

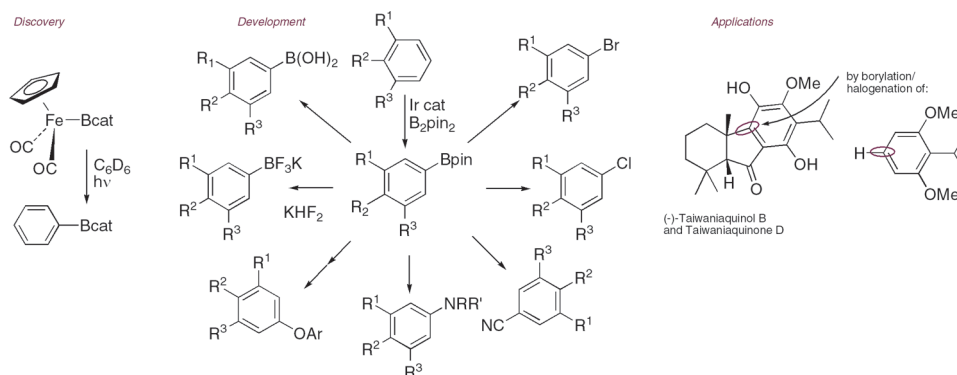
Borylation and Silylation of C–H Bonds: A Platform for Diverse C–H Bond Functionalizations

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CONSPECTUS



Methods that functionalize C–H bonds can lead to new approaches for the synthesis of organic molecules, but to achieve this goal, researchers must develop site-selective reactions that override the inherent reactivity of the substrates. Moreover, reactions are needed that occur with high turnover numbers and with high tolerance for functional groups if the C–H bond functionalization is to be applied to the synthesis of medicines or materials. This Account describes the discovery and development of the C–H bond functionalization of aliphatic and aromatic C–H bonds with borane and silane reagents. The fundamental principles that govern the reactivity of intermediates containing metal–boron bonds are emphasized and how an understanding of the effects of the ligands on this reactivity led us to broaden the scope of main group reagents that react under mild conditions to generate synthetically useful organosilanes is described.

Complexes containing a covalent bond between a transition metal and a three-coordinate boron atom (boryl complexes) are unusually reactive toward the cleavage of typically unreactive C–H bonds. Moreover, this C–H bond cleavage leads to the formation of free, functionalized product by rapid coupling of the hydrocarbonyl and boryl ligands. The initial observation of the borylation of arenes and alkanes in stoichiometric processes led to catalytic systems for the borylation of arenes and alkanes with diboron compounds (diborane(4) reagents) and boranes. In particular, complexes based on the Cp*Rh (in which Cp is the cyclopentadienyl anion) fragment catalyze the borylation of alkanes, arenes, amines, ethers, ketals, and haloalkanes. Although less reactive toward alkyl C–H bonds than the Cp*Rh systems, catalysts generated from the combination of bipyridines and iridium(I)-olefin complexes have proven to be the most reactive catalysts for the borylation of arenes. The reactions catalyzed by these complexes form arylboronates from arenes with site-selectivity for C–H bond cleavage that depends on the steric accessibility of the C–H bonds. These complexes also catalyze the borylation of heteroarenes, and the selectivity for these substrates is more dependent on electronic effects than the borylation of arenes. The products from the borylation of arenes and heteroarenes are suitable for a wide range of subsequent conversions to phenols, arylamines, aryl ethers, aryl nitriles, aryl halides, arylboronic acids, and aryl trifluoroborates.

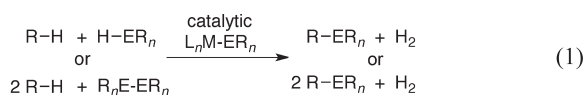
Studies of the electronic properties of the ancillary ligand on the rate of the reaction show that the flat structure and the strong electron-donating property of the bipyridine ligands, along with the strong electron-donating property of the boryl group and the presence of a *p*-orbital on the metal-bound atom, lead to the increased reactivity of the iridium catalysts. Based on this hypothesis, we studied catalysts containing substituted phenanthroline ligands for a series of additional transformations, including the silylation of C–H bonds. A sequence involving the silylation of benzylic alcohols, followed by the dehydrogenative silylation of aromatic C–H bonds, leads to an overall directed silylation of the C–H bond ortho to hydroxyl functionality.

Introduction

The catalytic activation and functionalization of C–H bonds with halogens, deuterium, and oxidizing agents has a long history spanning five decades,¹ but the selective functionalization of C–H bonds in the context of fine chemical synthesis germinated more recently.² Triggered by a serendipitous observation of the borylation of C–H bonds,³ my group has developed the selective functionalization of C–H bonds with main group reagents, focusing predominantly on C–H bond functionalization with boron reagents (eq 1). Because organoboron compounds, as well as organosilicon compounds, are common synthetic intermediates, this C–H bond functionalization chemistry has many potential applications for the synthesis of fine chemicals.

The processes for the functionalization of C–H bonds described in this Account resulted from our interest in understanding the relationships between the reactivity of classic organometallic compounds with metal–carbon bonds and related transition-metal complexes containing metal–heteroatom bonds.⁴ The sets of compounds relevant to this work are those containing bonds between a transition metal and a main group element, particularly compounds containing a covalent bond between a transition metal and a three-coordinate boron atom. Because boron is more electropositive than the metal-bound elements of most ligands and of the late transition metals, and because three-coordinate boron possesses a p-orbital that is available for π bonding with the transition metal or for binding of a substrate, we anticipated that metal–boryl complexes would undergo new transformations with small molecules or would undergo existing transformations by new mechanisms.

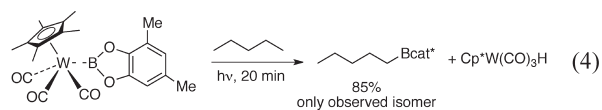
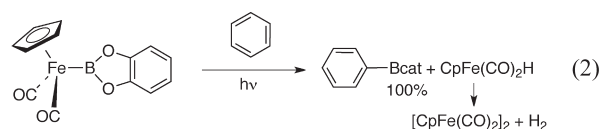
This Account will describe the discovery of the borylation of C–H bonds, the development of this stoichiometric reactivity into a catalytic process, the evolution of catalysts that create a platform for practical aromatic C–H bond functionalization, mechanistic information on these C–H bond functionalization reactions, and the use of this information to create catalysts for new classes of transformations, including mild and selective functionalization of C–H bonds with silicon reagents. The main-group products we form by the C–H bond functionalization are sufficiently stable to be purified by common methods, stored on the benchtop, and carried through a variety of synthetic transformations before the main-group moiety is transformed into the final desired functionalized product.



H-ER_n = boron or silicon hydride reagent, R_nE-ER_n = diborane(4) reagent

Initial Discovery of C–H Borylation in High Yields

Initial studies to probe the reactivity of transition metal–boryl complexes led to the functionalization of aryl C–H bonds. Simple metal–boryl complexes based on the Fp fragment [CpFe(CO)₂] were prepared because of their accessibility through the Fp anion and because of their potential to reveal fundamental properties of the metal–boron bond. While surveying the reactivity of these complexes, we found that FpBcat (cat = catecholate) reacts with benzene under photochemical conditions to generate the phenylboronate ester in quantitative yields (eq 2).³ This C–H activation process differs from typical C–H activation by metal–alkyl and metal–aryl complexes observed at that time.^{5,6} Most previous reactions led to exchanges of alkyl groups between the metal and a hydrocarbon (eq 3). In contrast, the reactions in eq 2 generate free functionalized products and could be part of a catalytic cycle.

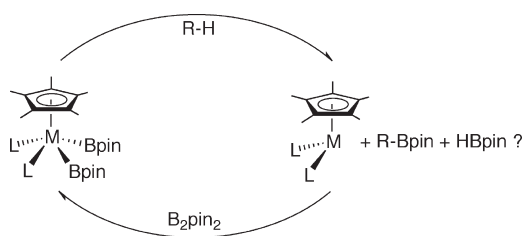


Eliminating or blocking sp²-C–H bonds in the boryl complex and changing from a first-row metal to a third-row metal led to the selective borylation of alkanes (eq 4).⁷ Most striking, the only product from this reaction was the linear alkylboronate ester. In contrast to related reactions of metal–oxo complexes that typically occur at the weaker C–H bonds (and also transfer a ligand to a hydrocarbon),⁸ the borylation process selectively functionalizes the strong primary C–H bond. This observation implies that the reaction occurs through an organometallic intermediate because linear alkyl complexes are typically more stable than branched alkyl complexes.⁹

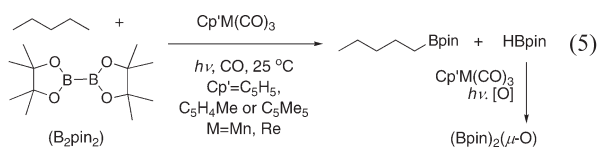
Discovery of Catalytic C–H Borylation in High Yields

To develop this stoichiometric reactivity into a catalytic process, a reagent must be used that allows the metal product to be converted to the starting metal–boryl complex.

SCHEME 1



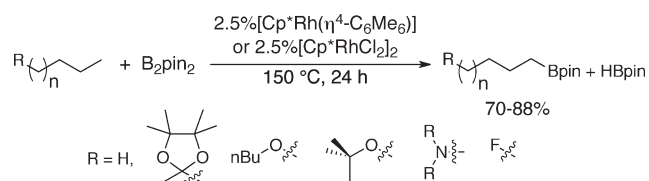
Commercially available reagents of the general formula $(RO)_2B-B(OR)_2$ readily undergo oxidative addition to transition-metal fragments.^{10–12} Thus, a Cp^* -metal complex could add the diboron reagent to generate an intermediate with a structure similar to the complexes we had shown to functionalize alkanes and arenes. A simple catalytic cycle for such a process is shown in Scheme 1. $Cp^*Re(CO)_3$ and $Cp^*Mn(CO)_3$ catalyzed the borylation of alkanes by such a pathway under photochemical conditions. This process was the first catalytic functionalization of an alkane that occurred with high selectivity for the primary C–H bond (eq 5).¹³



To develop a catalyst for thermal borylations of alkanes and arenes, the catalyst must contain a dative ligand that dissociates more readily under thermal conditions than CO dissociates from electron-rich metal centers. Smith reported the borylation of arenes with HBpin catalyzed by $Cp^*Ir(PMe_3)(Ph)(H)$, but this reaction occurred with only three turnovers, even in neat arene at 150 °C for 5 days.¹⁴ The slow rate of this reaction, most likely, results from a similar lack of a labile dative ligand. We considered that hexamethylbenzene in the known¹⁵ $Cp^*Rh(\eta^4-C_6Me_6)$ might dissociate more readily to allow addition of the diboron reagent to generate an intermediate that could functionalize alkanes and arenes in a catalytic cycle.

Indeed, the reaction of an alkane with $B_2(pin)_2$ (pin = pinacolate) catalyzed by 2.5 mol % $Cp^*Rh(\eta^4-C_6Me_6)$ formed alkylboronate esters in high yields with perfect selectivity for reaction at the primary C–H bond (Scheme 2).¹⁶ The commercially available and air-stable complex $[Cp^*RhCl_2]_2$ also catalyzes the functionalization of alkanes with the same selectivity.^{17,18} This result implies that both reactions occur through the same intermediate. The hexamethylbenzene

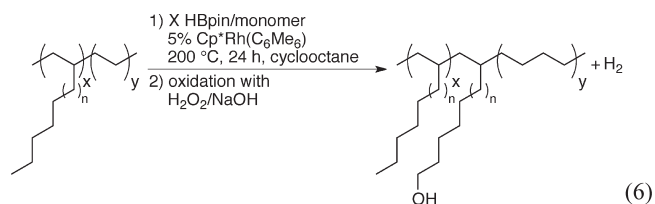
SCHEME 2



complex is more soluble and more reactive, but both species do catalyze the borylation of alkanes.

Further progress is needed to develop the borylation of aliphatic C–H bonds into a synthetic method because these reactions require high temperatures and occur in lower yields when conducted with stoichiometric amounts of substrate in an inert solvent.¹⁷ However, this rhodium catalyst is selective for the functionalization of the least sterically hindered primary C–H bond in a range of acetals, ethers, amines, and alkyl fluorides.¹⁷ In contrast to many other catalytic C–H bond functionalizations, this C–H bond functionalization is less reactive toward the C–H bonds alpha to the oxygen of an ether or the nitrogen of an amine than toward primary C–H bonds. Moreover, the C–H bonds in a *t*-butyl group or in a pinacol acetal were much less reactive than the primary C–H bonds of an alkyl chain. No product was detected from functionalization of the C–H bonds alpha to even a small, terminal fluoride.

The stability of the catalyst at high temperatures was exploited for the functionalization of polyolefins.^{19–21} Reaction of B_2pin_2 and HBpin with poly(propylene), poly(butene), and poly(ethylene-co-octene) led to the selective borylation of a fraction of the primary C–H bonds.^{19–21} A typical oxidative workup led to the hydroxymethyl-functionalized polyolefins (eq 6). This process occurred on scales sufficiently large to evaluate the materials properties and to grow graft copolymers.²⁰



Borylation of Aromatic C–H Bonds

Because the selectivity of the borylation of aliphatic C–H bonds suggests the intermediacy of organometallic species, and because C–H activation to generate metal–aryl complexes is typically faster than C–H activation to form metal–alkyl complexes,²² the borylation of aryl and heteroaryl

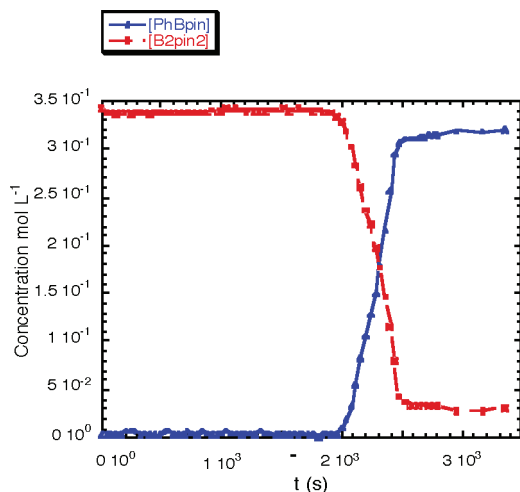
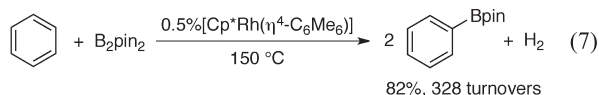
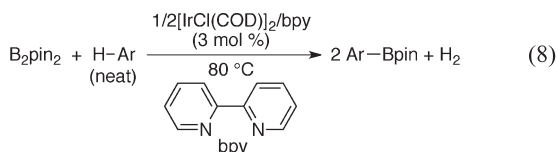


FIGURE 1. Profile of the decay of B_2pin_2 and appearance of $ArBpin$ from the reaction of B_2pin_2 with neat benzene at 80 °C catalyzed by 3 mol % $[Ir(COD)Cl]_2$ and 6 mol % bpy .

C–H bonds should occur faster, with higher turnover numbers, and with a greater tolerance of functional groups than the borylation of alkyl C–H bonds. Indeed, $Cp^*Rh(\eta^4-C_6Me_6)$ catalyzed the borylation of benzene solvent to generate $PhBpin$ in high yield and with >300 turnovers (eq 7).¹⁶ The temperature at which the rhodium-boryl intermediate reacts with arenes is lower than the temperature at which the same intermediate reacts with alkanes,²³ but it was still too high for the borylation to tolerate a wide range of functional groups.



The development of an iridium catalyst for the borylation of arenes resolved many of these issues.²⁴ We conducted studies in collaboration with Ishiyama, Miyaura and coworkers on iridium catalysts containing bipyridine ligands. This work was conducted contemporaneously with studies by Smith, Maleczka, and coworkers on catalysts containing bisphosphine ligands.²⁵ The catalysts containing heteroaromatic nitrogen ligands have proven to be more reactive (eq 8).



However, the original reactions catalyzed by Ir - bpy complexes were capricious. As shown by the data in Figure 1 obtained over 1 h,²⁴ the actual catalysis occurred in just a

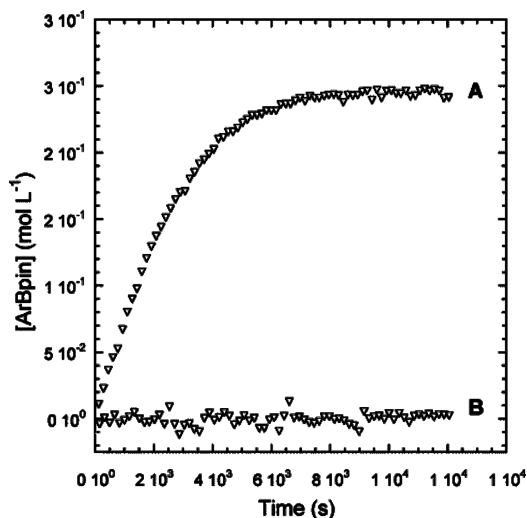


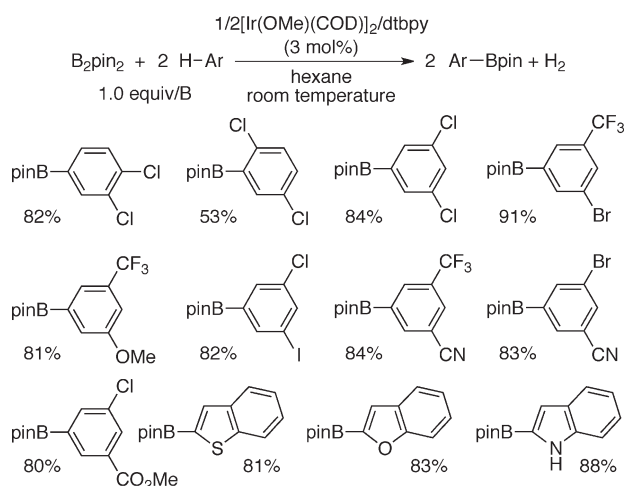
FIGURE 2. Profile of the reaction of B_2pin_2 with 1,2-dichlorobenzene in cyclohexane- d_{12} at 25 °C catalyzed by 5% $[Ir(COD)Cl]_2$ and 10% $dtbpy$ (relative to arene) initiated with 20 mol % of $HBpin$, relative to arene (curve A) and initiated without added $HBpin$ (curve B).

few minutes. Most of the reaction time involved generation of the active catalyst. If the active catalyst were used directly or generated rapidly in high yield, the catalytic reaction might occur with a 1:1 ratio of boron to arene, rather than with a large excess of arene, under milder conditions with low catalyst loadings.

We initially showed that the reduction of the cyclooctadiene ligand to cyclooctene generated a more active catalyst.²⁴ Later, we determined that the generation of pinacolborane from the diboron compound (by an unknown mechanism at the beginning of the reaction) led to the active catalyst.²⁶ Once a small portion of catalyst is generated, the reaction of the diboron compound with the arene generates more pinacolborane, and additional amounts of catalyst are generated. The effect of the borane on the generation of the active catalyst can be deduced from the reaction profile in Figure 2.²⁶ A smooth exponential appearance of product is observed at room temperature with a 1:1 ratio of boron to arene in the inert solvent cyclohexane for the reaction initiated with 20 mol % of added pinacolborane, but no reaction is observed under these conditions without added borane.

After several modifications of the iridium precursor and ligand, we found that the catalytic process could be conducted with a 1:1 ratio of boron to arene at room temperature in an inert solvent catalyzed by 4,4'-di-*tert*-butylbipyridine and $[Ir(COD)(OMe)]_2$.²⁷ As will be noted later, the yield of the active catalyst is higher when generated from $[Ir(COD)(OMe)]_2$ than when generated from $[Ir(COD)Cl]_2$, and

SCHEME 3

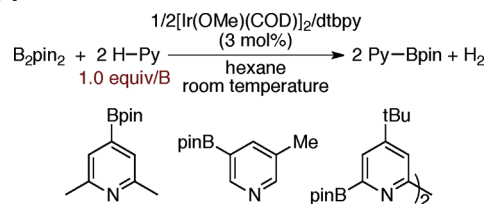


this higher yield is likely the origin of the increased reactivity under mild conditions with the methoxide precursor. Originally, we used *tert*-butyl-substituted bipyridine as ligand, instead of pyridine, to improve solubility of the catalyst in hydrocarbon solvents and to prevent borylation of the ligand. However, the electronic effect of the *tert*-butyl groups on the bipyridine ligand promotes the C–H bond functionalization process,²⁸ as will be described later in this Account.

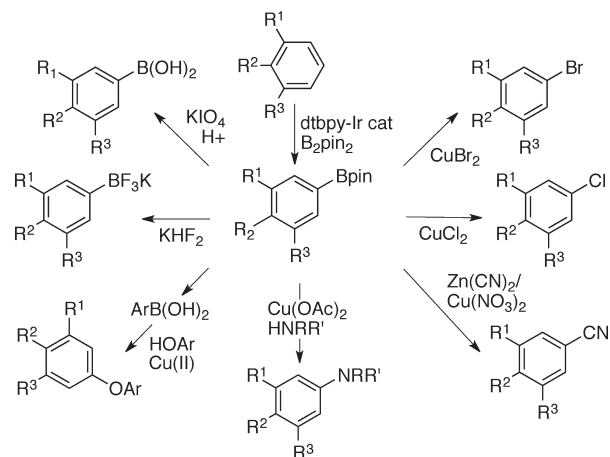
With this catalyst, the borylation of aromatic C–H bonds occurs with regioselectivity that is controlled by steric effects (Scheme 3). Reactions of symmetrically substituted 1,2- and 1,4-substituted arenes form a single product. Reactions of symmetrical or unsymmetrical 1,3-substituted arenes also lead to a single product because a single C–H bond is more sterically accessible than the others. These reactions occur in high yield with arenes containing substituents possessing potentially reactive functionality; they occur selectively at a carbon–hydrogen bond over a carbon–halogen bond, and they tolerate typical organic functional groups, such as nitriles and esters.^{27,29}

In contrast to the site-selectivity for the borylation of arenes, the site-selectivity for the borylation of heteroarenes is largely controlled by electronic effects.^{29–31} Furans, pyrroles, and thiophenes undergo reaction at the C–H bond alpha to the heteroatom. Reactions of benzo-fused heterocycles occur at the C–H bond alpha to the heteroatoms, without competing reaction at the aromatic ring. If the alpha positions are substituted, then the borylation occurs at the C–H bond beta to the heteroatom. The selectivity for reaction at a nitrogen heterocycle can be modified by steric effects: a large substituent on nitrogen causes the reaction to occur at the C–H bond beta to nitrogen.^{30,32} The selectivity

SCHEME 4



SCHEME 5



for the borylation of pyridines is distinct from that for five-membered ring heterocycles and arenes. For reasons that have not yet been elucidated, the borylation of pyridines occurs preferentially at the positions beta and gamma to nitrogen (Scheme 4).^{33,34} If the pyridine contains a substituent at the 3-position, the borylation occurs at the 5-position, and if the pyridine is 2,6-disubstituted, then the reaction occurs at the 4-position. If bipyridine contains a large substituent at the 4-position, then borylation occurs at the 2-position.

Creation of a Platform for Aryl C–H Bond Functionalization

The convenience of handling of the aryl boronate esters and diverse reactivity of the arylboronic acid analogues motivated us to develop processes involving C–H borylation, followed by derivatization of the arylboronate esters. By this sequence, a single type of C–H bond functionalization creates a platform for a range of aromatic C–H bond functionalizations (Scheme 5). Clearly, the products from the borylation of aromatic C–H bonds can be used as reagents for Suzuki–Miyaura cross coupling,³⁵ and the combination of borylation and oxidation has been shown to generate phenols from arenes.³⁶ However, we sought to develop sequences in which the combination of C–H borylation

and less traditional conversions of arylboronate esters generate functionalized products.

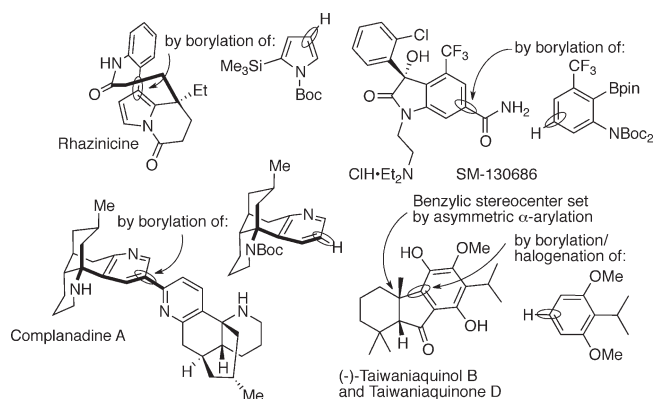
In one case, we showed that iridium-catalyzed arene borylations, followed by halogenation of the initial organoboronate product with cupric bromide,³⁷ formed aryl bromides.³³ This sequence constitutes a sterically controlled halogenation of an arene that complements the electronically controlled halogenation of arenes by electrophilic aromatic substitution. Published examples of this process show that halogens, carboalkoxyl, and cyano groups are tolerated by the two-step sequence. These examples also showed that the combined steric and electronic control of the reactions of pyridines³⁸ can lead to selective functionalizations. Related chlorinations were achieved with cupric chloride and demonstrated a tolerance for amides and both pivalate- and TIPS-protected phenols. Finally, Ritter and Furuya reported the formation of aryl fluorides by converting the aryl pinacolboronate to the arylboronic acid by a method described below, and then converting the arylboronic acid to the aryl fluoride by a silver-mediated process.³⁹

More common derivatizations of arylboronates include the amination and etherification initially reported by Lam, Chan, and Evans.⁴⁰ We extended the Lam–Chan functionalization of arylboronate esters to the functionalization of the pinacol boronate esters resulting from C–H borylation. Although the scope of the amination of the pinacolboronate esters is not as broad as that for the amination of arylboronic acids, we did identify conditions suitable for conducting a one-pot sequence involving borylation and amination. This sequence constitutes a sterically controlled amination of an aromatic C–H bond.⁴¹ Related sequences to form aryl ethers via the C–H borylation were also developed, but required the generation of the boronic acids as an intermediate.⁴¹

Most recently, we developed a protocol to convert pinacol boronate esters to aromatic nitriles. This reaction makes possible a one-pot synthesis of aromatic nitriles from arenes by the combination of iridium-catalyzed borylation, followed by cyanation of the arylboronate ester.⁴² Again, the regioselectivity of the overall process is controlled by steric effects that dictate the regioselectivity of the C–H borylation step.

Although the pinacolboronate esters are convenient to use because they are stable toward air and chromatography, a similar process that generates more reactive boronic acids or trifluoroborates would be desirable. A one-pot protocol for the generation of a boronic acid via the C–H bond functionalization chemistry was achieved⁴³ by iridium-catalyzed borylation, followed by an oxidative hydrolysis of the pinacol boronate ester with added periodate.^{44,45} The

CHART 1



added oxidant had been reported^{44,45} to allow the thermodynamically unfavorable hydrolysis of pinacolboronate esters by consuming free pinacol. A simple process for generating the trifluoroborates was achieved by the sequence of C–H borylation, followed by addition of excess KHF_2 to the pinacolboronate ester.⁴³ Further derivatizations that exploit this C–H activation reaction certainly will be developed.

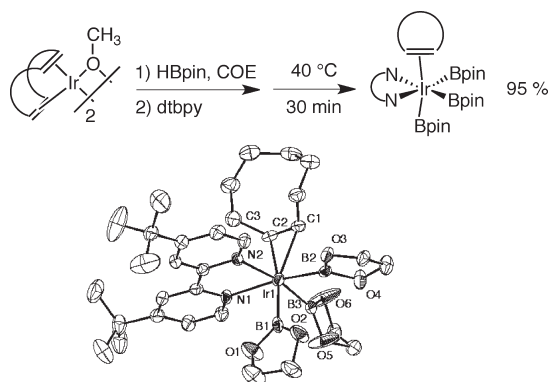
Applications of the C–H Borylation

Many other groups have now used C–H borylation catalyzed by iridium and dtbpy. Space does not permit a detailed description of each of these applications, but a comprehensive presentation of this work has been published recently.⁴⁶ Attesting to the versatility of the borylation of arenes, this reaction has been used to synthesize natural products and active pharmaceutical ingredients (Chart 1). Gaunt and co-workers reported the synthesis of rhazinicine initiated by the borylation of an N-Boc-pyrrole derivative at the 3 position,³² and Sarpong and Fischer exploited the selectivity for the borylation of pyridine beta to nitrogen when preparing a pyridylboronate acid for the key coupling reaction to form complanadine A.⁴⁷ Shibasaki et al. reported the synthesis of SM-130686 by the borylation of a 1,2,3-trisubstituted arene and subsequent conversion of the aryl boron unit to a primary amide.⁴⁸ Finally, our group prepared two members of the Taiwaniaquinoid family of natural products by the combination of C–H borylation and halogenation to generate an aryl halide that was used for a palladium-catalyzed asymmetric α -arylation.⁴⁹

Mechanism of the C–H Borylation of Arenes

Studies of the mechanism of the borylation of arenes revealed key intermediates and elucidated the factors that control reaction rates. The complex that reacts with arenes

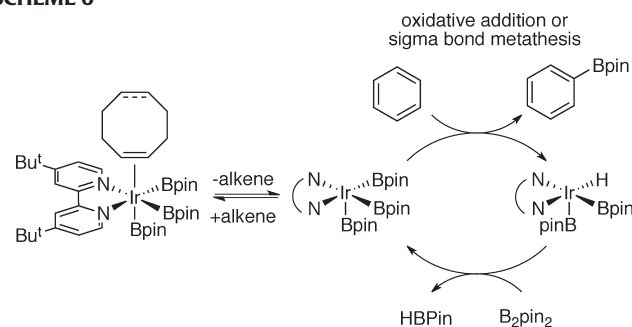
contains three pinacolboranyl ligands and one 4,4'-di-*tert*-butyl-bipyridine. The alkene adduct $[\text{Ir}(\text{dtbpy})(\text{Bpin})_3(\text{alkene})]$ (alkene = cyclooctene, cyclocadiene, or derivatives of them) of this fragment has been isolated and is observed in the catalytic system.^{24,26} $[\text{Ir}(\text{dtbpy})(\text{Bpin})_3(\text{COE})]$ was isolated initially, in low yield, from $[\text{Ir}(\text{COD})\text{Cl}]_2$, COE, and B_2pin_2 , and its structure was determined by X-ray diffraction.²⁴ Later, this complex was prepared in high yield by the reaction of $[\text{Ir}(\text{COD})(\text{OMe})_2]$ with HBpin and an excess of cyclooctene, followed by the addition of di-*tert*-butyl-bipyridine and slight warming (eq 9).²⁶ $[\text{Ir}(\text{dtbpy})(\text{Bpin})_3(\text{alkene})]$ does not form in high yield from the same reaction with B_2pin_2 in place of HBpin. This difference in yield of the active catalyst from B_2pin_2 and HBpin is the origin of the shorter induction period when the reaction is started with some added pinacolborane (*vide supra*).



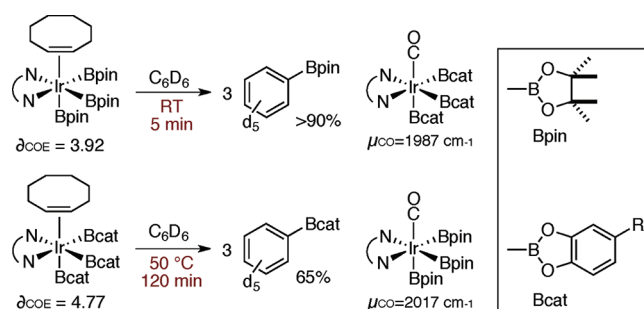
The isolated trisboryl complex reacts with arenes to generate aryl boronate esters.²⁶ In neat benzene, this reaction is rapid. Reactions of the trisboryl complex with a mixture of benzene and benzene-*d*₆ and parallel reactions of benzene and benzene-*d*₆ in cyclohexane occur with similar primary isotope effects. The catalytic process run in cyclohexane is first-order in arene and occurs with a primary KIE that is similar to that of the single turnover. Thus, C–H bond cleavage is the turnover-limiting step of the catalytic cycle. The catalytic and stoichiometric reactions were inhibited by added COE, indicating that dissociation of COE occurs prior to C–H bond cleavage, and reactions with labeled B_2pin_2 showed that the trisboryl intermediate resulting from dissociation of COE reacts with arene, not an Ir(I) species that could form by reductive elimination of B_2pin_2 .

A simple mechanism for the borylation of arenes catalyzed by $[\text{Ir}(\text{dtbpy})(\text{Bpin})_3(\text{alkene})]$ is shown in Scheme 6. Reversible dissociation of alkene from $[\text{Ir}(\text{dtbpy})(\text{Bpin})_3(\text{alkene})]$ forms the active 16-electron species. This species reacts with the arene to form the arylboronate ester and an iridium hydride product. This iridium hydride would then

SCHEME 6



SCHEME 7



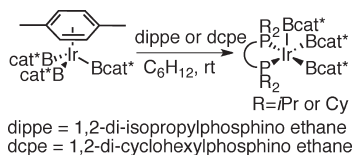
react with the B_2pin_2 to form HBpin and regenerate the trisboryl complex. Computational studies by Sakaki et al. suggest that the C–H bond is cleaved to form an iridium(V) trisboryl aryl hydride intermediate that undergoes rapid reductive elimination of the arylboronate ester.⁵⁰

Further Catalyst Development

Information on the effect of the substituents at boron and the ancillary ligand on the turnover-limiting C–H activation step would provide a foundation for the development of additional classes of C–H bond functionalizations. As shown in Scheme 7, the trisboryl complexes containing pinacolate and catechol groups on boron react with significantly different rates and yields.²⁸ The pinacolboryl complex reacts much faster and in higher yields than the catecholboryl complex. The CO infrared stretching frequencies of the respective carbon monoxide adducts show that the complex containing the pinacolboryl groups is significantly more electron rich than that containing catecholboryl groups. Thus, the more electron rich of the two iridium complexes undergoes C–H bond cleavage faster, a trend which is consistent with activation of the C–H bond by a mechanism closely related to oxidative addition to generate an iridium(V) intermediate.

To develop more active catalysts, we evaluated the electronic properties of potential ancillary ligands. As noted

previously, the iridium catalysts ligated by phosphines are less reactive than those ligated by bipyridines. Our group and Smith's group reported the synthesis and structural characterization of phosphine-ligated trisboryl complexes (eq 10).^{28,51} Complexes of cyclohexyl and isopropyl phosphines are five-coordinate and lack the alkene ligand, presumably due to the steric demand of the phosphine and the weak binding of alkenes to the higher-valent iridium(III). Although it contains an open coordination site, the bisphosphine analogues of the bipyridine complexes react much more slowly with arenes than do the bipyridine complexes. This low reactivity is presumably due, in part, to the steric congestion at the open coordination site.



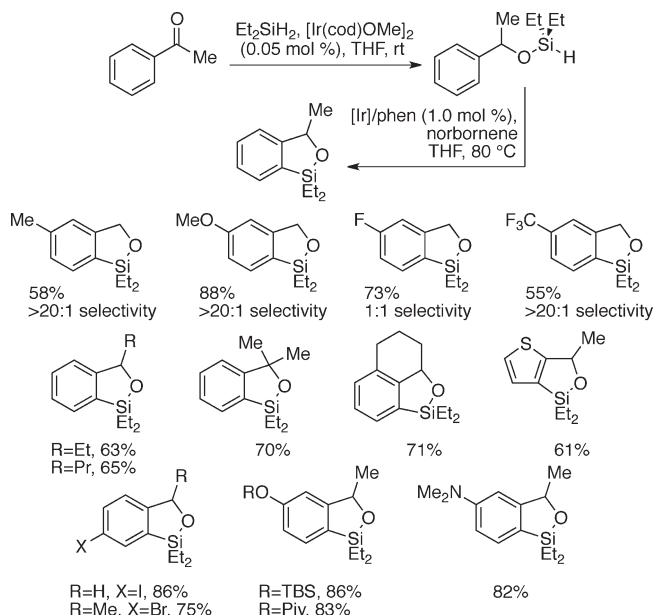
However, electronic effects likely contribute to the large difference in reactivity of bisphosphine and bipyridine complexes. Analysis of previously reported stretching frequencies of nickel–carbonyl compounds containing bipyridine⁵² and phosphine⁵³ ligands shows that the nickel–carbonyl adduct of bipyridine is more electron rich than nickel–carbonyl adducts of phosphine ligands, and the complex of 4,4-dimethyl-bipyridine is even more electron rich than that of the parent bipyridine. Thus, we surmised that the flat structure of the bipyridine, the strong electron-donating property of bipyridine, and the electron-donating property of the *tert*-butyl groups in dtbpy all contribute to the high activity of the Ir-dtbpy catalyst.

Iridium-Catalyzed Silylation of Arenes

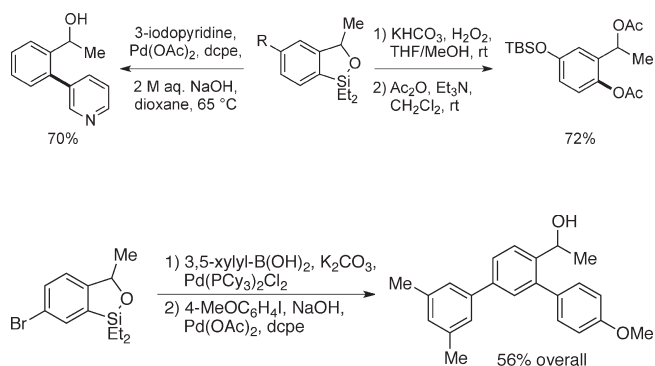
With this information about the electronic effects on the borylation reaction, we are developing catalysts that enable new classes of C–H bond functionalization with main group reagents. This information has led us to expand the scope of these reactions to the silylation of arenes. Silanes would be valuable reagents for the functionalization of aromatic and aliphatic C–H bonds for several reasons. First, they are less expensive and typically more stable than borane reagents. Second, cross couplings and oxidations of organosilane reagents can be conducted when the arylsilane contains a silicon–heteroatom bond.^{54–56} Third, one can envision directed silylation in which a silane docks at the oxygen of an alcohol.

Following this strategy, we developed intramolecular silylation of the C–H bond ortho to a benzylic alcohol to

SCHEME 8



generate benzoxasiloles.⁵⁷ As shown in Scheme 8, we generated the silyl ether from a dihydrosilane and an alcohol or ketone and cyclization of the silyl ether generates oxasilole products. Like the intermolecular borylation of aromatic C–H bonds, this intramolecular silylation is largely controlled by steric effects. An electron-donating substituent or an electron-withdrawing substituent at the 3-position of the aryl ring leads to reaction at the 6-position, whereas reaction of the 3-fluoro substrate leads to a 1:1 mixture of products. These reactions also tolerate auxiliary functionality, such as an aryl iodide or an aryl bromide, and they tolerate alcohols protected as the TIPS ether or pivalate ester. The silylation process occurs with benzylic silyl ethers derived from secondary alcohols or tertiary alcohols. It even occurs to form tricyclic benzoxasiloles and heteroaromatic analogues.



Because the products of the C–H bond functionalization process contain a Si–O bond, they are suitable for further

derivatization. The products undergo Hiyama coupling under conditions closely related to those developed by Denmark and Sweis to generate the biaryl product.⁵⁸ They also undergo Tamao–Fleming oxidation to generate the phenol,⁵⁵ which was acetylated prior to isolation. Because different bases are used for Suzuki and Hiyama coupling, Suzuki coupling of an auxiliary aryl halide can be conducted prior to Hiyama coupling at the carbon–silicon bond to form a triaryl product in good overall yield. Further studies on the silylation of sp^2 -hybridized C–H bonds with this catalyst and silylations of aliphatic C–H bonds are in progress.

Conclusions

Several properties of metal–boryl complexes lead to C–H bond functionalizations. First, because a B–C bond is stronger than a B–H or B–B bond,⁵⁹ the reaction of an alkane or arene with a borane or diborane(4) reagent is exothermic by 3–4 kcal/mol and ca. 20 kcal/mol, respectively. The thermodynamic properties of this reaction contrast with those of reactions with substrates containing an X–H bond in which X is electronegative. For example, a simple analysis of bond energies⁶⁰ shows that the reaction of an alkane with water to form an alcohol and hydrogen is thermodynamically unfavorable by 20–30 kcal/mol. Second, the strong σ -donation due to the electropositive property of the boron in the boryl ligand and the presence of the p-orbital lead to a low barrier for the C–H bond cleavage step.

Computational studies^{23,61} on the reactions of methane and higher alkanes with the iron, tungsten, and rhodium systems described in this Account suggest that these complexes react with alkanes by a mechanism related to σ -bond metathesis to form a borane complex. However, computational work on the C–H bond cleavage of arenes by an analogue of $[\text{Ir}(\text{dtbpy})(\text{Bpin})_3]$ implies that C–H bond cleavage by this system is closer to an oxidative addition than a σ -bond metathesis.⁵⁰

Perhaps most important, C–H bond cleavage is followed by rapid functionalization of the alkyl or aryl group. Coupling of the boryl and alkyl or aryl ligands is fast, in part, because the functionalizing group is bound to the metal when the C–H bond is cleaved. Moreover, the planarity at boron of the boryl unit and the electropositive property of the boron center appear to lead to rapid coupling to form a carbon–boron bond. The barrier for reductive elimination from the aryliridium(V) intermediate containing a boryl group was calculated to be only 3–4 kcal/mol.⁵⁰

Whether these principles translate directly to the silylation of C–H bonds is unknown. However, silane sigma

complexes are stable,⁶² making a related mechanism for C–H activation that generates a silane intermediate feasible. Moreover, reductive eliminations to form carbon–silicon bonds from organylmetal silane complexes are known.^{63,64} New catalysts and methods based on these fundamental principles will be the subject of future studies in our laboratory.

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BIOGRAPHICAL INFORMATION

John Hartwig was raised near Schenectady, New York, received his A.B. from Princeton University conducting research with Maitland Jones, obtained his Ph.D. from U.C. Berkeley with Bob Bergman and Richard Andersen, and conducted a postdoctoral fellowship at MIT with Stephen Lippard. In 1992, he began his independent career at Yale University and became the Irenée P. DuPont Professor in 2004. In 2006, he moved to the University of Illinois where he was the Kenneth L. Rinehart Jr. Professor of Chemistry. During the summer of 2011, he returned to U.C. Berkeley in the Henry Rapoport Chair. In addition to C–H bond functionalization with main group reagents, he is well-known for contributions to cross-coupling chemistry. He recently published the text “Organotransition Metal Chemistry: From Bonding to Catalysis.”

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