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Iridium-Catalyzed C−H Borylation of Heterocycles Using an Overlooked 1,10-Phenanthroline Ligand: Reinventing the Catalytic Activity by Understanding the Solvent-Assisted Neutral to Cationic Switch

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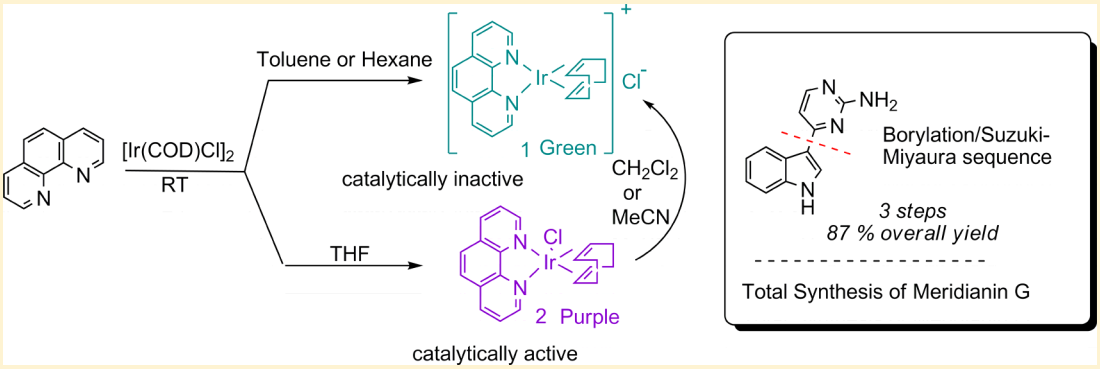
Supporting Information



ABSTRACT: The preformed catalyst [Ir(Cl)(COD)(1,10-phenanthroline)] (**2**; COD = cyclooctadiene) was found to be highly effective in a model reaction for the borylation of N-Boc-indole at the 3-position with B_2pin_2 (pin = pinacolato) as the borylating agent to give consistently 99% yield with 0.5 mol % catalyst loading. The corresponding in situ formed catalyst from $[Ir(Cl)(COD)]_2$ and 1,10-phenanthroline provided very inconsistent results for the same reaction (0−94% conversion). We propose this to be due to the competing formation of a catalytically inactive cationic complex, $[Ir(COD)(1,10\text{-phenanthroline})]^+Cl^-$ (**1**), in a noncoordinating solvent such as octane. Complexes **1** and **2** were characterized using solid-state NMR (^{13}C and ^{35}Cl) in conjunction with XPS to be cationic and neutral, respectively. The X-ray crystal structure of a pentavalent neutral Ir complex, [Ir(Cl)(COD)(2,2′-bipyridine)] (**3**), was also obtained for comparison purposes. Using catalyst **2**, the total synthesis of *Meridianin G* was accomplished in 87% overall isolated yield in a one-pot, three-step process.

INTRODUCTION

In recent years, Suzuki−Miyaura (SM) coupling has become the most prominent Pd-catalyzed cross-coupling reaction not only in academia but also in the fine chemical, agrochemical, electronics, and pharmaceutical industries, on the basis of a recent literature search.[1] This is mainly due to the fact that SM coupling utilizes environmentally benign, air- and moisture-stable organoboron reagents as coupling partners as well as the fact that it has extremely high functional group tolerance.[2] Therefore, the development of economically viable and operationally simple processes for the synthesis of organoboron reagents is highly desirable. The iridium-catalyzed direct C−H borylation of arenes[3] has emerged as an atom-economical green chemical process, as it involves direct functionalization of C−H bonds, as opposed to the classical methods which utilize either Grignard- or organolithium-mediated processes.[4] The Pd-catalyzed Miyaura borylation is another catalytic process, but it requires additional prefunctionalization steps, as the common starting materials are typically bromo or iodo arenes.[5]

The seminal reports of Ir-catalyzed processes were independently disclosed by the research groups of Maleczka/Smith III[6] and Hartwig/Ishiyama.[7] Maleczka/Smith III employed phosphines as supporting ligands, while Hartwig/Ishiyama used bipyridyl-type ligands. The regioselectivity of Ir-catalyzed borylations is generally controlled by steric interactions,[8] thereby providing access to products which would not have been possible through conventional aromatic electrophilic substitution. The functional group tolerance coupled with the complementary regioselectivity of Ir-catalyzed C−H borylation has led to the development of one-pot methods to convert these boronate esters to other useful products such as boronic acids and trifluoroborates,[9] 1,10-

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phenanthrolinols,[10] aryl halides,[11] aryl nitriles,[12] and anilines.[13] Ir-catalyzed C−H borylation and its subsequent functionalization has been successfully applied to the total synthesis of several complex natural products[14] and organic materials.[15]

Even though the borylation methodologies reported so far have found widespread use in the academic community, their sensitivity to the order of addition of the reagents and the batch to batch reproducibility dependence on the Ir precursors[16] cause great concern when the process is scaled up, especially in an industrial setup. During the past decade our group has been successful in demonstrating the superiority of the preformed Pd catalysts over in situ formed catalysts for various cross-coupling reactions, where well-defined precatalysts have generated the active catalytic species in a controlled manner.[17] These readily available preformed catalysts are now being used in multikilogram quantities in fine chemical and pharmaceutical processes.[18] As a continuation of this theme, we were interested in studying the effect of preformed vs in situ formed Ir catalysts for the direct C−H borylation of arenes. We were particularly interested in developing a robust and operationally simple method for C−H borylation of nitrogen-containing heterocycles, using relatively cheap ligands with low Ir loading. N-Boc-indole was chosen as a model system for this study.

Scheme 1 provides the recently reported Ir-catalyzed methods to make 3-borylated indoles. Hartwig and co-workers reported the use of N-TIPS-indole and B_2pin_2 with in situ formation of the catalyst from $[Ir(Cl)(COD)]_2$ (COD = cyclooctadiene) and dtbpy (4,4′-di-*tert*-butyl-2,2′-bipyridine) to make the product in 83% yield (**A**).[19] Maleczka, Smith, and co-workers developed a process for the 3-borylation of N-Boc-indole with HBpin using the $[Ir(OMe)(COD)]_2$/dtbpy system with 65% yield of the product (**B**).[20] While they are significant achievements, these methods employ relatively high loadings of Ir catalyst and ligand, and the yields in some cases were moderate. In addition, in the case of TIPS-indole, a 2-fold excess of the heterocycle is required, which is not economical. More recently, Krska, Maleczka, and Smith described a traceless directing group approach for 3-borylation of indole (**C**).[21] However, despite the lower loading of the Ir precursor, an excess of relatively expensive Me_4-1,10-phenanthroline ligand is required. Depending on the desired subsequent reactions to be carried out on the borylated product, the reaction in Scheme 1C may pose additional challenges due to the unprotected N−H functionality.

In summary, currently the most effective Ir catalysts for C−H borylation reactions are derived from readily available Ir precursors such as $[IrCl(COD)]_2$ and $[Ir(OMe)(COD)]_2$ in conjunction with electron-rich bipyridyl type ligands, in particular dtbpy and Me_4-1,10-phenanthroline.[22] We were intrigued, however, by one particular case reported by Hartwig, where dtbpy and the simple 1,10-phenanthroline ligand performed comparably in the borylation of benzylic C−H bonds.[23]

A simple cost comparison may show the financial benefits of using a catalyst formed from $[Ir(Cl)(COD)]_2$ and 1,10-phenanthroline. The dtbpy and the Me_4-1,10-phenanthroline ligands are respectively 5 and 13 times more expensive than 1,10-phenanthroline for research quantities (Table 1), while $[Ir(OMe)(COD)]_2$ is 1.5 times more expensive than the $[Ir(Cl)(COD)]_2$ precursor.

Scheme 1. Reported 3-Borylations of Indole[19−21]

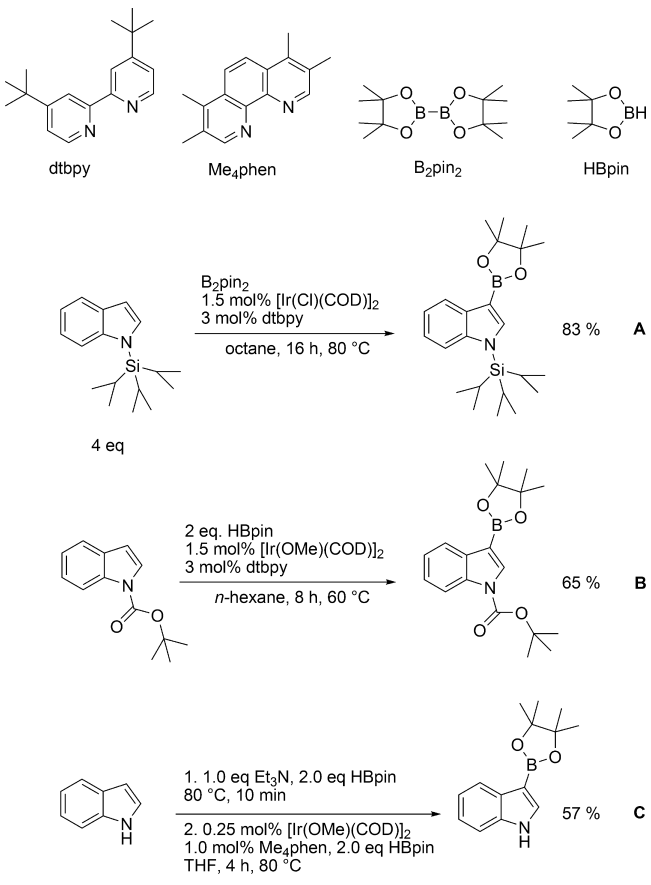

Table 1. Cost Comparisons of Reagents[a]

reagent	cost for 5 g (£)	rel cost
1,10-phenanthroline	9.80	1
dtbpy[b]	50.00	5
Me_4-1,10-phenanthroline	123.00	13
$[Ir(Cl)(COD)]_2$	471.00	1
$[Ir(OMe)(COD)]_2$	676.00	1.5

[a]Alfa Aesar UK prices as of November 2013. [b]Sigma-Aldrich UK price as of November 2013.

With the aim of studying the effect of preformed vs in situ formed catalysts in Ir-catalyzed C−H borylation reactions, we initially focused our attention on preparing preformed catalysts containing the cheaper 1,10-phenanthroline ligand for the direct borylation of N-Boc-indole as a model system. We developed a robust, operationally simple process with relatively low Ir loading and later extended the study to a few other nitrogen-containing heterocycles.

RESULTS AND DISCUSSION

Catalyst Synthesis and Characterization. The known cationic complex $[Ir(COD)(phen)]^+Cl^-$ (**1**; phen = 1,10-phenanthroline; Scheme 2) was synthesized according to literature procedures (Scheme 2).[24] This complex has previously only been investigated for oxidative addition reactions with a number of reagents: e.g., MeCN and MeOH.[24] During the characterization of **1**, it was observed that this green solid gives a purple solution on dissolution in $CDCl_3$.

As was observed in the literature procedure,[24] during the preparation of this complex in CH_2Cl_2, initially a purple

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Scheme 2. Preparation of Ir Complex 1

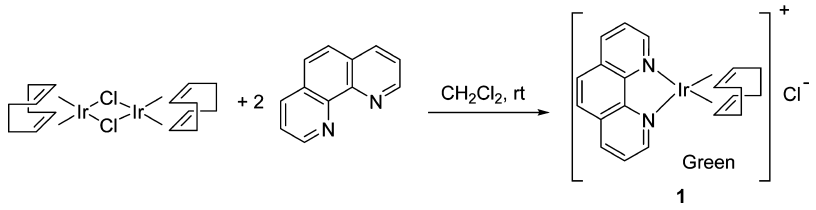
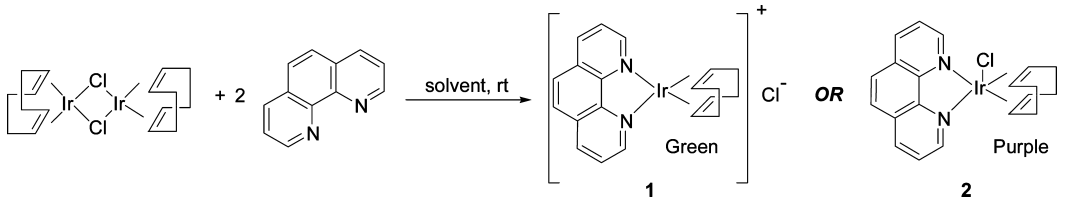


Table 2. Solvent-Dependent Preparation of 1 and 2



entry	solvent	complex	appearance	time before color change (min)	structure
1	THF	**2**	purple solution	N/A	neutral
2	CH_2Cl_2	**1**	purple solution to green solid	10	cationic
3	hexane	**1**	green solid	0	cationic
4	toluene	**1**	green solid	0	cationic
5	NMP	**1**	purple solution to green solid	75	cationic
6	CH_3CN	**1**	purple solution to green solid	10	cationic

reaction mixture, mostly in the solution phase, was obtained, from which a green solid precipitated after 10 min of stirring. The purple solution was proposed[24] to be the neutral pentavalent complex [Ir(Cl)(COD)(phen)] (**2**). However, to the best of our knowledge this neutral Ir complex has not previously been isolated or characterized. With the aim of isolating and characterizing this proposed species, a solvent screen was carried out (Table 2). It was revealed that, by reacting $[Ir(Cl)(COD)]_2$ with 1,10-phenanthroline in THF, purple complex **2** was isolated as a stable product (entry 1), in contrast to the reported reaction in CH_2Cl_2, which produced a green product **1** (entry 2). Importantly, in hexane, the typical solvent of choice for the C−H activated borylation reactions, the product formed was the green cationic complex **1** (entry 3). A similar observation (instantaneous green product formation) was observed when the reaction was carried out in toluene (entry 4). Although both NMP (*N*-methylpyrrolidone) and CH_3CN produced the green cationic product at different intervals of time (Table 2, entries 5 and 6) the reaction mixtures were initially purple, suggesting the conversion of the species from neutral to cationic. We have not carried out any detailed concentration studies to understand the neutral to cationic switch. This study suggests that polar solvents, preferably those with coordinating ability, tend to favor formation of the neutral complex, which in some cases transforms into the thermodynamically stable cationic complex. The exact mechanism of this solvent-assisted switch is yet to be determined.

As mentioned previously, interestingly the green cationic complex **1**, on dissolution in $CDCl_3$, gave a purple solution. Therefore, complexes **1** and **2** displayed identical ^1H NMR spectra when they were recorded in this solvent, consistent with the proposed structure **2** (Table 2). However, with time, precipitation of a green solid occurs from the purple solution. In addition, complex **1** was found to be insoluble, or decomposed, in most other solvents (H_2O, alcohols, DMSO, THF), making solution-state characterization extremely challenging.

The solid-state ^{13}C NMR spectrum, on the other hand, showed a clear structural difference between green complex **1** and purple complex **2** (Figure 1).

Solid-state ^{35}Cl NMR experiments supported the ionic nature of complex **1** and the covalent structure of complex **2** (Figure 2). In the ^{35}Cl spectra, a signal is clearly observed in the case of cationic $[Ir(COD)(phen)]^+Cl^-$ (**1**), whereas no signals can be seen in the case of covalent [Ir(Cl)(COD)(phen)]

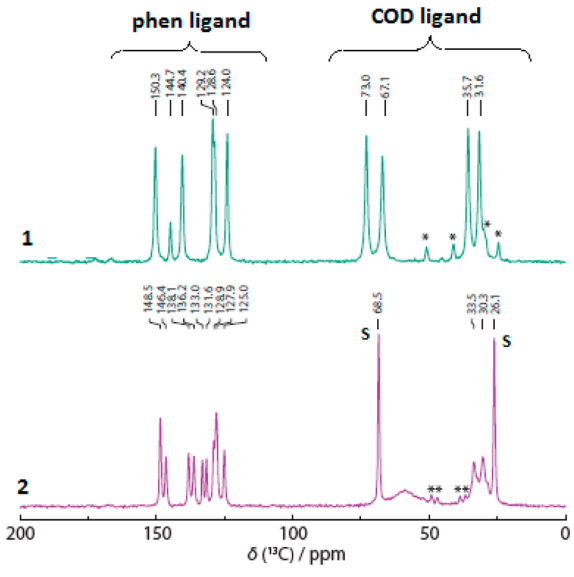


Figure 1. Solid-state ^{13}C NMR spectra of **1** (cationic) and **2** (neutral), showing the differences. Spinning side bands are marked with asterisks. Peaks corresponding to solvent molecules (THF) are marked with the letter S.

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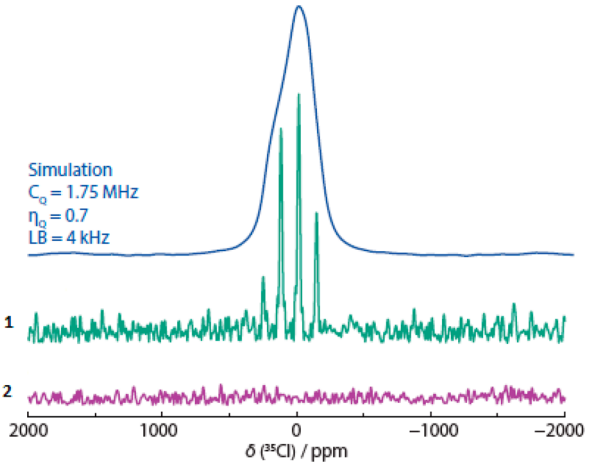


Figure 2. Normalized ^{35}Cl solid-state static NMR spectra of **1** and **2**, alongside a simulated ^{35}Cl line shape.

(**2**).[25] This behavior is consistent with what is typically observed for ionic and covalent chlorine sites, respectively.[26]

XPS studies further supported **1** being of ionic nature and **2** containing a covalent Ir−Cl bond (see the Supporting Information).

Therefore, it appears that THF is unique for isolation of the neutral species, while other nonpolar solvents (hexane, toluene) prefer the formation of the cationic complex. Polar solvents such as CH_2Cl_2, NMP, and CH_3CN favor initially the formation of the neutral species, which eventually changes to the cationic species with time. This switching of neutral to cationic in certain solvents was observed for the first time in this study, which helped us in understanding the poor activity of the 1,10-phenanthroline ligand. This phenomenon, resulting in a significant destructive effect on the borylation reaction when the catalyst is formed in situ, will be discussed later.

Due to the instability of **2** in solution over prolonged periods of time and the complete insolubility of **1**, it was not possible to grow crystals suitable for single-crystal X-ray diffraction. Therefore, an analogous bpy complex, [Ir(Cl)(COD)(bpy)] (**3**; bpy = 2,2′-bipyridine), was prepared in THF for a single-crystal X-ray determination. The crystal structure of the purple complex **3** revealed a pentavalent neutral Ir complex, further supporting the existence of such a species (Figure 3).

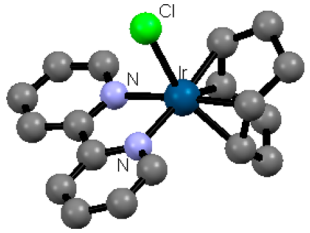
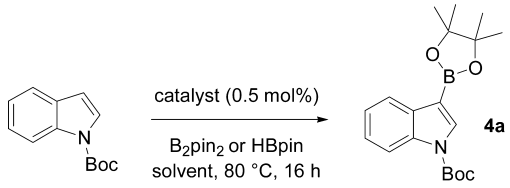


Figure 3. X-ray crystal structure of neutral [Ir(Cl)(COD)(bpy)] complex, **3**.

Interestingly, the crystallized structure of **3** is that of a slightly distorted square pyramidal Ir complex. The Ir−Cl bond is slightly longer (2.611 Å) in comparison to previously reported covalent Ir−Cl bonds (2.36−2.38 Å).[27]

Catalytic Activity Studies. With preformed catalysts **1** and **2** in hand, we evaluated their use in the direct C−H borylation of N-Boc-indole. Either B_2pin_2 or HBpin could be used as borylating agent to produce the expected product 3-Bpin-N-Boc-indole. The results are summarized in Table 3.

Table 3. Evaluation of Preformed Catalysts 1 and 2 in Borylation of N-Boc-indole



entry	[Ir] catalyst	structure	B source	solvent (0.17 M)	NMR conversn (%)[a]
1	**1**	cationic	B_2pin_2	octane	0
2	**2**	neutral	B_2pin_2	octane	100 (99)
3	**1**	cationic	B_2pin_2	2-MeTHF	0
4	**2**	neutral	B_2pin_2	2-MeTHF	94
5	**1**	cationic	B_2pin_2	$C_2H_4Cl_2$	0[b]
6	**2**	neutral	B_2pin_2	$C_2H_4Cl_2$	0
7	**2**	neutral	HBpin	octane	89
8	**2**	neutral	HBpin	octane	93[c]

[a]Isolated yield given in parentheses. [b]Reaction mixture instantaneously turned purple (indicating formation of neutral Ir species); however, no reaction took place. [c]0.33 M.

The cationic complex **1** resulted in no product formation at all, independent of the solvent used for the reaction (octane, 2-MeTHF, or $C_2H_4Cl_2$; Table 3, entries 1, 3 and 5). The reason for the catalytic inactivity of the ionic complex is not clear at the moment and is currently being investigated. Notably, 0.5 mol % of neutral [Ir(Cl)(COD)(1,10-phenanthroline)] (**2**) provided the borylated indole in 100% conversion by ^{1}H NMR with 99% isolated yield, from the reaction carried out in octane (entry 2). To the best of our knowledge, this is the best conversion with isolated yield reported for the borylation of the model substrate, with the lowest Ir loading. A simple filtration of the reaction mixture on silica gel followed by removal of volatiles under reduced pressure provided pure 3-Bpin-N-Boc-indole (**4a**). No borylation of octane was observed.[28]

The reaction using **2** in 2-MeTHF provided the product in 94% conversion (Table 3, entry 4), while no product formation was observed when the reaction was carried out in $C_2H_4Cl_2$ (entry 6).

HBpin has been described as superior to B_2pin_2 as a borylating reagent in many previous cases. It is proposed to result in faster generation of the catalytically active species, thereby providing enhanced results for the overall borylation reaction.[29] In this case, however, no beneficial effects were observed when changing B_2pin_2 for 2 equiv of HBpin (Table 3). Under standard reaction conditions, using 0.5 mol % of **2**, only 89% conversion was observed (entry 7). A very slight improvement was achieved by increasing the reaction concentration to 0.33 M (93%, entry 8). We have not made any effort to further optimize the reaction.

Subsequently, the performance of preformed [Ir(Cl)(COD)-(phen)] (**2**) was compared to that of the current state of the art in situ formed catalyst systems (Table 4). Both Me_4-1,10-phenanthroline and dtbpy have previously been demonstrated to outperform the unsubstituted simple 1,10-phenanthroline and bpy when they are employed in conjunction with $[Ir(Cl)(COD)]_2$ or $[Ir(OMe)(COD)]_2$.[30]

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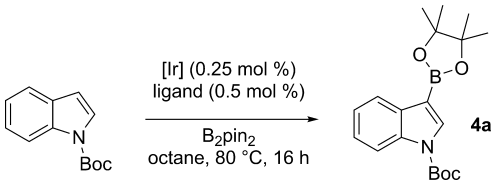
Table 4. In Situ Formed Ir Catalysts



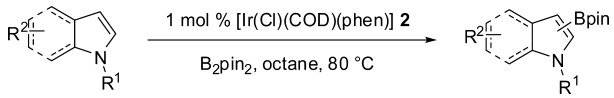
entry	[Ir]	ligand	NMR conversn (%)
1	$[Ir(Cl)(COD)]_2$	dtbpy	87
2	$[Ir(OMe)(COD)]_2$	dtbpy	94
3	$[Ir(Cl)(COD)]_2$	Me_4-1,10-phenanthroline	>90[a]
4	$[Ir(OMe)(COD)]_2$	Me_4-1,10-phenanthroline	>90[a]

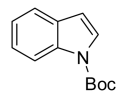
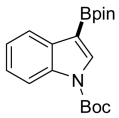
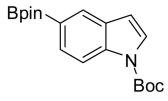
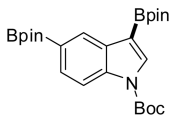
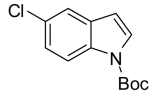
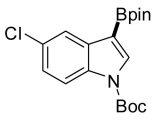
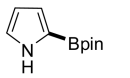
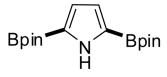
[a]Side products observed upon ^{1}H NMR analysis of the crude reaction mixture, proposed to be the result of multiple borylations.

In the current study, the in situ formed catalysts were less active than the preformed catalyst **2** (see Table 3, entry 2). Both $[Ir(Cl)(COD)]_2$ and $[Ir(OMe)(COD)]_2$ in conjunction with dtbpy provided the 3-borylated product in conversions of 87 and 94%, respectively (Table 4, entries 1 and 2). Using Me_4-1,10-phenanthroline as ligand gave conversions greater than 90%; however, multiple side products were observed in the ^{1}H NMR spectra (entries 3 and 4), suggesting the formation of a less selective catalyst.

Having identified [Ir(Cl)(COD)(phen)] (**2**) as the best-performing precatalyst, we continued to evaluate its use in the direct borylation of a few other nitrogen-containing heterocycles to establish the generality (Table 5).

Table 5. Borylation of Nitrogen-Containing Heterocycles using Neutral [Ir(Cl)(COD)(phen)] (2)[a]



entry	starting material	product		yield (%)
1			**4a**	99 %[b]
2			**4b**	93 %
3			**4c**	96 %
4			**4d**	47 %[c]
5			**4e**	96 %[d]

[a]Reaction conditions: 1 mol % of [Ir(Cl)(COD)(phen)] (**2**), heteroarene (1.0 mmol), B_2pin_2 (1 equiv), octane (6 mL), 80 °C, 16 h. [b]0.5 mol % of **2**. [c]3 mol % of **2**, 10 mmol of pyrrole, 1 mmol of B_2pin_2. [d]3 mol % of **2**, 1.5 equiv of B_2pin_2.

Both 5-chloro- and 5-Bpin-N-Boc-indole resulted in the formation of the 3-borylated products **4b**,**c** in excellent yields (96 and 93%; Table 5, entries 2 and 3), providing useful functionalities for further regioselective transformations.

Increased Ir loading had to be used in order to form 2-borylated pyrrole **4d** (Table 5, entry 4) in moderate yield. With a slight excess of B_2pin_2 with respect to pyrrole, 2,5-bis-borylated pyrrole **4e** (entry 5) was formed in excellent yield (96%), suggesting that the presence of free N−H functionalities does not influence the catalysis. Non-nitrogen-containing heterocycles, such as benzofuran and benzothiophene, did not undergo any borylation reaction using **2** under standard reaction conditions. The reaction mixture turned green instantaneously in both cases, suggesting that even some substrates are capable of turning covalent **2** into cationic **1** prior to the desired borylation reaction.

As mentioned previously, when aliphatic solvents are used for the borylation reaction, in the presence of the $[Ir(Cl)(COD)]_2$/1,10-phenanthroline system (in situ) catalytically inactive cationic species **1** (see Table 2) may form. Our effort to optimize the reaction conditions for the 3-borylation of N-Boc-indole under in situ conditions was not successful, as it is difficult to reliably control the formation of the desired catalytically active covalent species (Scheme 3). This might be the reason the cheaper 1,10-phenanthroline ligand was previously reported to underperform, in comparison to the more costly Me_4-1,10-phenanthroline or dtbpy ligand, by earlier researchers during the ligand screens and hence was overlooked in subsequent studies. This hypothesis has been tested in the current study, where inconsistent results have been obtained while repeating the in situ catalysis experiment several times, using $[Ir(Cl)(COD)]_2$/1,10-phenanthroline for the 3-borylation of N-Boc-indole. Even when the reactions are carried out under identical conditions (addition of the solvent to a flask containing $[Ir(Cl)(COD)]_2$, 1,10-phenanthroline, B_2pin_2, and N-Boc-indole), conversions vary from 0 to 94%, suggesting the sensitivity of the in situ conditions. However, no such inconsistencies were observed when the preformed neutral complex was used as a catalyst.

Since there have been some reports on the importance of the order of addition of reagents in room-temperature borylations,[22] we also investigated the effect in our 80 °C reaction. The results are summarized in Table 6. Conditions A involved adding the ligand to a suspension of the Ir precursor, B_2pin_2, and N-Boc-indole in octane. Conditions B involved adding the N-Boc-indole to a suspension of the Ir dimer precursor, ligand, and B_2pin_2 in octane.

None of the desired product was formed in the $[Ir(Cl)(COD)]_2$/1,10-phenanthroline case, when the ligand was added last (Table 6, entry 1). However, using $[Ir(OMe)(COD)]_2$/1,10-phenanthroline under conditions A did provide a catalytically active species, and 97% conversion was observed by ^{1}H NMR (entry 2). Notably, a number of side products were observed in the ^{1}H NMR spectrum after filtration on silica gel.[25]

When the order of addition was reversed, and the aryl reagent was added last, the in situ $[Ir(Cl)(COD)]_2$/1,10-phenanthroline system did result in good catalytic activity: 96% conversion to the product (Table 6, entry 3, reaction carried out in duplicate). Notably, this is slightly less active than the preformed **2**, which consistently provided 100% conversion to the product. Using conditions B, the in situ catalyst formed from $[Ir(OMe)(COD)]_2$ and 1,10-phenanthroline provided

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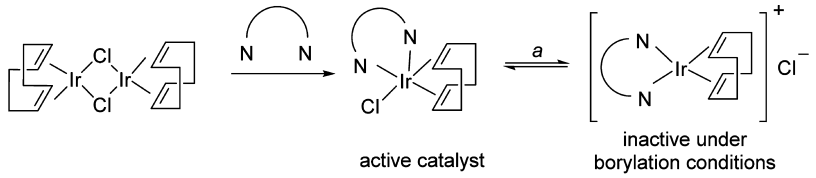
Scheme 3. Reaction between Ir Dimer Precursor and N,N Ligands in Octane



a is irreversible under the reaction conditions if N,N = 1,10-phen

Table 6. Investigation of In Situ Conditions at 0.5 mol % Ir Loading[a,b]

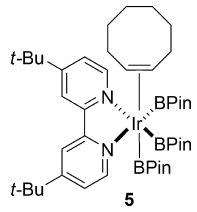
entry	catalyst	ligand	order of addition	NMR conversn (%)
1	$[Ir(Cl)(COD)]_2$	1,10-phenanthroline	A	0
2	$[Ir(OMe)(COD)]_2$	1,10-phenanthroline	A	97[c]
3	$[Ir(Cl)(COD)]_2$	1,10-phenanthroline	B	96
4	$[Ir(OMe)(COD)]_2$	1,10-phenanthroline	B	97[c]

[a]Reaction conditions: N-Boc-indole (1 mmol), B_2pin_2 (1 mmol), [Ir] catalyst (0.5 mol %), ligand (0.5 mol %), octane (0.17 M), 80 °C, 16 h. [b]Order of addition: (conditions A) (i) Ir dimer, B_2pin_2, (ii) N-Boc-indole, solvent, (iii) ligand; (conditions B) (i) Ir dimer, B_2pin_2, ligand, (ii) solvent, (iii) N-Boc-indole. [c]Side products observed upon ^1H NMR analysis of the crude reaction mixture.

results comparable to those for the reaction under conditions A (entry 4).

On the basis of preliminary results, the reason for the order of addition of reagents and catalysts not affecting the borylation reaction when the $[Ir(OMe)(COD)]_2$ precursor is used can be tentatively explained by the fact that the $[Ir(OMe)(COD)]_2$/1,10-phenanthroline combination does not form a cationic complex but rather a neutral tetravalent Ir complex where the ligand is monodentate (see the Supporting Information). The same observation can also be used to explain why the order of addition for catalyst systems formed in situ from $[IrCl(COD)]_2$ and dtbpy or Me_4-1,10-phenanthroline ligand does not affect the outcome of the borylation reaction. When catalysts are prepared from this precursor and dtbpy or Me_4-1,10-phenanthroline, the precatalysts formed in both THF and CH_2Cl_2 are identical on the basis of solid-state ^{13}C NMR studies and are therefore proposed only to exist as neutral complexes (see the Supporting Information). These results indicate that the $[Ir(Cl)(COD)]_2$/1,10-phenanthroline combination is unique in terms of its dependence on the order of addition. When the ligand is added last, formation of the desired catalytically active species is inhibited. When the aryl reagent is added last, the catalytically active species is formed in order for the borylation reaction to take place. This suggests that the aryl reagent in some way may hinder the formation of the catalytically active neutral species. This can be avoided by using the precatalyst [Ir(Cl)(COD)(phen)] (**2**), where the ligand is already bound to Ir.

In previous mechanistic work, it has been suggested that the Ir dimer reacts with the boron reagent prior to reacting with the ligand.[29] Complex **5**, formed from this reaction, is proposed to be an important intermediate in the catalytic cycle, generating the catalytically active species by dissociation of the COE ligand (Figure 4).

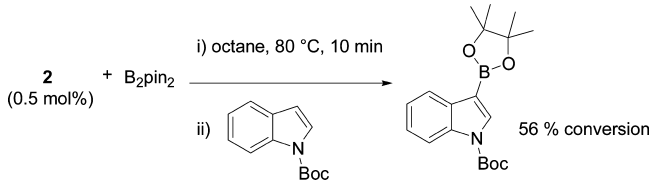


5

Figure 4. Catalytic intermediate proposed by Hartwig.[29]

In this study, however, prestirring **2** with B_2pin_2 for 10 min at 80 °C before adding N-Boc-indole gave only 56% conversion to the product (Scheme 4).

Scheme 4. Stepwise Addition of Reagents using Precatalyst 2



This suggests that the reaction between **2** and B_2pin_2 leads to a detrimental side reaction, producing a boron species that is unreactive in the subsequent borylation of N-Boc-indole.[31] It is therefore not clear whether or not the preformed complex [Ir(Cl)(COD)(phen)] (**2**) follows the same initial reaction pathway as in the case of the in situ system. Further studies are currently being undertaken to gain more insight into understanding the reaction pathway.

On the basis of these results, the protocol for using preformed **2** has to involve a one-time addition of Ir catalyst **2**, B_2pin_2, and aryl reagent followed by solvent.

In addition to the above advantages, preformed Ir catalyst **2** is easy to handle and stable to storage for a longer period of time under inert conditions. Shelf life studies indicate that after storage under air for 60 days, a slight drop in conversion in a test reaction from 100 to 95% has been observed, with 0.5 mol % Ir loading.

Total Synthesis of Meridianin G. A one-pot C−H borylation followed by Suzuki−Miyaura coupling and a deprotection methodology was demonstrated using the same catalytic system to synthesize the natural product meridianin G in excellent overall yield (Scheme 5).[32,33] The three-step reaction sequence uses only commercially available starting materials. The 3-borylated indole **4a** was generated using the standard Ir-catalyzed procedure. The volatiles were subsequently removed, and the resulting crude residue was used directly in the subsequent Suzuki coupling reaction, catalyzed by the preformed Pd complex dtbpfPdCl$_2$ (dtbpf = di-*tert*-butylphosphinoferrocene) with trade name Pd-118.[34] Under

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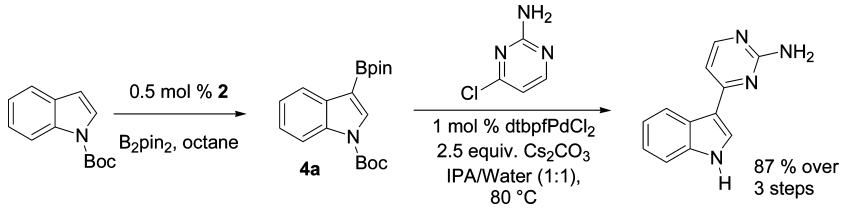
Scheme 5. One-Pot Total Synthesis of Meridianin G



the chosen reaction conditions, with Cs_2CO_3 as a base in aqueous isopropyl alcohol solvent, the Boc protecting group was also removed and the desired product meridianin G was obtained in 87% overall yield, over three reaction steps.

Further application studies using preformed catalyst **2** and related examples are in progress.

CONCLUSIONS

[Ir(Cl)(COD)(phen)] (**2**) was identified as an efficient precatalyst for the direct 3-borylation of N-Boc-indole and other nitrogen-containing heterocycles. This system provides a cost-effective and highly active alternative to the well-established in situ $[Ir(OMe)(COD)]_2$/dtbpy system. The in situ protocol using $[Ir(Cl)(COD)]_2$ and 1,10-phenanthroline was found to give irreproducible results due to the competing formation of catalytically inactive cationic Ir species $[Ir(COD)(phen)]^+Cl^-$ (**1**) in aliphatic solvents. The neutral to cationic switch was established for the first time to understand the structure–activity relationship of the catalyst and the reaction conditions.

EXPERIMENTAL SECTION

General Considerations. Unless otherwise stated, all reactions were carried out under a dry nitrogen atmosphere using standard Schlenk techniques. Iridium catalyst preparation reactions were carried out in 50 mL Schlenk tubes with magnetic stirring bars. Catalyst screening reactions were carried out in individual Schlenk tubes with magnetic stirring. Anhydrous tetrahydrofuran, dichloromethane, *n*-hexane, octane, toluene, and NMP were purchased from commercial sources in Sure/Seal bottles and used as received. N-Boc-indole and 4,4′-di-*tert*-butylbipyridine were purchased from Sigma-Aldrich and used as received. Bis(pinacolato)diboron, 2,2′-bipyridine, 1,10-phenanthroline, and 3,4,7,8-tetramethyl-1,10-phenanthroline were purchased from Alfa Aesar and used as received. $[Ir(Cl)(COD)]_2$ and $[Ir(OMe)(COD)]_2$ are available from Johnson Matthey Catalysis & Chiral Technologies, as are precatalysts **1**–**3**.

The identity of known isolated products was confirmed by comparison with reported literature spectroscopic data. Both ^1H and $^{13}C\{^1H\}$ NMR spectra were recorded on a 400 MHz spectrometer referenced to the residual ^1H and $^{13}C\{^1H\}$ signals of the solvents. NMR multiplicities are abbreviated as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad signal. Coupling constants *J* are given in Hz.

Solid-state NMR spectra were recorded at a static magnetic field strength of 9.4 T ($\upsilon_0(^1H)$ = 400.16 MHz). For ^{13}C, the probe was tuned to 100.63 MHz and the spectra were referenced to the alanine CH_3 signal at 20.5 ppm. For ^{35}Cl, the probe was tuned to 39.21 MHz and referenced to KCl.

The radiation for the XPS studies was monochromatized aluminum Kα radiation with a 650 μm spot size. Charge compensation was provided by the in-lens electron flood gun at a 2 eV setting and the "401" unit for "zero energy" argon ions.

General Method for Preparation of Ir Complexes. $[IrCl(COD)]_2$ (0.372 mmol) and the bidentate N–N ligand (0.748 mmol) were weighed and transferred to a 50 mL Schlenk tube. Then 10 mL of solvent was added and the reaction mixture was stirred at room temperature for 3 h. Subsequently, the solvent was removed in vacuo to provide the desired product.

*[Ir(COD)(phen)]Cl (**1**):*[24] $[IrCl(COD)]_2$ (0.250 g, 0.372 mmol); 1,10-phenanthroline (0.135 g, 0.748 mmol); CH_2Cl_2 (10 mL). The product was obtained as a green solid (98% yield). ^{13}C SS-NMR (100 MHz): δ 150.3, 144.7, 140.4, 129.2, 128.6, 124.0, 73.0, 67.1, 35.7, 31.6. Anal. Calcd for $C_{20}H_{20}ClIrN_2$: C, 46.55; H, 3.91; N, 5.43. Found: C, 46.12; H, 3.85; N, 5.27.

*[Ir(Cl)(COD)(phen)] (**2**):* $[IrCl(COD)]_2$ (0.250 g, 0.372 mmol); 1,10-phenanthroline (0.135 g, 0.748 mmol); THF (10 mL). The product was obtained as a dark purple solid (99% yield). ^1H NMR ($CDCl_3$, 400 MHz): δ 8.69 (dd, *J* 5.6, 1.2, 2H), 8.54 (dd, *J* 8.0, 1.2, 2H), 7.97 (s, 2H), 7.84 (dd, *J* 8.0, 5.2, 2H), 3.95 (m, 4H), 2.49–2.47 (m, 4H), 1.80–1.76 (m, 4H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 147.9, 146.5, 135.0, 131.2, 127.4, 125.3, 59.8, 31.9. ^{13}C SS-NMR (100 MHz): δ 148.5, 146.4, 138.1, 136.2, 133.0, 131.6, 128.9, 127.9, 125.0, 33.5, 30.3. Anal. Calcd for $C_{20}H_{20}ClIrN_2$: C, 46.55; H, 3.91; N, 5.43. Found: C, 46.49; H, 3.89; N, 5.39.

*[Ir(Cl)(COD)(bpy)] (**3**):* $[IrCl(COD)]_2$ (0.250 g, 0.372 mmol); 2,2′-bipyridyl (0.117 g, 0.748 mmol); THF (10 mL). The product was obtained as a purple solid (90% yield). ^1H NMR ($CDCl_3$, 400 MHz): δ 8.32 (4H, m), 8.08 (2H, m), 7.53 (2H, m), 3.80 (4H, m), 2.46 (4H, m), 1.79 (4H, m). Anal. Calcd for $C_{18}H_{20}ClIrN_2$: C, 43.94; H, 4.10; N, 5.69. Found: C, 43.43; H, 4.21; N, 5.21; CCDC 985451.

General Method for Ir-Catalyzed Borylation Reactions. The Ir catalyst, ligand (if applicable), B_2pin_2, and heteroaryl species (if a solid) were weighed and transferred to a Schlenk flask. The flask was evacuated and refilled with nitrogen five times. Then the heteroaryl species (if a liquid) was added, immediately followed by the solvent. The reaction mixture was stirred at 80 °C for 16 h, cooled to room temperature, and subsequently passed through silica gel to remove iridium catalyst residue. The silica gel was washed with 2 × 2 mL of dichloromethane. The combined fractions were evaporated to dryness using a rotary evaporator to provide the desired borylated compound. If required, the product was further purified by column chromatography.

*3-Bpin-N-Boc-indole (**4a**):*[20] N-Boc-indole (202 μL, 1.0 mmol); B_2pin_2 (254 mg, 1.0 mmol); **2** (2.6 mg, 0.005 mmol); octane (6 mL). The product was obtained as a white solid (342 mg, 99%). No further purification required. ^1H NMR ($CDCl_3$, 400 MHz): δ 8.16 (m, 1H), 8.0 (s, 1H), 7.99 (dd, *J* 6.8, 0.8, 1H), 7.32–7.24 (m, 2H), 1.66 (s, 9H), 1.37 (s, 12H).

*3,5-di-Bpin-N-Boc-indole (**4b**):* 5-Bpin-N-Boc-indole (343 mg, 1.0 mmol); B_2pin_2 (254 mg, 1.0 mmol); **2** (5.2 mg, 0.01 mmol); octane (6 mL). The product was obtained as a white solid (438 mg, 93%). No further purification required. ^1H NMR ($CDCl_3$, 400 MHz): δ 8 40 (s, 1H), 8.17 (d, *J* 8.4, 1H), 7.99 (s, 1H), 7.76 (dd, *J* 8.0, 0.8, 1H), 1.65 (s, 9H), 1.39 (s, 12H), 1.38 (s, 12H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 151.3, 140.3, 137.4, 134.8, 132.7, 131.4, 116.2, 85.9, 85.5, 85.4, 30.1, 26.9, 26.8. mp 204–209 °C. Anal. Calcd for $C_{25}H_{37}B_2NO_6$: C, 64.00; H, 7.95; N, 2.99. Found: C, 63.81; H, 7.97; N, 2.96.

*3-Bpin-5-Cl-N-Boc-indole (**4c**):* 5-Cl-N-Boc-indole (251 mg, 1.0 mmol); B_2pin_2 (254 mg, 1.0 mmol); **2** (5.2 mg, 0.01 mmol); octane (6 mL). The product was obtained as a white solid (361 mg, 96%). No further purification required. ^1H NMR ($CDCl_3$, 400 MHz): δ 8.08 (d, *J* 8.8, 1H), 8.01 (s, 1H), 7.95 (d, *J* 2.0, 1H), 7.26 (dd, *J* 8.8, 2.0, 1H), 1.65 (s, 9H), 1.37 (s, 12H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 149.1, 136.1, 134.7, 128.6, 124.4, 122.2, 115.9, 84.3, 28.2, 24.9. mp 179–183

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°C. Anal. Calcd for: $C_{19}H_{25}BClNO_4$: C, 60.42; H, 6.67; N, 3.71. Found: C, 60.15; H, 6.72; N, 3.69.

2-Bpin-pyrrole (4d):[35] Pyrrole (693 μL, 10 mmol); B_2pin_2 (254 mg, 1.0 mmol); **2** (15.5 mg, 0.03 mmol); octane (6 mL). Crude product was purified by flash column chromatography (0–20% MTBE/PE) to give the product as a colorless oil (91 mg, 47%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.82 (s, 1H), 7.01–6.99 (m, 1H), 6.86–6.85 (m, 1H), 6.31–6.29 (m, 1H), 1.32 (s, 12H).

2,5-di-Bpin-pyrrole (4e):[36] Pyrrole (69 μL, 1.0 mmol); B_2pin_2 (381 mg, 1.5 mmol); **2** (15.5 mg, 0.03 mmol); octane (6 mL). The product was obtained as a white solid (306 mg, 96%). No further purification required. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.28 (s, 1H), 6.83 (d, *J* 2.4, 2H), 1.31 (s, 24H).

Meridianin G:[33] **4a** (1.0 mmol) was prepared according to the general method for Ir-catalyzed C–H borylation reactions described above. After completion of the reaction by GC monitoring, octane was removed under reduced pressure. To the resulting residue was added 4-chloropyrimidin-2-amine (130 mg, 1.0 mmol), Cs_2CO_3 (0.815 g, 2.5 mmol), and dtbpfPdCl$_2$ (6.4 mg, 0.01 mmol), followed by the addition of a 1:1 mixture of IPA and water (6 mL). This mixture was heated to 80 °C with stirring for 16 h under an N_2 atmosphere. Then the reaction mixture was extracted with water (6 mL) and brine (6 mL). The organic phase was dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel with a solvent mixture of 5% MeOH and 95% hexane. The desired product was obtained as a pale yellow powder (0.183 g, 87% overall yield). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 11.66 (s, 1H), 8.58 (d, *J* 7.8, 1H), 8.19 (d, *J* 2.9, 1H), 8.10 (d, *J* 5.3, 1H), 7.44 (d, *J* 7.8, 1H), 7.14 (m, 2H), 7.01 (d, *J* 5.3, 1H), 6.41 (s, 2H).

■ ASSOCIATED CONTENT

Supporting Information

A table regarding lower catalyst loading, text giving additional details on SS NMR ^{35}Cl and XPS spectra of **1** and **2**, figures giving ^{1}H and ^{13}C NMR spectra for compounds **2**, **3**, **4a–e**, and meridianin G, DSC traces of **2** and **3**, comparison of solution-state ^{1}H NMR spectra of **2** and [Ir(OMe)(COD)(phen)], solution and SS NMR spectra of Ir(Cl)(COD)(Me$_4$phen) and Ir(Cl)(COD)(dtbpy), and the ^{11}B NMR spectrum of the reaction of [Ir(Cl)(COD)(dtbpy)] with B_2pin_2, and a CIF file giving X-ray crystallographic data for **3**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare the following competing financial interests: The catalysts used in this study are commercially available from Johnson Matthey Catalysis and Chiral Technologies.

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