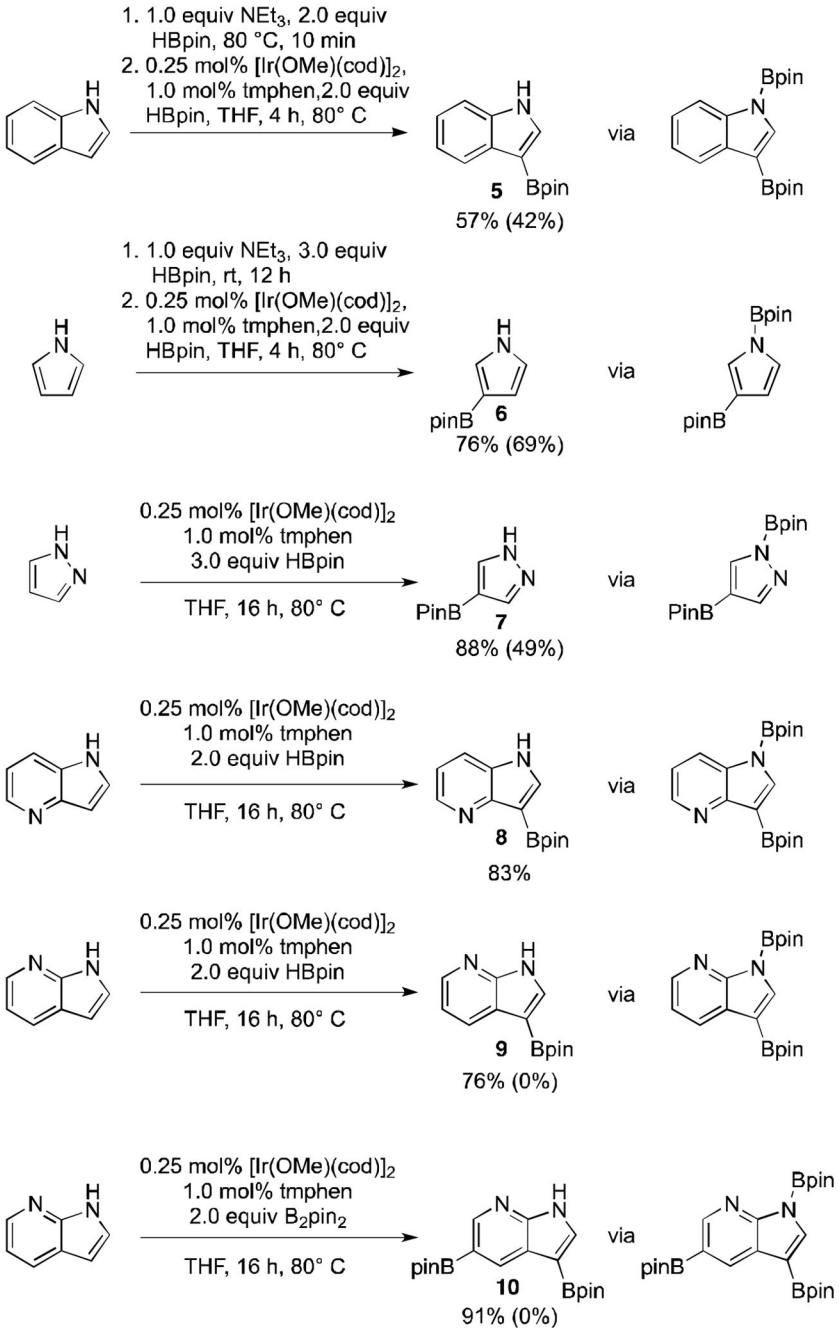


Scheme 2.

Comparison between Boc-directed and traceless Bpin-directed synthesis of 3-Bpin-indole.

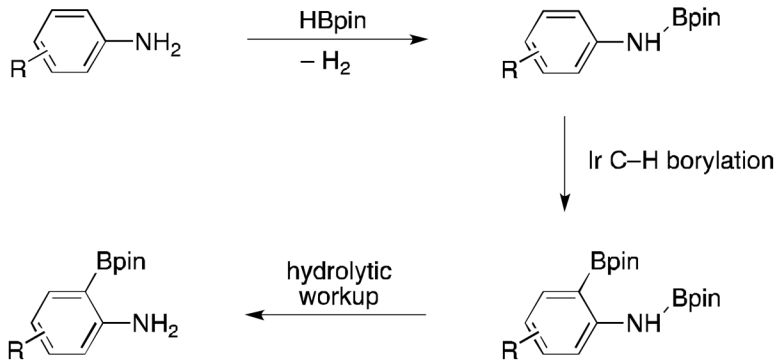


Scheme 3.
Selective 2 and 3-borylation of indole.



Scheme 4.

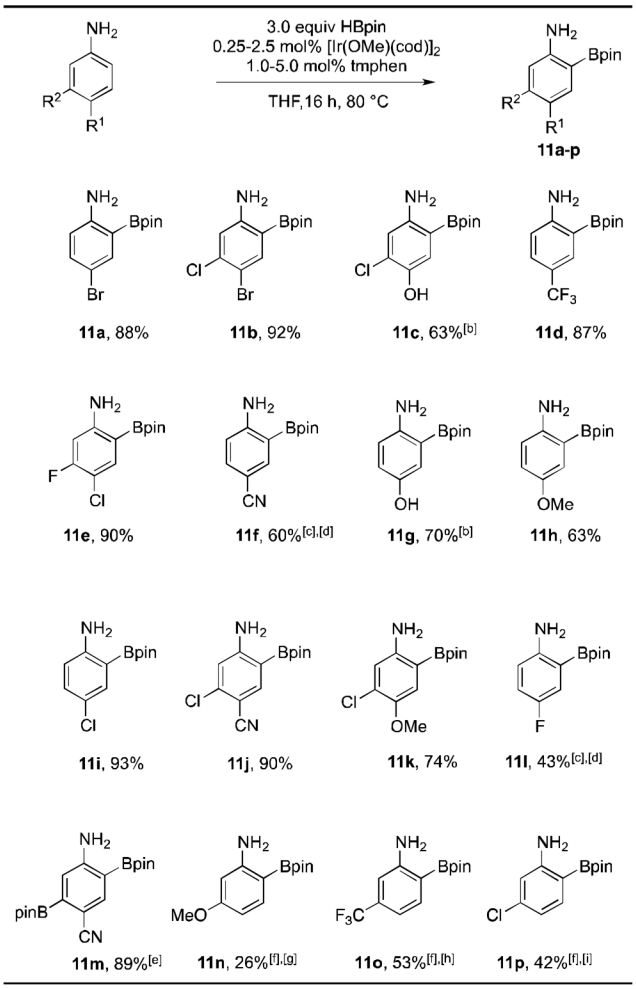
N–Bpin directed borylations of selected N-heterocycles. Isolated yields given. Yields in parentheses are for the Boc directed route from parent heterocycles using reported yields for Boc protection.[15] The borylation of *N*–Boc-4-azaindole has not been reported.



Scheme 5.
Intermediates in Bpin directed aniline borylation.

Table 1

Traceless Bpin directed borylation of anilines.[a]



[a]Yields are for isolated materials. Unless otherwise noted, the borylation catalyst was generated from 0.25 mol% $Ir(OMe)(COD)]_2$ and 1 mol% tmphen. See Supporting Information for details.

[b]4 equiv HBpin used for this substrate.

[c]2 equiv HBpin used for this substrate.

[d]4,4′-bisdimethylamino-2,2′-dipyridyl (3 mol%) was used in place of tmphen and reaction was run in hexanes with 1.5 mol% $[Ir(OMe)(COD)]_2$.

[e]The substrate is 4-aminobenzonitrile

[f]Reaction carried out with 5 mol% tmphen and 2.5 mol% $[Ir(OMe)(COD)]_2$.

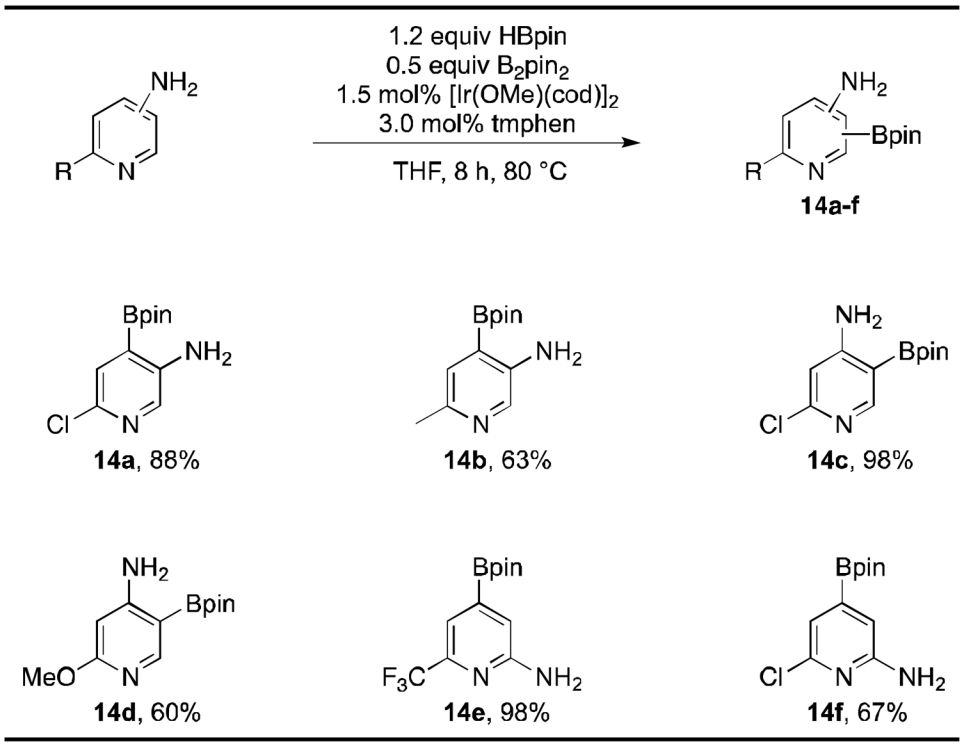
[g]Reaction gave 47% yield of 5-borylated product.

[h]Reaction gave 21% yield of 5-borylated product.

[i]Reaction gave 17% yield of 5-borylated product.

Table 2

Traceless Bpin directed borylations of aminopyridines.



[a]Yields are for isolated materials. See Supporting Information for details.