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High-Throughput Optimization of Ir-Catalyzed C−H Borylation: A Tutorial for Practical Applications

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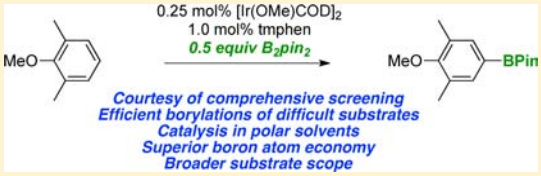
Supporting Information

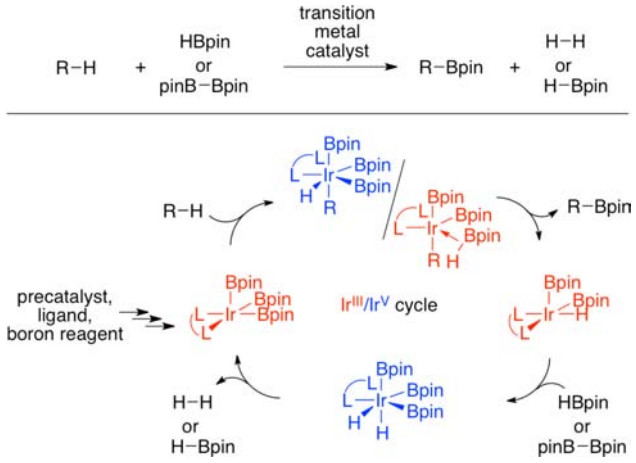
ABSTRACT: With the aid of high-throughput screening, the efficiency of Ir-catalyzed C−H borylations has been assessed as functions of precatalyst, boron reagent, ligand, order of addition, temperature, solvent, and substrate. This study not only validated some accepted practices but also uncovered unconventional conditions that were key to substrate performance. We anticipate that insights drawn from these findings will be used to design reaction conditions for substrates whose borylations are difficult to impossible using standard catalytic conditions.



INTRODUCTION

The development of iridium catalyzed C−H borylation over the past decade has provided a simple, atom economical route to arylboronate esters.[1] Studies of precatalysts such as (η^6-mesitylene)Ir(Bpin)$_3$[2] and (dtbpy)Ir(Bpin)$_3$(coe)[3] (**1**, dtbpy =4,4′-di-*tert*-butyl-2,2′-bipyridine, coe = cyclooctene) support a mechanism where species of the formula $L_2Ir^{III}Bpin_3$ are the intermediates that mediate C−H cleavage (Scheme 1). This

Scheme 1. Mechanism for Ir-Catalyzed C−H Borylation



picture has been corroborated by computational studies[4] and more recently by the isolation of 16-electron complexes (dippe)IrBpin$_3$ and (dcpe)IrBpin$_3$ that react directly with C−H bonds at room temperature.[5]

In an early communication by Ishiyama, Takagi, Hartwig, and Miyaura (hereafter ITHM), a set of precatalysts and ligands were screened for borylations.[6] From this screen, conditions for utilizing [Ir(cod)(μ_2-OMe)]$_2$ (**2**, cod = 1,5-cyclooctadiene) as the precatalyst, dtbpy as the ligand, B_2pin_2 as the borylating agent, and hexane as the solvent gave excellent results for a panel of electron-deficient substrates. In this report, it was noted that reaction conversions were solvent dependent, following the order hexanes > DME > DMF. The ability to carry out the reaction with an air-stable boron reagent (B_2Pin_2) using the precatalyst [Ir(cod)(μ_2-OMe)]$_2$, which has been described as being air stable, has made the ITHM protocol the preferred method for carrying out Ir-catalyzed C−H borylation.[7]

To date, many unique combinations of precatalyst, boron reagent, ligand, and solvent have been described in the literature.[8] Not surprisingly, many of these are variants of the ITHM protocol, where modifications have been made based on mechanistic work and/or empirical findings. Since the initial reports, the substrate scope for C−H borylation has expanded considerably. Yet, there has been no comprehensive study of the synergistic roles that substrate, solvent, precatalyst, borylating agent, temperature, order of addition, etc. might have on borylations. Such a study is important because it is likely that conditions that are optimal for one substrate class (e.g., electron-deficient arenes) might have limited success, or fail entirely, for another substrate (e.g., an azaindole).

Comprehensive studies of this type are challenging for a number of reasons. First, exploration of *n* variables creates an *n*-dimensional reaction space to be surveyed, making most undertakings labor intensive. Second, collection and processing of experimental data must be reliable and fast to avoid an analysis bottleneck. Third, the analysis and interpretation of *n*-dimensional data are nontrivial, and it is critical that they are presented such that underlying themes are clear so scientists

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can use the information to solve specific problems. Lastly, variability in any experimental endeavor is unavoidable. This means that multiple runs must be carried out for conclusions from the data to be made with confidence.

The advent of high-throughput reaction screening techniques and modern analytical methods has provided a means of overcoming the obstacles listed above, enabling a comprehensive study to be undertaken with a reasonable investment of time and resources.[9] Given the potential value of Ir-catalyzed C−H borylation, a comprehensive study would provide a roadmap for practitioners of this method. For these reasons, we have undertaken a systematic study of multiple reaction variables affecting Ir catalyzed C−H borylation. While this study validates some accepted practices, there are some surprising findings and several cases where unconventional conditions are the key to substrate performance.

RESULTS

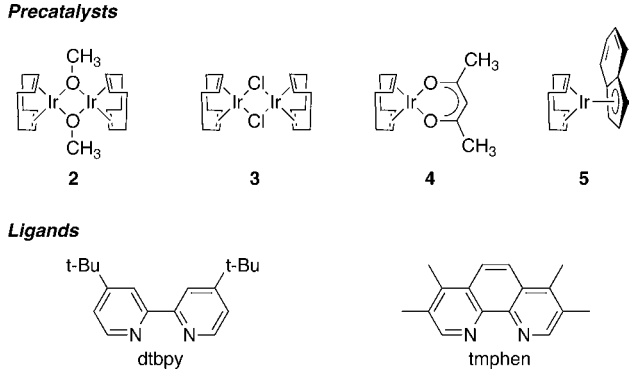
Methods. To expedite the process of running the number of reactions required in this study, reactions were conducted in a glovebox using microscale 96-well plate reactors. To ensure that results from this study mirrored typical laboratory applications, commercially supplied anhydrous solvents and reagents were used as received, except for THF and 2-methyltetrahydorfuran, which were distilled from Na/benzophenone to remove inhibitors. Reagents were dispensed to each well from stock solutions to accurately control stoichiometries, and reactions were run in duplicate on each plate to test for consistency. Furthermore, entire reaction screens were periodically repeated to further certify reproducibility. Temperatures and time points were chosen so that the fastest reactions were stopped before completion. Reaction products were verified by comparing ^{1}H NMR spectra of crude mixtures to data of authentic compounds. Product yields were determined from HPLC data calculated from peak areas, relative to an internal standard.

Order of Addition Effects. Compound **1** is most likely the major catalyst resting state in borylations utilizing **2** as the Ir precatalyst. In the synthesis of **1** from **2** it was noted that the order in which HBpin and dtbpy were added greatly affected isolated product yields.[3] Consequently, it might be expected that orders of addition might impact borylation efficiencies for in situ generated catalysts. The nature of the borane reagent has also been shown to influence relative rates of borylation[6]—a somewhat surprising finding given that kinetic studies show catalytic reactions with B_2pin_2 are zero order in $[B_2pin_2]$.[3] Variations have also been observed depending on the nature of the precatalyst. For example, borylations with B_2pin_2 using the precatalyst $[Ir(\mu_2\text{-Cl})(cod)]_2$ (**3**) exhibit induction periods that can be eliminated when catalytic amounts of HBpin are added to the reaction mixture.[3]

The present study uses catalysts generated in situ because this is the typical practice reported for C−H borylations. Given this and the influences of reagents and catalysts noted above, examination of the effects of the order of addition of precatalyst, ligand, and boron reagent on the outcome of C−H borylation was deemed the most logical starting point. Two conditions for in situ catalyst formation were tested and found to significantly impact borylation efficiency. These are designated as conditions **A** and **B** in the text. For condition **A**, the order of addition is precatalyst, boron reagent, and ligand. The order for condition **B** is precatalyst, ligand, and boron reagent. The precatalyst, boron reagent, and ligand were dispensed as stock solutions in the designated solvent. After the catalyst components were combined, aliquots from a stock solution of the substrate and internal standard (typically dodecahydrotriphenylene) were added to the well plates. The reaction plate was then sealed and stirred at the desired temperature for an allotted amount of time, at which point the reaction was cooled to room temperature and quenched by exposure to atmospheric O_2.

The four precatalysts used in the screens were the commercially available compounds **2**, **3**, Ir(acac)(cod) (**4**), and (Ind)Ir(cod) (**5**) (Chart 1). The ligands chosen were the commonly employed dtbpy and the electron-rich ligand 3,4,7,8-tetramethyl-1,10-phenanthroline (tmphen).[10] The reaction in the initial screen was the borylation of 3-bromotoluene carried out in THF at room temperature. The results are shown in Figure 1.

Chart 1



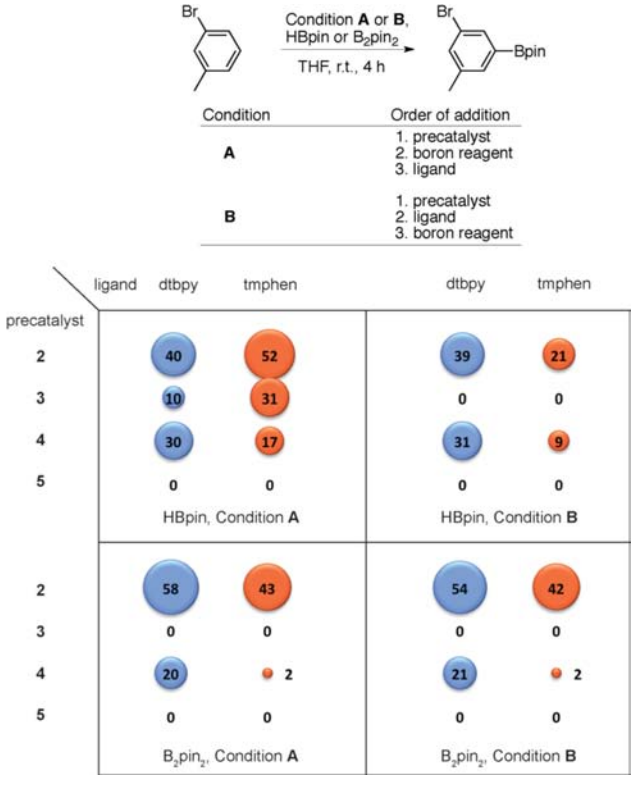


Figure 1. Order of addition effects for room temperature C−H borylations. Data plotted are product yields determined by HPLC.

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Some general trends emerge. First, the relative ordering of precatalyst activity is **2** > **4** > **3** > **5**. This is consistent with the literature for **2**, **3**, and **5**, with **5** being ineffective at room temperature.[2] While precatalyst **4** has not been used in any borylations to date, it outperforms more commonly employed **3** in most cases and is more effective than Ir(OAc)(cod).[6]

The order of addition had little effect on the performance of the precatalyst/ligand combination **2** or **4**/dtbpy, which is somewhat unexpected given the influence of addition order in synthesis of **1** from **2**.[3] For **2**/dtbpy borylation conversions with B_2pin_2 were ∼50% greater than those with HBpin, while HBpin was ∼50% *more* effective than B_2pin_2 for precatalyst **4**/dtbpy.

Surprisingly, the order of addition greatly affected the performance of precatalyst **2**/HBpin when the more electron-rich ligand tmphen was used. For example, the performance of the combination **2**/tmphen/HBpin rivals that of **2**/dtbpy/B_2pin_2 when the borane is added before the ligand. This reactivity is attenuated 2.5-fold when tmphen is added before HBpin. In contrast, borylations with the combination **2**/tmphen/B_2pin_2 were insensitive to the order of addition and had conversions that were intermediate to those for HBpin. It is particularly noteworthy that the highest borylation conversions for **2**/tmphen are achieved with HBpin, even though the thermodynamic driving force is less than the analogous reaction with B_2pin_2.

Of the precatalysts that operated at room temperature, **3** was most sensitive to addition order and borane reagent. Specifically, the only combination that gave conversion at room temperature was condition **A** with HBpin. The effectiveness of HBpin over B_2pin_2 is consistent with the previously noted induction period for borylations employing the latter with precatalyst **3**;[3] however, the influence of addition order with HBpin was unexpected.

Temperature Effects. Substrate electronic effects influence Ir-catalyzed C−H borylation rates with electron-deficient substrates being the most reactive.[4a] Consequently, room temperature borylations of electron-rich substrates are less practical. This is illustrated by reactivity of 1,2,3-trimethoxybenzene. In Figure 2, borylation conversions are given at 25 and 80 °C. In all cases the reaction duration was 2.5 h, and precatalyst **2** was used. In addition to temperature, the ligand, boron reagent, and order of addition were varied.

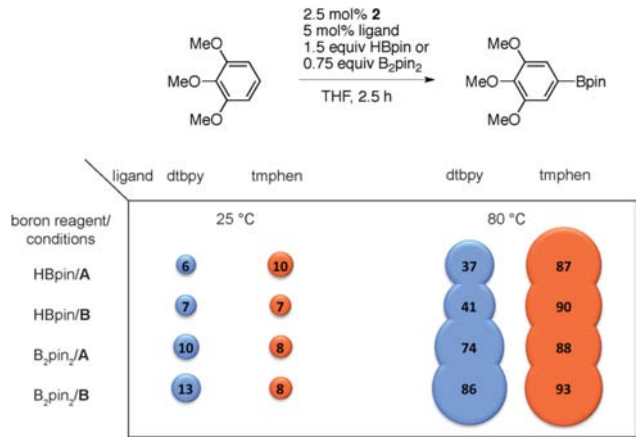

Figure 2. Temperature and ligand effects on borylation of 1,2,3-trimethoxybenzene with precatalyst **2**. Data plotted are product yields determined by HPLC.

As expected, conversions at 80 °C were much greater than those at 25 °C. In contrast to the observations made with room temperature borylation of 3-bromotoluene, conversions in the present case were only slightly influenced by order of addition with condition **B** (precatalyst, ligand, then boron reagent) giving marginally higher conversions. At 80 °C the pairing of ligand and boron reagent had pronounced effects. For the typically employed dtbpy ligand, conversions with HBpin were considerably lower than those for B_2pin_2. Borylation conversions with tmphen-ligated catalysts were superior to those for dtbpy, and the choice of boron reagent was less important with HBpin and B_2pin_2 performing similarly.

To more broadly assess the effects of elevated temperatures on C−H borylation, the reaction of 3-methyl-*N*,*N*-dimethylaniline was screened at 80 °C. The combination of precatalysts, boron reagent, and orders of addition was identical to that in Figure 1. Because this substrate is particularly unreactive, the data in Figure 3 were recorded after 8 h reaction time.

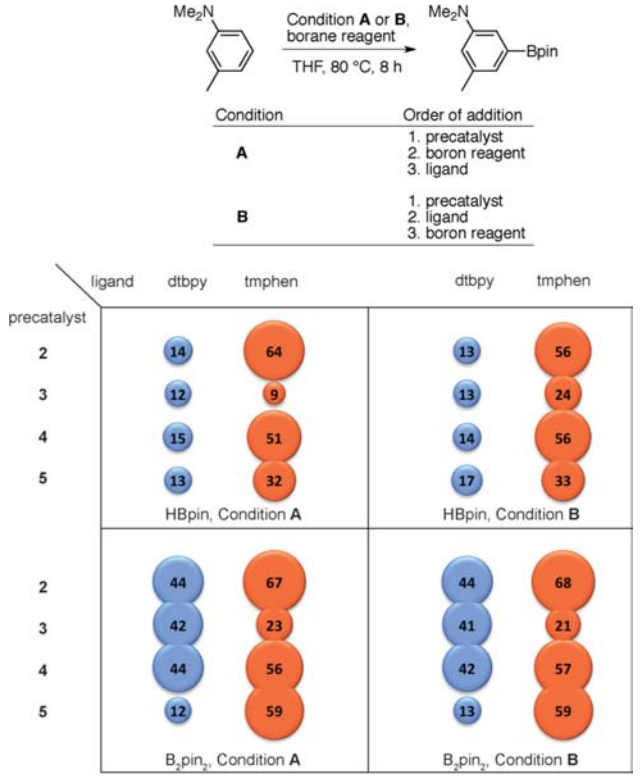

Figure 3. Effects of precatalyst, boron reagent, and order of addition, on C−H borylation of 3-methyl-*N*,*N*-dimethylaniline at 80 °C.

The effects of the ligand were dramatic with tmphen outperforming dtbpy with every precatalyst except for **3**. For all other catalysts conversions with tmphen were 1.5−4.5 times greater than those with dtbpy. This is consistent with previous observations that more electron-rich catalysts are more reactive.[6]

The data in Figure 3 differ significantly from those in Figure 1 in several respects. For example, the order of addition did not affect conversions at elevated temperature, consistent with the observations on the borylation of 1,2,3-trimethoxybenzene (vide supra). Also the choice of precatalyst is less important when dtbpy is used. Specifically, conversions with precatalysts **2**−**5** with dtbpy/HBpin gave uniformly low conversions. For the combination dtbpy/B_2Pin_2, precatalysts **2**−**4** perform

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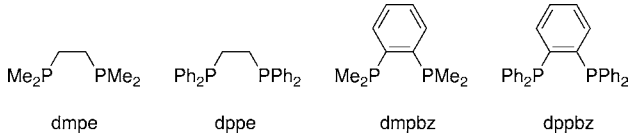
equally well and superior to reactions with **5**. As was the case in Figure 1, the combination dtbpy/B_2Pin_2 outperforms dtbpy/HBpin, but the increase (3-fold on average) was more pronounced at elevated temperature for precatalysts **2**–**4**.

In contrast, conversions with tmphen are sensitive to the choice of precatalyst. The performance of precatalyst **3** is particularly poor, mirroring the situation for borylation at room temperature. For the combination tmphen/HBpin the precatalyst activity is **2** > **4** > **5** ≫ **3** when the order of addition is condition **A**. For condition **B**, the activity of **2** decreases and **3** increases such that **2** ∼ **4** > **5** > **3**. When B_2Pin_2 is used with tmphen, the order of addition does not matter. Interestingly, the activities of **3** and **5** increase relative to **4** such that the overall ordering is **2** > **4** ∼ **5** > **3** with the performance of **4** and **5** being ∼85% of that for **2**.

Ligand Effects. Phosphine ligands have been used in catalytic borylations.[2] In practice, the catalyst ensemble that results is less active than the in situ generated nitrogen chelate ligands. Since quantitative comparisons have not been made, the borylation activity of 3-methyl-*N*,*N*-dimethylaniline was screened using the bidentate phosphine ligands in Chart 2.

Chart 2



Borylations with dmpe, dppe, and dmpbz in THF at 80 °C did not give product for any combination of ligand, precatalyst and boron reagent. In contrast, borylation with HBpin and dppbz gave appreciable yields of product. The activity of dppe, dtbpy, dppbz, and tmphen are compared in Figure 4. The best

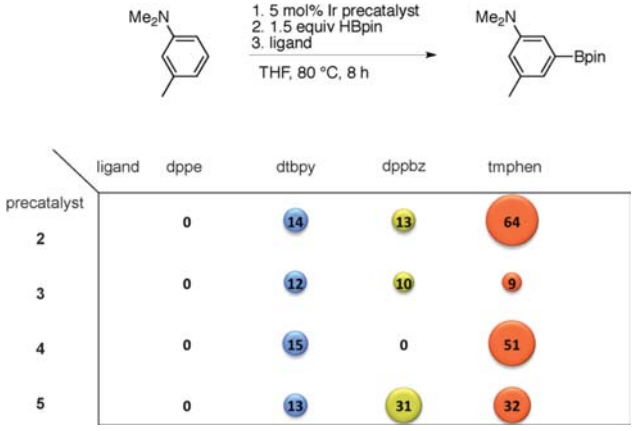


Figure 4. Comparison between dipyridyl and diphosphine ligated catalysts. Data plotted are product yields determined by HPLC. Results for dtbpy and tmphen are the same as shown in Figure 3.

precatalyst for dppbz is compound **5**. In fact, for the borylation of this electron-rich substrate with HBpin, when used with **5** dppbz outperforms all combinations of precatalyst and dtbpy, is competitive with tmphen/**3** or **5** but is less reactive than the pairing of tmphen with precatalysts **2** or **4**.

Solvent Effects. From the early report that solvent effects for borylation follow the order hexanes > DME > DMF it generally has been accepted that polar solvents are poor candidates for C–H borylation.[6] Since the order of addition effects can be attributed to efficiency of in situ catalyst assembly (vide infra), we wondered whether the poor performance in polar solvents might be due to inefficient catalyst assembly rather than performance of the catalyst itself. To address this question we synthesized precatalyst **1** according the literature procedure.[3] The tmphen analog (**6**) was prepared similarly. Compound **1** is one of the most efficient borylation precatalysts reported to date,[7] generating the active catalytic intermediate **7** by dissociation of cyclooctene. Intermediate **8** would be generated in analogous fashion from tmphen complex **6** (Scheme 2).

Scheme 2. Isolable Precatalysts and Equilibria Generating Active Intermediates

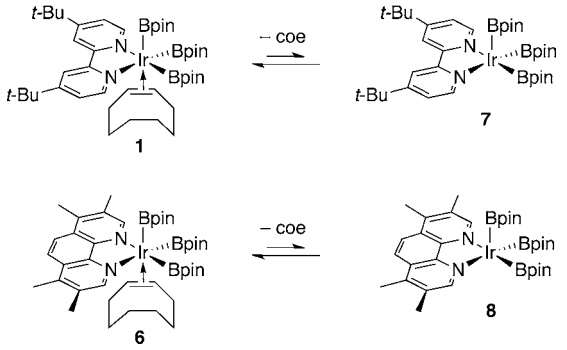


Figure 5 compares borylation conversions for 3-bromotoluene in 11 different solvents with a wide range of polarities.[11] The performance of catalysts generated in situ from precatalyst

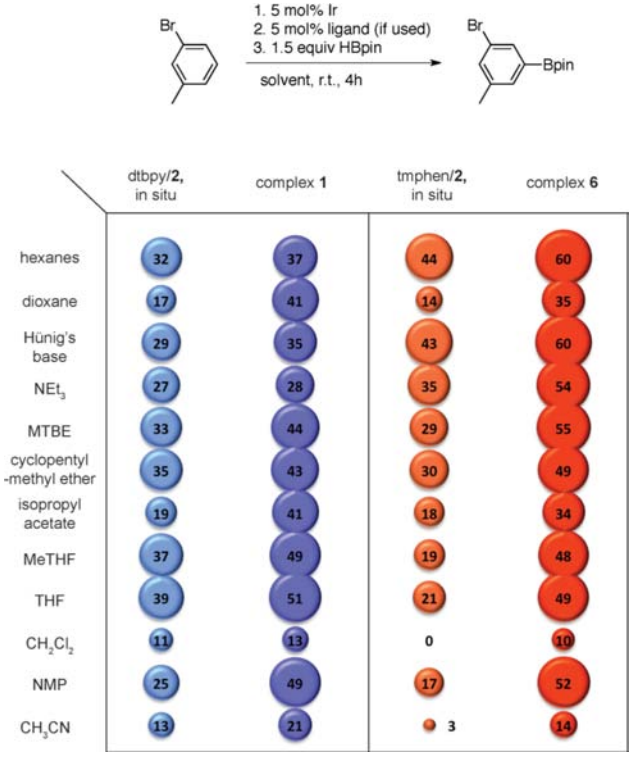


Figure 5. Solvent effects on activity in situ generated catalysts and isolated precatalysts **1** and **6**. Solvents are ordered by increasing dielectric constant.

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2 using HBpin and ligand (Condition A) were compared to borylations catalyzed by preassembled (ligand)Ir(coe)$(Bpin)_3$ precatalysts **1** and **6**.

The data in Figure 5 convincingly show that the in situ catalyst generation can be problematic since conversions for in situ generated catalysts are uniformly lower than those for **1** and **6**. Moreover, the efficiency of in situ catalyst generation varies considerably with the nature of the solvent. The best illustration of this is the comparison between the results obtained with in situ catalyst generation from precatalyst **2** and dtbpy as ligand versus those obtained with complex **1**, both in hexanes and dioxane as solvent. In line with the original literature report, when in situ catalyst generation is employed, hexanes is almost twice as effective as dioxane as solvent; however, borylation conversions in dioxane are higher in dioxane than hexane when preformed **1** is the precatalyst. While we have confirmed that borylations in DMF were poor for both in situ and preformed catalysts, *N*-methylpyrolidone (NMP) is an excellent solvent for borylations with preformed **1**. In fact, seven solvents, including THF, NMP, and isopropyl acetate (Ipac), are superior to hexane for borylations with preformed **1**. Thus, the data in Figure 5 dispel the notion that polar solvents are generally unsuitable for borylation.

Since it is desirable to carry out reactions with more electron-rich substrates at elevated temperatures, we examined borylations of dimethylresorcinol at 80 °C for a subset of solvents. These results are shown in Figure 6. For dtbpy, the

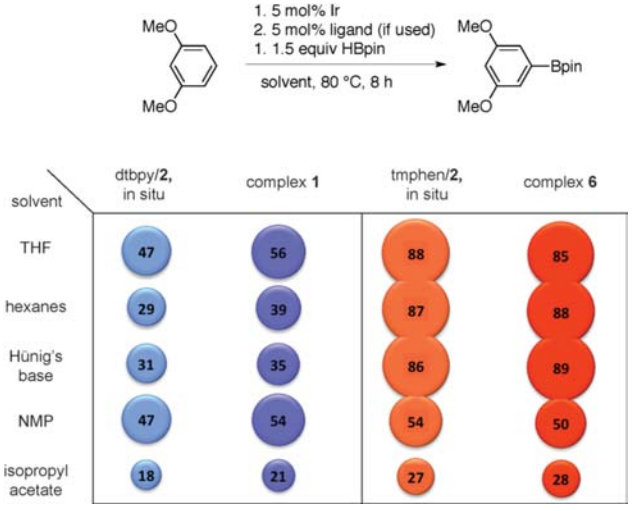

Figure 6. Solvent effects on activity at 80 °C of in situ generated catalysts and isolated precatalysts **1** and **6**. Data plotted are product yields determined by HPLC.

best solvents are THF and NMP, whereas for tmphen, THF, hexanes, and Hünig's base had superior performance. For both ligands, isopropyl acetate had the lowest conversions. Most importantly, the data clearly show that at elevated temperatures the performance of the in situ generated catalysts improved to the point that it rivaled that of the preformed complexes. This is consistent with previous observations for borylations carried out in neat, excess benzene-d_6.[3]

Ligand to Precatalyst Ratio Effects. For precatalysts like those depicted in Scheme 1, stoichiometry requires 1 equiv of bidentate ligand per Ir. It is not unusual to find that an excess of ligand gives optimum performance in reactions mediated by in situ generated catalysts. Thus, we examined the effect of the ligand to metal ratio on the borylation of 3-methyl-*N*,*N*-dimethylaniline. The results are shown in Figure 7.

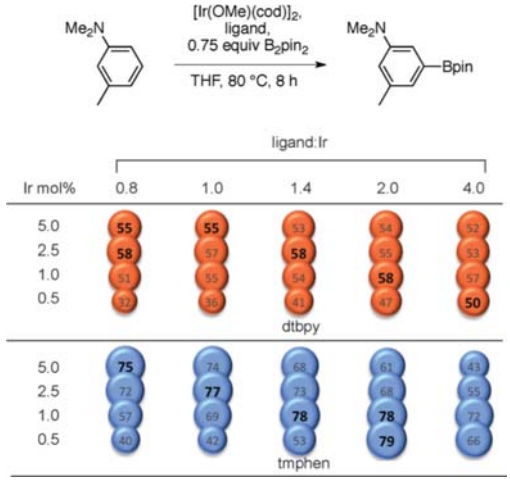

Figure 7. Effects of ligand to precatalyst ratio on performance of in situ generate C–H borylation catalysts. The highest yield for each respective catalyst loading is highlighted in boldface. Data plotted are product yields determined by HPLC.

For both dtbpy and tmphen, conversions were dependent on the ligand to metal ratio as a function of the catalyst loading. Specifically, increasing the ligand to metal ratio gives optimum yields as the catalyst loading is lowered. The effects for tmphen were more dramatic than for dtbpy. For example, identical conversions can be obtained with a 10-fold decrease in catalyst loading by simply doubling the ligand to metal ratio. It is noteworthy that tmphen conversions diminish when the ligand to metal ratio exceeds the optimal value. In contrast, exceeding the optimal value had less effect on conversions for dtbpy.

Precatalyst Stability. While precatalyst **2** is described as being air stable, we have observed that its activity diminishes when it is left on the benchtop. This prompted us to examine the effects of air exposure on the activity of precatalysts in Chart 1. This was accomplished by storing the catalyst for 100 days at ambient temperature at different relative humidity levels. The precatalysts were then assayed for activity by carrying out room temperature borylations of 3-bromotoluene using dtbpy as the ligand and comparing their performance that of control samples that were stored in a nitrogen filled drybox. As shown in Figure 8, catalytic activity of precatalyst **2** diminishes upon exposure to air. The fact that performance deteriorates as humidity increases indicates that moisture sensitivity of **2** is the primary issue. In contrast, the performance of precatalyst **3** was not compromised under the same conditions. Lastly, we note that the performance of precatalyst **2** was most batch dependent. This observed decrease in reactivity for samples of **2** upon aging in air was accompanied by the development of a green-yellow color of the solid, in contrast to the lemon-yellow color of fresh samples of **2**. These partially degraded samples of **2** were judged to be ~95% pure by ^{1}H NMR.

Open vs Closed Systems. In this study the reactions were carried out in closed systems. Borylations with B_2pin_2 generate HBpin as shown in eq 1. The HBpin can effect a second borylation that generates H_2 (eq 2). The H_2 generated will likely react with Ir–boryl complexes to form hydrides according to eq 3. Since effects from H_2 would be more pronounced in

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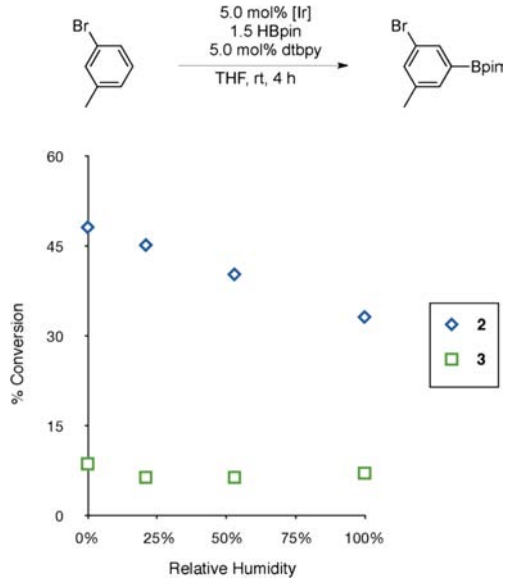

Figure 8. Aging effects on catalyst performance. Samples were stored at ambient temperature for 100 days. The data reported at 0% relative humidity refers to precatalyst samples stored under dry nitrogen. Other samples were stored under air at the reported relative humidities.

closed systems, we compared reactivities between open and closed systems for HBpin and B_2pin_2, and the results are shown in Figure 9. For HBpin, borylations in open systems were slightly more efficient than closed ones, while performance of open and closed systems was essentially identical for B_2pin_2.

$$\text{pinB}-\text{Bpin} + \text{Ar}-\text{H} \rightarrow \text{Ar}-\text{Bpin} + \text{pinB}-\text{H} \quad (1)$$

$$\text{pinB}-\text{H} + \text{Ar}-\text{H} \rightarrow \text{Ar}-\text{Bpin} + \text{H}-\text{H} \quad (2)$$

$$[\text{Ir}]-\text{Bpin} + \text{H}-\text{H} \rightleftharpoons \text{H}-\text{Bpin} + [\text{Ir}]-\text{H} \quad (3)$$

The kinetic behavior of the reactions with B_2pin_2 is interesting. In the case of dtbpy, the product initially forms more rapidly than when tmphen is the borylating ligand. Moreover, the B_2pin_2 reaction plateaus once the B_2pin_2 has been consumed. In contrast, the tmphen conversion is initially slower, which may indicate an induction period for the formation of active catalyst, but ultimately more product is formed because the tmphen system is more efficient for borylation with HBpin. While the detailed picture may be more complex and beyond the scope of this work, the improved conversion for HBpin has practical consequences for the boron atom economy of the reaction (vide infra).

DISCUSSION

Order of Addition Effects. The most pronounced effects were for borylations carried out at room temperature, where the choice of precatalyst, ligand, and boron reagent, combined with order of addition, can be critical. From Figure 1 it is clear that the order of addition has no effect on borylations carried out using B_2pin_2. In contrast, borylations with HBpin are sensitive to the order of addition, being more effective when the order is precatalyst, borane, followed by ligand (condition **A**).

The behavior can be attributed to precatalyst reactivity with HBpin and ligand. Precatalysts **2** and **3** react rapidly with HBpin. While the structures of the resulting iridium complexes are not known, oxidative additions of boranes typically generate

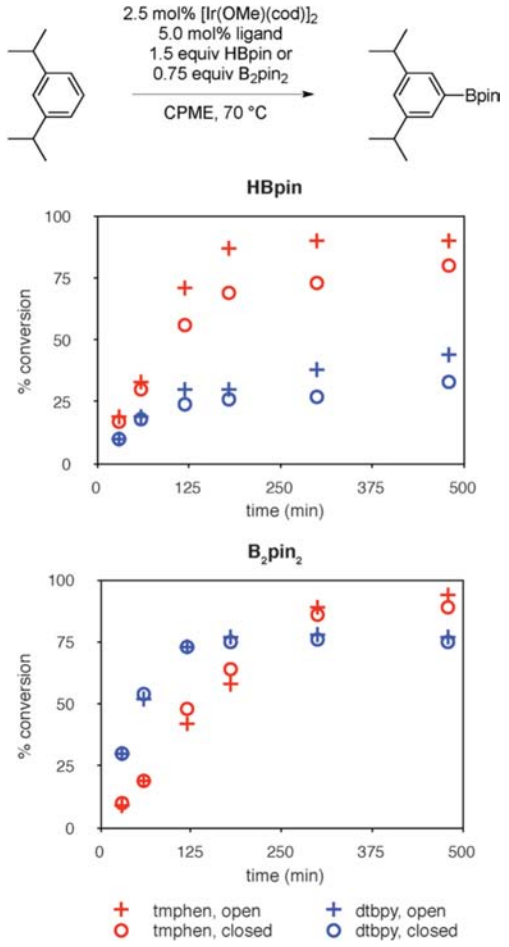

Figure 9. Comparisons between borylations with HBpin and B_2pin_2 in open and closed systems. Red and blue symbols represent tmphen and dtbpy, respectively; + = open system, o = closed system.

metal boryl complexes. These putative complexes could then react with chelating ligands to generate reactive boryl intermediates of the formula $(\text{ligand})\text{Ir}(\text{H})_x(\text{Bpin})_{3-x}$, where $x = 0-2$. Even though oxidative addition of B_2pin_2 to **2** and **3** should be thermodynamically favorable, no reaction was observed at room temperature. Interestingly, complex **3** was ineffective for room temperature borylations with B_2pin_2.

When dtbpy and tmphen are added to precatalyst **3** an immediate reaction occurs. ^{1}H NMR experiments (THF-d_8) show that a new complex forms when dtbpy is added to **3**. A single high-field resonance for the olefinic cod protons and chemically equivalent dtbpy t-Bu groups are consistent with generation of the 18-electron complex $\text{IrCl}(\kappa^2\text{-dtbpy})(\kappa^2\text{-cod})$ (**9**).[12] Oxidative addition to this coordinatively saturated complex will be slow, which accounts for the lack of reactivity. A similar complexation is seen in the reaction between tmphen and **3**.[13] The reactions of dtbpy and tmphen with precatalyst **3** are detrimental to catalyst performance at room temperature. Under these conditions it appears that generation of boryl intermediates prior to addition of the chelating ligand is essential to catalytic activity. If so, the success of HBpin over B_2pin_2 in the room temperature borylations with **3** can be attributed to the reactivity of the former over the latter.

For the combination of precatalyst **2** and dtbpy, the order of addition had no effect on reactivity. ^{1}H NMR experiments (THF-d_8) showed no evidence for complexation. Thus, dtbpy

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does not interfere with generation of active catalyst. In contrast, tmphen reacts rapidly with **2** to generate a green precipitate from THF, which explains the diminished reactivity when the order of addition is **2**, tmphen, followed by HBpin.

With respect to precatalyst, compound **2** had superior performance, regardless of ligand, boron reagent, or order of addition. This is consistent with the original report for the ITHM system. For the combination of dtbpy/**2**, order of addition had little effect on conversion (Figure 1). This is somewhat surprising given the report that yields in the synthesis of compound **1**, presumably an active species in the in situ generated reaction, were sensitive to the order of addition.

For the combination tmphen/**2**, Figure 1 shows that the order of addition is important when HBpin is the boron reagent. Specifically, conversion diminishes when the addition order is precatalyst, ligand, and boron reagent. When tmphen is added to solutions of **2**, a dark-green solid precipitates. While insolubility has hampered attempts to characterize the species that form, the low conversion under these conditions likely arises from inefficient generation of the homogeneous catalyst from the heterogeneous mixture.

Room temperature borylations with precatalyst **3** were most sensitive to order of addition, as no conversion was observed for the order: precatalyst, ligand, and boron reagent. Conversely, oxidative addition of HBpin to 16-electron complex **3** is more viable, and the boryl and hydride ligands will labilize ligands trans to them. This will facilitate coordination of dtbpy or tmphen ligands to generate active catalysts. Induction effects have been observed for borylations with precatalyst when the borane reagent is B_2pin_2. Presumably oxidative addition of B_2pin_2 to **3** is thermodynamically viable but kinetically slow.

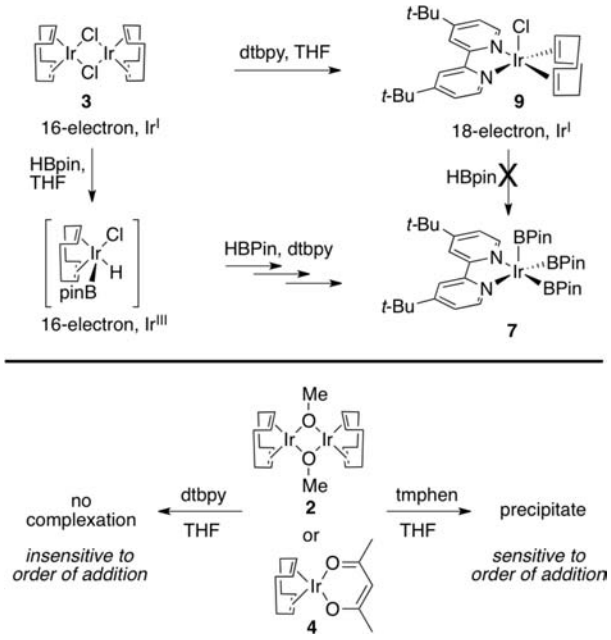
The performance of precatalyst **4**, the second most reactive at room temperature, was not affected by order of addition. Compound **4** does not react with dtbpy, but it forms an insoluble precipitate with tmphen, which accounts for the low conversions at room temperature.

The order of addition effects at room temperature correlates with interactions between the precatalysts and the nitrogen chelate ligands. When complexation between the Ir precatalyst and ligand occurs, catalysis is inhibited if the boron reagent is added after the chelating ligand. This is the case when tmphen is paired with precatalyst **2**, **3**, or **4** and for dtbpy/**3** as summarized in Scheme 3. For room temperature borylations with these precatalyst ligand pairings, the best conversions are obtained when the order of addition is precatalyst, boron reagent, then ligand. Conversely, borylation conversions for combinations of precatalyst **2**–**5** with dtbpy and tmphen carried out at elevated temperature (Figures 2 and 3) are not affected by order of addition.

Temperature Effects. There are many cases where it is desirable to carry out borylations at elevated temperatures to minimize reaction times, particularly in the case of electron-rich substrates. As most of the C–H borylations with the **2**/dtbpy precatalyst/ligand combination have been carried out at room temperature, it is important to assess catalytic viability at elevated temperatures. This is demonstrated for the borylations of 1,2,3-trimethoxybenzene in Figure 2, where conversions clearly improve with increased temperature.

As the room temperature data in Figure 2 show, conversions were more sensitive to the choice of boron reagent. Specifically, conversions with B_2pin_2 were 2.0 times higher than those for

Scheme 3. Precatalyst/Ligand Complexes Relevant to Order of Addition Effects

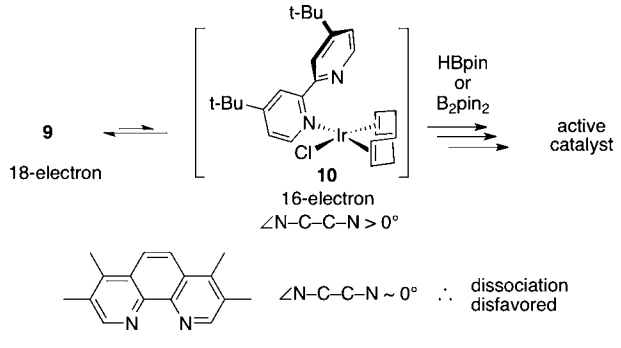


HBpin at 80 °C compared to the 1.4-fold improvement for B_2pin_2 over HBpin at room temperature in Figure 2.

The difference between the dtbpy and tmphen data is striking. In all cases, tmphen outperforms dtbpy, which is consistent with tmphen being the more electron-rich ligand. The surprising feature of the tmphen reactivity is that borylation conversions for HBpin rival those for B_2pin_2. This difference is more pronounced for the borylations of *N*,*N*-dimethyl-*m*-toluidine carried out with precatalyst **2** in Figure 3. For more electron-rich substrates the tmphen/**2** combination improves the atom economy for B_2pin_2 by utilizing both boron equivalents for borylation.

Precatalysts that performed poorly at ambient temperature were more viable at 80 °C. In particular, **3** performed just as well as **2** in borylations with dtbpy; however, complex **3** performed poorly with tmphen. The improvement for **3**/dtbpy can be rationalized as follows (Scheme 4). At elevated temperature pre-equilibrium dissociation of one dipyridyl arm in complex could generate 16-electron intermediate IrCl(κ^1-dtbpy)(κ^2-cod) (**10**) which can undergo oxidative addition with HBpin or B_2pin_2. In addition to being a stronger donor,

Scheme 4. Accessibility of κ^1-Intermediates for Dipyridyl and Phenanthroline Ligands



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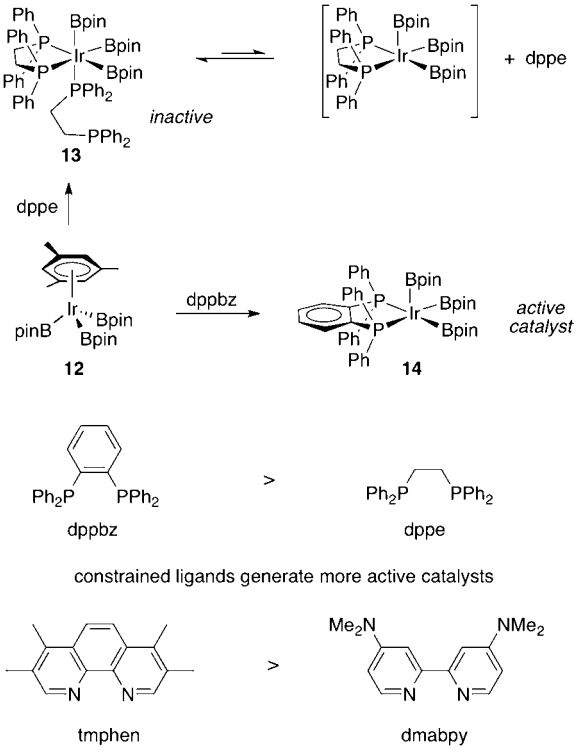
tmphen has a constrained geometry that will disfavor preequilibrium dissociation to IrCl(κ^1-tmphen)(κ^2-cod).

Catalysis with Constrained Geometry Ligands. Despite the fact that five-coordinate complexes with the formulas (κ^2-$R_2PCH_2CH_2PR_2$)Ir(Bpin)$_3$ (R = *i*-Pr (**11**) and Cy) borylate aromatic and heteroaromatic substrates at room temperature, dppe was ineffective for the borylation of *N*,*N*-dimethyl-*m*-toluidine at 80 °C. Attempts to prepare dppe analogs of **11** from dppe and (MesH)Ir(Bpin)$_3$ (**12**) yield the six-coordinate complex (κ^2-dppe) (κ^1-dppe)Ir(Bpin)$_3$ (**13**).[5,14] Complex **13** is much less reactive than five-coordinate complexes **11** because a phosphine ligand must dissociate to generate 16-electron intermediate (κ^2-dppe) Ir(Bpin)$_3$ that effects borylation. In contrast, analogs of dppbz react with (MesH)Ir(Bpin)$_3$ to afford five-coordinate structures (κ^2-dppbz)Ir(Bpin)$_3$ (**14**) that are reactive. Improved access to five-coordinate structures for dppbz relative to dppe is consistent with the enhanced reactivity of dppbz (Scheme 5).

Scheme 5. Effects of Ligand Geometries on Catalysis



It is interesting that the ligands where the dihedral angles in the chelate backbone are constrained, tmphen and dppbz, are more active than their unconstrained counterparts, dtbpy and dppe. The difference between tmphen and dtbpy could be due to the fact that tmphen is a stronger donor than dtbpy. If this were the main contributing factor, then 4,4′-bis-(dimethylamino)-2,2′-bipyridine (dmabpy) should be even more reactive because it is more electron rich than dtbpy or tmphen.[15,16] A comparison of relative conversions for borylation of 2,6-dimethylanisole with HBpin follows the order dtbpy < dmabpy < tmphen, indicating that tmphen outperforms a ligand that is more electron rich. Thus, the superior performance of tmphen may not solely be due to electronic effects. Perhaps, one contributing factor is the conformational rigidity of tmphen that enforces κ^2 coordination to the Ir center.

Solvent Effects. The notion that nonpolar solvents are privileged for Ir-catalyzed C−H borylation arose because a limited sample space was examined in early studies. While relative conversions for in situ generated catalyst for **2**/dtbpy follow the order hexanes > DME > DMF, the data in Figure 5 show no clear correlation between solvent polarity and conversions. In fact, the best solvent for room temperature borylations with in situ generated **2**/dtbpy is THF, which is one of the most polar of those surveyed. In contrast, the catalyst generated in situ from **2**/tmphen performs best in nonpolar solvents for room temperature borylations.

It has been shown in other catalytic systems that precatalysts where coligands are bound to the metal can be more effective than cases where ligand complexation is performed in situ.[17] Likewise, the data for preformed catalysts **1** and **6** clearly show that solvent effects for the in situ generated catalysts stem from catalyst generation as opposed to the borylation reaction itself. In fact, borylations with dtbpy ligated catalyst **1** become more efficient as solvent polarity increases. This trend is not followed for tmphen analog **6**, where hexanes is the best solvent at room temperature. Nevertheless, the borylation efficiency in polar solvents like NMP is acceptable for synthetic applications.

At elevated temperatures (Figure 6), precatalyst **1** still outperforms the in situ generated catalyst from **2**/dtbpy, and the more polar solvents, THF and NMP, are the best. Conversely, there is no particular advantage to using precatalyst **6** as conversions for in situ generated catalysts from **2**/tmphen were virtually identical. In addition, the performance of the tmphen ligated catalysts in NMP decreases at elevated temperatures.

In the second column in Figure 5, triethylamine and methylene chloride are the only outliers to the correlation between conversion and solvent polarity. Low conversions from triethylamine may be due solvent coordination to reactive intermediates **7** and **8**. Two observations support this notion. First, borylation activity improves for sterically hindered Hünig's base. Second the relative order THF > NEt_3 ≫ tetrahydrothiophene (not shown in Figure 5) is consistent with inhibition increasing with the softness of the donor atom (O < N < S).

It is instructive to comment on solvents that are poor candidates for borylations. For example, solvents with acidic hydrogens like alcohols (ROH) are ineffective because they react with the Ir−Bpin bonds to form ROBpin and Ir hydrides. Thus, C−H acidity of acetonitrile makes it a poor solvent for C−H borylation. Similarly, reactivity of the acetyl methyl protons may account for the relatively poor performance of isopropyl acetate in Figures 5 and 6. The poor conversions in methylene chloride result from reactions between the active catalysts and the solvent that generate catalytically inactive species. Other side reactions can interfere with borylation for solvents like DMSO where ^{11}B NMR spectra indicate formation of borates, presumably products of O-atom transfer from the solvent.

Despite these limitations, this study shows that a number of solvents, which practitioners of borylations might have not considered, are viable, and in some cases preferred options. The data in Figure 5 also show that poor performance for certain solvents for in situ generated catalysts is the result of inefficient catalyst generation. Given the number of steps involved in

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generating active catalyst from **2** + ligand, solvent effects are not surprising.

Ligand to Precatalyst Ratio Effects. For in situ generated catalysts, employing a 1:1 ratio of ligand to Ir frequently results in lower activity compared to preassembled catalysts. The data in Figure 7 clearly show that conversions at lower loading can be improved by increasing the equivalents of ligand per Ir precatalyst. Remarkably, comparable conversions can be obtained with a 10-fold reduction in catalyst loading by doubling the ligand to compound **2** ratio. Excess dtbpy does not inhibit borylation significantly, while for tmphen there is clearly an optimum ratio for a particular loading after which addition of more tmphen reduces conversion.[18]

When borylations were carried out using trisboryl catalysts **1** and **6**, conversions were not affected significantly by addition of dtbpy or tmphen. This suggests that there is a delicate balance between the in situ formation of active catalytic structures, such as **1** and **6**, and deleterious side reactions of dtbpy, and tmphen in particular, with Ir intermediates formed en route to **1** and **6**.

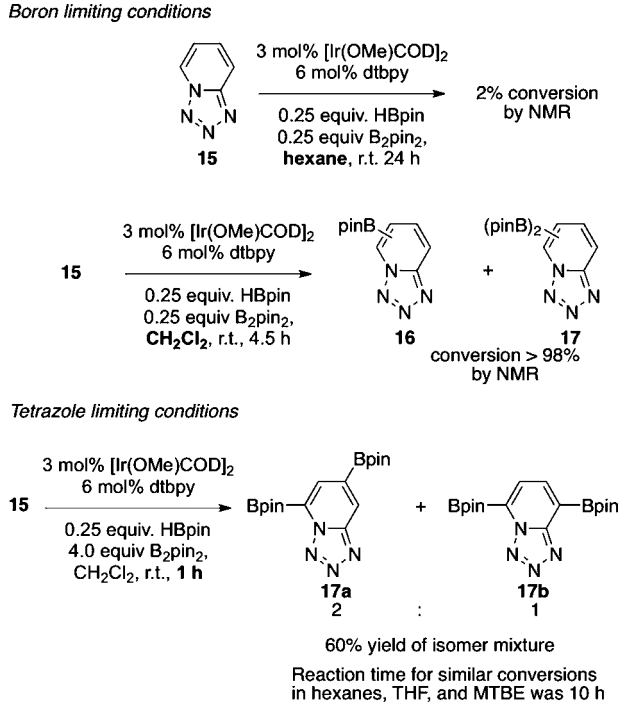
Precatalyst Stability. Despite reports to the contrary, the data in Figure 8 clearly show that **2** is not air stable. As relative humidities increase, the performance of precatalyst **2** markedly decreases. It is noteworthy that the precatalysts aged in dry air were as active as samples stored in a glovebox, showing that catalyst decomposition is accelerated by water. As the precatalyst **2** decomposes in the solid state, the color changes from lemon yellow to green and the solubility in $CDCl_3$ decreases. The latter factor may explain why samples with relatively clean NMR spectra can have marginal activity.

In contrast, precatalyst **3** was stable to air under identical conditions. Because **3** does not require special precautions and is prepared directly from $IrCl_3{\cdot}(H_2O)_x$, there are situations (e.g., the borylations with dtbpy in Figure 3) in which it may be the preferred precatalyst.

Open vs Closed Systems. The data in Figure 9 show that borylation reactivity in closed systems is diminished when HBpin is the borylating reagent. The higher H_2 concentrations in a closed system make the generation of hydride intermediates (eq 2) more likely. While it is not obvious a priori that these intermediates would be less reactive in borylation reactions, the propensity for Ir hydrides to bridge is well-known, and the resulting oligomers are typically less reactive than monomeric species.[19] The data in Figure 9 also highlight the fact that both HBpin and B_2pin_2 react similarly when tmphen is the coligand.

Borylation Case Studies. *Solvent Effects.* Relatively few borylations have been described for heteroatom rich substrates. This is unfortunate because many of these compounds are important pharmacophores. For example, tetrazolo[1,5-a]-pyridine scaffolds exhibit interesting antibacterial and anti-inflammatory properties.[20] Consequently, borylations of tetrazolo[1,5-a]pyridines could yield desirable building blocks for medicinal chemistry. However, borylation of tetrazolo[1,5-a]pyridine **15**, under conditions where boron reagents were limiting, gave only traces of products after 24 h when the reaction was carried out in hexane (Scheme 6). In contrast, the analogous borylation in CH_2Cl_2 gave complete conversion of boron reagents with formation of mono (**16**) and diborylated (**17**) products after 4.5 h (see SI for detailed analysis of products). Thus, despite the fact that methylene chloride gave the lowest conversions in Figure 5, it is an excellent solvent for borylation of **15**. Under tetrazole limiting conditions, two diborylated compounds form (**17a,b** Scheme 6) with complete

Scheme 6. Borylation of a Polar Heterocycle in Dichloromethane



conversion of tetrazole within 1 h in CH_2Cl_2. At higher B_2pin_2 concentrations, reaction rates in hexane, MTBE, and THF improved slightly; however, the reaction times required were still 10 times longer than those for reactions in CH_2Cl_2.

Based on electronic effects, the 5-position of **15** is expected to be the preferred site for the first borylation.[4a] Subsequent borylation at the 7- or 8-position would generate the **17a** and **17b**, respectively. The combination of nonselective borylation and modern separation methods is a potentially attractive approach for generating diverse compound libraries. In the case of **15**, the key to efficient functionalization is using a solvent that would normally be eschewed for the borylation reaction.

B_2pin_2 Atom Economy. Borylations of electron-rich structures are the most difficult, and it is desirable to carry them out as efficiently as possible. For the ITHM protocol, 1.0 equiv of B_2pin_2 per arene and higher catalyst loadings are typically used to achieve high conversion. This is because the HBpin that is generated is much less reactive when dtbpy is the ligand used for catalysis. This is evident from the data in Figure 9 where borylation of 1,3-diisoproylbenzene with 0.75 equiv B_2pin_2 plateaus at 75% conversion. For tmphen ligated catalysts the situation is different, as Figures 2 and 3 show that the rates of reaction for HBpin and B_2pin_2 are similar. Thus, using tmphen should make it possible to reduce the amount of B_2pin_2 to 0.5 equiv of per arene. Furthermore, the data in Figure 7 show that the Ir loading can be reduced if the ligand to Ir ratio is increased.

Scheme 7 shows results for borylating an electron-rich arene with 0.5 equiv of B_2pin_2. In this case, complete conversion to product requires efficient borylation by both B_2pin_2 and the HBpin that is produced when B_2pin_2 is consumed. The results clearly show that borylation with **2**/tmphen greatly improves the boron atom economy of the reaction when compared to the more widely used **2**/dtbpy combination.[21] It is noteworthy that the Ir catalyst loading with tmphen can be reduced 6-fold when

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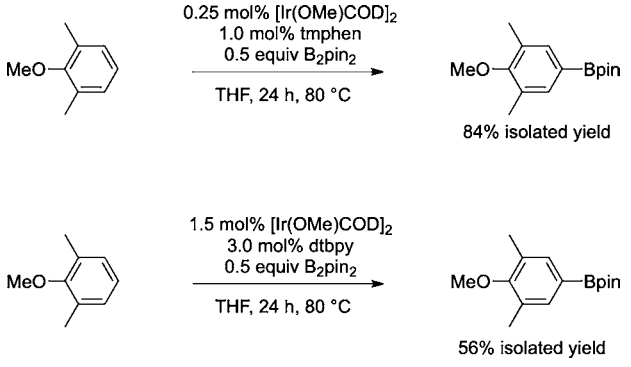
Scheme 7. Low Loading Borylation of an Electron-Rich Substrate



setting the ligand to Ir ratio to 2:1 according to the data in Figure 7.

SUMMARY

The following conclusions can be drawn from this study:

(1) Efficiencies of room temperature borylations are sensitive to order of addition as a function of precatalyst and boron reagent. Specifically, borylations with $[IrCl(cod)]_2$ are effective only with HBpin, which must be added to the precatalyst prior to addition of dipyridyl coligands.
(2) At elevated temperatures, order of addition had minimal influence on borylation efficiency.
(3) The most commonly used dipyridyl ligand, dtbpy, is outperformed by 3,4,7,8-tetramethyl-1,10-phenanthroline and in one case by a 1,2-diphosphino benzene, particularly for borylation of electron-rich substrates at elevated temperatures.
(4) Borylations with tmphen are highly efficient with B_2pin_2 or HBpin. Thus, reactions with B_2pin_2 are more atom economical with tmphen because both boron equivalents can be transferred.
(5) Polar solvents can be excellent candidates for C−H borylation.
(6) Ir loadings for in situ generated catalysts can be lowered significantly if the number of ligand equivalents per Ir is increased.
(7) Ligands with constrained geometries exhibit superior performance.
(8) By using appropriate precatalysts, ligands, boron reagents, solvents, and conditions, substrates that performed poorly under standard practices could be borylated efficiently.

ASSOCIATED CONTENT

Supporting Information

Full characterization, copies of all spectral data, and experimental procedures. 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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