

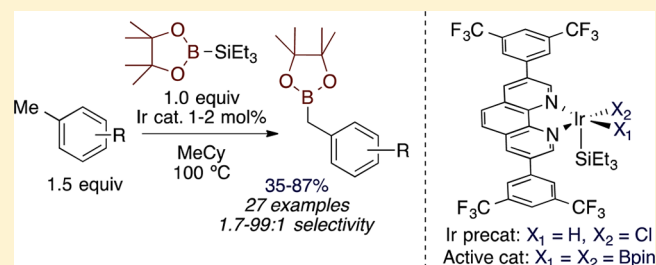
Iridium-Catalyzed Borylation of Primary Benzylic C–H Bonds without a Directing Group: Scope, Mechanism, and Origins of Selectivity

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S Supporting Information

ABSTRACT: Primary benzylic boronate esters are useful intermediates in organic synthesis, but these reagents cannot be prepared by hydroboration. The benzylic C–H borylation of methylarenes would be a method to form these products, but such reactions without neat methylarene or a directing group are unknown. We report an approach to divert the borylation of methylarenes from aromatic positions to benzylic positions with a silylborane as reagent and a new iridium catalyst containing an electron-deficient phenanthroline as ligand. This system forms benzylic boronate esters selectively over the corresponding aryl boronate esters. An Ir diboryl monosilyl complex ligated by the phenanthroline was isolated and determined to be the resting state of the catalyst. Mechanistic studies show that this complex is kinetically competent to be an intermediate in the catalytic process. Kinetic studies of benzylic and aryl C–H borylation catalyzed by various Ir complexes show that the rate of aryl C–H borylation decreases with decreasing electron density at the metal center of the Ir catalyst, but that the rate of benzylic C–H borylation is less sensitive to the degree of electron density at the metal center of the Ir catalyst. Kinetic and computational studies suggest that the two borylation reactions respond differently to the degree of electron density at the metal center because they occur with different turnover-limiting steps. The turnover-limiting step in the borylation of aryl C–H bonds is known to be C–H oxidative addition, but the turnover-limiting step of the borylation of benzylic C–H bonds appears to be an isomerization prior to C–B reductive elimination.



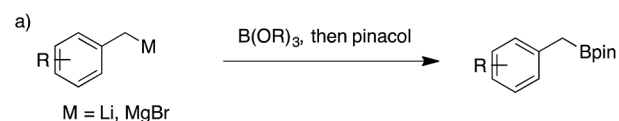
INTRODUCTION

Organoboron compounds are versatile intermediates in organic synthesis for the formation of carbon–carbon and carbon–heteroatom bonds. Such reagents have become essential building blocks for the synthesis of materials, pharmaceuticals, and agrochemicals.^{1–4} Arylboronic acids and the analogous esters and trifluoroborate salts are the most commonly used organoboron compounds. Commercial sources for these compounds are abundant, and methods for the synthesis of compounds containing the arylboron unit are well developed. However, the commercial availability of alkylboron compounds is more limited.

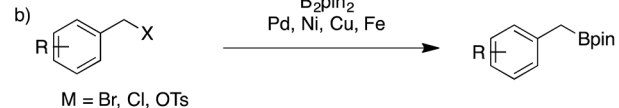
Like aryl boronate esters, alkyl boronate esters are often synthesized by quenching an organolithium or organomagnesium compound with a trialkylborate, followed by transesterification with a chelating diol (Scheme 1a).⁵ Although this method often forms boronate esters in high yield, it has limited functional group compatibility, due to the high reactivity of organolithium and organomagnesium species. The borylation of organic halides first developed by Ishiyama and Miyaura,^{6,7} and elaborated by others,^{8–13} is a milder method to convert aryl and alkyl halides directly to the desired organoboronate ester (Scheme 1b); however, the scope and yield of these reactions are often lower for the synthesis of alkyl boronate esters than for the synthesis of aryl boronate esters,

Scheme 1. Methods for the Synthesis of Primary Benzylic Boronate Esters

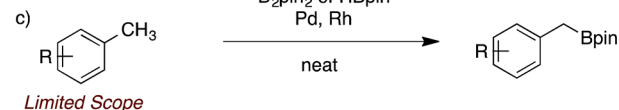
Metalation/Quech:



Cross-Coupling:



C–H Functionalization:



and the halide must be present in the organic reactant of this process.

Although alkyl boronate esters are often prepared by hydroboration of an alkene,^{14,15} this method cannot be used

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to form primary benzylic boronate esters. Such benzylic boronate esters are synthetically valuable because they can be converted to biologically relevant diarylmethanes, benzylic amines, and benzyl alcohols. Typically, the synthesis of primary benzylic boronate esters requires the intermediacy of a benzylic halide or pseudohalide, which are formed by the radical halogenation of a methylarene.

Iridium-catalyzed borylation of C–H bonds has created a route to aryl boronate esters without the intermediacy of aryl electrophiles.^{3,16,17} We envisioned a direct synthesis of primary benzylic boronate esters from methylarenes, but this approach faces the challenge of directing the borylation to a benzylic C–H bond over typically more reactive aryl C–H bonds. Although the selective borylation of benzylic C–H bonds has been achieved with Pd¹⁸ or Rh catalysts,^{19,20} these methods have poor functional group tolerance and require a large excess of methylarene (Scheme 1c). Ir-catalyzed borylation of primary and secondary benzylic C–H bonds has been reported with a hydrosilyl directing group,^{21,22} but the undirected, iridium-catalyzed borylation of benzylic C–H bonds with high benzylic:aryl (Bn:Ar) selectivity is unknown.

In 2008, our group reported that the borylation of toluene solvent with Et₃SiBpin catalyzed by iridium and di-*tert*-butylbipyridine as ligand gives a 1:1 mixture of benzyl boronate esters to aryl boronate esters.²³ Although this selectivity was poor, it did suggest that the selective borylation of a benzylic C–H bond could be achieved.

We report the selective borylation of benzylic C–H bonds in methylarenes with Et₃SiBpin, catalyzed by an Ir complex containing an electron-poor phenanthroline. These reactions occur with good functional group tolerance, require only a small excess of methylarene, and do not require a directing group. The benzylic boronate esters formed from this reaction can be converted to benzylic alcohols, benzylic amines, diarylmethanes, and benzylic iodides. Mechanistic studies reveal the resting state of the catalyst and show that the borylation of aryl C–H bonds is much more sensitive to the electronic properties of the catalyst than is the borylation of benzylic C–H bonds, most likely because of a difference in rate-determining step. This difference in electronic effects on the two processes created an opportunity to distinguish between the two sites for C–H borylation by the basicity of the dative ligand.

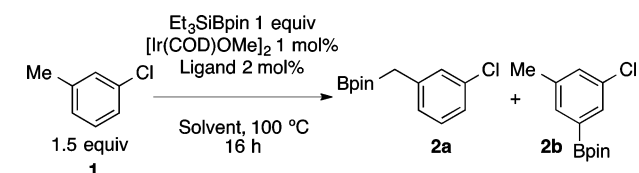
RESULTS AND DISCUSSION

Development of Conditions for Benzylic Borylation.

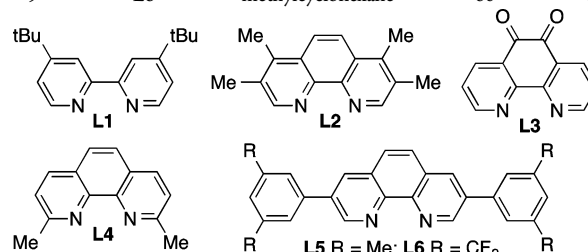
To create a catalyst and reagent for the borylation of benzylic C–H bonds, we built upon our preliminary observations of benzyl boronate esters forming as one product from the reaction of toluene with Et₃SiBpin catalyzed by iridium ligated by di-*tert*-butylbipyridine. We investigated reactions of *m*-chlorotoluene (**1**) with Et₃SiBpin catalyzed by a series of phenanthrolines possessing different steric and electronic properties. We used *m*-chlorotoluene **1** as a model substrate because the reaction of this neat arene with Et₃SiBpin catalyzed by iridium ligated by di-*tert*-butylbipyridine (dtbpy) gave a roughly 1:1 ratio of products from borylation at the benzylic position and 5-position of the arene, allowing the effect of the ligand on the selectivity for reaction at benzyl and aryl C–H bonds to be determined readily.

The results of reactions conducted with a series of ligands are shown in Table 1. These reactions were conducted with 1.5 equiv of arene, instead of the neat arene.²³ With THF as solvent

Table 1. Effect of Ligand and Solvent on the Borylation of Benzylic and Aryl C–H bonds^a



entry	ligand	solvent	yield ^b (%)	
			2a	2b
1	L1	THF	29	31
2	L2	THF	24	49
3	L3	THF	34	40
4	L4	THF	5	34
5	L5	THF	44	26
6	L6	THF	52	13
7	L6	dioxane	42	13
8	L6	cyclohexane	60	6
9	L6	methylcyclohexane	60	6



^aReactions were conducted on a 0.125 mmol scale. ^bDetermined by GC analysis.

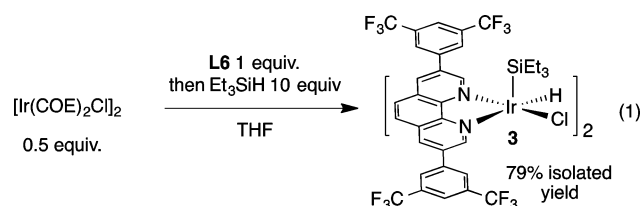
and dtbpy (**L1**) as ligand, benzylic boronate **2a** and aryl boronate **2b** were formed in equal quantities (Table 1, entry 1). The reaction of 3-chlorotoluene catalyzed by the complex containing tmphen (**L2**) as ligand (recently shown to create a more reactive catalyst for the borylation of arenes,^{24,25} heteroarenes,²⁶ and alkanes^{27–30} than those containing dtbpy) led to a significantly smaller amount of product **2a** from benzylic borylation (Table 1, entry 2). Thus, we tested catalysts containing less electron-donating nitrogen ligands. The reaction with phenanthroline (**L3**) as ligand (Table 1, entry 3) occurred with selectivity similar to that with **L1** as ligand. The lowest selectivity for product **2a** was observed for the reaction with neocuprine (**L4**) as ligand (Table 1, entry 4), suggesting that a sterically congested environment around the metal center favors the formation of aryl boronate **2b** over the benzyl boronate **2a**. However, the reactions conducted with 3,8-diaryldiphenylphenanthrolines **L5** and **L6** as ligand (Table 1 entries 5 and 6) formed the benzyl boronate **2a** as the major product. The reaction with ligand **L6**, containing electron-deficient aryl rings at the 3 and 8 positions on the phen core, led to the highest ratio of **2a:2b** (4:1, entry 6) in favor of the benzyl boronate ester.

The selectivity was improved further by changing the solvent. Reactions in alkane solvents (entries 8 and 9), rather than the ethereal solvents THF and dioxane (entries 6 and 7), occurred with a selectivity that more strongly favored the benzyl boronate ester (**2a:2b** = 10:1). The reactions in cyclohexane and methylcyclohexane (MeCy) occurred with the same selectivity. Thus, we conducted our further studies with MeCy as solvent because its boiling point is higher than that of cyclohexane and matches the reaction temperature.

With the conditions in entry 9 of Table 1, we began to investigate the scope of the borylation of methylarenes. However, the reactions of methylarenes containing substituents other than alkyl groups or halogens formed benzylic boronate esters in low yield. These low yields appeared to result from a long induction period (observed to be >10 h in most cases), rather than an incompatibility of the substrate with the catalyst. Thus, further changes to the catalyst were necessary to create a process that occurred with broad scope.

To decrease the induction period, we developed a new precatalyst that could more readily enter the catalytic cycle than the combination of $[\text{Ir}(\text{COD})\text{OMe}]_2$, **L6**, and silylborane. Because the active catalyst likely contains at least one silyl ligand, a precatalyst that contains a silyl ligand might generate the active catalyst more rapidly than does $[\text{Ir}(\text{COD})\text{OMe}]_2$. Also, a precatalyst that contains the dative ligand **L6** could form the active species more readily than would a combination of **L6** and an Ir precursor.

To generate such a precatalyst, we combined a 1:1 mixture of $0.5[\text{Ir}(\text{COE})_2\text{Cl}]_2$ and **L6** in THF with 10 equiv of triethylsilane (eq 1). A brown/purple solid was isolated from this



solution and was characterized by NMR spectroscopy, IR spectroscopy, and combustion analysis. The ^1H NMR spectrum contained one set of signals that is consistent with the composition of chlorohydridosilyl complex **3**. X-ray crystallographic analysis showed that, in the solid state, the product adopted the structure of the unsymmetrical dimer shown in Figure 1. In this structure, each metal center is bound to a

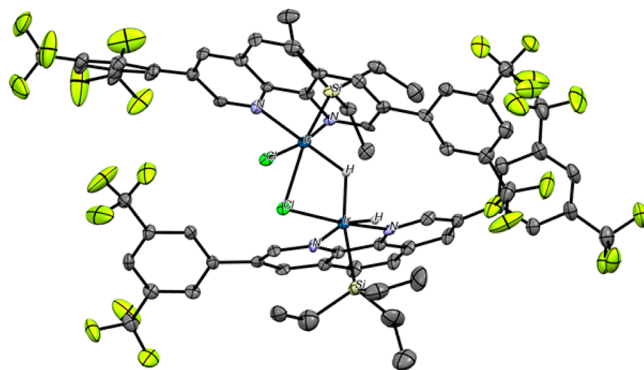


Figure 1. Structure of complex **3** determined by X-ray diffraction. Hydrogen atoms have been omitted, except for the hydrides bound to iridium.

terminal chloride or a terminal hydride, and the two metal centers are bridged by a chloride ligand and a hydride ligand. Consistent with this assertion, the infrared spectra of **3** (Nujol mull) contains a sharp absorption at 2121 cm^{-1} (due to the terminal hydride) and a very broad absorption at 1841 cm^{-1} (due to the bridging hydride).³¹ In the IR spectrum of the Ir–D analogue of **3**, these peaks shifted, confirming that they originated from Ir–H stretching modes (see Supporting

Information (SI), pp S7–S8). The IR spectrum of **3** in THF contained both Ir–H peaks, suggesting that **3** exists as the dimer in solution. The bridging and terminal hydride and chloride ligands rapidly exchange with each other on the NMR time scale. One hydride resonance and one set of ligand resonances are observed in the ^1H and ^{31}P NMR spectra.

We compared the profile of the borylation of **1** catalyzed by the combination of $[\text{Ir}(\text{COD})\text{OMe}]_2$ and **L6** (Figure 2,

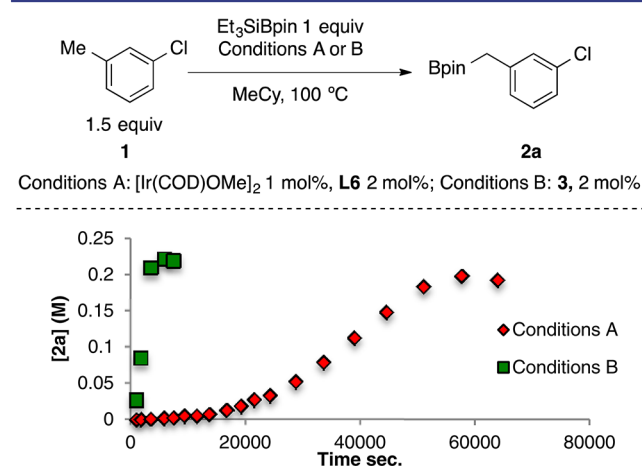
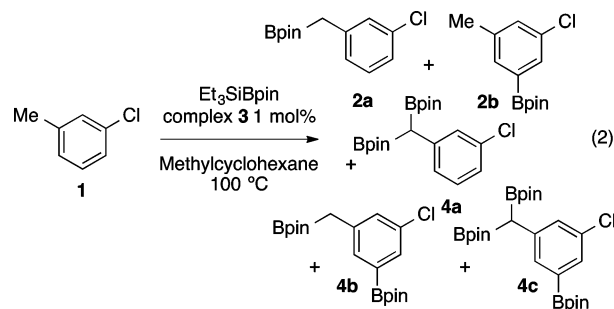


Figure 2. Reaction profiles for the borylation of **1** with Et_3SiBpin catalyzed by Conditions A or Conditions B. Reactions were conducted on a 0.25 mmol scale. The concentration of **2a** was determined by GC analysis.

Conditions A) to that of the borylation of **1** catalyzed by complex **3** (Figure 2, Conditions B). Under conditions A, we observed a long induction period. However, under conditions B, the reaction was complete after 1 h with no observable induction period.

With this new precatalyst in hand, we investigated the mass balance of the reaction and the effect of the ratio of arene to Et_3SiBpin on the distribution of products. GC/MS analysis of the reaction mixture from the borylation of **1** with Et_3SiBpin , catalyzed by **3**, showed that two products from diborylation of the arene and one product of triborylation were present, in addition to the products of monoborylation **2a** and **2b**. One diborylated compound was shown to be **4a** (eq 2) after its isolation from the reaction mixture. The other diborylated product was shown to be **4b**, and the triborylation product was determined to be **4c** by independent synthesis.



The graph in Figure 3 summarizes the effect of the ratio of arene to Et_3SiBpin on the distribution of products **2a,b** and **4a–c**. For reactions conducted with limiting arene, less than 60% yield of benzylic boronate **2a** formed; instead, these reactions formed significant quantities of polyborylated

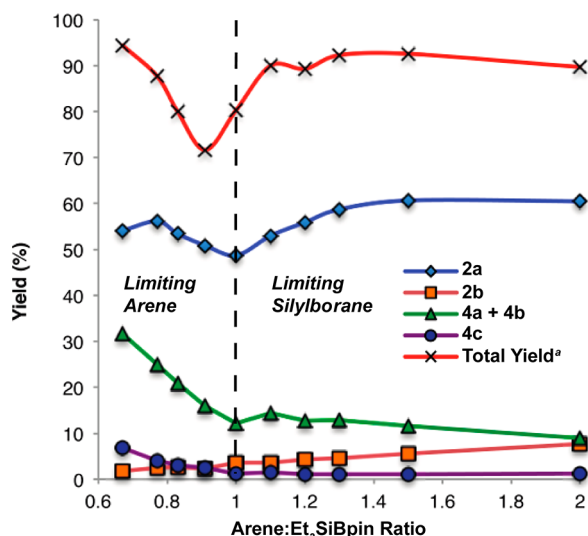


Figure 3. Effect of arene:Et₃SiBpin ratio on product distribution for the benzylic borylation of **1**. Reactions conducted on a 0.125 mmol scale. ^aTotal yield based on moles of boron incorporated for the limiting silylborane regime and on the moles of arene for the limiting arene regime. Yields determined by GC analysis.

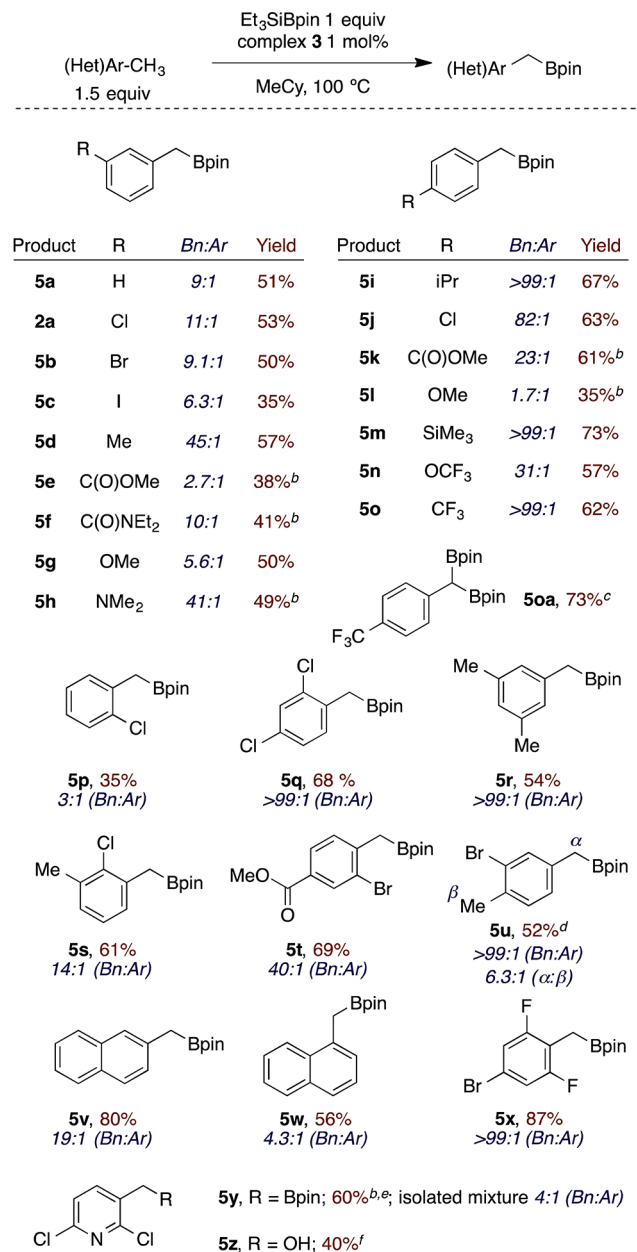
compounds **4a–c**. For reactions conducted with limiting silylborane, the yield of the desired product **2a** increased with increasing ratio of arene:Et₃SiBpin. However, no increase in the yield of **2a** was observed when the reaction was conducted with a ratio of arene to Et₃SiBpin higher than 1.5:1. Thus, we conducted the remainder of the study with a ratio of arene to Et₃SiBpin of 1.5:1.

Scope of the Borylation of Primary Benzylic C–H Bonds. The scope of the benzylic borylation was assessed under the reaction conditions shown in Chart 1. Methylarenes containing a variety of functional groups reacted with Et₃SiBpin catalyzed by 1–2 mol % of **3** at 100 °C in methylcyclohexane to form the corresponding benzylic boronate esters in moderate to excellent yields. (The reactions were conducted for 16 h, but many of the reactions were complete in less than 1 h.) The reactions of toluene and *meta*-substituted methylarenes formed moderate yields of benzylic boronates **5a–5h** with good to excellent selectivity for the benzylic boronate over the aryl boronate. Halogens, methoxy, carboalkoxy, carbamoyl, and dialkylamino groups were all tolerated.

The yield and selectivity of the benzylic boronate ester from the reactions of *para*-substituted methylarenes were higher than those observed from the reactions of *meta*-substituted methylarenes. With the exception of boronate **5l**, benzylic boronate esters **5i–5o** were formed in $\geq 23:1$ (Bn:Ar) selectivity and were isolated in yields ranging from 57 to 73%. This higher selectivity results from the greater steric hindrance at each aryl C–H bond of a 1,4-substituted arene than at the 5-position of a 1,3- or 1,2,3-substituted arene.

In general, the substituent *para* to the methyl undergoing borylation had a strong effect on the rate and selectivity of the reaction. For example, the borylation of *p*-methylanisole formed product **5l** slowly, and the selectivity for the benzylic product was only 1.7:1 (Bn:Ar). The reaction of *p*-(dimethylamino)-toluene with Et₃SiBpin in the presence of 10 mol % of complex **3** did not even form observable products from borylation. However, the reaction of *p*-methylbenzotrifluoride formed benzylic boronate **5o** in 62% yield and even generated

Chart 1. Scope of the Benzylic Borylation of Methylarenes^a



^aReactions were conducted on a 0.500 mmol scale. Yields are for isolated benzylic boronate ester. Selectivity determined by GC analysis. ^bReaction conducted with 2 mol % of complex **3**. ^cReaction conducted with 1 equiv of arene, 3 equiv of Et₃SiBpin, and 4 mol % of complex **3**. ^dIsolated as a 6.3:1 (α : β) mixture of products. ^eFormed inseparable mixture of aryl and benzylic boronate esters. ^fMixture of products **5y** was treated with aqueous NaOH and H₂O₂ in THF, and pyridyl methanol **5z** was isolated.

significant quantities of bisboryl product in less than 1 h. Bisboryl product **5oa** formed in 73% yield by conducting the reaction of 1 equiv of *p*-methylbenzotrifluoride with 3 equiv of silylborane, catalyzed by 4 mol % of complex **3**.

Ortho-substituted methylarenes also formed the corresponding benzylic boronate esters. However, these reactions occurred in lower yield and selectivity than the borylation of *meta*- or *para*-substituted methylarenes. For example, *o*-chlorotoluene formed benzylic boronate **5p** in 35% isolated yield with only 3:1 (Bn:Ar) selectivity. However, a similar methylarene

containing one additional chloro group at the *para*-position reacted to form benzylic boronate **5j** in 68% yield with complete selectivity for the benzylic boronate. This result shows that high yields and selectivity are attained if the aryl ring is sufficiently substituted to inhibit competing aryl C–H borylation, even when the steric properties of a substituent *ortho* to the methyl group undergoing borylation may hinder benzylic borylation.

The borylation of substrates containing two different methyl substituents occurred at the less hindered of the methyl groups. For example, the borylation of 2-bromo-1,4-dimethylbenzene occurred at the methyl group *meta* to the bromo substituent (α product) in preference to the methyl group *ortho* to the bromo substituent (β product). The ratio of these two products **5u** was 6.3:1 (α : β).

The borylation of methylnaphthalenes formed naphthylmethyl boronate esters **5v** and **5w** in good to excellent yields. Even though 2-methylnaphthalene possesses two sterically accessible aryl C–H bonds, naphthylmethyl boronate **5v** was formed in 80% yield with 19:1 (Bn:Ar) selectivity.

The borylation of methylarenes containing fluoride substituents formed benzylic boronates, albeit with lower selectivity (Bn:Ar) than did the borylation of methylarenes containing other electron-withdrawing groups. For example, the borylation of *p*-fluorotoluene formed the product of aryl C–H borylation at the site adjacent to fluorine as the major product. However, the borylation of fluorinated methylarenes in which all aryl C–H bonds are adjacent to at least one substituent larger than fluorine occurred in excellent yield and with high selectivity. For example, the borylation of 4-bromo-2,6-difluorotoluene formed benzylic boronate **5x** in 87% yield. No aryl C–H borylation or bisborylation was observed in this reaction.

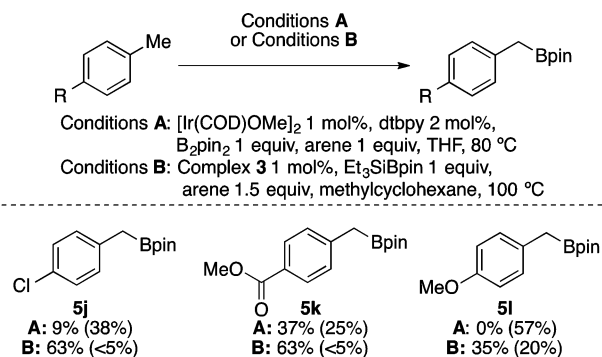
The reaction of picolines with Et_3SiBpin catalyzed by **3** did not form the corresponding heteroaryl or pyridylmethyl boronate ester except when the substrate contained substituents adjacent to nitrogen. We hypothesized that steric bulk adjacent to nitrogen in picolines might discourage coordination of the pyridine to the catalyst. Indeed, the borylation of 2,6-dichloro-3-picoline formed the pyridylmethyl boronate as the major product. We were unable to separate the heteroaryl and pyridylmethyl boronate products; therefore, **5y** was isolated as a 4:1 (Bn:Ar) mixture of isomers. However, pyridyl methanol **5z** was isolated in pure form in 40% yield after treatment of the initial mixture **5y** with H_2O_2 and NaOH.

In general, electron-deficient methylarenes reacted faster than electron-rich methylarenes. However, the selectivity for the benzylic boronate ester over the aryl boronate ester was often lower for reactions of electron-deficient methylarenes than for reactions of electron-rich methylarenes. For example, the lowest selectivity for the borylation of *meta*-substituted methylarenes was observed for the borylation of methyl *m*-toluate. This reaction formed **5e** with only 2.7:1 (Bn:Ar) selectivity, whereas the borylation of 3-dimethylaminotoluene formed benzylic boronate **5h** over the aryl boronate in a 41:1 (Bn:Ar) ratio. These results suggest that the rate of aryl C–H borylation is more sensitive to the electronic properties of the methylarene than is the rate of benzylic C–H borylation. A more detailed investigation of this phenomenon will be presented later in this paper.

Comparison of Catalysts for the Benzylic Borylation of Methylarenes Containing Hindered Aryl C–H Bonds. Because *para*-substituted toluenes do not contain any unhindered aryl C–H bonds, we compared the selectivity

obtained for the borylation of these substrates under the conditions developed in the current work to that obtained for aryl C–H borylation under the conditions originally published by Ishiyama, Miyaura, and Hartwig.³² We conducted the borylation of *p*-chlorotoluene, methyl *p*-toluate, and *p*-methylanisole with B_2pin_2 catalyzed by the combination of $[\text{Ir}(\text{COD})\text{-OMe}]_2$ and dtbpy (IMH catalyst, Conditions A, Chart 2). In

Chart 2. Comparison of Catalysts for Borylation of *para*-Substituted Methylarenes^a

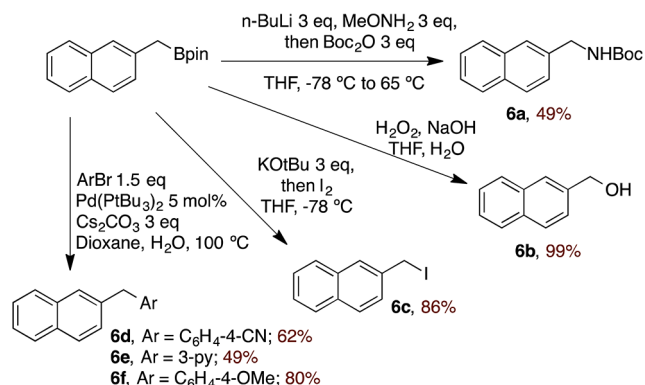


^aReactions were conducted on a 0.250 mmol scale. Yields were determined by GC analysis. Yields in parentheses are for the combined yield of all aryl boronate ester products.

contrast to the borylation of *para*-substituted methylarenes under our current conditions (Chart 2, Conditions B), the borylation of *para*-substituted methylarenes under Conditions A formed benzylic boronate esters in low yield and selectivity. For example, the borylation of methyl *p*-toluate under Conditions A formed the benzylic boronate **5k** in only 35% yield with selectivity less than 2:1 (Bn:Ar), whereas the same reaction under Conditions B formed **5k** in 63% yield with only trace amounts of competing arene borylation. Likewise, the borylation of *p*-chlorotoluene and *p*-methylanisole under Conditions A formed products **5j** and **5l** in 9% yield and <1% yield, respectively, but the borylation of the same substrates formed benzyl boronates **5j** and **5l** in 63% yield and 35% yield, respectively, under conditions B.

Functionalization of Primary Benzylic Boronate Esters. To illustrate the synthetic utility of primary benzylic boronate esters formed by the borylation of methylarenes, we conducted several reactions (Scheme 2) of naphthylmethyl boronate **5v**. Amination of **5v** under reaction conditions developed by Morken et al.³³ formed *N*-Boc-2-(aminomethyl)-

Scheme 2. Functionalization of Benzylic Boronate Esters

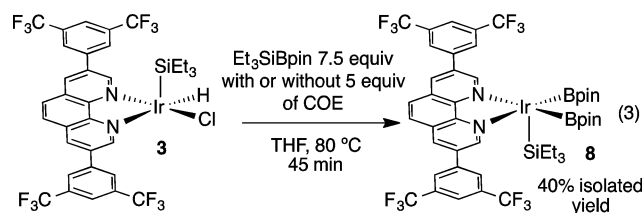


naphthalene **6a** in 49% yield. Oxidation of **5v** with hydrogen peroxide formed 2-(hydroxymethyl)naphthalene **6b** in quantitative yield. Inspired by recent work from Morken showing that bisboryl alkanes can be activated with *tert*-butoxide to form reactive nucleophiles for alkylation,³⁴ monobenzyl boronate **5v** was treated with KOtBu and quenched with iodine to give 2-(iodomethyl)-naphthalene **6c** in 86% yield. So far, reactions of the monobenzyl boronate with alkyl halides under these conditions did not occur.

The most conventional application of an organoboronate ester is Suzuki coupling to form diarylmethanes, but few examples of the coupling of primary benzylic boronate esters with aryl bromides have been reported.³⁵ Thus, we surveyed a series of bases and catalysts to identify a suitable protocol for coupling of the products of the benzylic borylation. The Suzuki coupling of boronate **5v** with several aryl bromides, catalyzed by Pd(PtBu₃)₂ gave diarylmethanes **6d–f** in good yield.

Mechanistic Studies and Investigation of the Origin of Selectivity. Having shown that the borylation reaction can be diverted from aryl C–H bonds to benzylic C–H bonds by changing the borane reagent and phenanthroline ligand on iridium, we sought to reveal the origin of this new site selectivity. First, we sought to reveal the effect of the reagent on this site selectivity by determining the structure of the active catalyst when conducting reactions with Et₃SiBpin in place of B₂pin₂. Second, we sought to reveal the origin of the electronic effect of the ligand on the site selectivity. As part of this study, we measured the rates for aryl C–H borylation and benzylic C–H borylation with B₂pin₂ or Et₃SiBpin catalyzed by iridium complexes bound by dtbpy or L6. With the structure of the active catalyst and detailed kinetic data as a foundation, we computed the structure of the transition states for the steps that cleave the C–H bond, form the B–C bond, and isomerize intermediates along the reaction coordinate.

Isolation of the Resting State. The reaction of silyl catalyst precursor **3** with 7.5 equiv of Et₃SiBpin in the presence or absence of 5 equiv of *cis*-cyclooctene (COE) led to the iridium diborylmonosilyl complex **8** ligated by L6 (eq 3). NMR spectral



data of the isolated material matched those of the material generated *in situ* and indicated that this complex lacked a bound alkene.³⁶ Single crystals of complex **8** were obtained, and the structure was determined by X-ray diffraction (Figure 4). Indeed, complex **8** adopts a slightly distorted square-based pyramidal geometry in which the sum of the angles in the square plane equals 360°, but the apical silyl ligand is tilted slightly toward the boryl ligands (Si–Ir–B angles = 86.3° and 87.9°). The Ir–B distances (2.044 and 2.050 Å) in **8** are similar to the Ir–B distances (2.027, 2.055, and 2.057 Å) in the previously reported COE-bound dtbpy complex containing three boryl ligands, rather than two boryl ligands and one silyl ligand.

Complex **8** is the resting state of the iridium catalyst during the benzylic borylation of methylarenes. Monitoring the borylation reaction by ¹H NMR spectroscopy during the

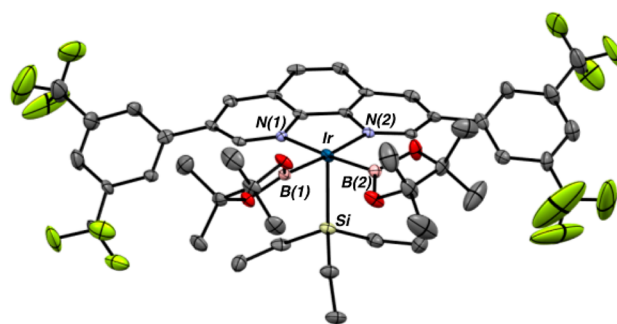


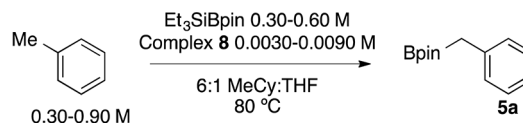
Figure 4. Structure of complex **8** determined by single-crystal X-ray diffraction. Hydrogen atoms omitted for clarity. Selected bond lengths (Å): Ir–N1 = 2.182(5), Ir–N2 = 2.195(5), Ir–B1 = 2.044(7), Ir–B2 = 2.050(7), Ir–Si = 2.353(2). Selected bond angles (deg): N1–Ir–Si = 93.2(1), N2–Ir–Si = 95.0(1), B1–Ir–Si = 86.3(2), B2–Ir–Si = 87.9(2).

reaction of 4-chlorotoluene with Et₃SiBpin catalyzed by complex **3** in methylcyclohexane-*d*₁₄ (see SI, pp S36–S38) showed that complex **8** was the major species ligated by L6 in solution (~80%). Triethylsilane was formed as a byproduct during this reaction (see SI, Figure S7).

Complex **8** is kinetically competent to be an intermediate in the benzylic borylation of methylarenes. The reaction of **2** with Et₃SiBpin catalyzed by the silyl hydride chloride complex **3** at 80 °C occurred with a short induction period (~30 min). However, the reaction of **2** catalyzed by diborylsilyl complex **8** occurred without an induction period (see SI, Figure S8). This lack of an induction period for the reaction catalyzed by **8** is consistent with it being a reaction intermediate. The reaction catalyzed by either complex formed benzylic boronate **2a** in 61% yield with 11:1 Bn:Ar selectivity, as determined by gas chromatography.

Determination of the Rate Law. To determine the order of the reaction in the different reagents, we measured the initial rates of reactions of toluene with Et₃SiBpin catalyzed by complex **8** with varying concentrations of the three components. The concentrations for this kinetic study are shown in Scheme 3 (also see SI, Table S2, for a table of

Scheme 3. Order in Reagents for the Benzylic Borylation of Methylarenes



Rate of Reaction: 1st order in [toluene], 1st order in [**8**], and 0th order in [Et₃SiBpin].

reaction conditions and initial rates). The rates of the reactions were determined to be first order in toluene, zeroth order in Et₃SiBpin, and first order in complex **8**. These orders are analogous to those for the borylation of arenes with B₂pin₂ catalyzed by (dtbpy)Ir(COE)(Bpin)₃.³⁷

Reactivity of the Catalyst Resting State. Stoichiometric reactions of complex **8** with methylarenes were conducted to assess further the role of this complex in the catalytic system. The reaction of fluorinated methylarene **10** with complex **8** (Figure 5a) forms a 1:1.4 ratio of benzylic boronate to aryl boronate esters, as determined by ¹⁹F NMR spectroscopy (see SI, Figure S10, for the reaction profile). The yield of this

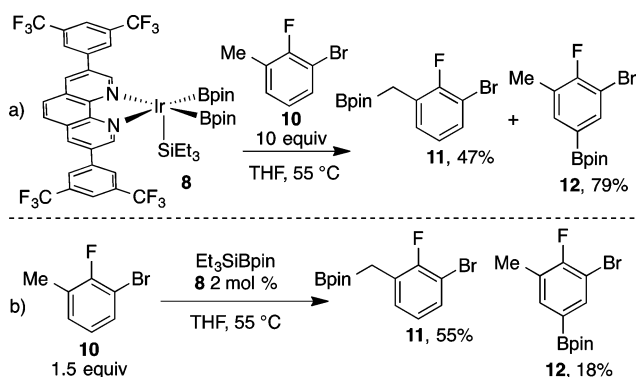


Figure 5. (a) Reaction of complex **8** with **10**. (b) Reaction of **10** with Et_3SiBpin catalyzed by complex **8**. Yields determined by ^{19}F NMR spectroscopy.

stoichiometric reaction was over 100% based on iridium, suggesting that the Ir-byproducts of the reaction of **8** with **10** also react with **10** to form boronate ester products. However, the catalytic reaction of **10** with Et_3SiBpin catalyzed by complex **8** (Figure 5b) forms a 3:1 ratio of benzyl boronate to aryl boronate esters, as determined by ^{19}F NMR spectroscopy. This observation implies that complex **8** is not a true intermediate or that it reacts in the absence of added silylborane by a pathway that is distinct from the one by which it reacts in the presence of silylborane.

To reveal the origin of the difference in selectivity between the stoichiometric reaction of complex **8** with arene **10** and the catalytic reaction, we determined the rate law for formation of aryl and benzyl boronates from the reaction of **8** with **10**. The rate of borylation of aryl and benzyl C–H bonds are both first order in arene **10** and first order in iridium complex **8**. However, the rate of benzylic C–H borylation is independent of the concentration of Et_3SiBpin , while the aryl C–H borylation is approximately inverse first order in the concentration of Et_3SiBpin at low ratios of Et_3SiBpin to Ir (Figure 6). At high ratios of Et_3SiBpin :Ir, the arene borylation was zeroth order in Et_3SiBpin . Thus, the effect of the concentration of Et_3SiBpin on the selectivity of the reaction of **8** with **10** results from the suppression of the rate of arene borylation by the Et_3SiBpin that is present in the catalytic reaction. These data are consistent with the intermediacy of **8**

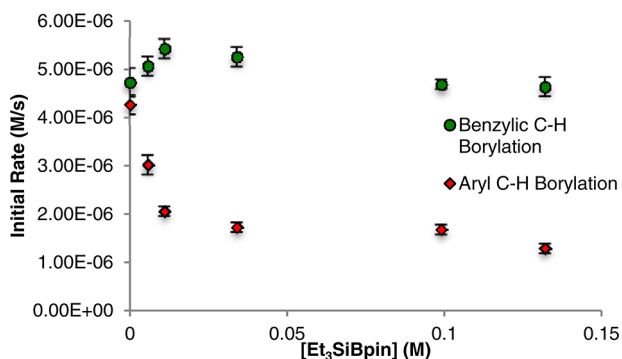
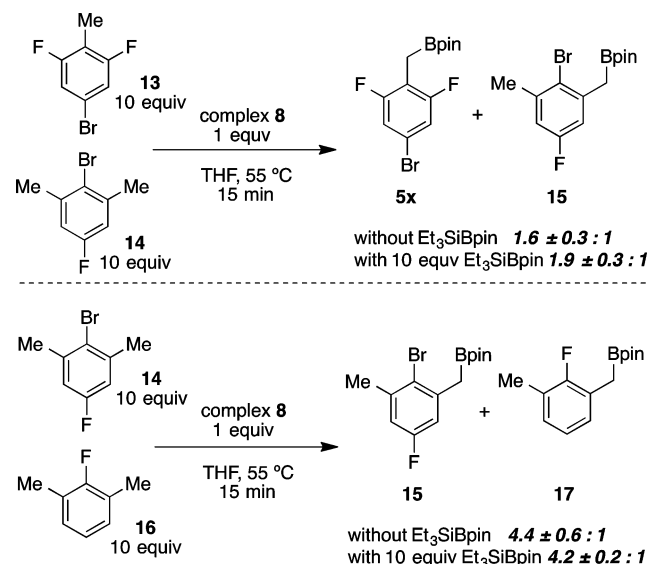


Figure 6. Dependence of the rate of aryl and benzylic C–H borylation on the concentration of Et_3SiBpin . Reactions conducted with **8** (14 mM), **10** (72 mM), and Et_3SiBpin (0–0.13 M) in THF. Initial rates for the formation of **11** and **12** were determined by ^{19}F NMR spectroscopy.

and a change in the selectivity of the reaction of **8** in the presence and absence of Et_3SiBpin .

The intermediacy of **8** in the benzylic borylation is also supported by experiments that compare the selectivity of the stoichiometric and catalytic reaction for the borylation of different fluorinated methylenes (Scheme 4). The reaction of

Scheme 4. Competition Experiments for the Borylation of Fluorinated Methylenes with Complex **8** and with Et_3SiBpin Catalyzed by **8**^a



^aReactions were conducted on a 0.0043 mmol scale. Ratios of products were determined by ^{19}F NMR spectroscopy.

10 equiv each of the two methylenes **13** and **14** with complex **8** formed a 1.6 ± 0.3 :1 ratio of benzylic boronate products **5x** and **15**, respectively as determined by ^{19}F NMR spectroscopy after 15 min (<30% conversion of **8**). The analogous reaction of **13** and **14** with 10 equiv of Et_3SiBpin catalyzed by **8** gave a similar ratio of **5x** to **15** (1.9 ± 0.3 :1).

The same experiment conducted with the two methylenes **14** and **16** gave a ratio of benzylic boronate products of 4.4 ± 0.6 :1 (**15**:**17**) for the stoichiometric reaction and 4.2 ± 0.2 :1 (**15**:**17**) for the catalytic reaction. The similar ratios for these two competition experiments suggest that the active species for benzylic borylation in the stoichiometric reaction is the same as the active species for benzylic borylation in the catalytic reaction.

Thus, we favor the intermediacy of **8** in the borylation of benzylic C–H bonds, rather than the conversion of **8** to a species on a distinct catalytic cycle. We draw this conclusion for several reasons. First, the selectivities are the same for the stoichiometric and catalytic reaction of this complex with different benzylic C–H bonds. Second, complex **8** is the only phenanthroline-bound species observed by ^1H NMR spectroscopy, and it reacts with rates that are similar to those of the catalytic process. If a small amount of complex generated from **8** were the true catalyst, then the catalytic reaction must be significantly faster than the stoichiometric reaction to account for the higher Bn:Ar selectivity observed during the catalytic reaction than during the stoichiometric reaction. Third, our data show that the rate of aryl borylation differs in the catalytic and stoichiometric reaction, not the rate of benzylic borylation. The catalytic borylation of arenes is slower than the

stoichiometric borylation of arenes because the silylborane inhibits the aryl C–H borylation reaction.

The origin of the difference in rate of arene borylation in the presence and absence of added Et_3SiBpin is unclear, but it may be due to the presence of complexes in equilibrium with **8** that can react with arenes to form aryl boronate esters. The formation of these complexes may be suppressed in the presence silylborane. Although we have been unable to identify such species, one possibility is the formation of a trisboryl complex by disproportionation of the silyldiboryl complex **8** initiated by reversible reductive elimination of Et_3SiBpin or generation of a highly reactive Ir(I) boryl species by the same reversible reductive elimination of Et_3SiBpin . This trisboryl complex would then react rapidly with an aryl C–H bond.

Investigation of the Turnover-Limiting Step. If oxidative addition of a C–H bond is the turnover-limiting step in the iridium-catalyzed borylation of benzylic C–H bonds with Et_3SiBpin , one would expect to observe (1) a primary kinetic isotope effect (KIE), (2) faster benzylic borylation of electron-deficient methylarenes than of electron-rich methylarenes, and (3) faster rates for the benzylic borylation of methylarenes catalyzed by electron-rich Ir complexes than by electron-poor Ir complexes. Experimental and theoretical studies on the iridium-catalyzed borylation of arenes with B_2pin_2 have shown previously that oxidative addition of an aryl C–H bond is the turnover-limiting step of that process.

The KIE for benzylic borylation was determined by measuring the rate of the catalytic borylation of toluene and toluene- d_8 in separate vessels. In contrast to the large primary isotope effect (5.0) for the iridium-catalyzed borylation of benzene,³⁶ the isotope effect from the independent reactions of toluene and toluene- d_8 with Et_3SiBpin catalyzed by **8** was only 2.2. Although a KIE of 2.2 could imply that C–H oxidative addition is the turnover-limiting step, this value is lower than most KIEs for reactions occurring with rate-limiting C–H bond cleavage.

The effect of the electronic properties of the methylarenes on the cleavage of the benzylic C–H bond was revealed by conducting reactions of a series of *para*-substituted methylarenes with Et_3SiBpin catalyzed by complex **8**. The initial rates for the formation of the benzylic boronate esters was correlated with Hammett substituent constants calculated from the ^{19}F NMR chemical shifts of substituted fluorobenzenes (Figure 7).³⁸ The rho value from this correlation was 2.1. Thus, the rate of borylation of electron-deficient methylarenes is faster than the rate of borylation of electron-rich methylarenes.

The analogous effect of the electronic properties of the arene on the borylation of an aryl C–H bond with Et_3SiBpin as the reagent catalyzed by complex **8** was measured by conducting the borylation of 1,3-disubstituted arenes. The rho value from these studies was 3.3, which is larger than the rho value obtained from the benzylic borylation of methylarenes. This result indicates that the rate of the borylation of aryl C–H bonds is more sensitive to the electronic properties of the arene undergoing functionalization than is the rate of borylation of benzylic C–H bonds. This result explains why the Bn:Ar selectivity for the borylation of electron-poor methylarenes is lower than that for the borylation of electron-rich methylarenes.

The effect of the electron density at iridium on the rate of benzylic and aryl C–H borylation was revealed by conducting the catalytic borylation of 1,3-di-*tert*-butylbenzene and mesitylene with B_2pin_2 or Et_3SiBpin catalyzed by a series of iridium complexes. We conducted these reactions with the four

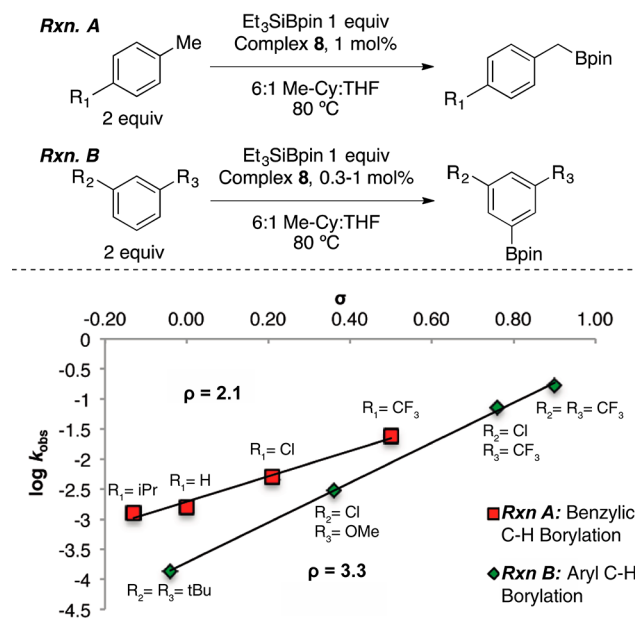


Figure 7. Hammett correlation for the benzylic C–H borylation of *para*-substituted toluenes and the aryl C–H borylation of 1,3-disubstituted arenes. Reactions conducted on a 0.125 mmol scale. The formation of aryl and benzylic boronate esters was monitored by gas chromatography.

iridium catalysts **8**, **18–20**, which are trisboryl complexes (**18** and **20**) and diborylmonosilyl complexes (**8** and **19**) bound by **L6** (**8** and **18**) and by **dtbpy** (**19** and **20**). Trisboryl complexes have been shown previously to be intermediates in the borylation reactions conducted with B_2pin_2 as the boron-containing reagent, and diborylmonosilyl complexes appear to be the active catalysts during borylation reactions conducted with Et_3SiBpin as the boron-containing reagent.

The second-order rate constants for the aryl C–H borylation of 1,3-di-*tert*-butylbenzene and for the benzylic C–H borylation of mesitylene were obtained by the method of initial rates, and the values are given in Table 2. These data show that the rate constants for benzylic borylation vary little with the change in boron source and the electronic properties of the iridium catalyst. In contrast, the rate constants for aryl C–H borylation span nearly 3 orders of magnitude.

From the rate constants for reactions conducted with each combination of catalyst and reagent, we calculated the difference in overall barrier for the borylation of a single benzylic C–H bond of mesitylene and the barrier for the borylation of a single aryl C–H bond of 1,3-di-*tert*-butylbenzene ($\Delta G_{\text{Bn}}^{\ddagger} - \Delta G_{\text{Ar}}^{\ddagger}$). For reactions in which the active catalyst is expected to be an Ir-diboryl monosilyl complex (reagent = Et_3SiBpin , catalyst = **8** or **19**) the borylation of a benzylic C–H bond was preferred over the borylation of an aryl C–H bond. The reactions catalyzed by **8** occurred with the largest preference ($\Delta G_{\text{Bn}}^{\ddagger} - \Delta G_{\text{Ar}}^{\ddagger} = -1.2$ kcal/mol) for reaction at the benzylic C–H bonds over the aryl C–H bonds. However, for reactions in which the active catalyst is expected to be a trisboryl complex (reagent = B_2pin_2 , catalyst = **18** or **20**) the borylation of an aryl C–H bond of 1,3-di-*tert*-butylbenzene is strongly favored over the borylation of a benzylic C–H bond of mesitylene ($\Delta G_{\text{Bn}}^{\ddagger} - \Delta G_{\text{Ar}}^{\ddagger} = +2.2$ – 4.1 kcal/mol).

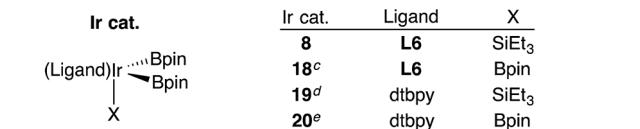
To assess the relative electron density at iridium in complexes **8** and **18–20**, we synthesized the CO adducts **21–24** (Table 3) and measured their ν_{CO} values (in THF).

Table 2. Effect of Different Catalysts on the Rate Constant of Benzylic C–H Borylation and Aryl C–H Borylation^a

Aryl Borylation

Benzylic Borylation

Ir cat./reagent	Aryl Borylation		Benzylic Borylation		$\Delta G_{Bn}^\ddagger - \Delta G_{Ar}^\ddagger$ (corrected for # of C–H bonds)
	k (M ⁻¹ s ⁻¹)	k_{rel}	k (M ⁻¹ s ⁻¹)	k_{rel}	
8/Et ₃ SiBpin	1.36(7) × 10 ⁻⁴	1	6.3(2) × 10 ⁻³	2	-1.2 kcal/mol
18/B ₂ pin ₂	9.2(4) × 10 ⁻³	67	3.4(3) × 10 ⁻³	1.1	+2.2 kcal/mol
19/Et ₃ SiBpin	2.85(4) × 10 ⁻⁴	2.1	3.8(1) × 10 ⁻³	1.2	-0.3 kcal/mol
20/B ₂ pin ₂	1.25(5) × 10 ⁻¹	919	3.2(1) × 10 ⁻³	1	+4.1 kcal/mol



^aReactions were conducted on a 0.125 mmol scale. Formation of aryl and benzylic boronate esters monitored by gas chromatography. ^bReaction conducted with 2 mol % catalyst. ^cFormed *in situ* from **L6** and (η^6 -mes)Ir(Bpin)₃.³⁹ ^dFormed *in situ* from (dtbpy)IrCl(SiEt₃)H and Et₃SiBpin. ^eFormed *in situ* from dtbpy and (η^6 -mes)Ir(Bpin)₃.

Table 3. C–O Stretching Frequencies of Carbonyl-Bound Ir-Trisboryl and Ir-Diborylmonosilyl Complexes^a

Ir-CO	Ir-CO	Ligand	X	ν_{CO} (cm ⁻¹)
	21	L6	SiEt ₃	1985
	22	L6	Bpin	1977
	23	dtbpy	SiEt ₃	1981
	24	dtbpy	Bpin	1972

^aMeasured by solution (THF) IR spectroscopy.

These values indicate that (1) complex **8** is the least electron-rich of the four complexes, (2) dtbpy is more electron donating than **L6**, (3) the Bpin ligand is more donating than the SiEt₃ ligand, and (4) the difference between a silyl ligand and boryl ligand on the metal affected the electron density more than the difference between the dative ligands.

A plot of the $\ln k_{obs}$ for the reactions catalyzed by the corresponding complexes **8** and **18–20** versus the ν_{CO} values for complexes **21–24** is shown in Figure 8. This graph shows that $\ln k_{obs}$ for the borylation of aryl C–H bonds decreases with increasing ν_{CO} , while $\ln k_{obs}$ for benzylic borylation changes little with increasing ν_{CO} . The difference in these trends explains why the ratio of benzylic borylation to aryl borylation for reactions catalyzed by complex **8** is larger than the corresponding ratio for reactions catalyzed by the more electron-rich iridium catalysts. The catalyst containing a less electron-rich metal center undergoes borylation of the aryl C–H bond more slowly than that containing the more electron-rich metal center, but the rate of the borylation of benzylic C–H bonds is not sensitive to the degree of electron density at the

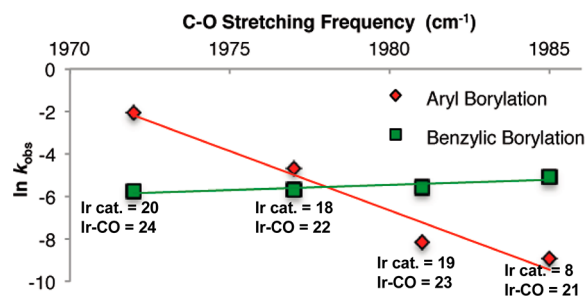


Figure 8. Dependence of the $\ln k_{obs}$ for benzylic and aryl C–H borylation on the electronic properties of the catalyst. Rate constant (k_{obs}) determined for the benzylic C–H borylation of mesitylene and the aryl C–H borylation of 1,3-di-*tert*-butylbenzene catalyzed by complexes **8**, **18–20**. C–O stretching frequency determined for complexes **21–24**.

metal center. The origin of this difference in electronic effects was revealed by DFT calculations.

Investigation of the Turnover-Limiting Step by DFT. Although the KIE and the rho value for benzylic borylation are consistent with turnover-limiting C–H oxidative addition, the lack of an influence of the electron density at Ir on the rate of benzylic borylation argues against turnover-limiting oxidative addition of a C–H bond. Recently, Himo et al. conducted a computational study on the mechanism of the borylation of the C–H bonds in chlorosilanes, and they determined that an isomerization process occurs prior to reductive elimination to form the C–B bond. This isomerization process yields an intermediate that is computed to undergo reductive elimination with a barrier that is lower than that for reductive elimination without isomerization.⁴⁰ This isomerization was computed with the B3LYP-D3 functional to be the turnover-limiting step, but oxidative addition of the C–H bond was computed with the M06 functional to be turnover limiting.

We calculated possible reaction pathways for the borylation of a benzylic C–H bond of toluene with complex **8**. The structures of intermediates and transition states were optimized using the B3LYP functional with Grimme's dispersion correction (B3LYP-D3) with the lan12dz basis set for Ir and the 6-31G(d,p) basis set for all other atoms. Single-point energy calculations with a solvent correction (cyclohexane, IEFPCM) were conducted with the M06 functional with the lan12tz basis set for Ir and the 6-31++G** basis set for all other atoms.⁴¹

We considered two pathways (Figure 9) that begin with diborylsilyl complex **I** and proceed through the transition state for oxidative addition of a benzylic C–H bond **TS-I** to form the seven-coordinate intermediate **II** containing a partial B–H bond. In one pathway (Path A) intermediate **II** reacts through the transition state **TSA-II** for reductive elimination to form the B–C bond in benzyl boronate ester and iridium product **IV**. In a second pathway (Path B) intermediate **II** undergoes isomerization through transition state **TSb-II** in which the hydride is exchanged between the boryl ligands, forming intermediate **III**. Intermediate **III** then undergoes reductive elimination to form the boronate ester and product **IV** through transition state **TSb-III**.

Our calculations predict that Path B is favored over Path A by 3.1 kcal/mol. In Path B, the transition state for isomerization through **TSb-II** prior to reductive elimination (**TSb-III**) is computed to lie at a slightly higher energy than that for the C–H bond cleavage. In contrast to Himo's calculations, our calculations find that the isomerization step is higher in energy

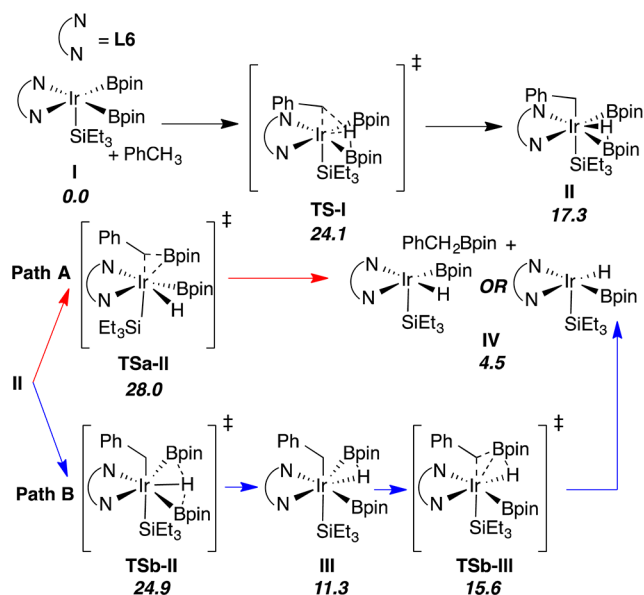


Figure 9. Computed pathways for the benzylic borylation of toluene with complex **8**. Structures optimized at B3LYP-D3 level with lan12dz (Ir) and 6-31G(d,p) basis sets. Single-point energy calculations conducted at M06 level with lan12tz (Ir) and 6-31++G** basis sets and a solvent correction (cyclohexane, IEFFCM). Values given for Gibbs free energy (kcal/mol).

than C–H activation when either the M06 or the B3LYP-D3 functionals are used (see SI, p S56, for B3LYP-D3 energies). To probe these relative energies, we compared our experimental KIE to the theoretical KIE calculated for Path A and Path B (see SI, pp S57–S60). The theoretical KIEs for Path A and Path B were calculated to be 1.5 and 1.8, respectively. Although the difference is small, the isotope effect calculated for Path B is closer to the experimental value of 2.2.

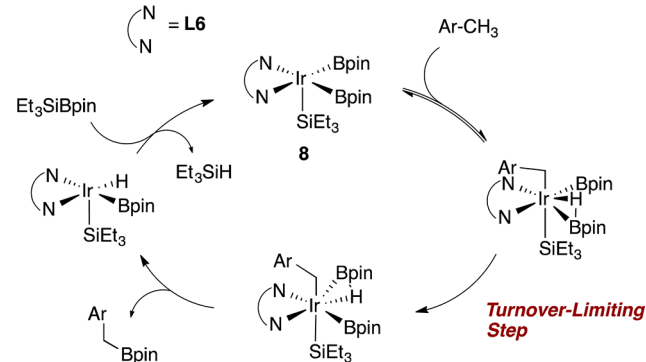
The relative energies of these transition states suggest that the isomerization could be the rate-limiting step of the benzylic borylation. Consistent with this hypothesis, the benzylic borylation is relatively insensitive to changes in electron density at iridium. This electronic effect is consistent with a rate-limiting, redox-neutral isomerization, rather than an oxidative addition of a C–H bond. In contrast, the sensitivity of the aryl C–H borylation to electron density at iridium is consistent with turnover-limiting oxidative addition of the C–H bond. In other words, the effect of the electron density of the Ir catalyst on the selectivity of the reaction is consistent with a difference in the turnover-limiting step of the borylation of aryl C–H bonds and the borylation of benzylic C–H bonds.

Based upon our experimental and computational data, we propose that the benzylic borylation of methylarenes catalyzed by complex **8** occurs via the mechanism detailed in Scheme 5. From the resting state **8**, reversible oxidative addition of a benzylic C–H bond of the methylarene occurs, followed by an irreversible isomerization. Reductive elimination then forms the benzylic boronate ester, and the catalyst is regenerated by reaction with Et_3SiBpin to form the Et_3SiH byproduct.

CONCLUSION

We have shown that the selective borylation of the benzylic C–H bonds of methylarenes can be achieved with Et_3SiBpin as reagent and an iridium catalyst containing a more weakly donating dative ligand than the commonly used di-*tert*-

Scheme 5. Proposed Mechanism for the Benzylic C–H Borylation of Methylarenes with Et_3SiBpin Catalyzed by Complex **8**



butylbipyridine. Unlike previously reported methods for the borylation of benzylic C–H bonds, our method occurs with good functional group tolerance and occurs without the need for a directing group or solvent quantities of the methylarene. The benzylic boronate esters formed during this reaction undergo a series of transformations to form diverse products.

The key to the development of this reaction was the discovery of an iridium diborylmonosilyl complex that is more electron-deficient than the previously reported iridium trisboryl complex for C–H borylation. This reduced electron density at the metal center significantly reduced the rate of aryl C–H borylation while not significantly affecting the rate of benzylic C–H borylation. This difference in effect of electronic properties on the rate of borylation appears to result from a difference between the turnover-limiting step for aryl C–H borylation and benzylic C–H borylation.

The ancillary dative ligand and one of the X-type ligands in the iridium diborylmonosilyl catalyst **8** of the current work are different from those of the iridium trisboryl IMH catalyst **20**. Instead of the strongly electron-donating dtbpy as the ancillary ligand in **20**, a less electron-donating **L6** is the ancillary ligand in catalyst **8**, and instead of three boryl groups in **20**, one less electron-donating triethylsilyl ligand and two boryl ligands are present in catalyst **8**. Both of these differences in the ligands cause the electron density at iridium in complex **8** to be less than that in the IMH catalyst **20**. This difference in electron density gives rise to the ca. 5 kcal/mol difference in the value of $\Delta\Delta G^\ddagger$ for the borylation of the two types of C–H bonds catalyzed by **8** and by **20**.

Our study, as well as those of several recent publications,^{42–45} demonstrates a direction for the design of new iridium catalysts for the borylation of C–H bonds. In the IMH catalyst, boryl ligands are both reactive and ancillary ligands. In the system we report here, one of the ancillary boryl ligands is replaced by a silyl ligand, thereby changing the electronic properties of the metal center for cleavage of the C–H bond. This property leads to novel selectivity for C–H borylation, and we are currently investigating the effect of altering the electronic and steric properties of the ancillary silyl ligand on the selectivity for various classes of C–H bond functionalization reactions.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectra for all new compounds, Cartesian coordinates and energies of calculated ground states

and transition states, crystallographic information, and CIF files. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b04899.

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Notes

The authors declare no competing financial interest.

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