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Iridium-Catalyzed C–H Borylation of Heteroarenes: Scope, Regioselectivity, Application to Late-Stage Functionalization, and Mechanism

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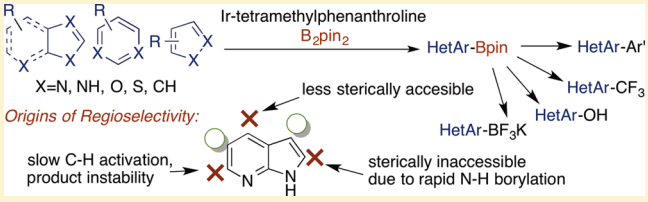
Supporting Information

ABSTRACT: A study on the iridium-catalyzed C–H borylation of heteroarenes is reported. Several heteroarenes containing multiple heteroatoms were found to be amenable to C–H borylation catalyzed by the combination of an iridium(I) precursor and tetramethylphenanthroline. The investigations of the scope of the reaction led to the development of powerful rules for predicting the regioselectivity of borylation, foremost of which is that borylation occurs distal to nitrogen atoms. One-pot functionalizations are reported of the heteroaryl boronate esters formed in situ, demonstrating the usefulness of the reported methodology for the synthesis of complex heteroaryl structures. Application of this methodology to the synthesis and late-stage functionalization of biologically active compounds is also demonstrated. Mechanistic studies show that basic heteroarenes can bind to the catalyst and alter the resting state from the olefin-bound complex observed during arene borylation to a species containing a bound heteroarene, leading to catalyst deactivation. Studies on the origins of the observed regioselectivity show that borylation occurs distal to N–H bonds due to rapid N–H borylation, creating an unfavorable steric environment for borylation adjacent to these bonds. Computational studies and mechanistic studies show that the lack of observable borylation of C–H bonds adjacent to basic nitrogen is not the result of coordination to a bulky Lewis acid prior to C–H activation, but the combination of a higher-energy pathway for the borylation of these bonds relative to other C–H bonds and the instability of the products formed from borylation adjacent to basic nitrogen.



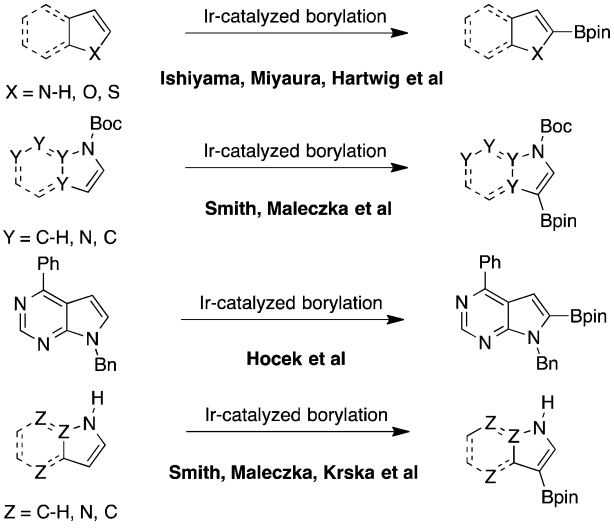
1. INTRODUCTION

The C–H bond functionalization of heteroarenes is an important synthetic method because heteroarenes are common units in the structures of pharmaceuticals, agrochemical products, and electronic materials.[1] Although transition-metal catalyzed reactions of arenes, such as cross-coupling reactions, typically occur with some heteroarenes,[2−4] the more basic the heteroarene and the more nitrogen atoms contained in the ring system of the heteroarene, the more challenging the translation of the catalytic reaction of an arene is to the catalytic reaction of the heteroarene.

In the past decade, the iridium-catalyzed C–H borylation of arenes has become a widely used method for the functionalization of arenes because of its ability to produce highly versatile aryl organoboronate ester intermediates from arenes without the need for reactive groups, such as halides or sulfonates.[5,6] C–H borylation occurs with some heteroarenes, and the reactions of benzo-fused or non-benzo-fused five-membered ring heteroarenes containing one heteroatom are some of the most reactive substrates for C–H borylation.[7−9] A few examples of the borylation of heteroarenes containing multiple heteroatoms and high nitrogen content also have been reported (Scheme 1), but the scope of these reactions has not been explored.[10−14]

In addition to improving methods for the modification of heteroarene building blocks, an understanding of the borylation of heteroarenes could allow for rapid derivatization of more complex medicinally important compounds and natural

Scheme 1. Examples of the Borylation of Heteroarenes



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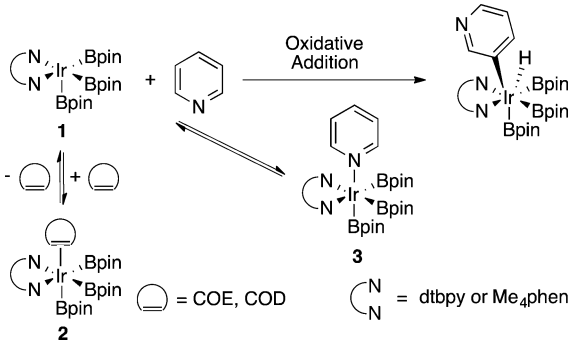
products. The combination of C−H borylation and elaboration of the heteroarylboronate ester by methods such as Suzuki coupling,[15] Chan−Lam−Evans coupling,[16] trifluoromethylation,[17] and oxidation[18] can lead to many derivatives after a single C−H bond functionalization reaction.

One challenge facing the application of catalysis to heteroarenes is the diversity of electronic properties of heteroarenes. The electron density at different positions of the heteroarene varies with the distribution of heteroatoms. Moreover, binding of a basic atom to the catalyst can poison its activity. The propensity of different heteroarenes to poison the catalyst varies because the basicity of the nonbonded electron pairs on the nitrogen atoms vary.[19] Thus, it is important to understand the trends in rate and selectivity for the borylation of these substrates and the mechanistic origin of these trends. There are many five- and six-membered ring heteroarenes, and all of these rings can contain substituents that have the potential to affect the rate and selectivity of the reaction. Thus, we sought to understand how the nitrogen atoms in the heteroaryl rings affect the reaction rates and the site selectivity.

The regioselectivity for the borylation of heteroarenes differs substantially from the regioselectivity for the borylation of arenes, and the regioselectivity for the borylation of various heteroarenes differs from each other. For the borylation of arenes, the regioselectivity is controlled almost exclusively by steric effects,[5] and this sterically controlled selectivity is complementary to the origin of selectivity during classical arene functionalization reactions, such as directed ortho metalation or Friedel−Crafts reactions. In contrast, the regioselectivity for the borylation of heteroarenes is controlled by a combination of electronic and steric effects. The regioselectivity for the borylation of pyrrole, indole, furan, and thiophene tends to occur at the most acidic C−H bond.[20] However, the regioselectivity for the borylation of heteroarenes containing a basic nitrogen, such as pyridine, quinoline, and other azines, undergoes borylation at the C−H bond located beta or gamma to the basic nitrogen.[9]

Basic heteroaryl substrates, such as pyridine, could occupy the vacant coordination site necessary for C−H activation in the 16-electron, five-coordinate Ir(III) species **1** (Scheme 2).[21]

Scheme 2. Coordination of Heteroarenes to the Active Catalyst



When the heteroarene binds more strongly than the olefin bound to the precatalysts or when the concentration of the heteroarene is sufficiently high, relative to the olefin, the resting state of the catalyst could shift from the alkene complex **2** to heteroarene complex **3**. In such a scenario, the reaction will be slower, relative to the analogous reaction with **2** as the resting state. The binding constant of the heteroarene to the catalyst could also be sufficiently high to form **3** irreversibly, preventing any appreciable formation of borylated product.

With these challenges associated with the borylation of heteroarenes in mind, we sought to explore the boundaries of the reaction scope, assess the applicability of this reaction to late-stage functionalization, reveal differences between the mechanism of the borylation of heteroarenes and the borylation of arenes, and investigate the origins of observed regioselectivities.

Here, we report a detailed study on the borylation of heteroarenes. The scope of the reactions we studied encompasses benzoxazoles, pyrimidines, as well as unprotected benzimidazoles, pyrazoles, and azaindoles. These heteroarenes are common heteroaryl motifs in medicinal chemistry[22−31] and are present in several currently marketed drugs (Figure 1).

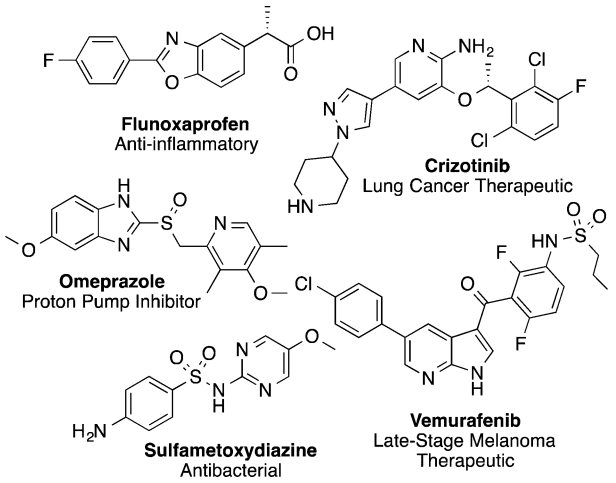


Figure 1. Pharmaceuticals containing benzoxazole, benzimidazole, pyrimidine, pyrazole, or azaindole moieties.

These reactions are amenable to one-pot sequences involving borylation and functionalization for the late-stage modification and the synthesis of biologically active heteroarenes. Finally, we report findings from mechanistic and computational studies that elucidate the origin of the regioselectivity. These studies show why borylation tends to occur at positions distal to nitrogen more rapidly than it occurs at positions adjacent to the nitrogen of azines and the nitrogen of azoles containing multiple heteroatoms.

2. RESULTS AND DISCUSSION

2.1. Method Development. The most common reaction system for the borylation of arenes is B_2pin_2 (bis(pinacolato)-diboron) as the boron source and a combination of $[Ir(COD)OMe]_2$ (bis(1,5-cyclooctadiene)di-iridium(I)-dimethoxide) and dtbpy (4,4′-di-*tert*-butyl bipyridine) as catalyst. Recently, the borylations of octane,[32] cyclic ethers,[32] chloromethylsilanes,[33] benzylic C−H bonds,[34] and arenes[35] have been shown to occur in higher yield when catalyzed by the combination of $[Ir(COD)OMe]_2$ and Me_4phen (3,4,7,8-tetramethyl-1,10-phenanthroline) than when catalyzed by the combination of $[Ir(COD)OMe]_2$ and dtbpy. The increased reactivity of the Me_4phen-Ir system over the dtbpy-Ir system is presumably due to the greater electron-donating ability and backbone rigidity of Me_4phen compared to those of dtbpy.

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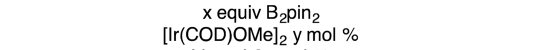
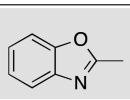
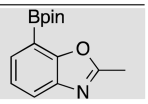
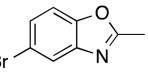
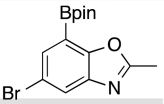
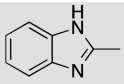
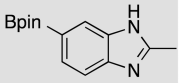
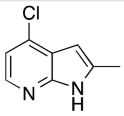
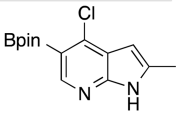
We began our studies on the borylation of basic heteroarenes containing multiple heteroatoms by investigating both of the catalytic systems for the borylation of benzo-fused azoles (Table 1). Initially we observed low conversion for the

Table 1. Effect of Ligand on the Borylation of Selected Azoles[a]



Entry	Substrate	x	y	Ligand	Yield[b]	Product
1a[c]		1.0	0.25	dtbpy	43%	
1b[c]		1.0	0.25	Me_4phen	68%	
2a[c]		0.75	0.25	dtbpy	85%	
2b[c] Br		0.75	0.25	Me_4phen	86%	
3a[d]		1.5	0.5	dtbpy	27%	
3b[d]		1.5	0.5	Me_4phen	94%	
4a[d]		1.5	1.0	dtbpy	27%	
4b[d]		1.5	1.0	Me_4phen	72%	

[a]Reactions were conducted on a 0.25 mmol scale. [b]Determined by ^{1}H NMR spectroscopy. [c]Reaction conducted at room temperature. [d]Reaction conducted at 80 °C.

reactions of 2-methylbenzoxazole and 5-bromo-2-methylbenzoxazole (entries 1 and 2) catalyzed by the combination of Me_4phen and $[Ir(COD)OMe]_2$ at temperatures below 50 °C. This lack of reactivity was most likely due to the low solubility of Me_4phen in THF. However, heating a mixture of B_2pin_2, Me_4phen, and $[Ir(COD)OMe]_2$ in THF at 80 °C and subsequent addition of this mixture to the heteroarene led to high conversions, even at room temperature.

The yields from the borylation reactions of 5-bromo-2-methylbenzoxazole conducted with dtbpy-Ir and Me_4phen-Ir as catalyst were similar to each other (Table 1, entry 2). However, the difference in yield between the two catalyst systems was significant for the borylations of azoles containing free N−H bonds, such as 2-methylbenzimidazole and 4-chloro-2-methyl-7-azaindole (entries 3 and 4). In these cases, the combination of iridium and Me_4phen was more active than the combination of iridium and dtbpy.

Reaction progress for the borylation of 5-bromo-2-methylbenzoxazole (Figure 2a) and 4-chloro-2-methyl-7-azaindole (Figure 2b) conducted with dtbpy-Ir or Me_4phen-Ir as catalyst was followed by gas chromatography (GC). Initial rates for formation of the product from the two substrates were similar with both catalyst systems, and the reaction profiles for the borylation of 5-bromo-2-methyl benzoxazole were essentially identical. However, the borylation of 4-chloro-2-methyl-7-azaindole catalyzed by the dtbpy-Ir system stalled at 78 min with a product yield of 27% and only 70% conversion of starting material. Borylation of this substrate under identical conditions, but with Me_4phen-Ir as catalyst, formed product in 72% yield with a standard exponential appearance of product.

Further reaction development with Me_4phen-Ir complexes as catalyst revealed that the stoichiometry of B_2pin_2 relative to heteroarene significantly influenced the yields for reactions of

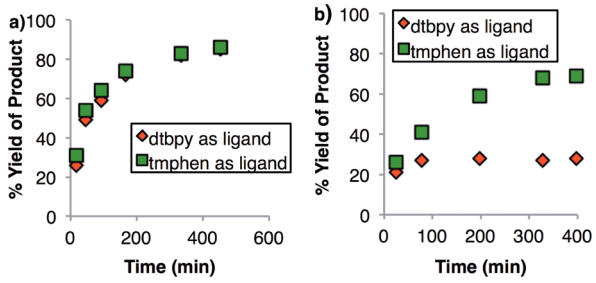
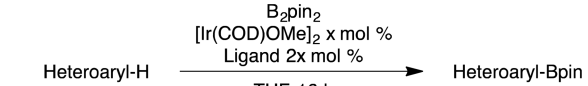
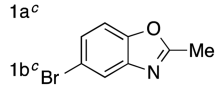
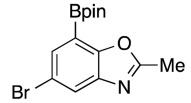
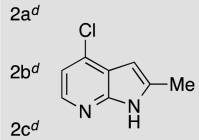
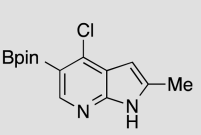


Figure 2. (a) Reaction profile for the borylation of 5-bromo-2-methylbenzoxazole with B_2pin_2 (1.0 equiv), 0.25 mol % $[Ir(COD)OMe]_2$ and 0.5 mol % ligand in THF at RT. (b) Reaction profile for the borylation of 4-chloro-2-methyl-7-azaindole with B_2pin_2 (1.5 equiv), 1.0 mol % $[Ir(COD)OMe]_2$ and 2.0 mol % ligand. Yields were determined by GC analysis.

Table 2. Effect of B_2pin_2 Stoichiometry on Product Yield[a]



Entry	substrate	x	B_2pin_2 (equiv)	Yield[b]	Product
1a[c]		0.25	0.75	86%	
1b[c] Br		0.25	1.0	85%	
2a[d]		1.0	0.75	15%	
2b[d]		1.0	1.0	46%	
2c[d]		1.0	1.5	72%	

[a]Reactions were conducted on a 0.25 mmol scale. [b]Determined by GC analysis. [c]Reaction conducted at RT. [d]Reaction conducted at 80 °C.

heteroarenes containing N−H bonds, but had little effect on reactions of heteroarenes lacking N−H bonds (Table 2). The borylation of substrates containing free N−H bonds (Table 2, entry 2) required 1.5 equiv of B_2pin_2 to form the product in high yield. The requirement for additional B_2pin_2 to obtain a high yield was found to result from the formation of an *N*-Bpin species, a finding that was also reported by Smith, Maleczka, and Krska during the preparation of this document. A detailed investigation of the N−H borylation phenomena will be presented later.

2.2. Scope of the Borylation of Heteroarenes. With Me_4phen-Ir as catalyst, we found that benzoxazoles and pyrimidines, as well as unprotected benzimidazoles, pyrazoles, and azaindoles, underwent the borylation process in good yield. Benzoxazoles underwent borylation at room temperature (Chart 1), provided that a substituent was present at the 2-position, leading to heteroaryl boronate esters **4a**−**f** in good to excellent yields. Borylation occurred almost exclusively at the 7-position, ortho to oxygen (confirmed via independent synthesis of **4a**). Smith, Maleczka, and Singleton proposed that the regioselectivity of the borylation of benzodioxole ortho to oxygen resulted from the greater acidity of the corresponding C−H bond at this position.[20] The same effect might be leading to borylation adjacent to oxygen in benzoxazoles. The borylation of 2-methylbenzothiazole led to a mixture of products **4g** within a substantially lower yield than was observed for borylation of the oxygen analogue.

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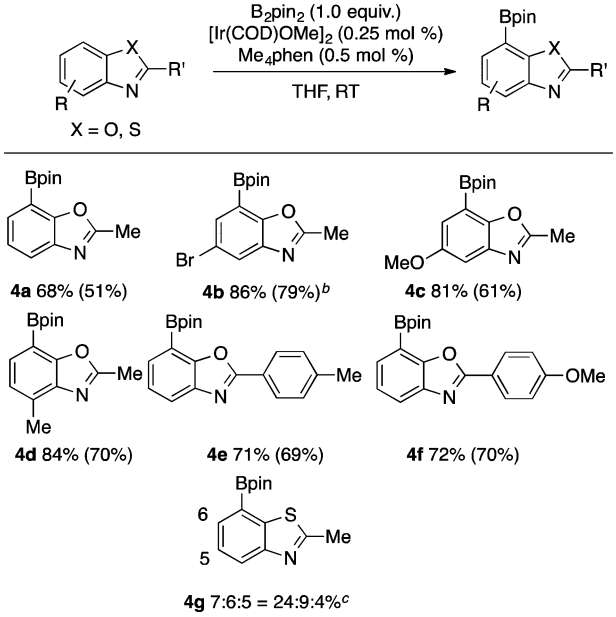
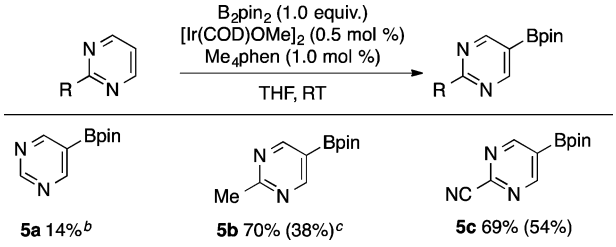
Chart 1. Borylation of Benzoxazoles and Benzothiazoles[a]



[a]Reactions were conducted on a 0.25 mmol scale. Yields were determined by ^{1}H NMR spectroscopy, and isolated yields are reported in parentheses for reactions conducted on a 0.50 mmol scale. [b]Reaction conducted with 0.75 equiv of B_2pin_2. [c]Reaction conducted at 50 °C with 1.0 mol % $[Ir(COD)OMe]_2$ and 2.0 mol % Me_4phen. Yields were determined by GC chromatography.

Chart 2. Borylation of Pyrimidines[a]

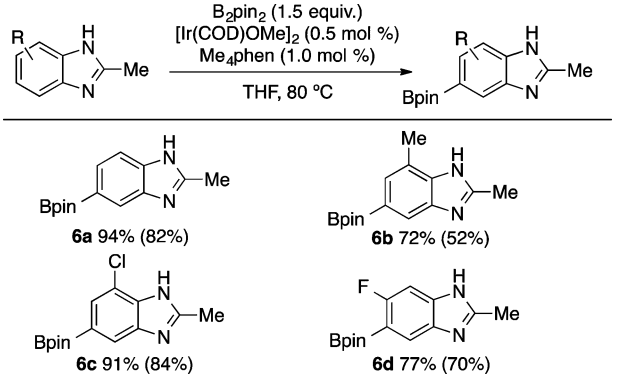


[a]Reactions were conducted on a 0.25 mmol scale. Yields were determined by ^{1}H NMR spectroscopy, and isolated yields are reported in parentheses for reactions conducted on a 0.50 mmol scale. [b]Reaction was conducted with 2.5 mol % $[Ir(COD)OMe]_2$ and 5.0 mol % Me_4phen. [c]Reaction was conducted with 0.75 equiv of B_2pin_2.

The borylation of pyrimidines led to formation of heteroaryl boronate esters **5a**–**c** (Chart 2), bearing the boryl group exclusively at the 5-position. This selectivity is complementary to the selectivity of radical C–H functionalizations of pyrimidines recently reported by the Baran group.[36] Once again, the heteroarene containing a substituent at the 2-position was more reactive than the analogue lacking a substituent at this position. For example, the reaction of the parent pyrimidine **5a** occurred in 14% yield, whereas the reaction of the 2-methyl analogue **5b** occurred in 70% yield. Heteroaryl boronates **5a**–**c** were not stable to silica gel chromatography; therefore, we purified these materials by Kugelrohr distillation. However, heteroaryl boronate esters also can be elaborated *in situ*, as will be shown later.

Benzimidazoles substituted at the 2-position led to the formation of products **6a**–**d** (Chart 3) from borylation distal to nitrogen at the 5- or 6-positions. Only one set of ^{1}H NMR

Chart 3. Borylation of Benzimidazoles[a]

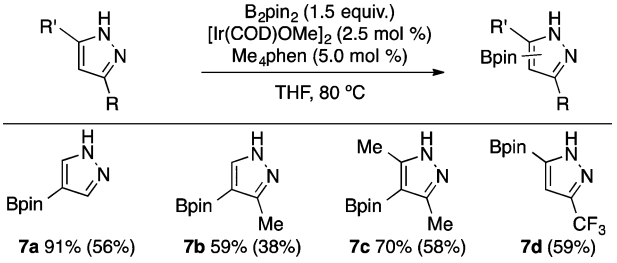


[a]Reactions were conducted on a 0.25 mmol scale. Yields were determined by ^{1}H NMR spectroscopy, and isolated yields are reported in parentheses for reactions conducted on a 0.50 mmol scale.

resonances were observed for these products due to the rapid tautomerism of benzimidazoles. A slightly lower yield was obtained for 4-methyl **6b** than for the less electron-rich **6a**, **6c**, and **6d**, but the yield for the reaction of **6b** was still at a useful level.

Smith, Maleczka, and Krska reported, during our current study, the borylation of unsubstituted pyrazoles and azaindoles. Here we present a more complete scope of these classes of substrates, particularly those containing varying substitution patterns. In analogy to the regioselectivity observed for benzimidazoles, the borylation of pyrazoles (Chart 4) occurred

Chart 4. Borylation of Pyrazoles[a]



[a]Reactions were conducted on a 0.25 mmol scale. Yields were determined by ^{1}H NMR spectroscopy, and isolated yields are reported in parentheses for reactions conducted on a 0.50 mmol scale.

beta to nitrogen in most cases. This site is the one at which electrophilic aromatic substitution typically occurs in these heterocycles.[37] The exception to this trend of reaction at the position beta to nitrogen was the reaction of trifluoromethyl-substituted **7d**, which underwent borylation adjacent to nitrogen. Borylation beta to nitrogen was also observed by Smith and Maleczka for Boc-protected pyrazole.[10] In contrast, the borylation of *N*-methylpyrazole has been reported to occur adjacent to the *N*-methyl moiety.[38] The borylation of unprotected pyrazole to generate **7a**, as has been previously reported,[11] occurs with selectivity that is similar to the selectivity for the borylation of the bulky Boc-protected pyrazole, due to rapid formation of a bulky *N*-Bpin species, which will be discussed later in this report.

Reactions of unprotected azaindoles formed boryl-azaindoles **8a**–**e** (Chart 5) in moderate to excellent yields. Products **8a**–**c** all resulted from borylation at the 3-position. Like the

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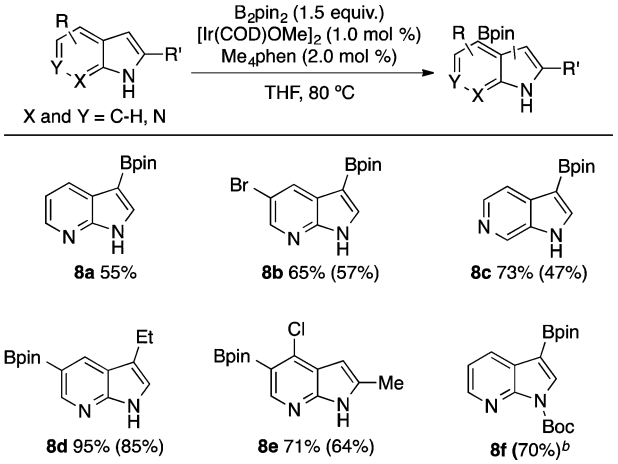
Chart 5. Borylation of Azaindoles[a]



[a]Reactions were conducted on a 0.25 mmol scale. Yields were determined by ^{1}H NMR spectroscopy, and isolated yields are reported in parentheses for reactions conducted on a 0.50 mmol scale. [b]Reaction conducted on a 0.50 mmol scale at RT with 1.0 equiv of B_2pin_2.

borylation of pyrazoles, the site for the borylation of azaindoles is the site at which electrophilic aromatic substitution typically occurs.[39] This selectivity contrasts that for the borylation of indole; the reaction of indole occurs at the 2-position.[40] This regioselectivity was also observed for the borylation of *N*-Boc-7-azaindole, which yielded compound **8f**.[41] However, when a substituent was present at the 3-position, borylation of the azaindole occurred at the 5-position. For example, the borylation of 3-ethyl azaindole occurred selectively at the 5-position to form boryl-azaindole **8d**. In addition, the borylation of 4-chloro-2-methyl-7-azaindole led to functionalization at the 5-position; this selectivity is analogous to that reported for the ortho metalation of *N*-TIPS-4-chloro-7-azaindole.[42]

2.3. Guidelines for Predicting the Regioselectivity of the Borylation of Heteroarenes. Our results show clearly that the regioselectivity for borylation of heteroarenes containing two heteroatoms is high in many cases. However, these selectivities might seem difficult to predict at first glance. Thus, it is important to provide some guidelines that allow one to predict the regioselectivity of the borylation of heteroarenes. Just a few trends allow one to make these predictions (Figure 3).

First, the borylation rarely occurs adjacent to nitrogen, whether the nitrogen atom is contained in the ring (e.g., pyrazoles) or is external to the ring (e.g., benzimidazoles). This result is consistent with the selectivity for the borylation of N–H bearing heterocycles reported by Smith and Maleczka.[11] Only one exception to this trend was observed, and this case (the borylation of trifluoromethyl-substituted pyrazole **7d**, Chart 4) involved the reaction of a heteroarene containing a strong electron-withdrawing group that presumably perturbed the electronic properties of the ring.[43] This trend also was followed whether the nitrogen was contained in an N–H bond or was unsaturated and basic. Although a simple trend, the origins of this trend are due to multiple factors, and these factors will be presented later in this paper.

Steel and Marder recently discussed the relationship between the site of borylation of disubstituted arenes and the ^{1}H NMR chemical shift of the aryl hydrogens.[44] They showed that the

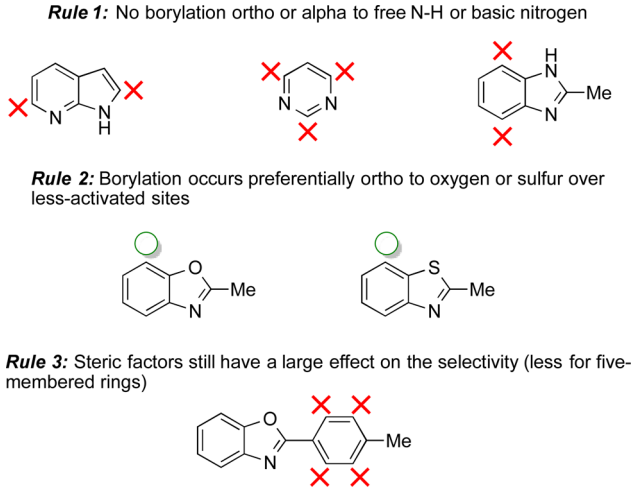


Figure 3. Rules for predicting regioselectivity.

aryl hydrogen with the furthest downfield chemical shift was typically the site of reactivity. The ^{1}H NMR chemical shifts of aryl hydrogens adjacent to basic nitrogen atoms and free N–H bonds are typically downfield of those for other aryl hydrogens. Thus, the lack of borylation adjacent to nitrogen is a deviation from Steel's observation, and the correlation between chemical shift and site selectivity does not extend in a general fashion to the borylation of basic heteroarenes. Factors beyond the electronic properties of the C–H bond control the position of the borylation of these heteroarenes.

Second, substrates containing sulfur or oxygen in their aromatic systems undergo borylation ortho to these heteroatoms with moderate to excellent selectivity. Our scope demonstrates this trend in the borylation of benzothiazoles and benzoxazoles, with the borylation of benzothiazoles being significantly less selective than the borylation of the analogous benzoxazoles. This selectivity does correlate with the predicted site selectivity for C–H borylation postulated by Steel et al. because its origin is likely electronic.[44]

Third, the borylation of basic heteroarenes has a large steric effect on regioselectivity. For example, no borylation is observed on the tolyl ring of 2-(*p*-tolyl)benzoxazole (Chart 1, **4e**). The main difference between the regioselectivity for the borylation of heteroarenes and the borylation of arenes is that the electronic properties of the heteroarenes can sometimes override the steric preference (benzoxazoles undergo ortho-borylation, rather than meta-borylation).

2.4. Tandem Reactions. In several cases, we experienced a significant difference between spectroscopic yields and isolated yields of the heteroaryl boronate esters formed from C–H borylation. This difference results from several of the products being unstable or immobile on silica. The difference in the two yields was as large as 32% (product **5b**, Chart 2). However, one valuable aspect of the borylation of C–H bonds is the ability to use the arylboronate esters *in situ* because the reaction gives only volatile HBpin or H_2 as side product and occurs with low loadings of iridium.[45−49]

Thus, to avoid isolation of the heteroaryl boronate ester intermediates, one-pot tandem reaction sequences are used, and several reports describe tandem borylation/functionalization sequences.[15,17,47,49,50] Here, we report several new applications of this methodology to the functionalization of heteroarylboronate esters generated by C–H bond borylation.

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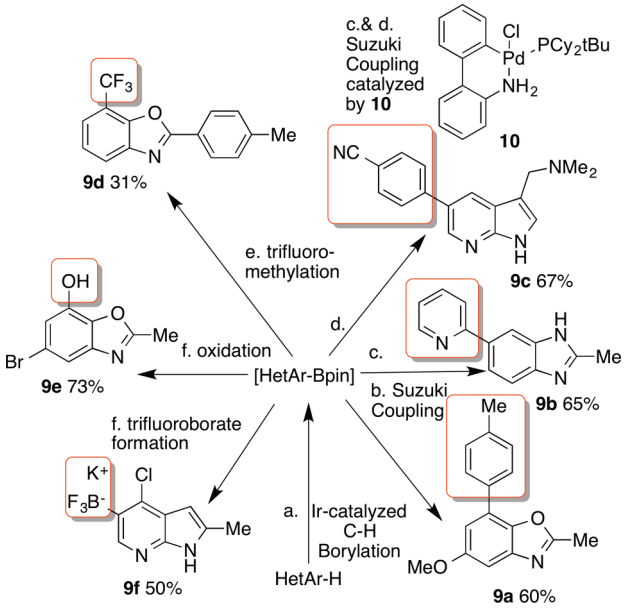
Scheme 3. C−H Functionalization via Tandem Borylation/Functionalization Sequences[a]



[a]Conditions: (a) B_2pin_2 (1−1.5 equiv), $[Ir(COD)OMe]_2$ 0.25−1.0 mol %, Me_4phen 0.5−2.0 mol %, THF, RT−80 °C, 16−48 h, removal of solvents. (b) 4-Bromotoluene (1.3 equiv), Pd(dba)2 5 mol %, QPhos 5 mol %, CsF (3 equiv), dioxane, H_2O, 100 °C, 21 h. (c) 2-Bromopyridine (1.3 equiv), complex 10.5 mol %, K_2CO_3 (3 equiv), dioxane, H_2O, 100 °C, 2 h. (d) 4-Bromobenzonitrile (1.3 equiv), complex 10.5 mol %, K_2CO_3 (3 equiv), dioxane, H_2O, 100 °C, 2 h. (d) $[(phen)CuCF_3]$ (1.2 equiv), KF (1 equiv), DMF, 50 °C, 21 h. (e) $NaBO_3{\cdot}4\ H_2O$ (3 equiv), THF, H_2O, RT, 15 min. (f) KHF_2 (4.6 equiv), MeOH, H_2O, 5 h.

Scheme 3 shows several different methods for the functionalization of the crude products of heteroaryl borylation, including Suzuki coupling, copper-mediated functionalization, and oxidation. For example, biaryl **9a** formed in good yield by a Suzuki coupling catalyzed by the combination of QPhos and $Pd(dba)_2$. Application of this catalytic system to the synthesis of biaryl **9b** containing multiple nitrogen atoms gave no product. However, conducting the reaction with the single-component precatalyst **10**, which is similar to a precatalyst shown to be highly active for Suzuki couplings,[51] led to the formation of **9b** in 65% yield, based on the starting heteroarene.

We were unable to isolate the heteroaryl boronate ester formed by the borylation of 3-dimethylamino azaindole. However, the product of C−H borylation of this substituted heteroarene generated *in situ* underwent Suzuki coupling with **10** as catalyst to form the 5-aryl derivative **9c** in 67% yield based on the starting heteroarene. The reactions that yielded **9b** and **9c** are rare examples of Suzuki couplings of basic heteroaryl boronate esters containing free N−H moieties.

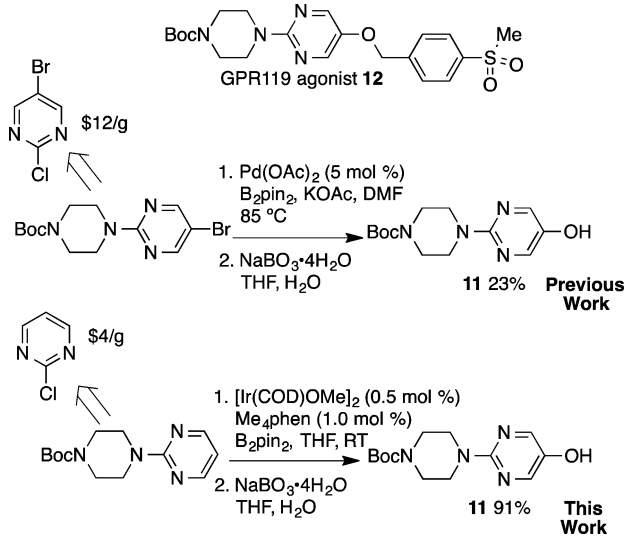
The trifluoromethyl-substituted heteroarene **9d** was synthesized by a protocol developed by our group for the oxidative trifluoromethylation of arylboronate esters.[17] Borylation of the benoxazole, followed by treatment of the heteroarylboronate ester with $(phen)Cu(CF_3)$ gave the 7-trifluoromethyl-substituted benzoxazole **9d**. A similar sequence[52] conducted with Togni's reagent as the source of the CF_3 group also generated **9d**, but the product was not isolable from the side products.

Related sequences formed heteroaryl alcohols. Borylation and oxidation of the intermediate with sodium perborate gave **9e** in high yield and with minimal side products.

We also showed that the products could be converted to trifluoroborates, which are stable, crystalline reagents for a range of transformations. Treatment of the crude product from the borylation of 4-chloro-2-methyl-7-azaindole with KHF_2 led to formation of the trifluoroborate **9f** in 50% yield. These tandem reaction sequences demonstrate the versatility of boronate ester intermediates for the synthesis of complex heteroaryl compounds.

2.5. Applications to Synthesis and Late-Stage Functionalization. We next sought to assess the suitability of the combination of C−H borylation and functionalization for the late-stage functionalization of biologically active compounds. Compound **11** (Scheme 4) is an intermediate in

Scheme 4. Tandem C−H Borylation and Oxidation as a Route to a Potential Diabetes Therapeutic



a synthesis, developed by AstraZeneca, of the potential type II diabetes therapeutic **12**.[53] As described in AstraZeneca's report, the synthesis of **11** was accomplished by a tandem sequence of Miyaura borylation and oxidation to give a 23% yield of the desired product. In contrast, the tandem sequence of C−H borylation and oxidation occurred to form **11** in a 91% yield and with a less expensive starting material.

A benzoxazole-containing c-Met kinase inhibitor has been identified as a potential cancer therapeutic.[54] The penultimate product **13** (Scheme 5) in the synthesis is converted to the inhibitor by removal of the Boc and *tert*-butyl groups. Structure−activity relationship (SAR) studies varying the substitution pattern on the benzoxazole moiety led to the discovery of several species with high c-Met kinase inhibition. The substitution patterns on the benzoxazole moieties were established in the second step of the reported synthesis (see Supporting Information [SI] for synthetic scheme). Thus, SAR studies could be greatly accelerated if a structure formed later in the synthetic sequence could be modified.

Using our rules for prediciting the regioselectivity, we predicted that borylation would occur selectively ortho to oxygen. Indeed, the heteroarylboronate ester intermediate **14** formed in 51% yield (as determined by ^1H NMR spectroscopy) from the borylation, and the Suzuki coupling of 2-

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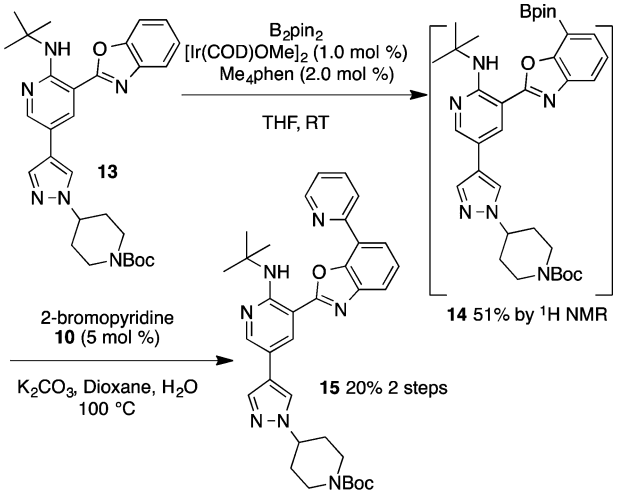
Scheme 5. Late-Stage Functionalization of a c-Met Kinase Inhibitor

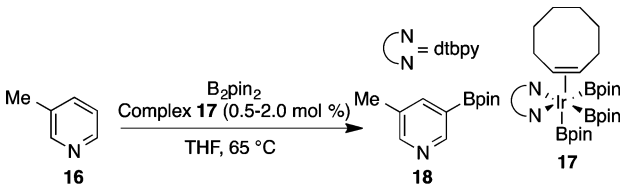


bromopyridine with **14** led to **15** (a highly potent c-Met kinase inhibitor) in 20% isolated yield from the parent arene. Although **15** was obtained in low yield, the amount of material would be sufficient for initial testing. Thus, this sequence further demonstrates the utility of C−H borylation for rapid derivatization of biologically active compounds.

2.6. Mechanistic Studies of Heteroarene Borylation. Our studies of the scope and applications of heteroaryl C−H borylation demonstrate that the iridium-catalyzed C−H borylation is a powerful tool for the functionalization of heteroarenes, even those containing multiple nitrogen atoms. The scope of the reaction encompasses several heteroaryl motifs that are prevalent in medicinal chemistry. However, to predict the regioselectivity and to understand the factors controlling the rate and scope, an understanding of the mechanism for the borylation of these heteroarenes is needed. Thus, we conducted experimental mechanistic studies and computational studies on the reported reactions.

2.6.1. Kinetic Studies of the Borylation of Representative Heteroarenes. We began our mechanistic investigations by conducting kinetic studies on the borylation of 3-picoline **16** catalyzed by complex **17** (Table 3). We chose **16** as a model basic heteroarene because of its simple structure and because the borylation of **16** yields a single product.[50] Complex **17** was chosen as catalyst because thermal dissociation of COE leads to the catalytically active 16-electron species and because **17** can be synthesized in gram quantities.[21] The synthesis of the Me_4phen-ligated analogue of **17** has been reported;[11] however, we were unable to synthesize this complex in an acceptable amount and purity for these studies.

Table 3. Kinetic Data for the Borylation of 3-picoline[a]



entry	$[B_2pin_2]$ (M)	3-picoline (M)	[catalyst] (M)	initial rate ($M \cdot s^{-1}$)
1	0.50	0.50	0.0025	$1.6 \pm 0.1 \times 10^{-6}$
2	0.50	0.50	0.0050	$3.6 \pm 0.1 \times 10^{-6}$
3	0.50	0.50	0.010	$7.6 \pm 0.4 \times 10^{-6}$
4	1.5	0.50	0.010	$7.9 \pm 0.3 \times 10^{-6}$
5	0.50	1.5	0.010	$8.2 \pm 0.3 \times 10^{-6}$

[a]Reactions were conducted on a 0.25 mmol scale. The formation of product **18** was observed by gas chromatography.

We measured initial rates for the borylation of **16** with varied concentrations of **16**, B_2pin_2, and **17** (Table 3). We observed a first-order dependence of the rate on the concentration of the catalyst (Figure 4), zero-order dependence of the rate on the concentration of B_2pin_2, and zero-order dependence of the rate on the concentration of the heteroarene. The zero-order dependence in substrate is distinct from the first-order dependence in substrate of the rate of arene borylation measured previously.[21]

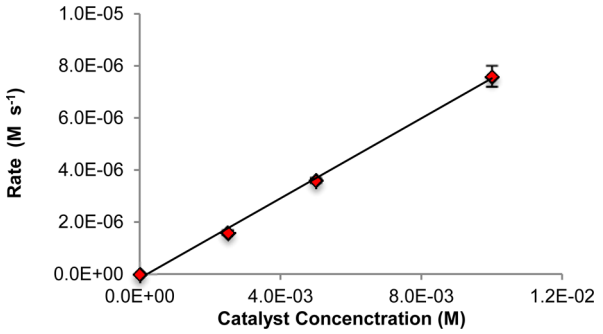
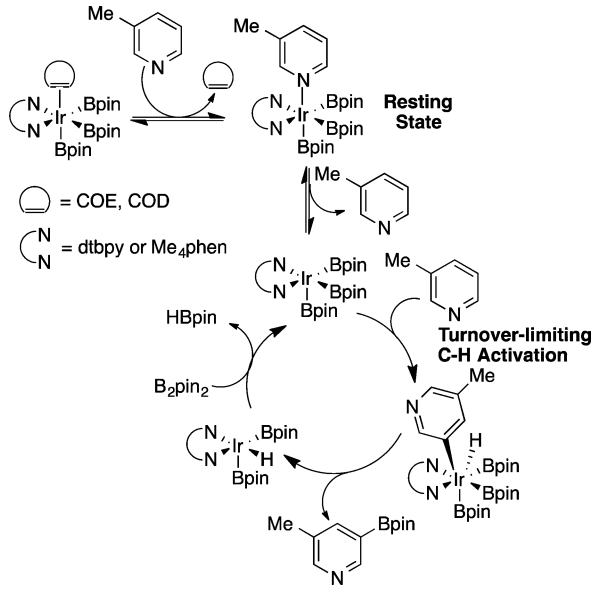


Figure 4. Dependence of the initial rate for the formation of **18** on the concentration of catalyst **17**.

This result is consistent with the mechanism shown in Scheme 6. In this scheme, the resting state of the catalyst contains the heteroarene, instead of the olefin of the precursor. Dissociation of the heteroarene, followed by reaction of the released heteroarene at the C−H bond, or simple rearrangement of the heteroarene from a nitrogen ligand to a π-arene or C−H σ complex would then lead to the transition state for C−H bond cleavage.

Scheme 6. Proposed Catalytic Cycle for the Borylation of 3-Picoline



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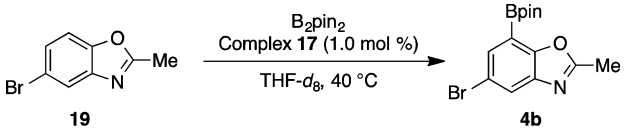
To assess the generality of the observed zero-order dependence in heteroarene, we conducted kinetic studies on the borylation of benzoxazole **19** (Table 4) by ^{1}H NMR spectroscopy. Benzoxazole **19** contains more steric bulk around the basic nitrogen than does **16** (Table 3). In this case, benzoxazole **19** would bind more weakly to the catalyst than the parent oxazoles, and the resting state of the catalyst could be the alkene complex. However, when we measured the initial rates for the formation of **4b** with varying concentrations of **19** we observed a weak dependence of the rate on the concentration of **19**. On the basis of the initial rates, we approximated the order of the reaction in **19** to be ~0.4 under the conditions detailed in Table 4.

Table 4. Kinetic Data for the Borylation of 5-Bromo-2-methylbenzoxazole 19[a]

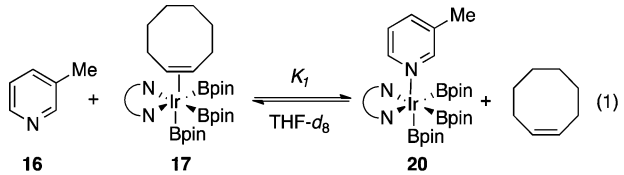


Entry	[benzoxazole] (M)	Initial Rate (M•s^{-1})	
1	0.50	1.1 ± 0.1 × 10^{-3}	~0.4 order in [19]
2	0.75	1.3 ± 0.1 × 10^{-3}	
3	1.0	1.5 ± 0.1 × 10^{-3}	

[a]Reactions were conducted on a 0.25 mmol scale. The formation of product **4b** was observed by ^{1}H NMR spectroscopy.

2.6.2. Relative Binding Affinities of the Heteroarenes and Cyclooctene. NMR spectroscopic studies were conducted to determine the relative binding constants of the heteroarenes and COE to iridium, as well as to determine the resting state of the catalyst. We conducted studies with 3-picoline **16** and 5-bromo-2-methyl-benzoxazole **19**, so that we could compare the trends in binding of these substrates to iridium with the kinetic data for the borylation of these substrates.

We first mixed 3-picoline **16** and COE-ligated iridium trisboryl complex **17** in THF-d_8 at room temperature and analyzed the composition of the iridium complex by ^{1}H NMR spectroscopy. Significant amounts of free COE were generated, as determined by the observation of a broad olefinic proton resonance for COE at 5.20 ppm. COE bound to this Ir fragment resonates at 3.93 ppm, and free COE resonates at 5.60 ppm. Thus, the observed signal indicates rapid exchange of free and bound COE on the NMR time scale, with approximately 75% of the COE in the free state. The resonance for the 6- and 6′- protons of bound dtbpy was also shifted downfield from those of complex **17**. We assigned this resonance to the picoline adduct **20** (eq 1).

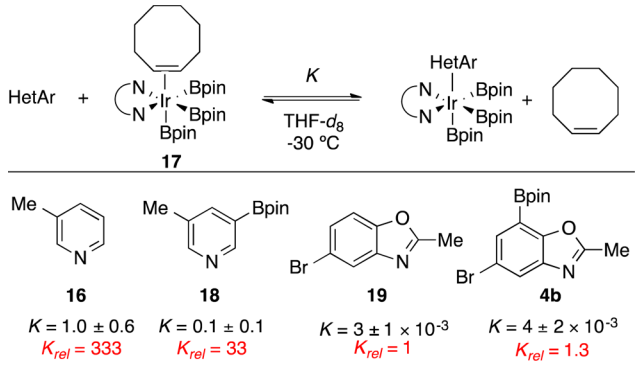


The borylation of 3-picoline was monitored by ^{1}H NMR spectroscopy with 2 mol % of **17** as catalyst to determine the resting state of the catalyst for this process. Sharp resonances corresponding to 3-picoline complex **20** and free COE were observed over the course of the reaction, allowing us to assign **20** as the resting state.

We determined the constant K_1 for the equilibrium depicted in eq 1. However, due to the fast exchange that occurred at RT, we conducted the ^{1}H NMR spectroscopic measurements at −30 °C, so that the free (δ = 5.60 ppm) and bound (δ = 3.93 ppm) olefinic proton resonances would be independently discernible. The equilibrium constant K_1 was determined to be 1.0 ± 0.6. Under the conditions of our kinetic studies, 3-picoline is present in a 50−200-fold excess over iridium complex **17**. The equilibrium constant indicates that picoline adduct **20** will be present in a similar excess over olefin adduct **17** during the catalytic reaction.

Unlike the borylation of 3-picoline, the rate of the borylation of benzoxazole **19** was found to have a partial order dependence on the concentration of the heteroarene (vide supra). To determine if this difference in order was due to poorer binding of **19** to iridium than of 3-picoline to iridium, we determined the equilibrium constant for the exchange of COE with the heteroarene **19**. This equilibrium constant was determined to be 3 ± 1 × 10^{-3} (Chart 6). This small equilibrium constant indicates that the resting state of the catalyst would likely consist mostly of the alkene complex.

Chart 6. Equilibrium Between Heteroarene-Bound and COE-Bound Forms of the Trisboryl Complex



However, when we monitored by ^{1}H NMR spectroscopy the borylation of **19** at 40 °C catalyzed by 1 mol % of complex **17** (Table 4), we observed a broad COE resonance at 5.40 ppm and a broad resonance corresponding to the 6,6′-proton of dtbpy at 9.82 ppm. The chemical shift of the COE under these conditions is closer to that of free COE than to that of bound COE, and the dtbpy resonance is closer to that of the heteroarene-bound complex (9.98 ppm) than the COE-bound complex (9.41 ppm), implying that most of the catalyst was bound by the heteroarene instead of COE.

From the ^{1}H NMR spectrum we approximated the equilibrium constant for the displacement of COE by **19** to be 2 × 10^{-2} at 40 °C, which is ~6 times larger than the equilibrium constant at −30 °C. This apparently greater preference for the heteroarene-complex at 40 °C than at −30 °C is likely due to the endothermicity of the displacement of the olefin by **19**. Indeed, a van't Hoff analysis of this process, revealed that ΔH = +4.7 ± 0.2 kcal/mol and ΔS = +3.8 ± 0.4 eu. With these thermodynamic data, we calculated the theoretical equilibrium constant at 40 °C to be 2.5 × 10^{-2} which is consistent with our experimental value. Finally, on the basis of the observed chemical shift of the dtbpy resonance, the

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ratio of olefin-bound **17** to benzoxazole bound complex is 0.4, which is roughly consistent with our kinetic data in Table 4.

Chart 6 shows the equilibrium constants for the displacement of COE by substrates **16** and **19** as well as by the products of borylation **18** and **4b**. 3-Picoline **16** binds much more strongly to iridium than does benzoxazole **19**. This observation is consistent with our initial rate data for the borylation of these two substrates, since the borylation of **19** (Table 4) is much more rapid than the borylation of **16** (Table 3). Substrate **16** undergoes stronger binding to iridium than the corresponding product of borylation **18**, which shows why the borylation of **16** occurs without significant product inhibition. However, some product inhibition is expected for the borylation of **19**, since the product of borylation **4b** has essentially the same ability to bind to iridium as the starting material.

2.7. Investigations of the Origin of the Regioselectivity. Several studies were conducted to reveal the origin of the regioselectivity of the borylation of basic heteroarenes. These studies included analyzing if the borylation of N−H bonds would create a large substituent on nitrogen and which heteroarenes would undergo this process, as well as competition studies with pyridines to address the question of whether binding of nitrogen to iridium or boron would be preventing the borylation at the C−H bonds adjacent to basic nitrogen atoms. We also concluded DFT calculations of the reaction pathways for the borylation of pyiridine adjacent to basic nitrogen.

2.7.1. N−H Borylation. To determine whether the borylation of N−H bonds affects regioselectivty, we investigated the origin of the lack of borylation α to free N−H moieties of basic heteroarenes. The lack of borylation adjacent to the N−H bond of the heteroarenes in this study was unexpected because indole undergoes borylation at the 2-position.[40]

We hypothesized that borylation occurs beta to free N−H moieties in the heteroarenes in the current study because of the steric bulk of an *N*-Bpin species resulting from N−H borylation. The following observations led to this hypothesis: (1) more than one equivalent of B_2pin_2 was required to achieve high yields of heteroaryl boronate ester, (2) borylation beta to nitrogen is the same regioselectivity observed for the borylation of *N*-Boc-protected heteroarenes, and (3) evolution of gas (presumed to be H_2) was observed upon addition of a mixture of B_2pin_2, ligand, and Ir precatalyst to the substrates containing N−H bonds.

If N−H borylation proceeds by a mechanism analogous to that of C−H borylation with B_2pin_2 as the boron source, one would expect HBpin to be the byproduct, not H_2. However, the HBpin generated by this pathway could react rapidly with the free N−H bond without catalysis, generating H_2 as a byproduct. To test whether HBpin reacts with the N−H bonds of the azoles, 4-chloro-2-methyl-7-azaindole **23** (Figure 5a) was mixed with HBpin in THF. No gas evolution was observed, and ^{1}H NMR spectroscopy confirmed that the N−H proton was still intact. However, when the same experiment was conducted in the presence of 0.5 mol % of iridium complex **17** (Figure 5b), vigorous gas evolution was observed, and a new species that lacked an N−H ^{1}H NMR resonance was formed. Also, the ^{11}B NMR spectrum of this species contained a new signal at 22.8 ppm. We assigned this new species as *N*-borylated azaindole **24**. This result is consistent with the recent findings from Smith

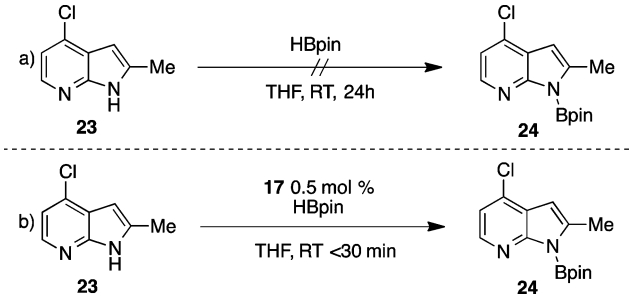

Figure 5. (a) Reaction of free N−H containing **23** with HBpin. (b) Reaction of **23** with HBpin catalyzed by **17**, which rapidly forms **24**.

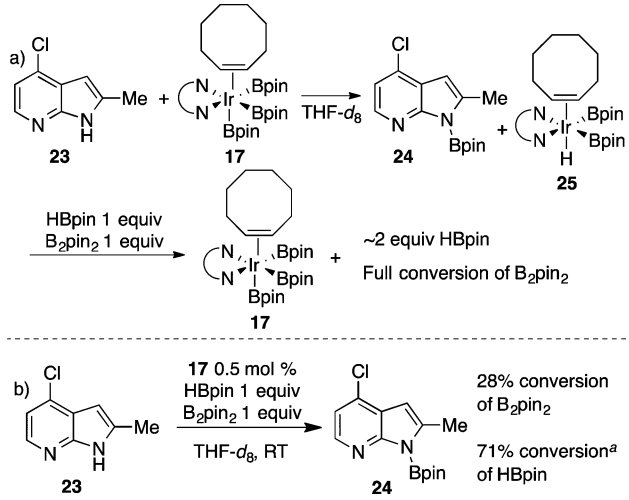

Figure 6. (a) Reaction of **23** with trisboryl complex **17** to form **24** and Ir−H species **25** as observed by ^{1}H NMR spectroscopy, followed by preferential reaction of **25** with B_2pin_2 to form **17**. (b) Preferential reaction of **23** with HBpin catalyzed by **17** to form **24**. Footnote *a*: Corrected for the generation of HBpin.

and Maleczka that the *N*-borylation of 7-azaindole occurs in the presence of an iridium catalyst and B_2pin_2.[11]

To investigate the mechanism of the formation of *N*-boryl **24**, azaindole **23** was mixed with equimolar amounts of trisboryliridium complex **17** (Figure 6a) in THF-d_8. The ^{1}H NMR spectrum of this reaction contained an iridium hydride signal (δ −4.72 ppm) as well as complete conversion of **23** to **24**. The observed iridium hydride **25** appeared to be identical to the bisboryl hydride observed previously.[21] The formation of **25** suggests an N−H activation/N−B reductive elimination pathway for the formation of **24**.

To determine if the iridium hydride would be recycled to the trisboryl **17**, we investigated the reactivity of iridium hydride **25** with HBpin and B_2pin_2. Addition of one equivalent of both HBpin and B_2pin_2 to the mixture containing **25** resulted in the formation of **17** and full conversion of B_2pin_2, suggesting that **25** reacts selectively with B_2pin_2 over HBpin. However, the N−H borylation of **23** with one equivalent of both HBpin and B_2pin_2 catalyzed by **17** (Figure 6b) results in the quantitative formation of **24** with only 28% conversion of B_2pin_2 and 71% conversion of HBpin, correcting for the generation of HBpin from the reaction of B_2pin_2 with **23**. These experiments demonstrate that HBpin must react with **23** via a pathway that does not involve the N−B reductive elimination to form **25**.

On the basis of these results we propose that N−H borylation under our reaction conditions occurs first by N−H

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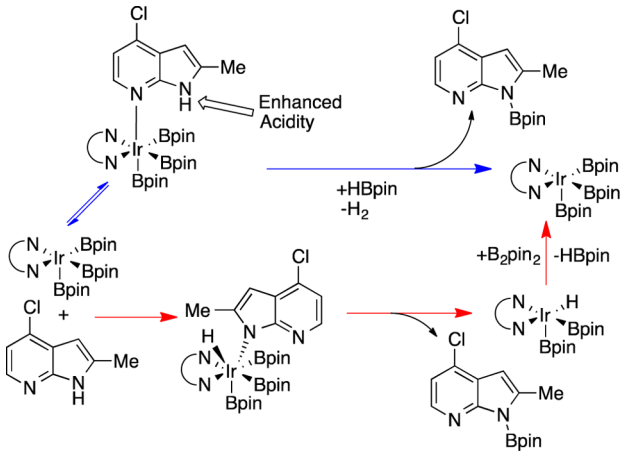
activation and N−B reductive elimination (red pathway, Scheme 7). This pathway produces HBpin, which can then

Scheme 7. Proposed Mechanism for the N−H Borylation of Basic Heteroarenes



react with **23** to produce **24** and H_2 gas by a different pathway, perhaps via coordination of **23** to the trisboryl complex, enhancing the N−H acidity (blue pathway, Scheme 7).

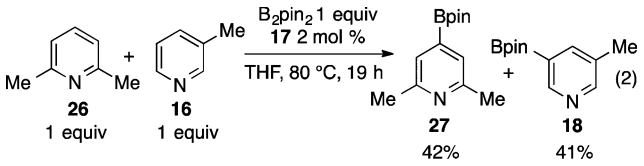
In summary, the mechanism proposed in Scheme 7 accounts for the rapid N−H borylation of basic heteroarenes and the formation of H_2 gas observed under our conditions. The ability of basic heteroarenes to coordinate to iridium, which may enhance the acidity of the N−H bond, explains why N−H borylation of basic heteroarenes occurs faster than the catalytic C−H borylation, whereas the N−H borylation of indoles and pyrroles does not occur on the time scale of C−H borylation.[55] We also considered the possibility that a catalytic amount of N-borylated product formed from the N−B reductive elimination pathway could act as a Lewis base to activate HBpin, in analogy to the activation of HBpin by triethylamine reported by Smith and Maleczka for the *N*-borylation of pyrrole and indole.[11] However, when azaindole **23** was treated with HBpin and 10 mol % of *N*-borylated **24** in THF, no appreciable reaction was observed over the course of 30 min. In contrast, the *N*-borylation of azaindole **23** in the presence of iridium occurs in less than 5 min. Therefore, the *N*-borylation of azaindole **23** in the absence of iridium is not competitive with the Ir-catalyzed reaction.

2.7.2. Origin of the Lack of Borylation Ortho to Basic Nitrogen. *2.7.2.1. Experimental Studies.* Finally, we investigated the origin of the absence of products from the borylation of C−H bonds located alpha to basic nitrogen atoms. This regioselectivity was first observed in a study on the borylation of pyridine.[40] Pyridine was found to form products from borylation at only the 3- and 4-positions in a statistical ratio without formation of product from borylation at the more kinetically acidic 2-position. This regioselectivity is general among the reactions of basic heteroarenes, except for a few examples involving the borylation of pyrazines and dtbpy adjacent to nitrogen.[13,14] At the time, it was proposed that precoordination of the basic nitrogen to a Lewis acidic species, creating steric bulk around nitrogen, would disfavor borylation at the 2-position. Under the reported conditions for the borylation of pyridine, there are only two Lewis acidic species at the start of the reaction: B_2pin_2 and iridium.

The observed regioselectivity could originate from coordination of pyridine to B_2pin_2 in either of two ways: (1) the two species could form a stable adduct quantitatively, or (2) the transition state for the C−H activation of a transiently formed adduct could be much lower in energy than the transition state for C−H activation of free pyridine.

The first proposal was shown to be invalid by measuring the ^{11}B NMR spectrum of a 1:1 mixture of pyridine and B_2pin_2 in THF. Only B_2pin_2 was observed; no upfield shift that would correspond to a Lewis acid−base N−B adduct was observed.

The second proposal was assessed by conducting competition studies and by analysis of our kinetic data. We conducted a competition experiment involving the borylation of one equivalent of 2,6-lutidine **26** and 3-picoline **16** with one equivalent of B_2pin_2 catalyzed by **17** (eq 2). If the transition



state for the C−H activation of a transiently formed N−B adduct is much lower in energy than that of the free heteroarene, then one would expect the borylation depicted in eq 2 to be much more selective for picoline **16** over lutidine **26** because **26** would bind much more weakly to a Lewis acid than would **16** due to the steric properties of **26**. In the event, the heteroaryl boronate esters **27** and **18** were formed in equal amounts, as determined by ^1H NMR spectroscopy: 42% and 41% yield, respectively.

Finally, a reaction of the catalyst with an adduct of the heteroarene with B_2pin_2 generated in small quantities by an unfavorable equilibrium would be first order in B_2pin_2. This prediction is inconsistent with the zero-order dependence of the reaction of **3**-picoline on the concentration of B_2pin_2. Thus, our experimental data strongly argue against binding of the heteroarene to the diboron reagent as the origin of the regioselectivity for the borylation of basic heteroarenes.

Having ruled out the binding of pyridines to B_2pin_2 during the reaction mechanism, we considered the potentiality that the heteroaryl substrate would bind to one equivalent of iridium while a second equivalent of iridium would react with the C−H bond of the bound pyridine. Such a mechanism would be second order in the concentration of catalyst if C−H activation is turnover limiting. Inconsistent with this pathway, the borylation of 3-picoline is first order in catalyst (Table 3).

However, if dissociation of heteroarene from a complex analogous to picoline adduct **20** (eq 1) were rate-limiting, then the reaction would be first order in catalyst and zero order in substrate and B_2pin_2. These are the kinetic orders we observed for the borylation of 3-picoline (Table 3). Yet rate-limiting dissociation of heteroarene can be discounted because the heteroarene and COE undergo exchange on the NMR time scale (vide supra). These data are inconsistent with precoordination of heteroarene to a Lewis acidic species as the origin of the observed selectivity.

2.7.2.2. Computational Studies. Having concluded that the origin of the lack of reactivity adjacent to a basic nitrogen atom was likely to result from electronic effects, we conducted DFT calculations of the reaction pathway for the borylation of pyridine at the 2-, 3-, and 4-positions. We calculated the pathway for the reaction of pyridine at these positions with the

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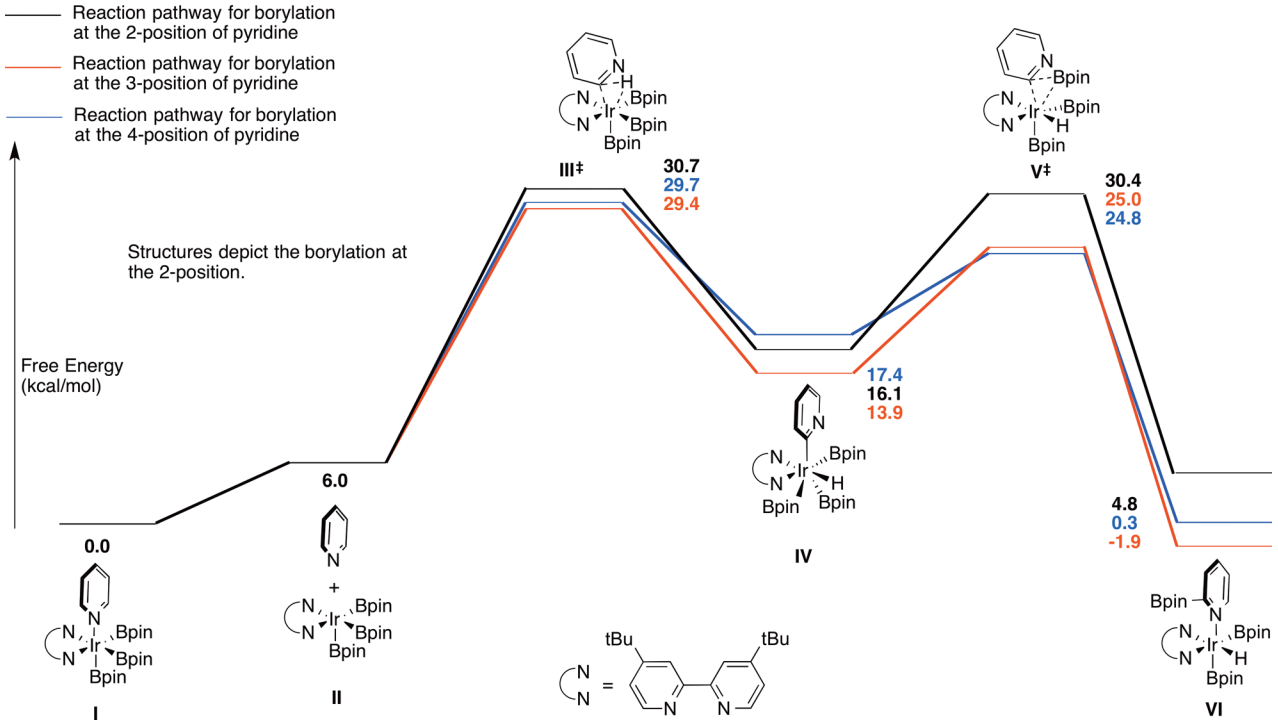

Figure 7. Reaction pathways for the borylation of pyridine at the 2-, 3-, and 4-positions calculated at the M06L level with lanl2dz and 6-31g(d,p) basis sets and IEFPCM THF solvation model.

16-electron complex generated from thermal dissociation of COE from **17**. The calculations were conducted with M06L functionals, the lanl2dz basis set for iridium, and the 6-31g(d,p) basis set for all other atoms. Solvation in THF was modeled using the IEFPCM formalism. The computed pathways describing the borylation of pyridine at the 3- and the 4-postions (red and blue pathways, respectively, Figure 7) predict turnover-limiting C−H activation. This computational result is consistent with experimentally determined side-by-side kinetic isotope effects of 2.9 and 2.4 for reaction at the 3- and the 4-positions, respectively (see SI for details). However, the pathways depicted in Figure 7 do not predict the high selectivity for borylation at the 3- and 4-positions over the 2-position. The highest energy along the pathway for reaction at the 2-position is only about 1 kcal/mol higher than that along the pathway for reaction at the 3- or 4-position.

2.7.2.3. Assessment of the Stability of the 2-Borylpyridine Products under the Reaction Conditions and Conclusion on the Origin of Regioselectivity for the Borylation of Pyridines and Diazines. Considering the results of the computational studies, we considered that the lack of observable products from borylation alpha to the basic nitrogen atom in pyridines and diazines might originate from the combination of the higher barrier of reaction at this site over other sites and the instability of the products formed from borylation alpha to basic nitrogen under the reaction conditions.

To test the second part of this hypothesis, we conducted the borylation of pyridine-d_5 in the presence of 5 mol % of unlabeled 2-borylpyridine **28** and monitored the fate of the 2-borylpyridine (Figure 8a). Heating of this reaction mixture led to the decomposition of 2-borylpyridine to multiple unidentifiable products. This decomposition was faster than the borylation of pyridine-d_5; only about 5% yield (based on B_2pin_2) of the pyridine-d_5 borylation products was observed at the time that the decomposition of the 2-borylpyridine was

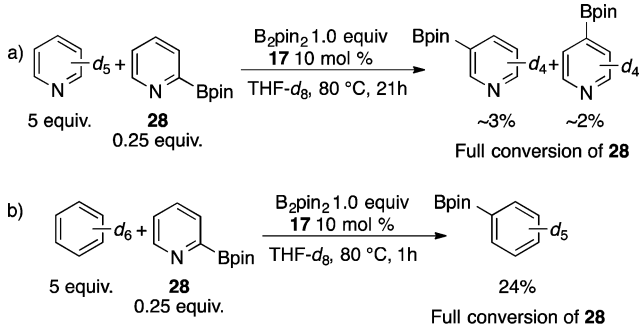

Figure 8. (a) Decomposition of 2-borylpyridine **28** during the borylation of pyridine-d_5. (b) Decomposition of 2-borylpyridine **28** during the borylation of benzene-d_6.

complete. Thus, the more rapid decomposition of 2-borylpyridyl products than the formation of borylpyridine products is likely the origin of the lack of observation of such products during the borylation of pyridines.

We also conducted the borylation of benzene-d_6 in the presence of 5 mol % of 2-borylpyridine **28** (Figure 8b). Under these conditions only a 24% yield of PhBpin was observed at the time of complete consumption of the 2-borylpyridine. Thus, even in the presence of benzene-d_6, a noncoordinating substrate containing six reactive C−D bonds, the decomposition of the 2-borylpyridine was faster than the C−H borylation process.

We also assessed the mass balance of the reaction of **4**-picoline (**29**) with B_2pin_2. Because of the substituent at the 4-position, 4-picoline should not form significant amounts of the borylation product. However, it has not been reported whether pyridines lacking sterically accessible C−H bonds are stable to the reaction conditions or undergo decomposition, perhaps through borylation at the 2-position. If 4-picoline undergoes

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slow reaction at the 2-position, followed by more rapid decomposition, we should observe (1) conversion of 4-picoline to a set of decomposition products, (2) conversion of B_2pin_2 to HBpin, and (3) catalyst decomposition.

Indeed, heating of 4-picoline (Figure 9) with B_2pin_2 at 80 °C in the presence of 10 mol % of complex **17**, led to the

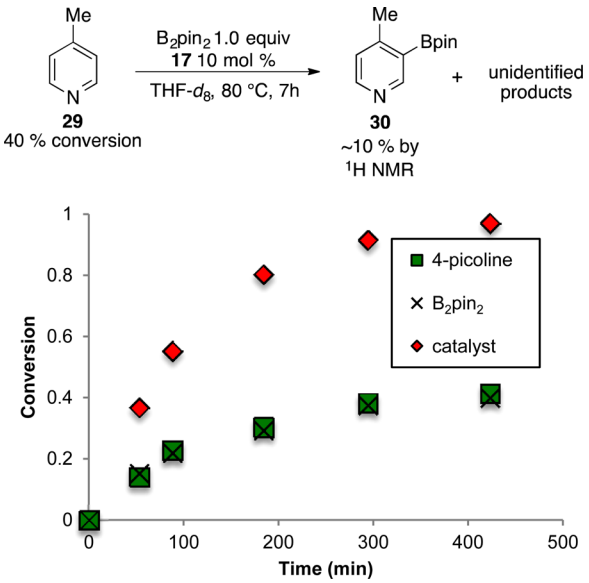

Figure 9. Decomposition of 4-picoline **29**, B_2pin_2, and catalyst as determined by ^{1}H NMR spectroscopy.

formation of several unidentifiable aromatic compounds, according to ^{1}H NMR spectroscopy, a small amount of heteroaryl boronate **30**, the distinctive broad quartet of HBpin, and complete decomposition of the trisboryl complex after 7 h. At this time, the conversion of 4-picoline was 40%, but the yield of 3-boryl-4-picoline **30** was only ~10%, implying that 4-picoline was converted to a series of products resulting from decomposition of the product of borylation at the 2-position. The conversion of B_2pin_2 paralleled the conversion of 4-picoline, which suggests that C–H borylation is leading to the formation of the multiple aromatic products. At this time we do not speculate on the mechanism of decomposition of the proposed 2-borylpyridyl products or the catalyst, but the instability of 2-borylpyridine derivatives is well documented.[56−58]

3. CONCLUSIONS

Our studies have demonstrated the potential of the iridium-catalyzed borylation to functionalize heteroarenes with predictable selectivities. Several important conclusions about the origin of the reactivity and selectivity can be drawn from our data.

(1) Investigations of the borylation of basic heteroarenes catalyzed by the combination of $[Ir(COD)OMe]_2$ and either Me_4phen or dtbpy revealed that the Me_4phen-Ir catalyst is more active for this transformation than the dtbpy-Ir catalyst.

(2) With the Me_4phen-Ir catalyst, the borylation of benzoxazoles, pyrimidines, and unprotected benzimidazoles, pyrazoles, and azaindoles occurred in good yield and with high selectivity.

(3) Much of the high selectivity was derived from the effect of free N–H and basic nitrogens on selectivity.

(4) No borylation occurred alpha or ortho to free N–H moieties, due to the rapid formation of a bulky *N*-Bpin species.

(5) Our studies also showed that borylation did not occur alpha or ortho to basic nitrogen moieties. This selectivity was not due to binding of the heteroarene to a Lewis acidic species through the basic nitrogen, as we proposed earlier, but this selectivity may be due to the combination of a higher-energy pathway for the borylation adjacent to basic nitrogen relative to the borylation at other sites and the instability of the products from borylation adjacent to basic nitrogen under the reaction conditions

(6) Heteroarenes were shown to bind to the catalyst, and the strength of this binding determines the resting state of the catalyst and ultimately the dependence of the rate of the reaction on the concentration of substrate.

We expect that our studies will greatly broaden the applications of iridium-catalyzed borylation in the field of medicinal chemistry due to our demonstration of the high and predictable selectivity of the reaction as well as the tolerance of the reaction to high nitrogen content of the substrates.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectra for all new compounds. Cartesian coordinates and energies of calculated ground states and transition states. 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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■ REFERENCES

(1) Welsch, M. E.; Snyder, S. A.; Stockwell, B. R. *Curr. Opin. Chem. Biol.* **2010**, *14*, 347.
(2) Ge, S.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2012**, *51*, 12837.
(3) Ye, M.; Gao, G.-L.; Edmunds, A. J. F.; Worthington, P. A.; Morris, J. A.; Yu, J.-Q. *J. Am. Chem. Soc.* **2011**, *133*, 19090.
(4) Meng, L.; Kamada, Y.; Muto, K.; Yamaguchi, J.; Itami, K. *Angew. Chem., Int. Ed.* **2013**, *52*, 10048.
(5) Mkhalid, I. A. I.; Barnard, J. H.; Marder, T. B.; Murphy, J. M.; Hartwig, J. F. *Chem. Rev.* **2009**, *110*, 890.
(6) Hartwig, J. F. *Acc. Chem. Res.* **2011**, *45*, 864.
(7) Ishiyama, T.; Takagi, J.; Yonekawa, Y.; Hartwig, J. F.; Miyaura, N. *Adv. Synth. Catal.* **2003**, *345*, 1103.
(8) Ishiyama, T.; Nobuta, Y.; Hartwig, J. F.; Miyaura, N. *Chem. Commun.* **2003**, *0*, 2924.
(9) Ishiyama, T.; Miyaura, N. *Pure Appl. Chem.* **2006**, *78*, 1369.
(10) Kallepalli, V. A.; Shi, F.; Paul, S.; Onyeozili, E. N.; Maleczka, R. E.; Smith, M. R. *J. Org. Chem.* **2009**, *74*, 9199.
(11) Preshlock, S. M.; Plattner, D. L.; Maligres, P. E.; Krska, S. W.; Maleczka, R. E.; Smith, M. R. *Angew. Chem., Int. Ed.* **2013**, *52*, 12915.

(12) Klecka, M.; Pohl, R.; Klepetarova, B.; Hocek, M. *Org. Biomol. Chem.* **2009**, *7*, 866.
(13) Mkhalid, I. A. I.; Coventry, D. N.; Albesa-Jove, D.; Batsanov, A. S.; Howard, J. A. K.; Perutz, R. N.; Marder, T. B. *Angew. Chem., Int. Ed.* **2006**, *45*, 489.
(14) Harrisson, P.; Morris, J.; Marder, T. B.; Steel, P. G. *Org. Lett.* **2009**, *11*, 3586.
(15) Robbins, D. W.; Hartwig, J. F. *Org. Lett.* **2012**, *14*, 4266.
(16) Tzschucke, C. C.; Murphy, J. M.; Hartwig, J. F. *Org. Lett.* **2007**, *9*, 761.
(17) Litvinas, N. D.; Fier, P. S.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2012**, *51*, 536.
(18) Webb, K. S.; Levy, D. *Tetrahedron Lett.* **1995**, *36*, 5117.
(19) Revuelta, J.; Machetti, F.; Cicchi, S. In *Modern Heterocyclic Chemistry*; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, Germany, 2011.
(20) Vanchura, I. I. B. A.; Preshlock, S. M.; Roosen, P. C.; Kallepalli, V. A.; Staples, R. J.; Maleczka, J. R. E.; Singleton, D. A.; Smith, M. R. *Chem. Commun.* **2010**, *46*, 7724.
(21) Boller, T. M.; Murphy, J. M.; Hapke, M.; Ishiyama, T.; Miyaura, N.; Hartwig, J. F. *J. Am. Chem. Soc.* **2005**, *127*, 14263.
(22) Ertan, T.; Yildiz, I.; Tekiner-Gulbas, B.; Bolelli, K.; Temiz-Arpaci, O.; Ozkan, S.; Kaynak, F.; Yalcin, I.; Aki, E. *Eur. J. Med. Chem.* **2009**, *44*, 501.
(23) Kumar, D.; Jacob, M. R.; Reynolds, M. B.; Kerwin, S. M. *Bioorg. Med. Chem.* **2002**, *10*, 3997.
(24) Potashman, M. H.; Bready, J.; Coxon, A.; DeMelfi, T. M.; DiPietro, L.; Doerr, N.; Elbaum, D.; Estrada, J.; Gallant, P.; Germain, J.; Gu, Y.; Harmange, J.-C.; Kaufman, S. A.; Kendall, R.; Kim, J. L.; Kumar, G. N.; Long, A. M.; Neervannan, S.; Patel, V. F.; Polverino, A.; Rose, P.; van der Plas, S.; Whittington, D.; Zanon, R.; Zhao, H. *J. Med. Chem.* **2007**, *50*, 4351.
(25) Bansal, Y.; Silakari, O. *Bioorg. Med. Chem.* **2012**, *20*, 6208.
(26) Adler, T. K.; Albert, A. *J. Med. Chem.* **1963**, *6*, 480.
(27) Hong, S.; Kim, J.; Seo, J. H.; Jung, K. H.; Hong, S.-S.; Hong, S. *J. Med. Chem.* **2012**, *55*, 5337.
(28) Vangveravong, S.; Taylor, M.; Xu, J.; Cui, J.; Calvin, W.; Babic, S.; Luedtke, R. R.; Mach, R. H. *Bioorg. Med. Chem.* **2010**, *18*, 5291.
(29) El-Deeb, I. M.; Lee, S. H. *Bioorg. Med. Chem.* **2010**, *18*, 3961.
(30) Orjales, A.; Mosquera, R.; López, B.; Olivera, R.; Labeaga, L.; Núñez, M. T. *Bioorg. Med. Chem.* **2008**, *16*, 2183.
(31) Shao, H.; Shi, S.; Huang, S.; Hole, A. J.; Abbas, A. Y.; Baumli, S.; Liu, X.; Lam, F.; Foley, D. W.; Fischer, P. M.; Noble, M.; Endicott, J. A.; Pepper, C.; Wang, S. *J. Med. Chem.* **2013**, *56*, 640.
(32) Liskey, C. W.; Hartwig, J. F. *J. Am. Chem. Soc.* **2012**, *134*, 12422.
(33) Ohmura, T.; Torigoe, T.; Suginome, M. *J. Am. Chem. Soc.* **2012**, *134*, 17416.
(34) Cho, S. H.; Hartwig, J. F. *J. Am. Chem. Soc.* **2013**, *135*, 8157.
(35) Preshlock, S. M.; Ghaffari, B.; Maligres, P. E.; Krska, S. W.; Maleczka, R. E.; Smith, M. R. *J. Am. Chem. Soc.* **2013**, *135*, 7572.
(36) O'Hara, F.; Blackmond, D. G.; Baran, P. S. *J. Am. Chem. Soc.* **2013**, *135*, 12122.
(37) Ichikawa, H.; Nishioka, M.; Arimoto, M.; Usami, Y. *Heterocycles* **2010**, *81*, 1509.
(38) Kallepalli, V. A., .Maleczka R. E., Jr., Onyeozili E., Smith M. R., III U.S. Patent 7,709,654, 2007.
(39) Schneider, C.; David, E.; Toutov, A. A.; Snieckus, V. *Angew. Chem., Int. Ed.* **2012**, *51*, 2722.
(40) Takagi, J.; Sato, K.; Hartwig, J. F.; Ishiyama, T.; Miyaura, N. *Tetrahedron Lett.* **2002**, *43*, 5649.
(41) For a prior report of this reaction see: Kallepalli, V. A.; Shi, F.; Paul, S.; Onyeozili, E. N.; Maleczka, R. E.; Smith, M. R. *J. Org. Chem.* **2009**, *74*, 9199.
(42) L'Heureux, A.; Thibault, C.; Ruel, R. *Tetrahedron Lett.* **2004**, *45*, 2317.
(43) The observed regioselectivity also could originate from the larger size of the CF_3 group relative to the Bpin group.
(44) Tajuddin, H.; Harrisson, P.; Bitterlich, B.; Collings, J. C.; Sim, N.; Batsanov, A. S.; Cheung, M. S.; Kawamorita, S.; Maxwell, A. C.; Shukla, L.; Morris, J.; Lin, Z.; Marder, T. B.; Steel, P. G. *Chem. Sci.* **2012**, *3*, 3505.
(45) Maleczka, R. E.; Shi, F.; Holmes, D.; Smith, M. R. *J. Am. Chem. Soc.* **2003**, *125*, 7792.
(46) Kikuchi, T.; Nobuta, Y.; Umeda, J.; Yamamoto, Y.; Ishiyama, T.; Miyaura, N. *Tetrahedron* **2008**, *64*, 4967.
(47) Murphy, J. M.; Liao, X.; Hartwig, J. F. *J. Am. Chem. Soc.* **2007**, *129*, 15434.
(48) Beck, E. M.; Hatley, R.; Gaunt, M. J. *Angew. Chem., Int. Ed.* **2008**, *47*, 3004.
(49) Liskey, C. W.; Liao, X.; Hartwig, J. F. *J. Am. Chem. Soc.* **2010**, *132*, 11389.
(50) Murphy, J. M.; Tzschucke, C. C.; Hartwig, J. F. *Org. Lett.* **2007**, *9*, 757.
(51) Kinzel, T.; Zhang, Y.; Buchwald, S. L. *J. Am. Chem. Soc.* **2010**, *132*, 14073.
(52) Liu, T.; Shao, X.; Wu, Y.; Shen, Q. *Angew. Chem., Int. Ed.* **2012**, *51*, 540.
(53) Scott, J. S.; Birch, A. M.; Brocklehurst, K. J.; Broo, A.; Brown, H. S.; Butlin, R. J.; Clarke, D. S.; Davidsson, Ö.; Ertan, A.; Goldberg, K.; Groombridge, S. D.; Hudson, J. A.; Laber, D.; Leach, A. G.; MacFaul, P. A.; McKerrecher, D.; Pickup, A.; Schofield, P.; Svensson, P. H.; Sörme, P.; Teague, J. *J. Med. Chem.* **2012**, *55*, 5361.
(54) Lee, J.; Han, S.-Y.; Jung, H.; Yang, J.; Choi, J.-W.; Chae, C. H.; Park, C. H.; Choi, S. U.; Lee, K.; Ha, J. D.; Lee, C. O.; Ryu, J. W.; Kim, H. R.; Koh, J. S.; Cho, S. Y. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 4044.
(55) Paul, S.; Chotana, G. A.; Holmes, D.; Reichle, R. C.; Maleczka, R. E.; Smith, M. R. *J. Am. Chem. Soc.* **2006**, *128*, 15552.
(56) Abraham, M. H.; Grellier, P. L. In *The Metal—Carbon Bond (1985)*; John Wiley & Sons, Ltd.: New York, 2010; p 25.
(57) Campeau, L.-C.; Fagnou, K. *Chem. Soc. Rev.* **2007**, *36*, 1058.
(58) Liu, Y.; Milo, L. J., Jr.; Lai, J. H. *ARKIVOC* **2013**, 135.