C−H Activation for the Construction of C−B Bonds

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1. Introduction

A long-standing challenge in synthetic chemistry is the direct, selective functionalization of alkyl, alkenyl, and aryl C−H bonds. Much research has been devoted to the selective oxidation of alkyl C−H bonds, but the development of a catalyst for the conversion of methane to methanol, for example, remains an important, unsolved problem in catalysis.[1] Several groups have made great progress toward selective conversions of aryl C−H bonds to C−C, C−O, C−N, and C−X (X = F, Cl, Br, and I) bonds,[2,3] and several groups have made progress toward the conversion of alkyl C−H bonds to C−C, C−O, and C═C bonds.[4,5] In contrast, the direct conversion of C−H bonds to C−B bonds is a more recently developed class of metal-catalyzed C−H bond functionalization. Significant progress has been made toward the development of systems that catalyze such borylation reactions of C−H bonds in alkanes, alkenes, and arenes in high yields and with high selectivity. In a period of about one and one-half decades, this reaction has developed from curious stoichiometric reactions of transition metal−boryl complexes to a synthetic method now being studied by several groups and being used by synthetic chemists in the fields of materials science, fine chemical synthesis, and natural product synthesis.

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Ibraheem Mkhalid was born in Jeddah, Saudi Arabia, in 1976. He received his B.Sc. from King Abdul Aziz University (1999) and his Ph.D. from Durham University (2006) for work on transition metal catalyzed borylation of C−H bonds carried out under the supervision of Professor Todd B. Marder. In 2006, he returned to King Abdul Aziz University as Assistant Professor in the Chemistry Department and has served as Deputy Dean of the English Language Institute at the same University.

Jonathan H. Barnard was born in Coalville, Leicestershire, United Kingdom, in 1982. He received his undergraduate degree (M.Sc. in Chemistry) from Durham University in 2005. He is currently completing a Ph.D. under the supervision of Prof. Todd Marder and Dr. Andrew Whiting at Durham University, studying the development of transition metal-catalyzed C−H borylation reactions and applications of these and cross-coupling reactions to the synthesis of biologically active retinoids for use as triggers of stem cell differentiation.

Todd Marder received his B.Sc. in Chemistry from M.I.T. (1976) where he worked with Professor A. Davison, and his Ph.D. from the University of California at Los Angeles (1981), where he was a University of California Regents Intern Fellow working with Professor M. F. Hawthorne. Following postdoctoral research with Professor F. G. A. Stone at the University of Bristol in England, he spent two years as a Visiting Research Scientist at DuPont Central Research in Wilmington, DE, where he developed one of the first catalytic processes for the intermolecular hydroacylation of alkenes. He joined the faculty at the University of Waterloo in Canada in 1985, and in 1995 was the recipient of the Rutherford Memorial Medal for Chemistry of the Royal Society of Canada. He moved to the University of Durham in England in 1997 to take a Chair in Inorganic Chemistry. He has carried out pioneering studies on metal boryl complexes and diboron reagents, and their role in catalyzed borylation processes, often involving fruitful collaborations with Tom Baker (then at DuPont), Nick Norman (Newcastle and Bristol Universities), and Zhenyang Lin (Hong Kong University of Science and Technology), and on the use of 3-coordinate boron as a p-acceptor in nonlinear optical materials. In 2008, he was the recipient of the Royal Society of Chemistry Award in Main Group Element Chemistry. He has held Visiting Professorships in the UK, France, Hong Kong and Japan, and holds an Adjunct Professorship in Chemistry at the Hong Kong University of Science and Technology, and an Honorary Professorship at Newcastle University through the North-East England Stem Cell Institute. He has published over 225 papers and presented over 275 invited lectures worldwide. His diverse research interests include synthesis, structure, bonding and reactivity of organometallic and metal-boron compounds, homogeneous catalysis, small molecule triggers of stem cell differentiation, luminescence, nonlinear optics, liquid crystals, and crystal engineering.

Jaclyn Murphy received her Bachelors of Science degree in chemistry from the University of Massachusetts, Amherst, in 2004. In 2009, she earned her Ph.D. from Yale University under the guidance of Professor John F. Hartwig, studying the development of transition metal catalysts for the borylation of alkanes and arenes. She is currently a NIH postdoctoral fellow in the laboratory of Professor Gregory C. Fu at the Massachusetts Institute of Technology. In her spare time, Jaclyn enjoys reading, listening to music, and playing sports.

The conversion of C−H bonds to C−B bonds is both thermodynamically and kinetically favorable. On the basis of calculated bond energies for methylboronates and dioxaborolanes, the reaction at a primary C−H bond of methane or a higher alkane with $B_2(OR)_4$ to form an alkylboronate ester R′-$B(OR)_2$ and the accompanying borane H−$B(OR)_2$ is thermodynamically downhill. The reaction of the primary C−H bond of methane with $HB(OR_2)_2$ to form an alkylboronate ester R′-$B(OR)_2$ and H_2 is approximately thermoneutral (Scheme 1). The B−C bond energy of a higher alkylboronate than a methylboronate has not been calculated, but the thermodynamics for reactions with higher alkanes are presumably similar to those with methane.[6,7]

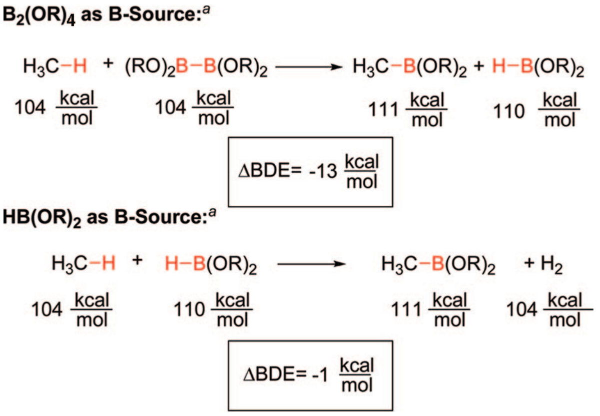
The rates of key steps along the reaction pathway for the conversion of a C−H bond in an alkane or arene to the C−B bond in an alkyl or arylboronate ester are also favorable. The accessible barriers for C−H bond cleavage and B−C bond formation during the borylation of alkanes and arenes, as will be discussed in this review, are attributed to the combination of the strong σ-donor properties of the boryl group, and the presence of an unoccupied p_z-orbital on boron in a boryl complex. The presence of a low-energy LUMO (lowest unoccupied molecular orbital) on the boryl ligand due to the p_z-orbital stabilizes the transition state for C−H bond cleavage,

John F. Hartwig is the Kenneth L. Rinehart Professor of Chemistry at the University of Illinois, Urbana−Champaign. Professor Hartwig received his A.B. degree from Princeton in 1986 and his Ph.D. from the University of California, Berkeley, in 1990. Subsequently, he was an American Cancer Society Postdoctoral Fellow at the Massachusetts Institute of Technology and joined the Yale University faculty in 1992. Dr. Hartwig joined the University of Illinois chemistry faculty in July 2006. Professor Hartwig's research focuses on the discovery and mechanistic understanding of organic reactions catalyzed by organometallic complexes. He was one of the originators of palladium-catalyzed cross-coupling reactions to form carbon−heteroatom bonds, palladium catalyzed coupling of enolates, the functionalization of C−H bonds with boron reagents, asymmetric iridium-catalyzed allylic substitution, and a variety of catalysts for olefin hydroamination. He was recently the recipient of the 2009 Mitsui Catalysis Award, the 2008 Mukaiyama Award from the Society of Synthetic Organic Chemistry, Japan, the 2008 International Catalysis Award from the International Association of Catalysis Societies, the 2008 Paul N. Rylander Award of the Organic Reactions Catalysis Society, the 2007 Tetrahedron Young Investigator Award in Organic Synthesis, the 2007 Raymond and Beverly Sackler Prize in the Physical Sciences, and the 2006 ACS Award in Organometallic Chemistry. His new organometallic textbook, "Organotransition Metal Chemistry: From Bonding to Catalysis", will appear this fall. In his spare time, he enjoys cooking, the outdoors, and making his two daughters Amelia and Pauline laugh.

the basicity of boron helps to deprotonate the acidic alkane σ-complex, and the electrophilicity of the p_z-orbital at boron matches with the nucleophilicity of the hydrocarbyl ligand to allow facile coupling of the hydrocarbyl and boryl group to form the B−C bond in the final product.[8,9] The borylation of C−H bonds in alkenes, in most cases, occurs by a different pathway in which the C−H bond is cleaved by β-hydrogen elimination reactions.

Selective C−H bond functionalization has been called one of the "holy grails" of chemistry,[10] and perhaps one of the most difficult problems in C−H functionalization is the selective functionalization of the primary C−H bonds in alkanes.[4,5,11] Primary C−H bonds are stronger than secondary or tertiary C−H bonds, and most uncatalyzed functionalizations of alkanes, such as halogenations and autoxidations, occur at the internal positions of alkanes. Because the products of alkane functionalization are generally more reactive than alkanes, subsequent functionalizations, such as multiple halogenations or combustion of alkanes, are a common problem.[12] The first catalytic functionalizations of alkanes selectively at the terminal position by small-molecule catalysts were the rhenium catalyzed and rhodium catalyzed borylations of alkanes reported by Hartwig and co-workers described in this review.[13,14] In contrast to enzymatic oxidations by ω-hydroxylases,[15] this selective functionalization of primary aliphatic C−H bonds occurs with alkanes of all chain lengths tested.

Scheme 1. Thermodynamics of Methane Borylation with $B_2(OR)_4$ or $HB(OR)_2$



[a] Energies of the boron species are calculated. See ref 6 for details.

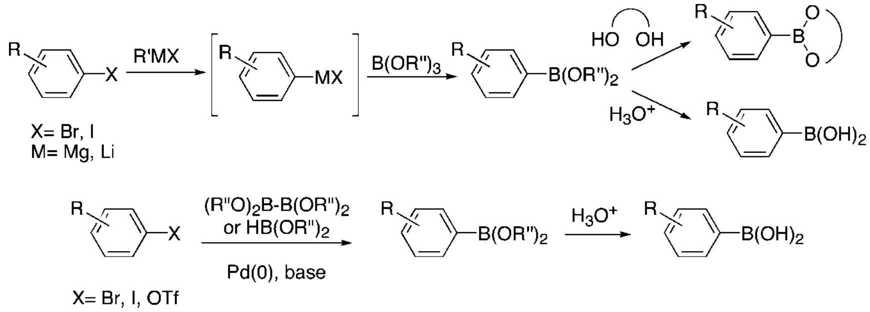
The functionalization of arenes without the need for directing groups has also been a challenge in the field of C−H bond functionalization. Several groups have developed methods for the directed functionalization of arenes.[3,16] For example, Murai, Ellman and Bergman, Sanford, Yu, and Shi, among others, have developed palladium-catalyzed and ruthenium-catalyzed methods for the acetoxylation, halogenation, alkylation, and arylation of arenes in the presence of basic directing groups, such as pyridines, pyrimidines, pyrazines, pyrazoles, and oximes.[17−23] Methods for the functionalization of arenes without directing groups provide products with complementary regioselectivity. In particular, the metal-catalyzed borylation of arenes produces functionalized arenes with regioselectivity that is typically determined by steric factors, and this process does not require a chelating substituent to trigger catalyst activity.

In addition to producing, in a single step, functionalized alkanes and arenes that typically require multistep synthesis involving directing groups, the borylation of alkanes and arenes alleviates the need for halogenated arene precursors to arylboron compounds. Arylboronates are now widely used in synthesis.[24] They undergo metal-catalyzed cross-coupling reactions, 1,2- and 1,4-additions to carbonyl compounds, oxidative aminations, and additions to imines and iminium ions.[25−30] Many arylboronates are now available, but most are prepared from aryl halides (Scheme 2). Therefore, the availability of the arylboronates depends on the availability of the appropriately substituted aryl halides.

There are two commonly used methods for the synthesis of arylboronic acids. One method for the synthesis of these materials involves the conversion of an aryl halide to a Grignard or lithium reagent, followed by the reaction of the main group organometallic reagent with a trialkylborate. Addition of either a diol or an acid converts the initial organoboron product to the final ester or the acid, respectively. Alternatively, one recently developed and widely employed route to boronate esters is the palladium-catalyzed coupling of an aryl halide with a mono- or diboron reagent.[31] In addition, analogous copper catalyzed borylation of aryl halides with diboron reagents has recently been reported.[32] In contrast, the direct borylation of arenes and alkanes provides access to synthetically useful compounds without relying on the accessibility of aryl or alkyl halides. This direct borylation, therefore, reduces steps, while providing simple access to isomers of arylboronates that would be difficult to access otherwise (vide infra).

Although studies on the conversion of typically unreactive C−H bonds in aliphatic and aromatic substrates to the C−B

Scheme 2. Common Syntheses of Arylboronate Esters and Acids



bonds in alkyl- and arylboronates have been conducted more recently than those on other classes of C−H bond functionalizations, the conversion of alkyl and aryl C−H bonds to C−B bonds can already be performed in a catalytic manner with high yields, excellent selectivities, and high turnover numbers. The direct borylation of alkanes is currently one of only a few methods that leads to the selective functionalization of primary alkyl C−H bonds. This review describes the early stoichiometric studies of the borylation of alkanes and arenes, the development of catalysts for the borylation of aliphatic, alkenyl, and aromatic C−H bonds, the mechanistic studies of these reactions, and the recent applications of the borylation of alkyl and aryl C−H bonds.

2. Stoichiometric Borylation of Arenes and Alkanes

In the Supporting Information of a paper in 1993 by Marder and co-workers on the synthesis of the first trisboryliridium complexes, a GC/MS total ion chromatogram was included that indicated the formation of a small amount (<1%) of two isomers of tolylboronate ester as side product arising from borylation of the toluene solvent.[33] The formation of this product was not discussed in the text of the paper, and studies to develop this observation into systems that react in higher yields or that catalyze C−H borylation were not pursued at that time.

In 1995, Hartwig and co-workers reported the first reactions of arenes and alkenes with defined metal−boryl complexes,[34−44] and these reactions formed free alkenyl- and arylboronate esters in high yields.[45] Irradiation of $CpFe(CO)_2(Bcat)$ (Cp = cyclopentadienyl, cat = $1,2\text{-}O_2C_6H_4$ = catecholate) in benzene yielded PhBcat in 87% yield (Scheme 3). In addition to the photochemical borylation of arenes by $CpFe(CO)_2(Bcat)$, the analogous borylation of arenes by $Mn(CO)_5(Bcat)$ and $Re(CO)_5(Bcat)$ was reported.

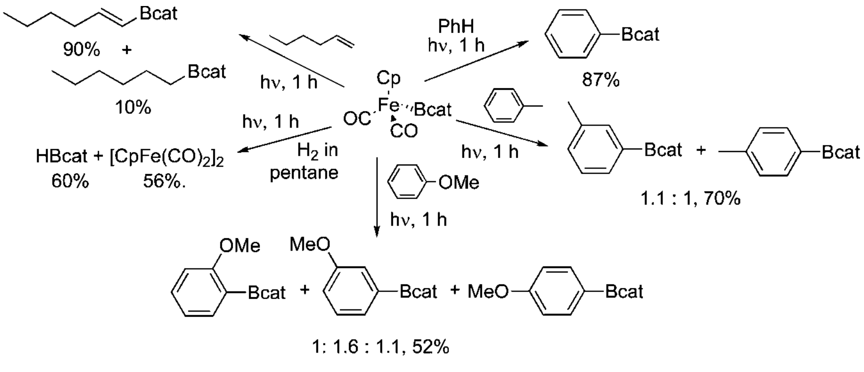
The reaction of most monosubstituted arenes, such as toluene or chlorobenzene, with $CpFe(CO)_2(Bcat)$ yielded a mixture of *meta*- and *para*-substituted arylboronate esters. However, the reaction of anisole with $CpFe(CO)_2(Bcat)$ yielded a mixture of *ortho*-, *meta*-, and *para*-borylated arenes in a 1.0:1.6:1.1 ratio. The authors also noted that the reaction of anisole with the less electron-rich $Re(CO)_5(Bcat)$ yielded *o*-anisylBcat as the major product.[46] The methoxy group may interact with either the metal center or the boryl ligand of $M(CO)_x(X)_y(Bpin)$ (pin = $OCMe_2CMe_2O$ = pinacolate), and this interaction may lead to the formation of products arising from C−H activation of the *ortho* C−H bond. The reaction of $CpFe(CO)_2(Bcat)$ with alkenes yielded a mixture of alkyl- and alkenylboronate esters, but the reaction of $CpFe(CO)_2(Bcat)$ with alkanes did not provide functionalized products (Scheme 3).

Soon after, Hartwig and co-workers reported the borylation of alkanes. These reactions were conducted with complexes containing pentamethylcyclopentadienyl (Cp*) ligands, to prevent C−H activation of the pseudoaromatic-cyclopentadienyl C−H bonds, and 3,5-dimethylcatecholboryl ligands (Bcat′), to prevent C−H activation of the aromatic C−H bonds in the boryl group.[47] A series of $Cp^*M(CO)_2(Bcat')$ (Bcat′ = $1,2\text{-}O_2C_6H_2\text{-}3,5\text{-}Me_2$) complexes were synthesized, and the photochemical-reactions of these complexes in alkanes were studied. The reaction of $Cp^*Fe(CO)_2(Bcat')$ in pentane yielded 20% pentylBcat′, the reaction of $Cp^*Ru(CO)_2(Bcat')$ in pentane yielded 40% pentylBcat′, and the reaction of $Cp^*W(CO)_3(Bcat')$ in pentane yielded 85% pentylBcat′.

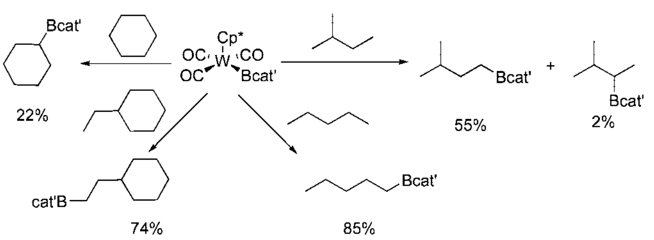
The photochemical reaction of $Cp^*W(CO)_3(Bcat')$ in a variety of alkanes produced alkylboron derivatives (Scheme 4).[47] Irradiation of $Cp^*W(CO)_3(Bcat')$ in either linear or branched alkanes produced linear alkylboronate esters from the functionalization of primary C−H bonds in moderate to good yields. $Cp^*W(CO)_3(Bcat')$ reacted with cyclic alkanes, such as cyclohexanes, lacking any primary C−H bonds to produce cyclohexylBcat′ in 22% yield and with cyclic alkanes containing alkyl substituents, such as ethylcyclohexane, at the terminal position of the ethyl group.

Hartwig and co-workers performed experiments to probe the mechanism of the reaction of $Cp^*W(CO)_3(Bcat')$ with

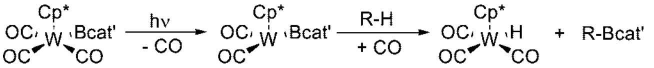
Scheme 3. Summary of the Reactions of the Iron Boryl Complex $CpFe(CO)_2(Bcat)$ with Hydrocarbons and Dihydrogen



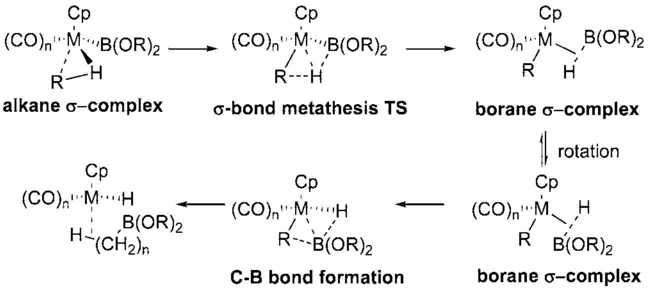
Scheme 4. Stoichiometric Reactions of Cp*W(CO)$_3$(Bcat′) with Various Alkanes



Scheme 5. Borylation of Hydrocarbons by Cp*W(CO)$_3$(Bcat′)



Scheme 6. Possible Mechanistic Pathway for the Borylation of Alkanes with CpM(CO)x Complexes



pentane.[48] The photochemical reaction of Cp*W-boryl complexes with a 1:1 mixture of pentane and pentane-d_{12} yielded a mixture of pentylBcat′ and pentyl-d_{11}Bcat′ that reflected a k_H/k_D of 5.0 ± 0.1. They also probed for reversible CO dissociation from the W complex. The rates of conversion of Cp*W(CO)$_3$(Bcat′) with respect to irradiation time were the same when the reaction was performed with 2 atm of CO or without added CO, and irradiation of Cp*W(CO)$_3$(Bcat′) with pentane in the presence of labeled ^{13}CO did not lead to Cp*W(CO)$_x$(^{13}CO)$_y$(Bcat′) at 50% conversion of the starting W complex. Also, irradition of Cp*W(CO)$_3$(Bcat′) and PMe$_3$ in pentane produced Cp*W(CO)$_2$(PMe$_3$)(Bcat′) and pentylBcat′.

On the basis of these data, Hartwig and co-workers proposed the following mechanism for the reaction of Cp*W(CO)$_3$(Bcat′) with alkanes. Initial photochemically induced dissociation of a carbonyl ligand results in the coordinatively unsaturated intermediate Cp*W(CO)$_2$(Bcat′). This dissociation of CO was revealed by trapping the resulting 16-electron intermediate with either a trialkyl or triarylphosphine to form Cp*W(CO)$_2$(PR$_3$)(Bcat′). In the absence of added phosphine ligands, the 16-electron intermediate cleaves a C−H bond of either an arene or an alkane faster than it recombines with CO, and the resulting alkyl complex was proposed to undergo reductive elimination of an aryl- or an alkylboronate ester (Scheme 5).

Hall, Hartwig, and co-workers conducted a study that combined experimental and computational methods to gain insight into this C−H bond functionalization process.[49] C−H bond cleavage by either σ-bond metathesis or oxidative addition was originally considered (Scheme 6).[48] However, computational results suggested that this reaction is a "boron-assisted, metal-mediated hydrogen transfer." The proposed pathway first involves the formation of an alkane σ-complex containing a boryl ligand. According to these studies, this alkane complex converts to a borane complex containing an alkyl ligand by a single-step process. The transition state for C−H bond cleavage that links these two structures is considered to form by transfer of the acidic C−H bond of the σ-alkane complex to the basic boryl group with accompanying transfer of electron density from the metal center to the empty p-orbital on the boron. The empty p-orbital on the boron atom thus assists this process by accepting electron density from the metal center via backbonding.

In the resulting borane σ-complex, the boryl and hydrocarbyl moieties are located *trans* to each other. In order to provide the necessary *cis* disposition of these two units, rotation of the borane σ-complex is proposed to occur. B−C bond formation then proceeds by a related σ-bond metathesis process, and the final organoboronate product dissociates.

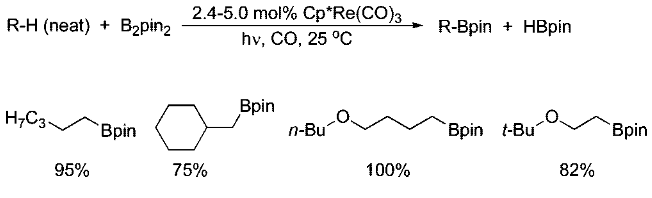
Calculations conducted in parallel by Lam and Lin[50] led them to propose a one-step mechanism proceeding by a similar "oxidatively added transition state" (OATS) for reaction of the iron complex but a two-step mechanism for reaction of the tungsten complex through a W(IV) intermediate resulting from oxidative addition of the C−H bond. This oxidative addition pathway was calculated by Hall, Hartwig, and co-workers[49] to be higher in energy by 4 and 11 kcal mol^{-1} for W and Fe, respectively, than that shown in Scheme 6.

3. Rhenium-Catalyzed Borylation of Alkanes

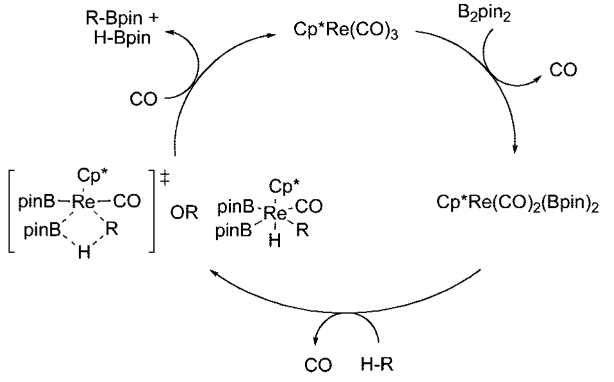
In 1999, Hartwig and co-workers described the first example of the reaction of an alkane with B$_2$pin$_2$ catalyzed by a metal complex to form an alkylboronate ester. These reactions occurred with essentially perfect regioselectivity for formation of products from functionalization of the primary C−H bond. More specifically, the photochemical reaction of pentane and methylcyclohexane with B$_2$pin$_2$ in the presence of 2.4−5.0 mol % Cp*Re(CO)$_3$, stabilized by 2 atm of CO, formed a single reaction product resulting from borylation of a single primary C−H bond.[13] In addition to alkanes, alkyl ethers underwent borylation at the least sterically hindered terminal methyl groups in moderate to excellent yields (Chart 1).

Hartwig and co-workers performed a series of mechanistic experiments on the rhenium-catalyzed borylation of alkanes. First, they isolated *trans*-Cp*Re(CO)$_2$(Bpin)$_2$ from the reaction of Cp*Re(CO)$_3$ and B$_2$pin$_2$ in cyclohexane under photochemical conditions.[13] Second, they showed that irradiation of *trans*-Cp*Re(CO)$_2$(Bpin)$_2$ in pentane formed 1-pentylBpin in quantitative yield. Thus, Cp*Re(CO)$_2$(Bpin)$_2$ is chemically competent to be an intermediate in the borylation of alkanes. To probe whether the observed single isomer resulted from thermodynamic or kinetic selectivity, the borylation of pentane was conducted in the presence of 2-butylBpin. No isomerization of this branched alkylboronate to the linear isomer was observed. Therefore, the high ratio of linear to branched C−H bond functionalization products results from kinetic selectivity, rather than from isomerization of a mixture of branched isomers to the most stable linear one.[51,52] On the basis of these experimental data, they proposed that the borylation of alkanes catalyzed by the Cp*Re complex occurs by the mechanism shown in Scheme

Chart 1. Cp*Re-catalyzed Borylation of Alkanes



Scheme 7. Proposed Mechanism for Cp*Re-Catalyzed Alkane Borylation



7. Following dissociation of carbon monoxide from the Cp*Re complex, B_2pin_2 undergoes oxidative addition to form $Cp^*Re(CO)_2(Bpin)_2$. This intermediate then dissociates CO, and the resulting unsaturated bisboryl complex reacts with alkane. If a discrete alkyl intermediate is formed, reductive elimination to form a C−B bond provides the experimentally observed alkylboronate ester product (Scheme 7).

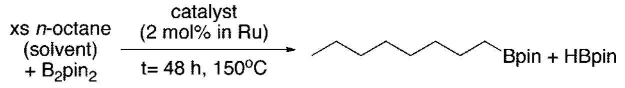
4. Ruthenium-Catalyzed Borylation of Alkanes

In 2006, Hartwig and co-workers reported a series of Cp*Ru complexes that catalyze the borylation of alkanes with B_2pin_2 at 150 °C.[53] The reaction of octane with B_2pin_2 in the presence of $[Cp^*RuCl_2]_2$ formed 1-octylBpin in 98% yield. The reaction of octane with B_2pin_2 catalyzed by $[Cp^*RuCl]_4$ also led to the complete consumption of B_2pin_2, but octylBpin was formed in only 65% yield. Except for $[Cp^*Ru(OMe)]_2$, all of the Cp*Ru complexes catalyzed the reaction of octane with B_2pin_2 to give moderate to high yields of 1-octylBpin (Table 1). (COD)Ru(η^3-2-methylallyl)$_2$ (COD = 1,5-cyclooctadiene) and $Ru(acac)_3$ catalyzed the borylation of octane with B_2pin_2 in poor yields.

Investigation of the scope of ruthenium catalyzed aliphatic borylations catalyzed by either $[Cp^*RuCl_2]_2$ or $[Cp^*RuCl]_4$ showed that branched alkanes, linear and cyclic tertiary amines, dialkyl ethers, and partially fluorinated alkanes all underwent the borylation process to form products arising from functionalization of primary C−H bonds in good yields (Chart 2).

Surprisingly, the reaction of arenes with B_2pin_2 in the presence of Cp*Ru-complexes did not form functionalized products in good yields. For example, the reaction of B_2pin_2 with benzene catalyzed by 2 mol % $[Cp^*RuCl_2]_2$ formed PhBpin in only 20% yield. Mechanistic data suggested that a catalytically inactive, $[Cp^*Ru(\eta^6\text{-arene})]^+$ complex is formed during the borylation of arenes catalyzed by Cp*Ru complexes.

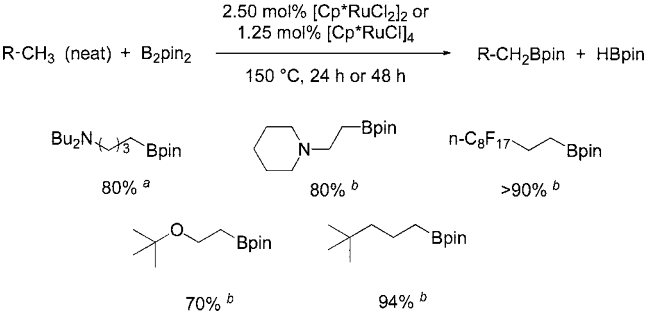
Table 1. Borylation of Octane with B_2pin_2 Catalyzed by Ru Complexes



catalyst	yield[a]	conversion[a]
$[Cp^*RuCl_2]_2$	98% (75%)[b]	99%
$[Cp^*RuCl]_4$[c]	65%	99%
Cp*Ru(H)(COD)	58%	80%
Cp*Ru(Cl)(TMEDA)	95%	98%
$[Cp^*Ru(OMe)]_2$	7%	65%
(COD)Ru(2-methylallyl)$_2$	7%	59%
$Ru(acac)_3$	4%	76%

[a] Determined by GC. [b] Isolated yield in parentheses. [c] 5 mol % Ru used.

Chart 2. Products from Ru-catalyzed Terminal Borylation of Heteroatom-Containing Substrates



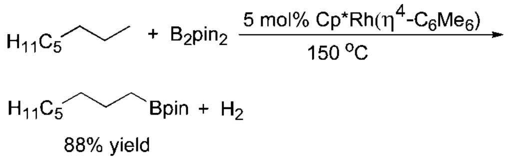
[a] Conditions: $[Cp^*RuCl]_4$ neat, 150 °C, 24 h, yield determined by GC. [b] Conditions: $[Cp^*RuCl_2]_2$ neat, 150 °C, 48 h, yield determined by GC.

5. Rhodium-Catalyzed Borylation of Alkanes and Arenes

5.1. Borylations of Alkanes and Arenes Catalyzed by Cp*Rh(η^4-C_6Me_6)

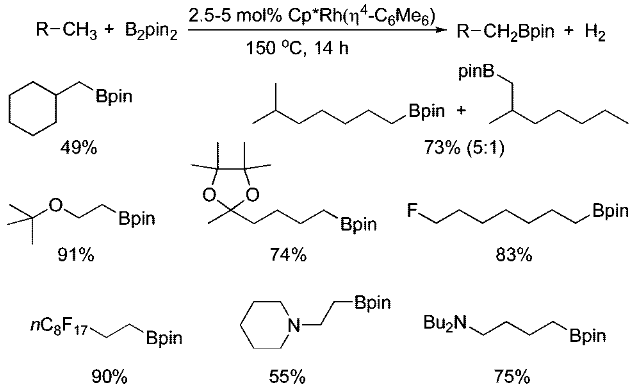
Cp*Rh complexes are the most active catalysts discovered thus far for the borylation of alkanes. In 2000, Chen and Hartwig reported a series of Cp^*ML_2 complexes that catalyze the borylation of arenes and alkanes under thermal conditions.[14] They investigated complexes containing Cp* ligands because the reactions of $Cp^*M(CO)_x(Bcat)$ with arenes and alkanes under photochemical conditions produced arylboronate esters and alkylboronate esters. They studied Cp*M complexes containing dative ligands, such as olefins and η^4-arenes, as catalysts because these ligands dissociate more readily under thermal conditions than the CO ligands of $Cp^*M(CO)_x(Bcat)$ complexes.

Initially, Hartwig and co-workers tested iridium complexes, such as Cp^*IrH_4 and $Cp^*Ir(C_2H_4)_2$, as catalysts for the borylation of octane, but the yields of octylBpin were low (<20%) and the reaction times were long (2 days). To increase catalytic activity, they investigated the typically more reactive, second-row, rhodium analogues as catalysts for the borylation of alkanes. $Cp^*Rh(C_2H_4)_2$, $Cp^*Rh(\eta^4\text{-}C_6Me_6)$, $Cp^*Rh(H)_2(SiEt_3)_2$, and $Cp^*Rh(C_2H_3SiMe_3)_2$ were shown to catalyze the borylation of octane with B_2pin_2.[14] Reactions catalyzed by the rhodium−silyl complexes occurred in lower yields than those catalyzed by the rhodium−bis(olefin) complexes. Reactions catalyzed by $Cp^*Rh(C_2H_4)_2$ formed side products resulting from borylation of the ethylene ligands; a mixture of monoborylated, diborylated, triborylated, and tetraborylated ethylene was observed by GC/MS. The hexamethylbenzene ligand of $Cp^*Rh(\eta^4\text{-}C_6Me_6)$ was more resistant to C−H bond functionalization, and the reaction of octane with B_2pin_2 catalyzed by 5 mol % $Cp^*Rh(\eta^4\text{-}C_6Me_6)$ provided the highest yield (88%) of octylBpin (eq 1).



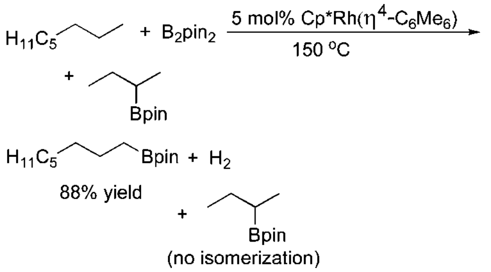
(1)

Chart 3. Scope of Cp*Rh(η^4-C$_6$Me$_6$) Catalyzed Borylation of Aliphatic Substrates[a]



[a] Conditions: 2.5−5 mol % Cp*Rh(η^4-C$_6$Me$_6$), 1 equiv of B$_2$pin$_2$ in neat substrate, 150 °C, 24 h. yields were determined by GC analysis.

The number of moles of octylBpin produced from the reaction of octane with B$_2$pin$_2$ is greater than the number of moles of B$_2$pin$_2$ converted during the course of the reaction. This observation suggests that the HBpin produced during the reaction of B$_2$pin$_2$ reacts with octane in the presence of Cp*Rh(η^4-C$_6$Me$_6$) to form the octylboronate ester. Indeed, in a separate experiment, the reaction of octane with HBpin catalyzed by 5 mol % Cp*Rh(η^4-C$_6$Me$_6$) yielded octylBpin in 65% yield. To assess whether the high selectivity reflected a kinetic or thermodynamic distribution of products, the reaction of octane with B$_2$pin$_2$ was conducted in the presence of 2-(2-butanyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane, the product that would result from functionalization of the 2-position of butane. No isomerization of the 2-butyl boronate ester to the 1-butyl isomer occurred (eq 2).



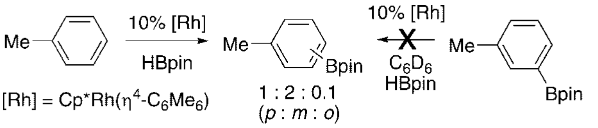
(2)

Hartwig and co-workers also demonstrated that Cp*Rh(η^4-C$_6$Me$_6$) catalyzes the borylation of terminal methyl groups in linear and branched alkanes, alkyl ethers, linear and cyclic tertiary amines, and partially fluorinated alkanes (Chart 3).[14,54] The presence of heteroatoms, such as nitrogen and oxygen, are known to activate the C−H bond α to the heteroatom toward cleavage by many metal complexes.[55−62] However, this property of the heteroatoms did not override the preference of the catalyst for the functionalization of the least hindered of the primary C−H bonds.

Further studies demonstrated that more electron-deficient C−H bonds in aliphatic substrates undergo borylation catalyzed by Cp*Rh(η^4-C$_6$Me$_6$) faster than more electron-rich C−H bonds. For example, the borylation of a 1:1 mixture of octane and (perfluoro-*n*-octyl)ethane with B$_2$pin$_2$, catalyzed by Cp*Rh(η^4-C$_6$Me$_6$), formed a 96:4 ratio of the fluoroalkylboronate ester to the alkylboronate ester. Also, the reaction of *n*-butyl ethyl ether with B$_2$pin$_2$ in the presence of 5 mol % Cp*Rh(η^4-C$_6$Me$_6$) produced a 1:4 mixture of 2-(4-ethoxybutyl)-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane and 2-(2-butoxyethyl)-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane (Scheme 8).

Cp*Rh(η^4-C$_6$Me$_6$) also catalyzes the reaction of B$_2$pin$_2$ with arenes in high yields with high turnover numbers and wide functional group compatibility. Hartwig and co-workers reported the reaction of benzene with B$_2$pin$_2$ catalyzed by 5 mol % Cp*Rh(η^4-C$_6$Me$_6$) to form PhBpin in 92% yield after 2.5 h and with only 0.5 mol % Cp*Rh(η^4-C$_6$Me$_6$) to form the same product in 82% yield. This latter reaction corresponds to a catalyst turnover number of 328.[14]

Smith and co-workers subsequently reported the reactions of a range of arenes with HBpin in the presence of this Cp*Rh(η^4-C$_6$Me$_6$) catalyst.[63] They showed that Cp*Rh(η^4-C$_6$Me$_6$) catalyzes the reaction of arenes containing alkyl, alkoxy, ester, amide, and amine functionalities, and that it catalyzes the reactions of heteroarenes in moderate to excellent yields (Chart 4). This work was followed by a demonstration that these reactions catalyzed by this rhodium system also occur with arenes in cyclohexane as an inert solvent.[64] These reactions occurred with similar selectivity to those conducted in neat arene. With a 1:1 to 4:1 ratio of HBpin to arene, depending on the reactivity of the arene, yields of the arylboronate ester products ranged from 59 to 88%. This work also included an example in which a silylated indole underwent borylation at the 3-position over the typically more reactive 2-position. This change in selectivity occurred when the silyl substituent was a bulky tri-isopropylsilyl group. Finally, as part of this work, the products were shown to result from kinetic selectivity. The borylation of benzene conducted with added, pure *meta*-tolylBpin did not lead to formation of the mixture of isomers observed from the direct borylation of toluene (eq 3).



(3)

Scheme 8. Electronic Effect on Aliphatic Borylations Catalyzed by Cp*Rh(η^4-C$_6$Me$_6$)

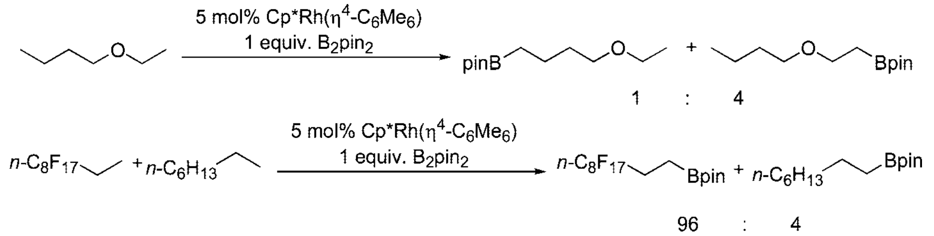
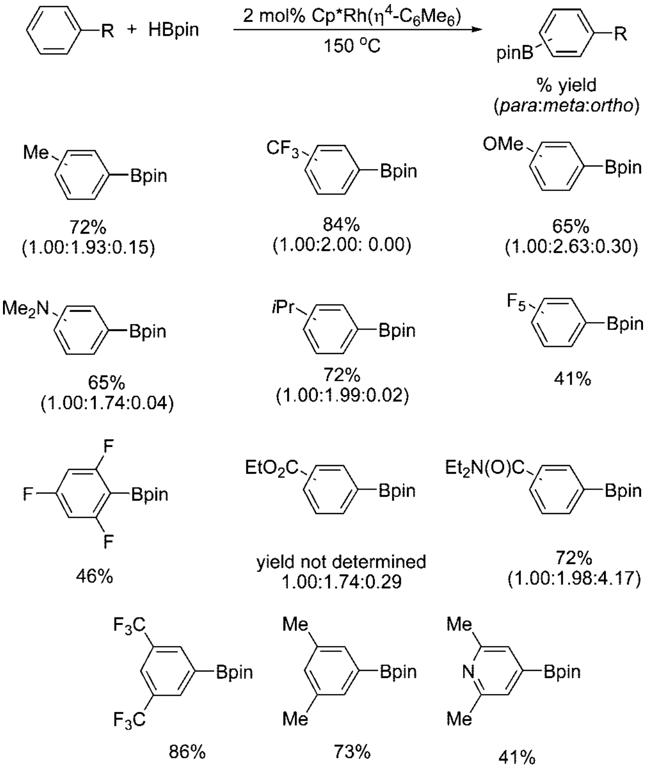


Chart 4. Rhodium Catalyzed Borylation of Arenes with HBpin



5.2. Borylations of Hydrocarbons Catalyzed by other Rhodium Complexes

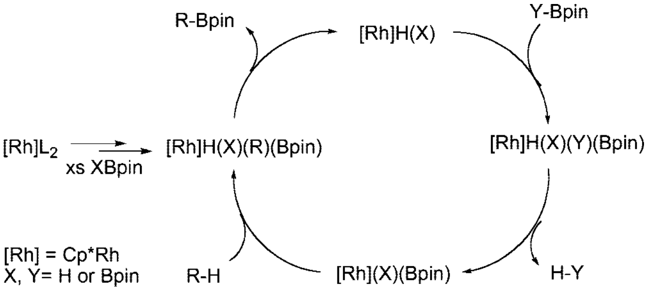
Other groups have reported other Rh complexes that catalyze the borylation of hydrocarbons. In 2001, Marder and co-workers reported that $[Cp^*RhCl_2]_2$ and $[Rh(Cl)(N_2)(PiPr_3)_2]$ catalyze the borylation of arenes with HBpin.[65] Nearly identical regioselectivities were observed for the borylation of toluene with $[Cp^*RhCl_2]_2$ ($o/m/p$ = 5:65:30) and $Cp^*Rh(\eta^4\text{-}C_6Me_6)$ ($o/m/p$ = 5:63:32); these data imply that these two catalyst precursors form the same catalytically active species. $[Rh(Cl)(N_2)(PiPr_3)_2]$ catalyzed the borylation of alkylarenes at the benzylic position, and this process will be discussed in section 5.3. In 2004, Beller and co-workers published the reaction of *o*-xylene and HBpin catalyzed by the combination of $[Cp^*RhCl_2]_2$ and 2,2′-bipyridine to yield 28% of 4,4,5,5-tetramethyl-2-(3,4-dimethylphenyl)-1,3,2-dioxaborolane at 80 °C.

Beller and co-workers also reported that the reaction of *o*-xylene with HBpin, catalyzed by Rh(COD)(acac), formed 4,4,5,5-tetramethyl-2-(*o*-tolylmethyl)-1,3,2-dioxaborolane in 67% yield.[66] In 2006, Murata and co-workers reported the reaction of arenes with HBpin catalyzed by the combination of $[Rh(COD)Cl]_2$ and potassium hydrotris(pyrazolyl)borate (KTp) or isolated $[Rh(Tp^{Me2})(COD)]$ (Tp^{Me2} = hydrotris(3,5-dimethylpyrazolyl)borate) to yield arylboronic esters. They also reported that the combination of $[Ir(COD)Cl]_2$ and KTp or isolated TpIr(COD) catalyzed the reaction of arenes with HBpin.[67]

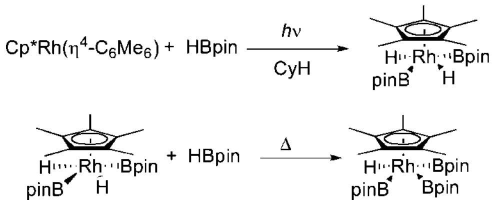
5.3. Mechanistic Investigations of the Borylation of Alkanes Catalyzed by Cp*Rh Complexes

The initial mechanism proposed by Hartwig and co-workers for the borylation of alkanes catalyzed by $Cp^*Rh(\eta^4\text{-}C_6Me_6)$ is shown in Scheme 9. The catalytically active boryl complex $Cp^*Rh(H)_x(Bpin)_{4-x}$ is generated by dissociation of hexamethylbenzene and addition of a combination of HBpin and B_2pin_2. Reductive elimination of HBpin from $Cp^*Rh(H)_x(Bpin)_{4-x}$ (x = 1, 2) would create a coordinatively unsaturated rhodium–boryl complex $Cp^*Rh(H)_x(Bpin)_{2-x}$ (x = 0, 1), which was proposed to react with an alkane C–H bond via oxidative addition to produce an alkylmetal–boryl complex from which reductive elimination would give the alkylboronate ester product (Scheme 9).[14]

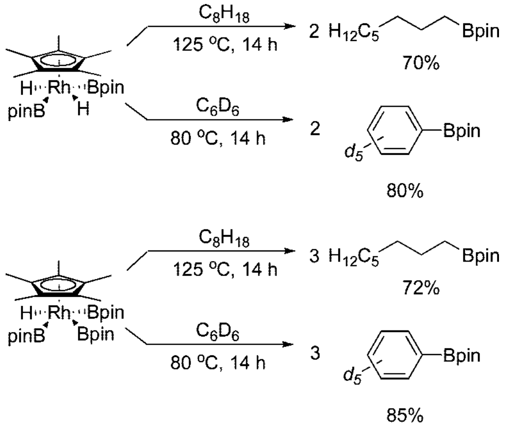
Scheme 9. Mechanism First Proposed by Hartwig et al. for Alkane Borylation Catalyzed by $Cp^*Rh(\eta^4\text{-}C_6H_6)$



Scheme 10. Synthesis of $Cp^*Rh(H)_2(Bpin)_2$ and $Cp^*Rh(H)(Bpin)_3$



Scheme 11. Borylation of Octane and Benzene with $Cp^*Rh(H)_2(Bpin)_2$ and $Cp^*Rh(H)(Bpin)_3$

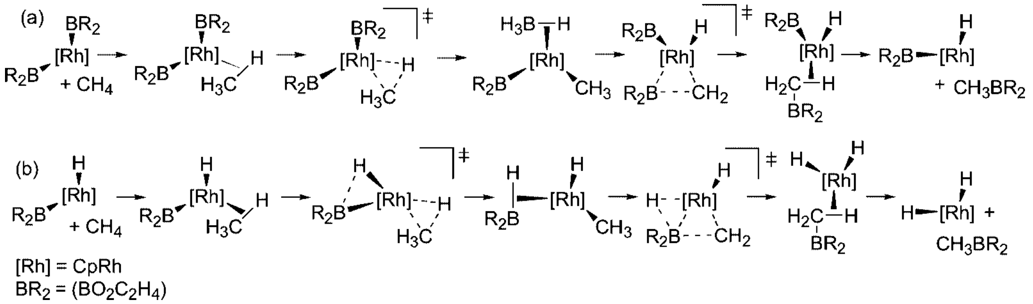


In 2005, Hartwig, Hall, and co-workers reported synthetic, kinetic, and computational data that revealed a likely mechanism for the borylation of alkanes catalyzed by Cp*Rh.[68] Several rhodium–boryl complexes that were possible intermediates were isolated.

Heating $Cp^*Rh(H)_2(SiEt_3)_2$ in the presence of B_2pin_2 in cyclohexane formed a mixture of $Cp^*Rh(H)_2(Bpin)_2$ and unreacted $Cp^*Rh(H)_2(SiEt_3)_2$.[14] Pure $Cp^*Rh(H)_2(Bpin)_2$ was isolated from the reaction of $Cp^*Rh(\eta^4\text{-}C_6Me_6)$ with HBpin under photochemical conditions, and $Cp^*Rh(H)(Bpin)_3$ was isolated from the reaction of $Cp^*Rh(H)_2(Bpin)_2$ with neat HBpin (Scheme 10).[8]

Both $Cp^*Rh(H)_2(Bpin)_2$ and $Cp^*Rh(H)(Bpin)_3$ reacted with octane and benzene to yield either 2 or 3 equivalents of octylBpin and PhBpin, respectively, (Scheme 11)[8] in yields

Scheme 12. Mechanism of C−H Bond Cleavage and C−B Bond Formation Supported by Density Functional Theory (DFT) Calculations for Hydridoboryl (a) and bis(Boryl) (b) CpRh Complexes



[Rh] = CpRh
$BR_2 = (BO_2C_2H_4)$

(70−85%) that were similar to those of the catalytic process and with comparable or faster rates. The reaction of Cp*Rh$(H)_2$$(Bpin)_2$ or Cp*Rh(H)$(Bpin)_3$ with benzene occurred at 80 °C in 82−85% yield, while the reaction with octane occurred at 125 °C, giving octylBpin in 70% and 72% yields, respectively. The reaction with octane formed 1-octylBpin as the only alkylboronate ester product. Therefore, Cp*Rh$(H)_2$$(Bpin)_2$ and Cp*Rh(H)$(Bpin)_3$ are chemically and kinetically competent to be intermediates in the borylation of arenes and alkanes.

After having identified likely reaction intermediates, the reactions of methane with CpRh$(H)_2$$(BO_2C_2H_4)_2$ and CpRh(H)$(BO_2C_2H_4)_3$ were studied by Harwig, Hall, and co-workers as models for the reactions of alkanes with Cp*Rh$(H)_2$$(Bpin)_2$ and Cp*Rh(H)$(Bpin)_3$ (Scheme 12). Novel conclusions were drawn from these studies.[8] The empty p-orbital of the boryl ligand in the CpRh$(BO_2C_2H_4)_2$ intermediate was found to be involved in the C−H borylation process in several ways.

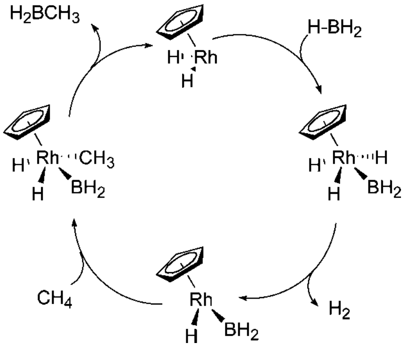
Reaction of the bisboryl intermediate with methane was calculated to occur by coordination of the alkane, followed by conversion of the alkane complex to a borane complex through a single transition state. This process occurs without formation of a discrete Rh(V) intermediate, much like the pathway lacking a high-valent intermediate calculated for the stoichiometric reactions of the iron and tungsten boryl complexes. Coupling of the alkyl group with the second boryl ligand is calculated then to form the final products (part (a) of Scheme 12).

Reaction of the boryl hydride intermediate with methane was calculated to occur by a related but distinct mechanism. After coordination of the alkane, simultaneous cleavage of the alkane C−H bond and formation of a borane B−H bond is calculated to form an alkyl complex containing a coordinated borane. Coupling of the boryl moiety with the alkyl group would then form the final products (part (b) of Scheme 12).

Miyamoto and co-workers[69] performed computational studies on the reaction of BH_3 with CH_4 catalyzed by CpRh. This set of calculations, like those conducted by Hall, Hartwig, and co-workers, indicated that the rate-determining step in the functionalization of alkanes catalyzed by Cp*Rh is C−H bond cleavage and that the reductive elimination of a C−B bond is rapid. However, these authors proposed that a pathway involving oxidative addition and reductive elimination through a high-valent rhodium intermediate is followed (Scheme 13).

The difference between the two sets of computational conclusions can be explained by some simplifications made by Miyamoto and co-workers. For example, HBpin and B_2pin_2 are the only reagents, so far, that undergo the rhodium-catalyzed borylation of alkanes and arenes. The alkoxy groups on HBpin modulate the strength of B−H interactions, which are critical to the catalytic process. Thus, BH_3 might be a poor computational model for HBpin and B_2pin_2 in these reactions. Second, the intermediates in the catalytic process are bisboryl dihydride and trisboryl monohydride complexes, not the monoboryl trihydride complexes studied by Miyamoto.

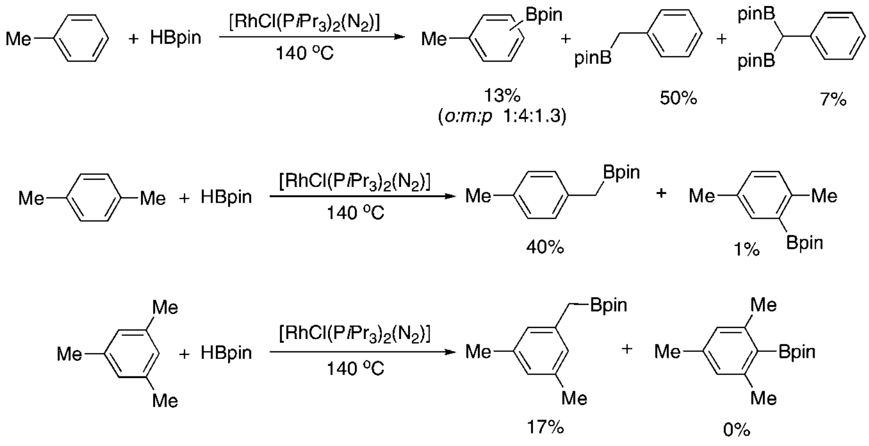
Scheme 13. Mechanism of the Borylation of Alkanes Catalyzed by Cp*Rh Proposed by Miyamoto and Co-workers



5.4. Rh-Catalyzed Borylation of Benzylic C−H Bonds

Rhodium complexes also catalyze the borylation of benzylic C−H bonds. After the observation of benzylic borylation as a side product from the reaction of B_2pin_2 with *m*-xylene reported by Smith[63] when using the Cp*Rh-based catalyst developed by Hartwig, Marder and co-workers described, in 2001, the benzylic borylation of toluene, *p*-xylene, and mesitylene with HBpin catalyzed by [Rh(Cl)(N_2)(P*i*$Pr_3)_2$].[65] [Rh(Cl)(N_2)(P*i*$Pr_3)_2$] (3 mol %) and 1 M HBpin were allowed to react with toluene at 140 °C, and the major product was 2-benzyl-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane (Scheme 14). Products resulting from the borylation of arene C−H bonds or from diborylation of the benzylic position were produced in low yields. The quantity of PhCH$(Bpin)_2$ produced indicated that borylation of the benzylic C−H bonds in toluene further activated one of the remaining benzylic hydrogens to C−H borylation. *para*-Xylene was borylated at the benzylic position in preference to the aromatic position (98:2). The reaction of mesitylene with HBpin catalyzed by [Rh(Cl)(N_2)(P*i*$Pr_3)_2$] yielded 2-(3,5-dimethyl-benzyl)-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane, resulting from the borylation of a benzylic C−H bond, as the sole monoborylation product, along with smaller amounts of bisborylation products and traces of trisborylation products.

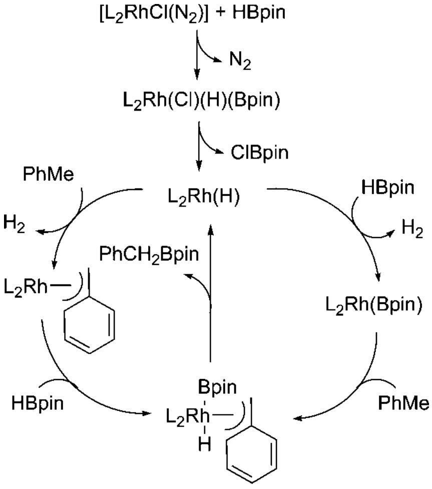
Scheme 14. Rhodium-Catalyzed Benzylic Borylation of Toluene



Experiments were conducted to probe the factors leading to products from benzylic borylation of alkylbenzenes by HBpin in the presence of $[Rh(Cl)(N_2)(PiPr_3)_2]$ as catalyst precursor. Marder and co-workers considered the possibility that this borylation reaction might occur by a radical mechanism. A benzylic radical is more stable than an aryl radical, and the generation of a benzylic radical would explain the product selectivity. However, no effect of 2,6-di-*tert*-butyl-4-methylphenol (BHT) as a radical inhibitor was observed on the yield or selectivity of the products. This result did not support a radical-based mechanism for the borylation of alkylbenzene with HBpin catalyzed by $[Rh(Cl)(N_2)(PiPr_3)_2]$. Although a black precipitate was apparent, addition of Hg did not affect the selectivity, and the decrease in yield was much less than the decrease that would be expected if the reaction were heterogeneous.

Thus, Marder and co-workers proposed an alternative mechanism based on other experimental data. They observed[70] that the oxidative addition of HBpin to $[Rh(Cl)(N_2)(PiPr_3)_2]$ at 140 °C yielded $[Rh(Cl)(H)(Bpin)(PiPr_3)_2]$, which was characterized by single-crystal X-ray diffraction and, subsequently, by neutron diffraction.[71] $[Rh(Cl)(H)(Bpin)(PiPr_3)_2]$ catalyzed the reaction of toluene with HBpin, and this reaction provided the same product distribution as the reactions catalyzed by $[Rh(Cl)(N_2)(PiPr_3)_2]$. The authors proposed that reductive elimination of ClBpin, observed by in situ ^{11}B NMR spectroscopy, from $[Rh(Cl)(H)(Bpin)(PiPr_3)_2]$ forms the rhodium-hydride intermediate $[Rh(H)(PiPr_3)_2]$. Two possible pathways involving $[Rh(H)(PiPr_3)_2]$ are shown in Scheme 15. DFT calculations by Lin, Marder, and co-workers[72] suggested that the left-hand cycle was the pathway followed for the catalytic borylation of benzylic C−H bonds. Thus, the C−H activation was proposed to occur directly from the rhodium(I) hydride intermediate, rather than from the Rh(I) boryl complex, because the strong *trans*-influence of the boryl ligand in the latter destabilized coordination of the C−H bond to Rh. The η^3-benzyl complex, $[Rh(iPr_3P)_2(H)(Bpin)(\eta^3\text{-benzyl})]$, is a key intermediate that explains the propensity of this system to activate benzylic C−H bonds in preference to aromatic ones. Importantly, reaction of HBpin with $[Rh(H)(PiPr_3)_2]$ could lead to the Rh(I) boryl complex $[Rh(Bpin)(PiPr_3)_2]$ shown at the right-hand side of Scheme 15. Reaction of this species with additional HBpin could be responsible for the generation of the small amounts of B_2pin_2 observed experimentally in these reactions, regenerating $[Rh(H)(PiPr_3)_2]$. Unfortunately, the dehydrodimerization of HBpin is thermodynamically uphill, and thus an efficient catalytic dehydrodimerization process would require removal of H_2 from the system.

Scheme 15. Two Potential Mechanisms for Rhodium-Catalyzed Benzylic Borylation of Toluene

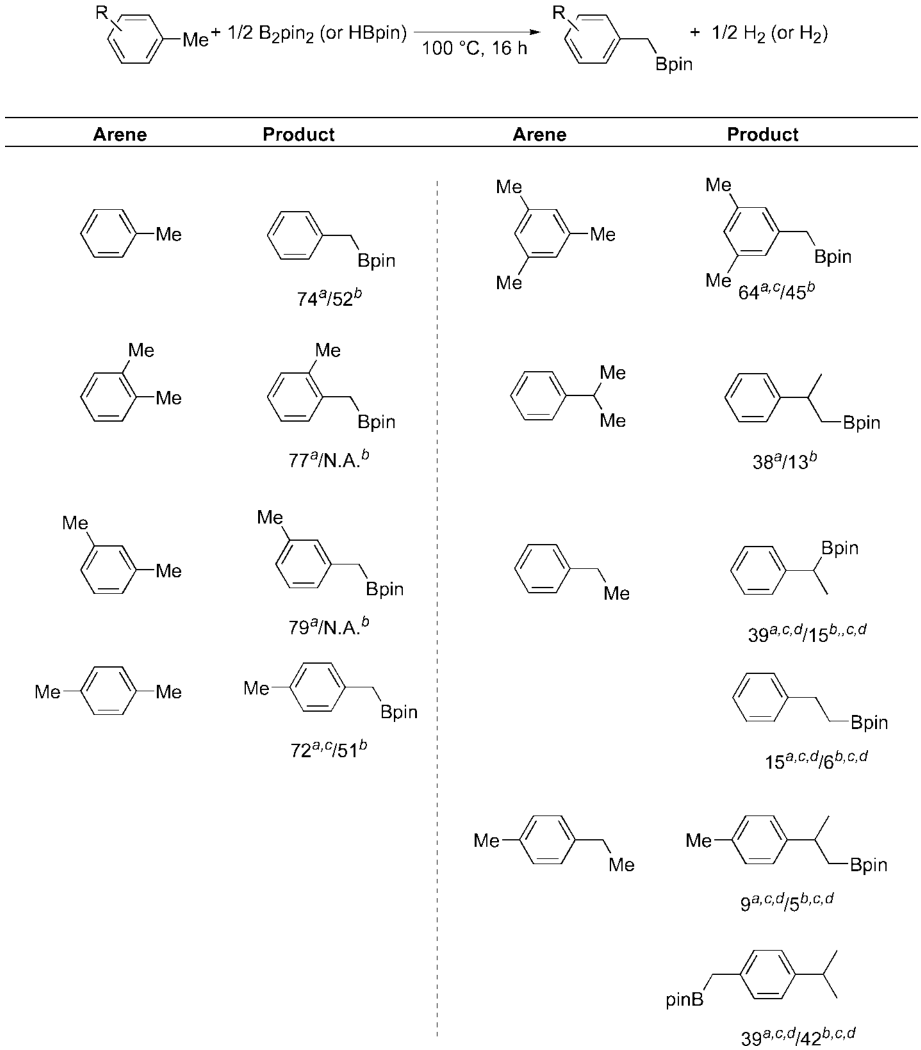


6. Palladium-Catalyzed Borylation of Benzylic C−H Bonds

In 2001, Ishiyama, Miyaura, and co-workers described a palladium-catalyzed borylation of alkylbenzenes with either B_2pin_2 or HBpin.[73] They reported that 10% palladium on carbon (Pd/C) catalyzed the reaction of toluene with HBpin or B_2pin_2 to form the product of functionalization at the benzylic position. In initial studies, they tested the reaction of toluene with HBpin catalyzed by either $Pd(OAc)_2$ or $PdCl_2$, and low yields of benzylboronate esters were obtained, whereas the combination of palladium and a ligand, such as PPh_3, PCy_3, $P(OPh)_3$, $AsPh_3$, or $SbPh_3$ did not yield the benzylboronate ester. These authors also investigated other metals, such as platinum, rhodium, and ruthenium on carbon as catalysts for the borylation of alkylbenzenes with either B_2pin_2 or HBpin.

The highest yield of benzylboronate esters was obtained when alkylbenzenes and B_2pin_2 or HBpin were allowed to react in the presence of palladium on carbon. Platinum, rhodium, or ruthenium on carbon failed to catalyze the borylation of benzene. A number of alkylbenzenes underwent the benzlic borylation process with either 1 mmol of B_2pin_2 or 1 mmol of HBpin in the presence of 3 mol % of 10% Pd/C at 100 °C (Chart 5).

Chart 5. Palladium Catalyzed Benzylic C−H Activation and Borylation[e]



[a] Yield of product using B_2pin_2. [b] Yield of product using HBpin. [c] Six mol % of 10% Pd/C was used. [d] A mixture of regioisomeric products was obtained. The yield listed is the isolated yield of isomer shown. [e] General procedure: in neat arene (60 mmol), 3 mol % of 10% Pd/C and 1 mmol of boron source were stirred at 100 °C for 16 h under nitrogen.

7. Iridium-Catalyzed Borylation of Arenes

7.1. Borylation of Arenes Catalyzed by Cp*Ir-Complexes

Like Cp*Rh complexes, Cp*Ir complexes catalyze the borylation of arenes, but with low turnover numbers. In 1999, Smith and co-workers reported the reaction of 5 equiv of HBpin with deuterated benzene at 150 °C catalyzed by 17 mol % of Cp*Ir(PMe_3)(H)(Bpin) to form C_6D_5Bpin in 53% yield (ca. 3 turnovers).[74] The scope of the borylation of arenes with HBpin catalyzed by Cp*Ir(PMe_3)(H)(Bpin) was investigated by the same group.[63] The borylation of monosubstituted arenes provided a mixture of arylboronate esters, and the borylation of 1,3-disubstituted arenes exclusively provided 3,5-disubstituted arylboronate esters. However, no studies on the reaction of arenes containing amines, esters, or amides, or of heteroarenes catalyzed by Cp*Ir(PMe_3)(H)(Bpin) were reported. The borylations of arenes catalyzed by Cp*Ir complexes occurred in higher yields and with faster reaction rates with electron-deficient substrates than with electron-rich substrates.

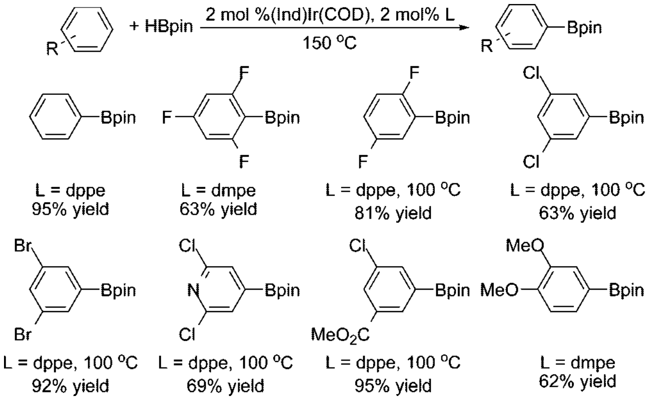
The mechanism of this catalytic process has never been clearly defined, but a few experiments provided some mechanistic insight.[75] Spectroscopic studies did not lead to the detection of free phosphine, and reactions of anisole catalyzed by Cp*IrH_4 formed a different distribution of products than did those catalyzed by Cp*Ir(PMe_3)$(H)_2$. Thus, the active catalyst was proposed to contain PMe_3 as a ligand, but the individual steps and actual intermediates in the catalytic cycle remain unknown.

7.2. Arene Borylation with Iridium Catalysts Containing Phosphine Ligands

Although Cp*Ir complexes were the first catalysts reported for the direct borylation of arenes, other combinations of iridium precursors and ligands generate more active catalysts for this process. Iridium systems containing phosphine- and nitrogen-based ligands have been shown to catalyze the borylation of arenes with faster rates and higher yields than those containing Cp* ligands, and these catalysts are described in the following sections.

On the basis of the observations of trisboryl complexes by Marder and co-workers,[33] Smith, Maleczka, and co-workers tested combinations of (Ind)Ir(COD) and trimethylphosphine, 1,2-bis(dimethylphosphino)ethane (dmpe), or

Chart 6. Borylation of Arenes with HBpin Catalyzed by the Combination of (Ind)Ir(COD) and Phosphine Ligands



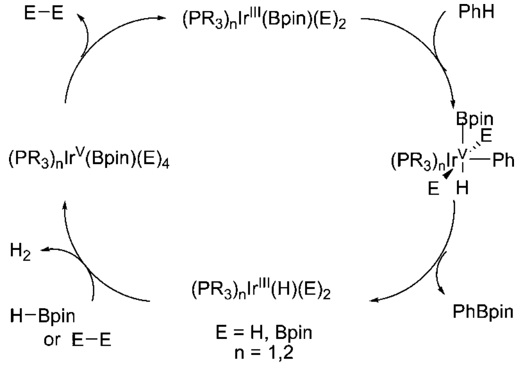
1,2-bis(diphenylphosphino)ethane (dppe) as catalysts for the borylation of arenes with HBpin.[75] The reaction of benzene with HBpin catalyzed by (Ind)Ir(COD) and PMe_3 at 150 °C yielded 88% PhBpin after 18 h. The reaction of benzene with HBpin catalyzed by (Ind)Ir(COD) and dppe at 150 °C yielded 95% PhBpin after 2 h. They obtained the highest yields of arylboronate esters when the catalyst was generated from a 2:1 ratio of PMe_3 to (Ind)Ir(COD) or a 1:1 ratio of dmpe or dppe to (Ind)Ir(COD). A number of electron-neutral and electron-deficient arenes reacted with HBpin in the presence of 2 mol % (Ind)Ir(COD) and either 2 mol % dmpe, 2 mol % dppe, or 4 mol % PMe_3 (Chart 6). The borylation of arenes catalyzed by the combination of (Ind)Ir(COD) and phosphine ligands tolerated halogens, alkoxides, and esters and occurred with heteroaromatic systems.

Smith and co-workers obtained data to distinguish between a catalytic cycle involving Ir(I) and Ir(III) intermediates and a cycle involving Ir(III) and Ir(V) intermediates. They prepared the Ir(I)−boryl complex $Ir(Bpin)(PMe_3)_4$, analogous to $Rh(Bcat)(PMe_3)_4$, which had previously been structurally characterized by Marder, Norman, and co-workers,[76] and the Ir(III)−boryl complex *fac*-$Ir(Bpin)_3(PMe_3)_3$, which is analogous to *fac*-$Ir(Bcat)_3(PEt_3)_3$[33] and *fac*-$Rh(Bcat)_3(PMe_3)_3$, the latter of which was structurally characterized by Marder, Norman, and co-workers.[76] Both $Ir(Bpin)(PMe_3)_4$ and *fac*-$Ir(Bpin)_3(PMe_3)_3$ reacted with benzene to produce PhBpin.[75] However, only the Ir(III) complex reacted with iodobenzene to give the same products as were formed from the catalytic borylation of this arene. The reaction of $Ir(Bpin)(PMe_3)_4$ with iodobenzene did not produce the iodophenylboronic ester, whereas the reaction of *fac*-$Ir(Bpin)_3(PMe_3)_3$ with iodobenzene yielded a mixture of *meta*- and *para*-borylated iodobenzene in 54% yield and PhBpin in 45% yield. The reaction of B_2pin_2 with iodobenzene in the presence 2 mol % (η^6-mesitylene)$Ir(Bpin)_3$, the Bpin analogue of the first trisboryl complex reported by Marder and co-workers,[33] and 2 mol % dppe formed a mixture of iodophenylboronate esters in 77% yield. Thus, the authors did not rule out a pathway involving Ir(I) and Ir(III) intermediates but favored a catalytic cycle involving Ir(III) and Ir(V) species (Scheme 16).

7.3. Arene Borylations Catalyzed by Complexes of Cp Analogues and Carbene Ligands

Arene borylation catalyzed by the combination of tris(pyrazolyl)borate ligands or carbene ligands and Ir(I) complexes have also been reported. In 2006, Murata and co-workers reported the reaction of arenes with HBpin catalyzed by the combination of $[Ir(COD)Cl]_2$ and KTp or isolated TpIr(COD).[67] Also in 2006, Herrmann and co-workers described a series of biscarbene iridium complexes that catalyzed the reaction of arenes with HBpin.[77] Along with iridium complexes of phosphine ligands, iridium complexes of nitrogen ligands have been investigated for the borylation of arenes. In 2004, Nishida and Tagata described the borylation of arenes and heteroarenes catalyzed by the combination of $[Ir(COD)Cl]_2$ and 2,6-diisopropyl-*N*-(2-pyridylmethylene)-aniline.[78] In 2007, Yinghuai and co-workers reported the borylation of arenes with HBpin catalyzed by the combination of iridium(I) salicylaldiminato−cyclooctadiene complexes and additives such as 2,2′-bipyridine (bpy), tetra-2-pyridinylpyrazine, and PPh_3.[79] Depending on the identity of the salicylaldiminato ligand, the yield of ArBpin was higher when the reactions were conducted in a mixture of an ionic liquid and methylene chloride.

Scheme 16. Proposed Mechanism for the Ir-Phosphine-Catalyzed Borylation of Arenes



7.4. Arene Borylations Catalyzed by Complexes of Bipyridine Derivatives

In 2002, Ishiyama, Miyaura, Hartwig, and their co-workers reported the borylation of arenes catalyzed by iridium complexes of bipyridine and di-*tert*-butylbipyridine. The initial paper on this system[80] was published concurrently with that of Smith, Maleczka, and co-workers on the borylation of arenes catalyzed by iridium complexes of phosphines.[75] The catalysts containing bipyridine derivatives are more reactive for most borylations of arenes and heteroarenes than those containing phosphine ligands. The reactions catalyzed by the iridium catalyst containing the bipyridine derivative occur at room temperature to 80 °C, in many cases with turnover numbers between 500 and 1 000, and with turnover numbers exceeding 24 000 in favorable cases.[81] In contrast, the reactions catalyzed by the phosphine-ligated iridium complexes occur at 150 °C with unactivated, electron-neutral arenes and at 100 °C with more electron-poor arenes.

In their initial report, Ishiyama, Miyaura, and Hartwig reported the borylation of arenes with B_2pin_2 in the presence of catalytic amounts of $[Ir(COD)Cl]_2$ and 2,2′-bipyridine (bpy) or 4,4′-di-*tert*-butyl-2,2′-bipyridine (dtbpy).[80] The reactions of excess amounts of arenes with B_2pin_2 catalyzed by the combination of $[Ir(COD)Cl]_2$ and bpy occurred at 80 °C. A variety of arylboronate esters was synthesized in moderate to good yields from the reaction of arenes with B_2pin_2 catalyzed by 1.5 mol % $[Ir(COD)Cl]_2$ and 3 mol % bpy (Table 2). In these reactions, both equivalents of boron in B_2pin_2 were converted to the arylboronate esters. HBpin was also shown to be a viable boron source for this reaction. For example, PhBpin was produced in 80% yield from the

Table 2. Borylation of Arenes with B_2pin_2 Catalyzed by the Combination of $[Ir(COD)Cl]_2$ and 2,2′-Bipyridine

$$\mathrm{ArH} + B_2pin_2 \xrightarrow[80\ ^\circ C,\ 16\ h]{1.5\ mol\%[Ir(COD)Cl]_2\ \ 3.0\ mol\%\ bpy} 2\ \mathrm{ArBpin} + H_2$$

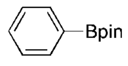
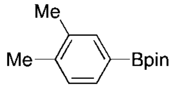
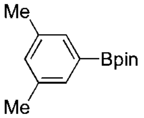
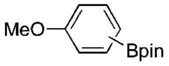
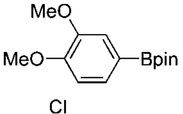
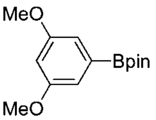
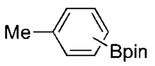
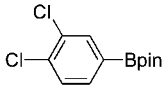
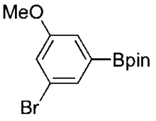
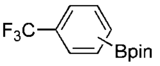
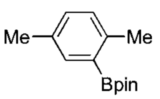
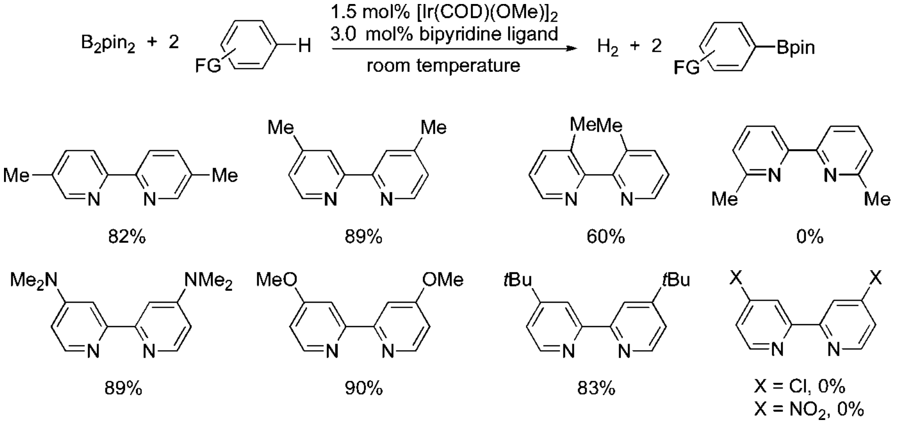
product	yield %	product	yield %	product	yield %
	95		83		86
	95 (1:74:25) (*o*: *m*: *p*)		86		72
	82 (0:69:31) (*o*: *m*: *p*)		83		73
	80 (0:70:30) (*o*: *m*: *p*)		58		

Chart 7. Borylation of Arenes at Room Temperature with B_2pin_2 Catalyzed by the Combination of $[Ir(COD)(OMe)]_2$ and 2,2′-bipyridine



reaction of HBpin with 60 equiv of benzene catalyzed by 1.5 mol % $[Ir(COD)Cl]_2$ and 3.0 mol % bpy after 16 h at 80 °C.[80]

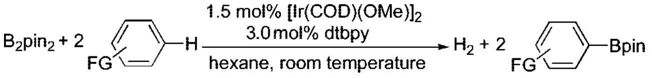
The regioselectivity of the reactions catalyzed by dtbpy-ligated iridium was, again, controlled by steric effects. The reaction of monosubstituted arenes, such as anisole, toluene, and trifluoromethylbenzene yielded an approximately statistical mixture of products arising from *meta*- and *para*-borylation, with the product from *ortho*-borylation being observed (1%) only from the reaction of anisole. However, the borylation of 1,3-disubstituted arenes formed 3,5-disubstituted arylboronate esters exclusively, and the reaction of the symmetric 1,4-disubstituted arene, *p*-xylene, with B_2pin_2 catalyzed by 1.5 mol % $[Ir(COD)Cl]_2$ and 3 mol % bpy yielded the 2,5-dimethylphenylboronic ester, but in somewhat lower yield.

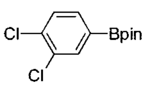
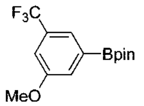
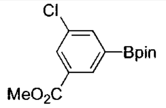
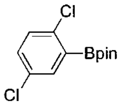
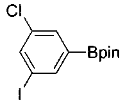
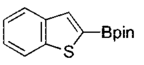
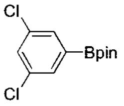
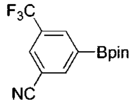
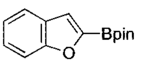
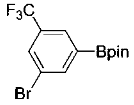
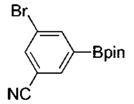
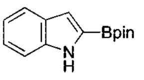
Ishiyama, Miyaura, Hartwig, and co-workers then developed related catalysts that were more active at lower temperatures and that reacted with higher turnover numbers than the initial system. They observed an induction period during the borylation of benzene-d_6 with B_2pin_2 catalyzed by the combination of $[Ir(COD)Cl]_2$ and bpy. During this induction period, the cyclooctadiene ligand was reduced to cyclooctene-d_2.[82] Thus, $[Ir(COE)_2Cl]_2$ (COE = cyclooctene) was investigated as the iridium precursor, and 4,4′-di-*tert*-butyl bipyridine (dtbpy) was used in place of bpy because the *tert*-butyl groups would make the catalyst more soluble in arenes and would protect the ligand against borylation. The reaction of benzene with B_2pin_2 catalyzed by the combination of $[Ir(COE)_2Cl]_2$ and dtbpy yielded 80% PhBpin at room temperature with no observable induction period.[80] This reaction was the first example of a metal-catalyzed borylation of an arene that occurred at room temperature.

To optimize the catalyst further, Ishiyama, Miyaura, Hartwig, and co-workers conducted a systematic study of substituted bipyridine ligands and Ir(I)-cyclooctadiene precursors.[83] $[Ir(COD)Cl]_2$, $[Ir(COD)_2]BF_4$, $[Ir(COD)(OH)]_2$, $[Ir(COD)(OPh)]_2$, $[Ir(COD)(OMe)]_2$, and $[Ir(COD)(OAc)]_2$ were tested as catalyst precursors for the reaction of 1.5 mol % $[Ir(COD)(X)]_2$, 3.0 mol % bpy, and 1.0 mmol B_2pin_2 in neat benzene. The iridium(I) precursor that led to the most active catalyst was $[Ir(COD)(OMe)]_2$.[83]

Ishiyama, Miyaura, Hartwig, and co-workers also studied the borylation of arenes catalyzed by iridium complexes of a series of disubstituted 2,2′-bipyridines to probe both the sensitivity and importance of the electronic and steric properties of the 2,2′-bipyridine ligand (Chart 7).[83] To probe the steric effects of the bpy ligand, they tested the combination of $[Ir(COD)(OMe)]_2$ and dimethyl-2,2′-bipyridine ligands as catalysts for the reactions of arenes with B_2pin_2. The combination of 1.5 mol % $[Ir(COD)(OMe)]_2$ and either 3.0 mol % 4,4′-dimethyl-2,2′-bipyridine or 3.0 mol % 5,5′-dimethyl-2,2′-bipyridine catalyzed the reaction of benzene with B_2pin_2 to form PhBpin in yields of 89% and 82%,

Table 3. Arene Borylation with B_2pin_2 Catalyzed by $[Ir(COD)(OMe)]_2$ and dtbpy



product	% yield	product	% yield	product	% yield
	82		81		80
	53		82		81
	84		84		83
	91		83		88

respectively. The reaction of benzene with B_2pin_2 catalyzed by the combination of $[Ir(COD)(OMe)]_2$ and 3,3′-dimethyl-2,2′-bipyridine yielded 60% PhBpin.

The steric hindrance of the methyl groups in the 3- and 3′-positions prevents the pyridine rings from adopting a coplanar arrangement, and this structural change was proposed to be responsible for the lower yields obtained from reactions catalyzed by complexes of this bipyridine derivative. The combination of $[Ir(COD)(OMe)]_2$ and 6,6′-dimethyl-2,2′-bipyridine did not catalyze the reaction of benzene and B_2pin_2. The steric hindrance around the nitrogen atoms in 6,6′-dimethyl-2,2′-bipyridine was proposed to prevent this ligand from binding tightly to the iridium complex.

To probe the electronic effects of the bpy ligand on arene borylation, Ishiyama, Miyaura, Hartwig, and co-workers studied arene borylations catalyzed by iridium complexes of a series of 4,4′-disubstituted-2,2′-bipyridine ligands (Chart 7).[83] The combination of $[Ir(COD)(OMe)]_2$ and bipyridine ligands containing electron-donating groups, such as NMe_2, OMe, or *t*Bu, catalyzed the borylation benzene with B_2pin_2 in yields of 89%, 90%, and 83%, respectively. However, the combination of $[Ir(COD)(OMe)]_2$ and bipyridine ligands containing electron-withdrawing groups, such as Cl and NO_2, did not catalyze the reaction of benzene with B_2pin_2.

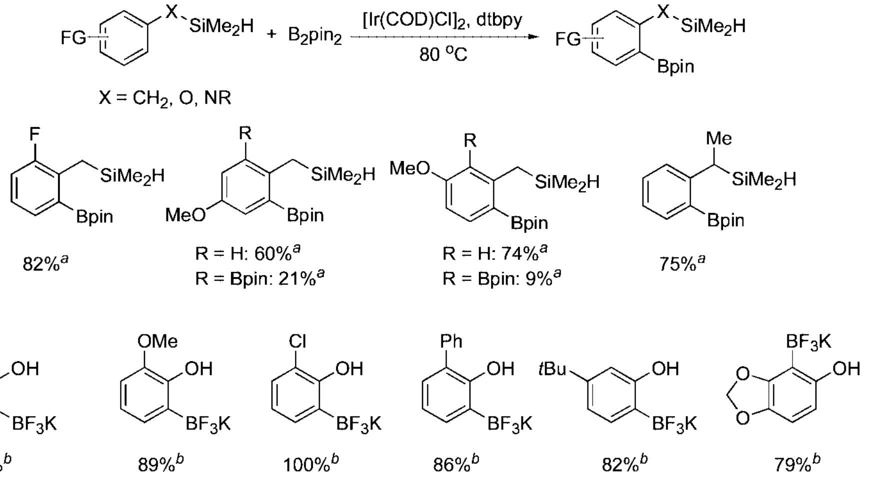
The initial arene borylations catalyzed by $[Ir(COD)(OMe)]_2$ and dtbpy were conducted in neat arene, but to increase the utility of this methodology, Ishiyama, Miyaura, and Hartwig investigated the iridium-catalyzed reaction of arenes with B_2pin_2 in common organic solvents.[83] The rate of borylation of arenes with B_2pin_2 (2:1 molar ratio) catalyzed by 1.5 mol % $[Ir(COD)(OMe)]_2$ and 3.0 mol % dtbpy was faster in nonpolar solvents, such as hexane, than in more coordinating, more polar solvents, such as dimethyl ether (DME) and dimethyl formamide (DMF). In the presence of 1.5 mol % $[Ir(COD)(OMe)]_2$ and 3.0 mol % dtbpy, a variety of arenes reacted with B_2pin_2 at room temperature in hexane to form arylboronate esters in moderate to high yields (Table 3).[83] A number of functional groups were tolerated, such as halides (Cl, Br, and I), alkoxides, esters, and nitriles. Heteroaromatic substrates also reacted to form heteroarylboronate esters in high yields.

7.5. Directed *ortho*-Borylation

Although the regioselectivity controlled by steric effects complements the regioselectivity of most other types of arene functionalization, a method to alter this selectivity would be valuable. In 2008, Hartwig and co-workers described the selective *ortho*-borylation of arenes catalyzed by the combination of $[Ir(COD)Cl]_2$ and dtbpy.[84] Several examples of this process are shown in Chart 8. In this method, the borylation of arenes was led to the *ortho* position by a new directing group, a dialkyl hydrosilyl group.[85] This method provides a mild alternative to *ortho*-metalation methods based on alkyl lithium or magnesium reagents.[85−87] The hydrosilyl group is also distinct from more typical directing groups that are Lewis basic.

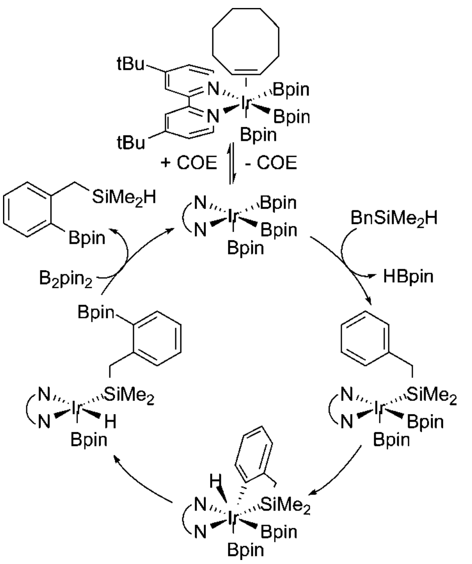
The directing effect of a hydrosilyl group also extended the scope of the *ortho*-borylation to the reaction of free phenols and *N*-alkylanilines. In this case, the hydrosilyl group was installed by dehydrogenative coupling of the phenol with

Chart 8. *ortho*-Directed Arene Borylation Observed with Benzylic Dimethylsilanes as Substrates



[a] Conditions: 0.25 mol % $[Ir(COD)Cl]_2$, 0.5 mol % dtbpy, 5 mol % HBpin, 1 equiv of B_2pin_2, tetrahydrofuran (THF), 80 °C. [b] Conditions: (1) 0.5 mol % $[Ir(COD)Cl]_2$, Et_2SiH_2 in PhH. (2) 1.0 mol % $[Ir(COD)Cl]_2$, 2.0 mol % dtbpy, 1 equiv of B_2pin_2, THF, 80 °C. (3) 4 M KHF_2 (aq) in THF.

Scheme 17. Proposed Mechanism for Hydrosilyl-Directed *ortho*-Borylation of Alkylarenes and Phenols



a dihydrosilane, and the silyl ether was used in situ for the subsequent *ortho*-borylation. Addition of potassium hydrogen difluoride provided stable, synthetically useful potassium trifluoroborates. Benzylic hydrosilanes and silylated phenols containing electron-donating and electron-withdrawing substituents were tolerated, and the desired products were obtained in moderate to excellent yields (Chart 8).

The mechanism of this *ortho*-borylation has not been studied in detail. However, a simple H/D exchange reaction between benzyldimethylhydrosilane and HBpin catalyzed by the combination of $[Ir(COD)(OMe)]_2$ and dtbpy led to the incorporation of deuterium only at the *ortho* positions. This result indicated that the hydrosilyl group triggers C−H cleavage at the *ortho* position.

The mechanism in Scheme 17 is envisioned to account for this *ortho*-borylation. Initial reaction of the trisboryl intermediate (vide infra) with the silane functionality could lead to free borane and a bisboryl silyl species. C−H bond cleavage by this intermediate would generate an iridium−aryl linkage, and B−C bond formation from this aryl intermediate would generate an *ortho*-borylated arylsilyl complex. Reductive elimination of silane would release the functionalized product, and addition of the boron reagent and silane would regenerate the bisboryl silyl intermediate.

Very recently, Ishiyama, Miyaura, and co-workers have described the use of a catalyst system consisting of $[Ir(COD)(OMe)]_2$ and 4 equiv of a monodentate phosphine ligand (i.e., 2 equiv of ligand per Ir) for the *ortho*-directed borylation of methylbenzoates using B_2pin_2 at 80 °C in octane solvent.[88,89] The ligand that generated the most selective catalyst was $(3,5\text{-}(CF_3)_2C_6H_3)_3P$, which contains strongly electron-withdrawing aryl groups. It is believed that the *ortho*-directing effect of the CO_2Me substituent is due to chelation control, although it is not yet clear exactly how many phosphine ligands are bound to iridium in the active species or whether the active catalyst is the ligated trisboryl Ir(III) analogue of the dtbpy system. Selectivity for *ortho*-borylation was high in most cases for compounds of the type $FG-C_6H_4-CO_2Me$ [FG = *o*-CF_3 (98%); *o*-NMe_2 (97%); *m*-Br (64%); *m*-NMe_2 (99%); *p*-Me (99%); *p*-OMe (66%)].

Recently, Sawamura and co-workers reported the first example of a supported catalyst for arene borylation.[90] The reaction of B_2pin_2 with a series of methylbenzoates catalyzed by the combination of $[Ir(COD)(OMe)]_2$ and the silica-supported monodentate, electron-rich, and compact phosphine ligand SMAP (a silica-supported phosphine ligand) resulted in *ortho*-directed borylation of a series of methylbenzoates under mild conditions (25−50 °C) in excellent yields (Table 4). In neat methylbenzoate, at 100 °C, up to 20 000 turnovers were observed with excellent regioselectivity. Reactions of arenes containing CO_2Et, CO_2tBu, $CONMe_2$, SO_3Me, $CH(O(CH_2)_3O)$, and OMOM also occurred to form products containing >99:1 *o*/(*m* + *p*) ratios (Table 4). Thus, an ether oxygen β- to the aryl group was an effective *ortho*-director, as was a C=O moiety. This selectivity is reminiscent of that of directed *ortho*-metalation (DoM), which is widely employed for the lithiation of arenes[91] and often applied in cross-coupling reactions.[92,93] Even a chlorine atom served as an *ortho*-directing group with the silica-supported iridium catalyst. The borylation of chlorobenzene gave a 92:8 ratio of *o*/(*m* + *p*) borylated products. Thus, the scope and utility of the iridium-catalyzed arene C−H borylation reaction has been significantly extended by the development of these several strategies to achieve *ortho*-directed borylation.

7.6. Borylation of Heteroarenes

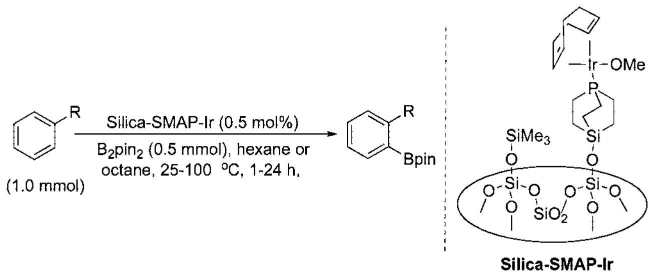
Several research groups have investigated the scope of iridium-catalyzed borylation of heteroarenes.[66,94−97] Early studies of the borylation of heteroarenes were focused on the selectivity of borylation of 5-membered heteroarenes. In 2002, Hartwig, Ishiyama, Miyaura, and co-workers reported the borylation of thiophene, pyrrole, and furan with B_2pin_2 catalyzed by the combination $[Ir(COD)Cl]_2$ and dtbpy in octane at 80 or 100 °C (Table 5).[95]

Several heteroarenes were shown to react with B_2pin_2 in the presence of the iridium−dtbpy catalyst to provide heteroarylboronate esters. The reaction of thiophene, furan, or pyrrole with B_2pin_2 in the presence of $[Ir(COD)Cl]_2$ and dtbpy yielded heteroarylboronate esters in high yields, and the borylation occurred selectively at the 2-position of these heteroarenes. Related reactions of thiophene, furan, or pyrrole with an excess of the diboron reagent produced 2,5-diborylated products. Thiophene, pyrrole, and furan 2,5-bisboronate esters were obtained in 80%, 80%, and 71% yields, respectively, when the Ir-catalyzed borylation of these heteroarenes was performed in the presence of 1.1 equiv of B_2pin_2.

Indole and benzofuran also underwent selective borylation at the 2-position in the presence of an iridium catalyst to form 2-boryl indole and 2-boryl benzofuran in moderate yields. The reaction of pyridine with B_2pin_2 catalyzed by $[Ir(COD)Cl]_2$ and dtbpy was conducted at a higher reaction temperature (100 °C), and a mixture of 3- and 4-borylated pyridine products was observed. Quinoline, however, underwent borylation exclusively at the 3-position in high yield. The origin of the regioselectivity of pyridine has not been established, but coordination of the pyridine to the boron reagent has been proposed to discourage C−H bond cleavage at the position α- to nitrogen.[95]

Borylated dtbpy was not observed in the product mixtures of reactions catalyzed by the combination of $[Ir(COD)X]_2$ and dtbpy. In 2006, Marder and co-workers investigated the iridium-catalyzed borylation of 2-substituted pyridines and the borylation of substituted 2,2′-bipyridines.[96] The reaction of 20 equiv of dtbpy with 40 equiv of B_2pin_2 in hexane catalyzed by $[Ir(COD)(OMe)]_2$ yielded 4,4′-tBu$_2$-6,6′-(Bpin)$_2$-

Table 4. *Ortho*-Directed Borylation of Arenes with B_2pin_2 Catalyzed by Silica-Supported Iridium Complexes



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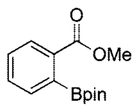
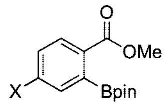
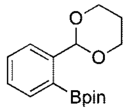
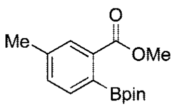
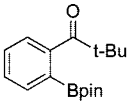
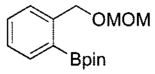
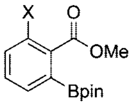
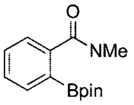
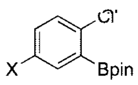
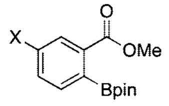
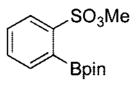
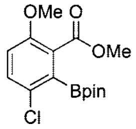
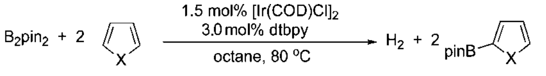
	89		X= OMe: 96 X= CF_3: 79		105 (>99:1)
	87		87 (>99:1)		72 (>99:1)
	X= OMe: 85 X= CF_3: 108		79 (>99:1)		X= H: 50 (92:8) X= CF_3: 75 (>99:1)
	X= OMe: 80 X= CF_3: 89		89 (>99:1)		85 (95:5)

[a] Yields given are isolated yields based on equiv of B_2pin_2 used. Numbers in parentheses indicate the ratio of *ortho*/(*meta* + *para*) products.

Table 5. Iridium-Catalyzed Borylation of Heteroaromatic Substrates



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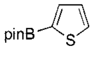
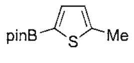
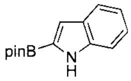
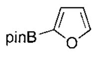
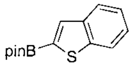
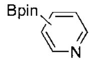
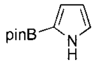
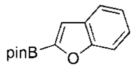
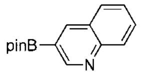
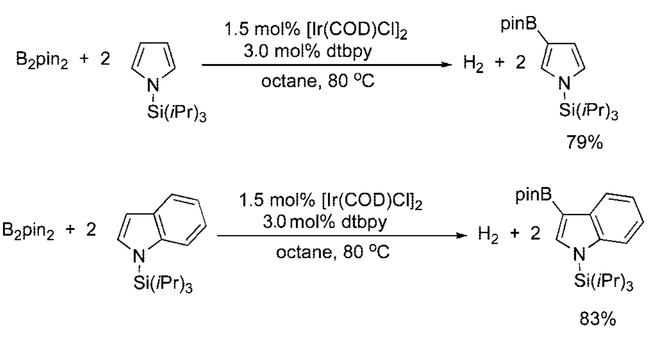
	83[a]		91		92
	83[a]		89		42[a,b,c]
	67[a]		91		84[b]

[a] Diborylated products were produced in 12−17% yield. [b] Reaction conducted at 100 °C. [c] Ratio of 3- and 4-boryl pyridine was 67:33.

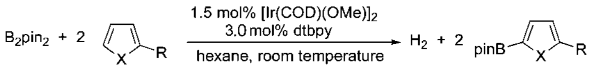
Scheme 18. Ir-Catalyzed Borylation of Tri(isopropyl)silyl-Protected Indoles



2,2′-bipyridine. This study shows that bipyridines undergo C−H borylation when they are present in excess with respect to the metal catalyst. In contrast to the regioselectivity observed from the borylation of dtbpy, 4,4′-$(MeO)_2$-2,2′-bipyridine reacted exclusively at the 5,5′ positions, i.e., adjacent to the two MeO groups, indicating that the directing effect of the pyridine nitrogen overrides the steric properties of the methoxy substituents. The compound 2-phenylpyridine, of significant interest in the synthesis or iridium-containing phosphors for OLED applications, was borylated at the 4- and 5-positions of the pyridine ring, indicating a clear preference for borylation to take place on the 6-membered heterocycle over the phenyl ring. This allowed, by one-pot borylation followed by Suzuki−Miyaura cross-coupling (a process to be addressed later), the synthesis of 4- and 5-(1′-naphthyl)-2-phenylpyridine derivatives.[96]

The regioselectivity of heteroaromatic borylation can be altered. By exploiting the slow rate of borylation at C−H bonds *ortho* to substituents, Hartwig, Ishiyama, Miyaura, and co-workers demonstrated that pyrrole and indole undergo borylation selectively at the 3-position when the nitrogen of these heterocycles bears a large protecting group. The reaction of *N*-tri(isopropyl)silylpyrrole with B_2pin_2 catalyzed by the combination of $[Ir(COD)Cl]_2$ and dtbpy yielded 79%

Table 6. Iridium-Catalyzed Borylation of 2-Substituted Thiophenes, Furans, And Pyrroles



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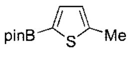
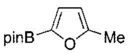
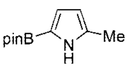
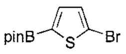
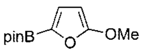
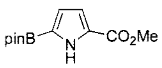
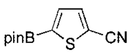
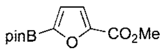
	95		85		96
	91		90		99
	60		80		

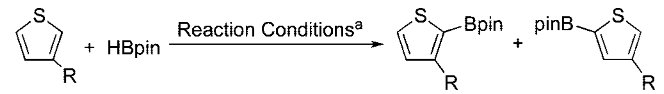
3-boryl-*N*-tri(isopropyl)silylpyrrole. The reaction of *N*-tri(isopropyl)silylindole and B_2pin_2 in the presence of [Ir(COD)Cl]$_2$ and dtbpy yielded 83% 3-boryl-*N*-tri(isopropyl)silylindole (Scheme 18).[95]

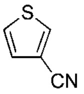
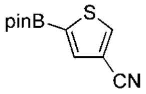
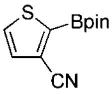
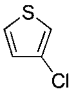
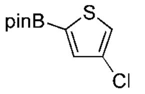
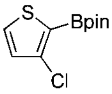
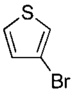
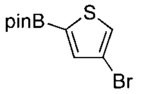
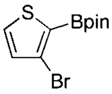
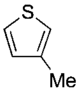
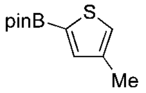
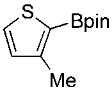
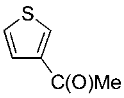
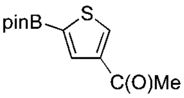
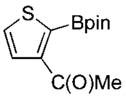
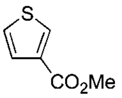
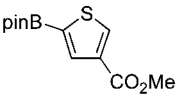
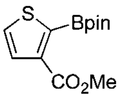
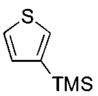
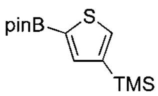
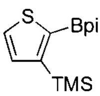
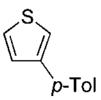
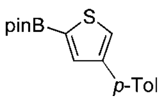
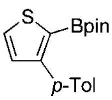
The effect of catalyst precursor and ligand on the yields for the borylation of heteroarenes was similar to that on the yields for the borylation of arenes. Heteroarenes react with B_2pin_2 to form heteroarylboronate esters in high yields at room temperature when the catalyst is generated from [Ir(COD)(OMe)]$_2$ and dtbpy. As observed for the borylation of arenes, the combination of [Ir(COD)(OMe)]$_2$ and 2,2′-bipyridine ligands containing electron-donating groups, such as NMe_2, OMe, and *t*Bu, catalyzed the reactions of heteroarenes with B_2pin_2 in higher yields than did the combination of [Ir(COD)(OMe)]$_2$ and 2,2′-bipyridine ligands containing electron-withdrawing groups, such as Cl and NO_2.

Ishiyama, Miyaura, Hartwig, and co-workers investigated the borylation of a variety of 2-substituted thiophenes, furans, and pyrroles with B_2pin_2 in hexane catalyzed by [Ir(COD)(OMe)]$_2$ and dtbpy (Table 6). The borylation of heteroarenes in the presence of this catalyst was shown to be compatible with several types of functional groups. The reaction of B_2pin_2 with heteroarenes containing alkyl groups, halides, alkoxides, nitriles, and esters provided heteroarylboronate esters in moderate to excellent yields.[94]

Smith and co-workers have recently studied the borylation of 2- and 3-substituted thiophenes catalyzed by [Ir(COD)(OMe)]$_2$ and dtbpy developed by Ishiyama, Miyaura, and Hartwig (Tables 7 and 8).[98] The reaction of 2-substituted thiophenes with HBpin (Table 7) yielded 2,5-disubstituted products, regardless of the electronic properties of the

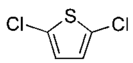
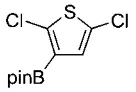
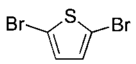
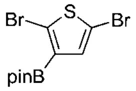
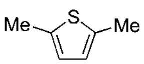
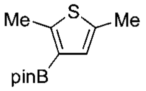
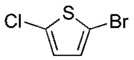
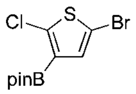
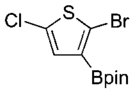
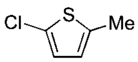
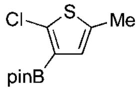
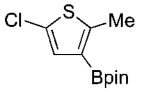
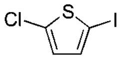
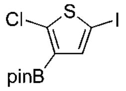
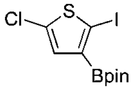
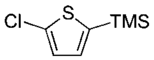
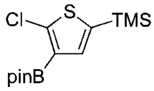
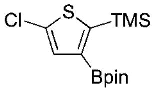
Table 7. Iridium-Catalyzed Borylation of 2-Substituted Thiophenes



arene	5-borylated thiophene	2-borylated thiophene	ratio of 5-borylated: 2-borylated thiophene[b]	% Yield[c]
			1:1.3	54
			3.5:1	66
			8.9:1	72
			8.9:1	67
			>99:1	82
			>99:1	95
			>99:1	79
			>32:1	74

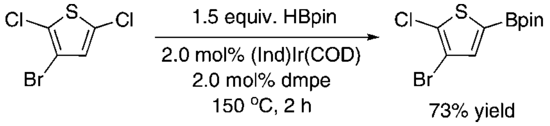
[a] Reaction conditions: 1.5 mol % [Ir(COD)(OMe)]$_2$ and 3.0 mol % dbtpy in hexanes at 25 °C with 1.5−2.0 equiv of HBpin. [b] Isomer ratios were determined by GC analysis. [c] Reported yields are the combined yield of both isomeric products, and yields are based on HBpin as the limiting reagent.

Table 8. Iridium-Catalyzed Borylation of 2,5-Disubstituted Thiophenes

thiophene	conditions	3-borylated Product	4-borylated Product	ratio of 3-:4-boryated products[c]	% yield[d]
	*a*		-----	n/a	86
	*a*		-----	n/a	56
	*b*		-----	n/a	97
	*a*			2.0:1	87
	*a*			2.3:1	86
	*a*			5.7:1	89
	*a*			>99:1	93

[a] Reactions conditions: 3−9 mol % [Ir]/dbtpy ([Ir] = $[Ir(COD)(OMe)]_2$), 1.5−2.5 equiv of HBpin, rt, 6−48 h. [b] Reaction conditions: 2 mol % (Ind)Ir(COD), 2 mol % dmpe, 1.5 equiv of HBpin, 150 °C, 16 h. [c] Isomer ratios determined by GC analysis and isomer identification based on NMR spectral data. [d] Isolated product. Isomers not separated.

substituent. The reaction of 3-substituted thiophenes with HBpin catalyzed by 1.5 mol % $[Ir(COD)(OMe)]_2$ and 3.0 mol % dtbpy yielded 2,3-disubstituted and 3,5-disubstituted thiophenes, but the major products were the 3,5-disubstituted thiophenes in most cases. 3-Cyanothiophene was the only substrate that yielded the 2,3-disubstituted thiophene as the major product, and there was only a slight preference for the formation of this product over the 3,5-disubstituted product. Reactions of 2,5-disubstituted thiophenes with HBpin in the presence of the combination of either $[Ir(COD)(OMe)]_2$ and dtbpy or (Ind)Ir(COD) and dmpe formed a mixture of 3- and 4-borylated thiophenes (Table 8). In general, the borylation of substituted thiophenes occurred adjacent to the more electron-withdrawing substituent.[98] Similar reactions of 2,3,5-trisubstituted thiophenes with HBpin did not yield borylated thiophenes. In one case, however, the reaction of 3-bromo-2,5-dichlorothiophene with HBpin catalyzed by the combination of (Ind)Ir(COD) and dmpe formed 2-(4-bromo-5-chloro-thiophen-2-yl)-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane in 73% yield (eq 4) from replacement of the less hindered chloride.



(4)

Along with the research groups of Ishiyama, Miyaura, Hartwig, Marder, and Maleczka and Smith, Beller and co-workers investigated the transition metal-catalyzed borylation of heteroaromatic systems.[66] Beller and co-workers tested 15 commercially available ruthenium, rhodium, iridium, and palladium complexes, in combination with a variety of phosphine and amine ligands, as catalysts for the borylation of arenes. All metal precursors tested in combination with PPh_3, PCy_3, TMEDA, or sparteine failed to catalyze the reaction of *m*-xylene with HBpin in high yield. Although they did not find a system to catalyze the reaction of HBpin with arenes, they did find conditions for the reaction of HBpin with thiophene, indole, benzothiophene, and benzofuran. The most reactive combination of iridium precursor and ligand for the borylation of heteroarenes was the combination of $[Ir(COD)Cl]_2$ and bpy previously described by Ishiyama, Miyaura, and Hartwig.[66]

Along with the borylation of 2-substituted thiophenes, furans, and pyrroles, the borylation of 2-substituted indoles with $[Ir(COD)(OMe)]_2$ and dtbpy has been investigated by several groups.[99,100] In 2006, Smith and co-workers reported that the borylation of 2-substituted indoles with this catalyst occurred selectively at the 7-position. They investigated the borylation of various indoles to probe selectivity and functional group compatibility, and these results are summarized in Table 9.[99] This iridium-catalyzed borylation of 2-substituted indoles containing halide, alkyl, nitrile, ester, amide, and silyl groups with HBpin yielded products exclusively from borylation at the 7-position. Smith and co-workers noted that the borylation of 2-phenyl indole with HBpin occurred selectively at the 7-position of the indole fragment without borylation of the 2-phenyl ring.

Beller and co-workers also investigated the borylation of 2-substituted indoles with B_2pin_2 catalyzed by $[Ir(COD)(OMe)]_2$ and dtbpy in heptane or dioxane at 50 or 100 °C. They conducted reactions of B_2pin_2 with indoles containing amide or ester substituents at the 2-position in the presence of $[Ir(COD)(OMe)]_2$ and dtbpy (Chart 9).[100]

Table 9. Borylation of 2-Substituted Indoles with HBpin Catalyzed by [Ir(COD)(OMe)]$_2$ and dtbpy

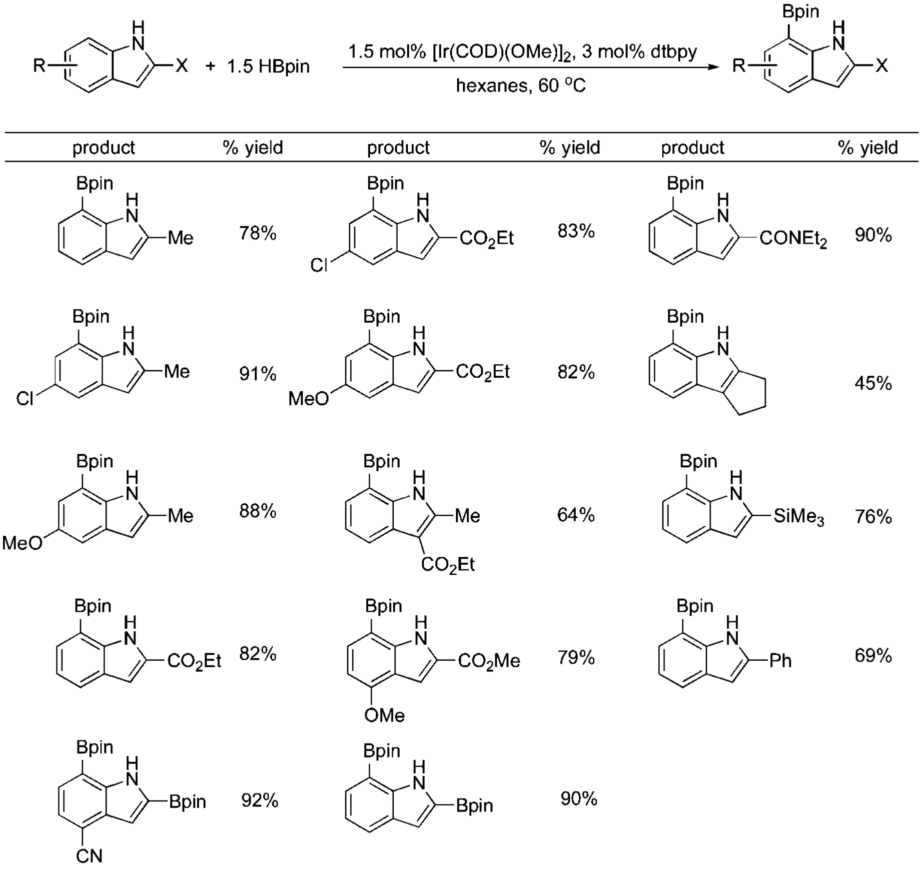
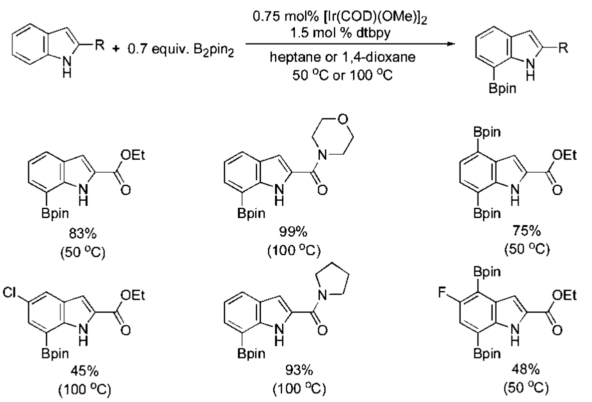


Chart 9. Borylation of 2-Substituted Indoles with B$_2$pin$_2$ Catalyzed by [Ir(COD)(OMe)]$_2$ and dtbpy



2,4,7-Trisubstituted indoles were selectively synthesized when the borylation reactions were run with excess B$_2$pin$_2$.[100] These authors hypothesized that the borylation of indole at the 7-position can be explained by an *ortho*-directing effect of the N−H bond of indoles.[100]

Smith and co-workers proposed three possible origins for the observed selectivity of the borylation of indoles: N−H activation of the indole, hydrogen bonding between a boryl ligand on the iridium center and the indole, or direct ligation of the indole to the iridium center (Figure 1). To test the potential that N−H activation leads to borylation at the 7-position, Smith and co-workers investigated the reaction of N-d_1-5-chloro-2-methylindole and HBpin in the presence of [Ir(COD)(OMe)]$_2$ and dtbpy. Inconsistent with a mechanism involving N−H activation, they did not observe incorporation of deuterium into HBpin or H$_2$ by ^{1}H and ^{11}B NMR spectroscopy. To test the potential that hydrogen bonding leads to borylation at the 7-position, they investigated the iridium-catalyzed reaction of *N*-methyl indole and benzofuran with excess HBpin, and they observed a mixture of diborylated products from both reactions. These studies, however, do not differentiate between hydrogen bonding or direct ligation because the observation of a mixture of diborylated *N*-methylindole products can be explained by either interaction. However, Hartwig and co-workers have identified Ir(dtbpy)(Bpin)$_3$ as the reactive intermediate in the iridium-catalyzed borylation of arenes,[80,81] and if this intermediate is the species that cleaves the C−H bond of indole, there are not a sufficient number of open coordination sites for both the direct ligation of the indole nitrogen at the metal center and the interaction of the C−H bond with the metal. A possible alternative interaction could

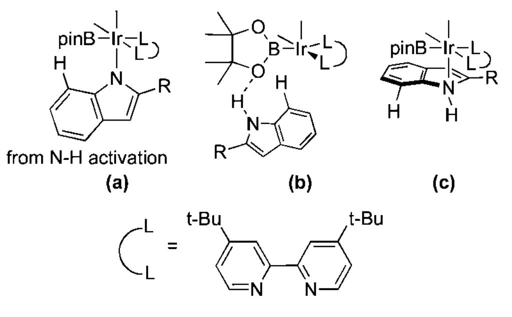


Figure 1. Possible interactions between Ir catalyst and indole leading to borylation of the 7-position.

Scheme 19. Borylation and Suzuki−Miyaura Coupling of 9-Benzyl-6-phenyl Pyrrolo[2,3-*d*]pyrimidine

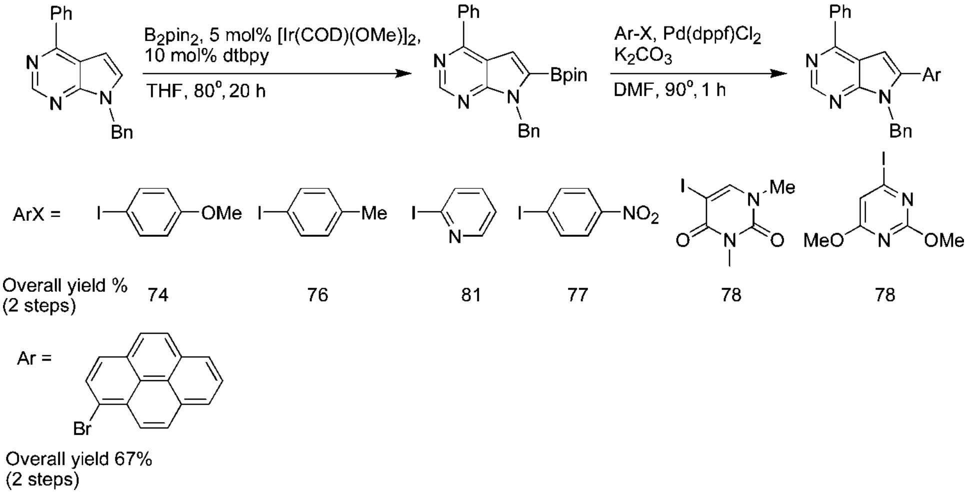
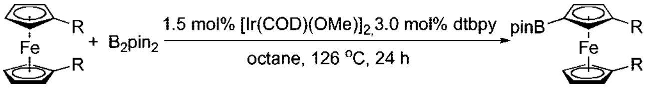


Table 10. Ir-Catalyzed Borylation of Substituted Ferrocenes



reactant	B_2pin_2 (equiv)	product	yield (%)
ferrocene	1.0	FcBpin	60
ferrocene	3.0	FcBpin	61
		1,1′-Fc(Bpin)$_2$	8
FcCO$_2$CH$_3$	1.5	1,3-FcBpin(CO$_2$CH$_3$)	42
		1,1′-FcBpin(CO$_2$CH$_3$)	31
FcBr	1.5	1,1′-FcBpin(Br)	28
		1,3′-FcBpin(Br)	35
1,1′-Fc(Br)$_2$	1.5	1,1′,3-FcBpin(Br)$_2$	81
1,1′-Fc(CH$_3$)$_2$	1.0	1,1′,3-FcBpin(CH$_3$)$_2$	12
1,1′-Fc(CH$_2$OCH$_3$)$_2$	1.0	1,1′,3-FcBpin(CH$_2$OCH$_3$)$_2$	15
CpMn(CO)$_3$	1.0	(CpBpin)Mn(CO)$_3$	79
CpMo(CO)$_3$Me	1.0	(CpBpin)Mo(CO)$_3$Me	82

involve the indole−nitrogen and a vacant p-orbital on a boryl ligand.

Hocek and co-workers[101] have employed the combination of [Ir(COD)(OMe)]$_2$ and dtbpy as catalyst for the borylation of pyrrolo[2,3-*d*]pyrimidines, followed by Suzuki−Miyaura cross-couplings. By this protocol, they prepared a series of 6,8-disubstituted 7-deazapurines (Scheme 19). In contrast, the reaction of 9-benzyl-6-phenylpurine did not form 8-borylated purine. This lack of reactivity was attributed to either the formation of a stable Ir−purine complex at N-7 or the possible instability of the purine-8-boronate ester to protodeborylation under the reaction conditions.

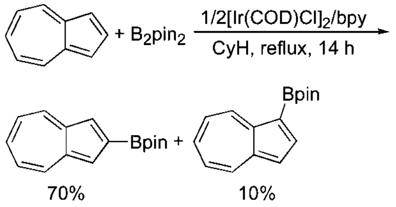
7.7. Borylation of Coordinated and Fused Arenes

The iridium-catalyzed borylation of arenes has also been used for the selective borylation of metallocenes and polycyclic arenes (Table 10). In 2004, Plenio and co-workers reported the reaction of ferrocenes with B$_2$pin$_2$ catalyzed by the combination of [Ir(COD)(OMe)]$_2$ and dtbpy.[102] The reaction of ferrocene with B$_2$pin$_2$ in the presence of [Ir(COD)(OMe)]$_2$ and dtbpy formed the monoborylated ferrocene (FcBpin) in 60% yield; diborylated ferrocene [1,1′-Fc(Bpin)$_2$] was observed as a side product in <5% yield. Reactions conducted with an excess of B$_2$pin$_2$ formed the monoborylferrocene as the major product. Studies on the scope of the reaction of substituted ferrocenes with B$_2$pin$_2$ catalyzed by [Ir(COD)(OMe)]$_2$ and dtbpy were conducted with ferrocenes containing electron-donating and electron-withdrawing substituents. The reactions of electron-deficient ferrocenes produced higher yields of ferrocenylboronic esters than did reactions of electron-neutral or electron-rich ferrocenes.

The borylation of half-sandwich complexes, such as CpMn(CO)$_3$ and CpMo(CO)$_3$Me, was also studied by Plenio and co-workers. CpMn(CO)$_3$ reacted with B$_2$pin$_2$ in the presence of [Ir(COD)(OMe)]$_2$ and dtbpy to form borylated CpMn(CO)$_3$ complexes in 79% yield. The reaction of CpMo(CO)$_3$Me with B$_2$pin$_2$ catalyzed by [Ir(COD)(OMe)]$_2$ and dtbpy yielded 82% (CpBpin)Mo(CO)$_3$Me from borylation of the Cp ligand (Table 10).

The iridium-catalyzed borylation has also been applied to the selective modification of polycyclic arenes. Like the borylation of heteroarenes and monocyclic arenes, this application highlights the complementary selectivity of iridium-catalyzed arene borylation, compared to that of other methods for arene functionalization, such as electrophilic aromatic substitution. For example, the direct borylation of azulene provides access to products that are difficult to obtain by electrophilic or nucleophilic aromatic substitution. Because of the polarization of the π-electrons of azulene, nucleophilic additions occur at the 4-, 6-, and 8-positions, whereas electrophilic substitutions occur at the 1- and 3-positions.[103,104] Functionalization at the 2-position commonly requires the installation of a directing group at either the 1- or 3-position, followed by subsequent functionalization at the 2-position.

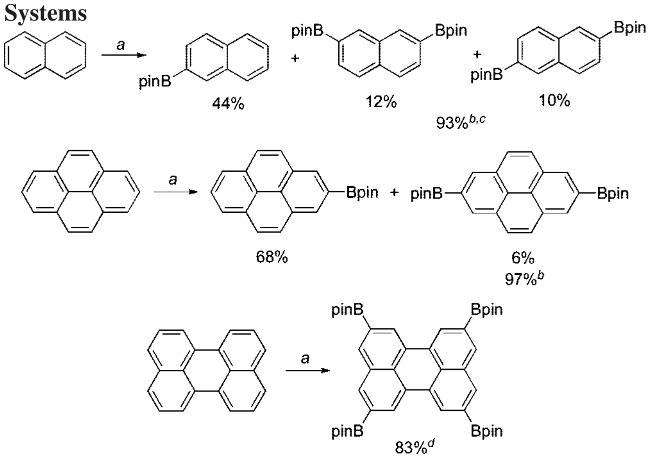
Sugihara and co-workers reported the reaction of azulene with B$_2$pin$_2$ catalyzed by [Ir(COD)Cl]$_2$ and bpy to yield 70% of the 2-borylated azulene and 10% of the 1-borylated azulene (eq 5).[105] Attempts by this group to conduct the alternative borylation of 2-iodoazulene with B$_2$pin$_2$ catalyzed by Pd(dppf)Cl$_2$ yielded only 42% of the desired 2-borylated azulene, along with 22% of an undesired dimeric byproduct.[106] While azulene underwent borylation in high yield, there were limitations in the scope of this process. Azulenes containing either formyl or hydroxymethyl substitutes did not react under these conditions. Also, azulenes containing alkyl substituents located *ortho* to the five-membered ring reacted to form borylated products in low yield. The authors postulated that the active iridium catalyst binds in an η^2-mode to the five-membered ring prior to borylation. Electron-withdrawing substituents would then decrease the π-basicity of the azulene, and substituents located *ortho* to the 5-membered ring would sterically hinder coordination. Both properties were proposed to decrease the binding of the substrate and, thereby, to decrease the yield of borylated azulene product.



(5)

Marder and co-workers have also investigated the borylation of polycyclic systems, such as naphthalene, pyrene, and perylene (Scheme 20).[107] The reaction of naphthalene with 1.1 equiv of B_2pin_2 in the presence of 5 mol % $[Ir(COD)(OMe)]_2$ and 10 mol % dtbpy in cyclohexane yielded 2-borylated naphthalene in 44% yield, 2,6-diborylated naphthalene in 10% yield, and 2,7-diborylated naphthalene in 12% yield. Reactions of naphthalene with excess B_2pin_2 catalyzed by 5 mol % $[Ir(COD)(OMe)]_2$ and 10 mol % dtbpy formed a 1:1 mixture of 2,6- and 2,7-diborylated naphthalene in 93% yield.

Scheme 20. Ir-Catalyzed Borylation of Polycyclic Aromatic Systems



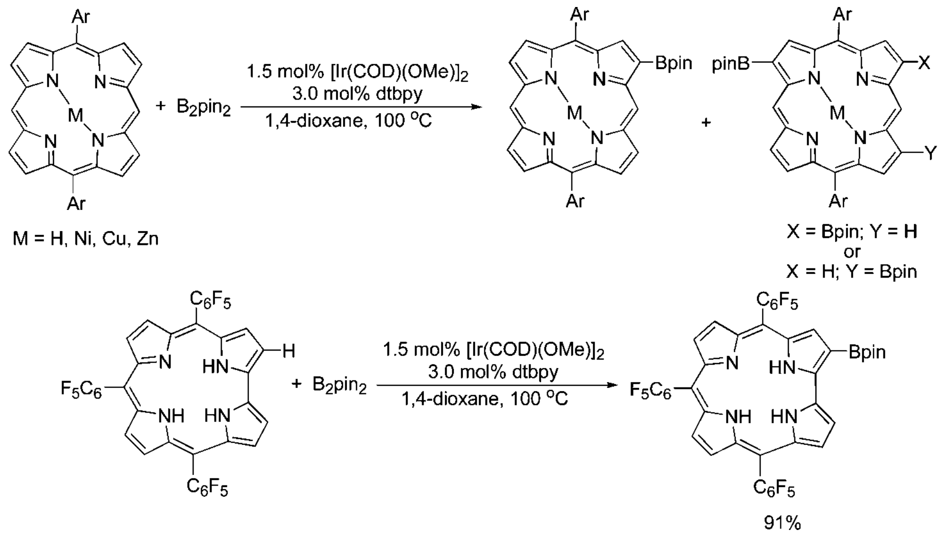
[a] Standard reaction conditions: 5 mol % $[Ir(COD)(OMe)]_2$, 10 mol % dtbpy, 1.1 equiv of B_2pin_2 in CyH at 80 °C for 16 h. [b] Five mol % $[Ir(COD)(OMe)]_2$, 10 mol % dtbpy, 2.2 equiv of B_2pin_2 in CyH at 80 °C. [c] Combined yield of both isomers. [d] Five mol % $[Ir(COD)(OMe)]_2$, 10 mol % dtbpy, 4.4 equiv of B_2pin_2 in CyH at 80 °C.

The analogous reactions of larger fused polycyclic arenes were more selective.[107] The reaction of pyrene with 1.1 equiv of B_2pin_2 catalyzed by $[Ir(COD)(OMe)]_2$ and dtbpy yielded 68% of 2-pyrylboronic ester and 6% of 2,7-diborylated pyrene. When 2.2 equiv of B_2pin_2 were employed, the 2,7-diborylated pyrene was isolated in 97% yield. It should be noted that electrophilic substitution takes place at the 1-, 3-, 6-, and 8-positions of pyrene, and thus, pyrene chemistry is dominated by derivatives at these positions. Thus, the sterically determined selectivity of the iridium-catalyzed borylation reaction allows, for the first time, the potential for direct synthesis of a wide variety of derivatives at the 2-, or 2,7-positions, which has important consequences for the design of luminescent reagents, electronic materials, and rigid-rod-based structural motifs. The borylation of perylene with 4.4 equiv of B_2pin_2 catalyzed by $[Ir(COD)(OMe)]_2$ and dtbpy yielded tetraborylated perylene in 83% yield (Scheme 20). As expected, the reaction of perylene with less than 4 equiv of B_2pin_2 yielded a mixture of monoborylated, diborylated (three isomers), triborylated (two isomers), and tetraborylated perylene.

Kobayashi and co-workers reported the borylation of tetracene with the combination of [Ir(COD)(OMe)] and dtbpy to give 80% yield of a 1:1 mixture of 2,8- and 2,9-diboryl tetracenes that were separated by recrystallization.[108] These products, which are homologues of the diboryl napthalenes prepared by Marder and co-workers,[107] were subsequently employed in the regiospecific synthesis of extended π-conjugated tetracenes of interest for applications in semiconductors and organic field-effect transistors (OFETs).

Along with the borylation of polyaromatic systems with B_2pin_2 catalyzed by iridium catalysts, researchers have reported the borylation of polyheteroaromatic systems catalyzed by iridium complexes. Shinokubo, Osuka, and co-workers have published several reports describing the borylation of porphyrin and corrole systems with B_2pin_2 catalyzed by the combination of $[Ir(COD)(OMe)]_2$ and dtbpy (Scheme 21).[109-112] The borylation of *meso*-arylporphyrins or corroles[109-111] with B_2pin_2 catalyzed by the combination of $[Ir(COD)(OMe)]_2$ and dtbpy yielded

Scheme 21. Ir-Catalyzed Borylation of Porphyrins and Corroles



porphyrins functionalized exclusively at the β-positions or 2-boryl corrole, respectively. They demonstrated the utility of the β-borylated porphyrins either by further functionalizing the porphyrins at the *meso*-position or performing Suzuki−Miyaura cross-coupling reactions with aryl halides. In addition, they investigated the borylation of extended porphyrins; specifically, reaction of hexakis(2,6-dichlorophenyl)[28]-hexaphyrin(1.1.1.1.1.1)[112] with 24 equiv of B_2pin_2 catalyzed by 10 mol % $[Ir(COD)(OMe)]_2$ and 20 mol % dtbpy yielded 81% of the hexaborylated hexaphyrin as a single isomer.

7.8. Mechanistic Studies of (bpy)Ir-Catalyzed Arene Borylations

Ishiyama, Miyaura, Hartwig, and co-workers reported extensive studies that provided insight into the mechanism of arene borylation catalyzed by the combination of iridium precursors and dtbpy.[80,81] Initial studies focused on the synthesis of iridium−boryl complexes from B_2pin_2, and both [Ir(COD)(dtbpy)Cl] and [Ir(COD)(dtbpy)]OTf. The reaction of [Ir(COD)(dtbpy)Cl] with B_2pin_2 did not provide an iridium−boryl complex. However, the reaction of [Ir(COD)(dtbpy)]OTf with B_2pin_2 in tetrahydrofuran (THF) formed the iridium(III) bisboryl complex *cis*-$[Ir(COD)(dtbpy)(Bpin)_2]$OTf. This complex catalyzed the borylation of benzene, yielding 80% PhBpin in 5 h at 80 °C, but it did not produce PhBpin when heated in C_6D_6. Instead, this complex extruded B_2pin_2. Therefore, *cis*-$[Ir(COD)(dtbpy)(Bpin)_2]$OTf generates an active catalyst, but this cationic species is not the iridium−boryl complex that directly reacts with arenes to form arylboronate esters.

Spectroscopic studies of the catalytic system and isolation of additional iridium−boryl complexes did lead to the identification of the active catalyst. From a catalytic reaction containing 10 mol % $[Ir(COE)_2Cl]_2$, 20 mol % dtbpy, and 10 equiv of B_2pin_2 in mesitylene, $[Ir(dtbpy)(\eta^2\text{-COE})(Bpin)_3]$ was isolated in 15% yield.[80] The reaction of $[Ir(dtbpy)(\eta^2\text{-COE})(Bpin)_3]$ with benzene yielded 3 equiv of PhBpin at room temperature. This reactivity of the trisboryl complex provided direct evidence that $[Ir(dtbpy)(\eta^2\text{-COE})(Bpin)_3]$ is an intermediate or leads directly to an intermediate in this borylation system (Figure 2).

Hartwig, Ishiyama, and Miyaura later reported an improved synthesis of $[Ir(dtbpy)(\eta^2\text{-COE})(Bpin)_3]$ that provided quantities that were sufficient for detailed mechanistic studies.[81] After much experimentation, $[Ir(dtbpy)(\eta^2\text{-COE})(Bpin)_3]$ was isolated in 80−95% yield by the sequence shown in eq 6.[81] Several features of this process were important. First, the reaction occurred in high yield with $[Ir(COD)(OMe)]_2$ as the iridium source. This result fits with the general result that the most active catalysts are generated from $[Ir(COD)(OMe)]_2$. Second, the reaction occurred in high yield when HBpin and COE were added before the bipyridine ligand. The species formed initially from these reagents was not identified, but the more intuitive addition of ligand before borane led to low yields of the trisboryl complex.

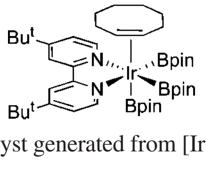
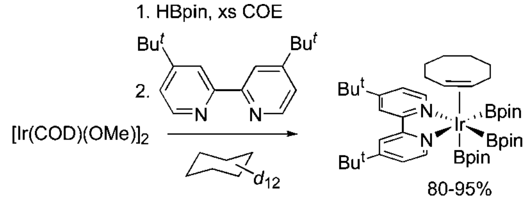


Figure 2. Active catalyst generated from $[Ir(COD)(OMe)]_2$, dtbpy, and B_2pin_2.



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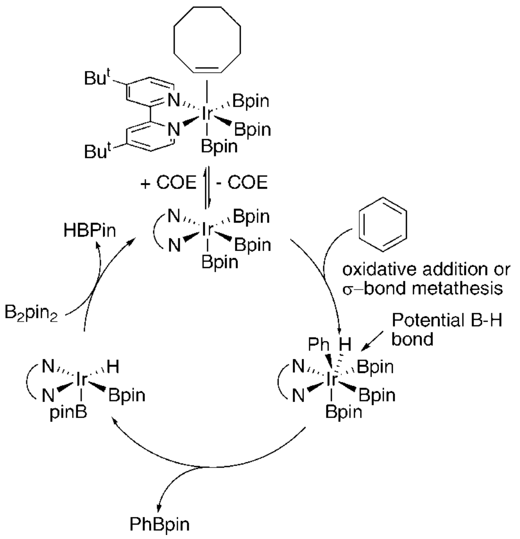
Hartwig and co-workers then conducted studies on the reactivity of $[(dtbpy)(\eta^2\text{-COE})Ir(Bpin)_3]$.[81] The reaction of $[Ir(dtbpy)(\eta^2\text{-COE})(Bpin)_3]$ with arenes yielded 3 equiv of ArBpin. The yields and regioselectivities of the borylated products observed from the reaction of $[Ir(dtbpy)(\eta^2\text{-COE})(Bpin)_3]$ and arenes were similar to those of the borylated products observed from the reaction of arenes and B_2pin_2 catalyzed by the combination of $[Ir(COD)(OMe)]_2$ and dtbpy.

Two different types of iridium complexes were considered as possible intermediates that cleave the C−H bond of the arene. Either the Ir(III) complex $[Ir(dtbpy)(Bpin)_3]$, formed by dissociation of COE, or the Ir(I) complex [Ir(dtbpy)(Bpin)], formed by a combination of dissociation of COE and reductive elimination of B_2pin_2, could cleave C−H bonds of arenes. To investigate the identity of the catalytic intermediates, Hartwig and co-workers studied the borylation of 1,2-dichlorobenzene with $[Ir(dtbpy)(\eta^2\text{-COE})(Bpin)_3]$ in the presence of $B_2pin_2\text{-}d_{24}$ in cyclohexane. The formation of ArBpin was observed by ^{1}H NMR spectroscopy, prior to the formation of B_2pin_2. If B_2pin_2 underwent reductive elimination from $[Ir(dtbpy)(\eta^2\text{-COE})(Bpin)_3]$, the formation of B_2pin_2 prior to the formation of ArBpin and ArBpin-d_{24} would be observed, but this was not the case. These results provided strong evidence that the trisboryl iridium−dtbpy complex is the active catalytic species generated from $[Ir(COD)(OMe)]_2$, dtbpy, and B_2pin_2. The observation by Marder and co-workers[96] that dtbpy undergoes borylation only when present in excess (vide supra) is consistent with the conclusion that the dtbpy ligand remains bound to the active catalyst.

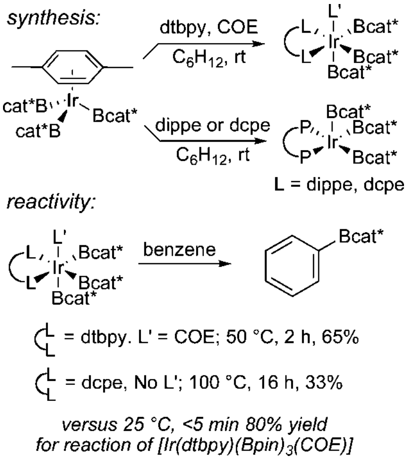
Detailed kinetic studies of the reaction of arenes with B_2pin_2 catalyzed by $[Ir(dtbpy)(\eta^2\text{-COE})(Bpin)_3]$ in a mixture of cyclohexane and cyclohexane-d_{12} revealed that the borylation of arenes is first-order in arene, zero-order in B_2pin_2, and inverse first-order in COE. The reaction is first-order in catalyst in the presence of added COE, but one-half-order in catalyst in the absence of added COE due to the reversible generation of equimolar amounts of COE and the 16-electron, trisboryl reactive intermediate. Isotope effects of the catalytic borylation reaction were measured by conducting the reaction with a mixture of protiated and deuterated arenes and by obtaining the rate constants for the separate reactions of protiated and deuterated arenes. Primary kinetic isotope effects were observed for reactions of benzene and 1,2-dichlorobenzene under both conditions. These data indicated that C−H bond cleavage occurs during the turnover-limiting step of the catalytic cycle.

On the basis of these data obtained from NMR spectroscopy of catalytic systems, isolation of kinetically competent intermediates, and kinetic data, Hartwig and co-workers proposed the mechanism shown in Scheme 22 for the borylation of arenes catalyzed by dtbpy-ligated complexes of iridium. First, COE dissociates reversibly from the stable iridium trisboryl complex. The resulting 16-electron complex then reacts with the arene in a turnover-limiting step to form the arylboronate ester. This latter process likely occurs by coordination of arene and subsequent oxidative addition of

Scheme 22. Proposed Mechanism for the Iridium-Catalyzed Borylation of Arenes



Scheme 23. Synthesis and Reactivity of Variants of [Ir(dtbpy)(Bpin)$_3$(COE)]



the aryl C−H bond to form an iridium(V) intermediate. Reductive elimination of Ph−Bpin from the iridium(V) intermediate then forms the free functionalized product and an iridium(III) species. A combination of oxidative addition of B$_2$pin$_2$ and reductive elimination of HBpin would then regenerate the active iridium trisboryl complex. Alternatively, a type of σ-bond metathesis between [Ir(dtbpy)(Bpin)$_3$] and Ph−H could produce an intermediate phenyliridium complex containing a coordinated borane [Ir(dtbpy)(Bpin)$_2$(HBpin)(Ph)]. This phenyliridium complex would eliminate PhBpin to generate the same bisboryliridium hydride complex as would be formed by the sequence of C−H oxidative addition and B−C reductive elimination.

Hartwig and co-workers recently reported studies to probe the electronic effects of the boryl and dative ligands on the rate of the C−H borylation by {IrL$_2$[B(OR)$_2$]$_3$} intermediates.[113] To do so, they prepared the dtbpy complex containing three 4-*tert*-butylcatecholboryl (Bcat*) ligands and a bisphosphine complex containing the same three catecholboryl ligands (Scheme 23). These studies show that the type of dioxaborolanyl ligand has a pronounced effect on the reactivity of the boryl complexes with arenes. The dtbpy-ligated tris-Bcat* complex reacted much more slowly with arenes than did the analogous Bpin complex. The substituents at oxygen on the boryl ligands significantly affected the electron density at the metal; the ν_{CO} value for the Bcat* complex was higher than that of the Bpin complex by 30 cm^{-1}. Calculations by DFT methods implied that this difference in electronic properties led to a larger difference in energy between 16-electron iridium(III) complexes and 18-electron iridium(V) aryl hydride complexes for the complex containing the Bcat ligands than for the complex containing Bpin ligands.

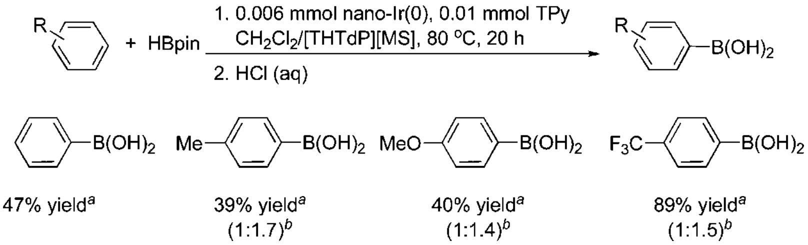
Hartwig and co-workers[113] and Smith and co-workers[114] also prepared 16-electron, phosphine-ligated complexes that were direct analogues of the 16-electron reactive intermediate [Ir(dtbpy)(Bpin)$_3$]. Hartwig and co-workers prepared the 1,2-bis(diisopropylphosphino)ethane (dippe) and 1,2-bis(dicyclohexylphosphino)ethane complexes containing Bcat ligands to compare the reactivity of this intermediate to that generated from [Ir(dtbpy)(Bcat*)$_3$]. One might expect that these complexes would react readily with arenes because they contain an open coordination site. However, consistent with the lower catalytic activity of the complexes containing bisphosphine ligands, this complex reacted more slowly than the tris-Bcat* complex containing dtbpy as ligand. The reaction of benzene with [Ir(dippe)(Bcat*)$_3$] required 100 °C over 16 h and gave only one equivalent of arylboronate ester per trisboryl complex. The reaction of [Ir(dippe)(Bpin)$_3$] with benzene was not reported in the paper by Smith et al.,[114] but the reaction of [Ir(dippe)(Bpin)$_3$] with the more reactive 1,3-bistrifluoromethylbenzene required 48 h at room temperature for full conversion. These times contrast with the reaction of 1,3-bistrifluoromethylbenzene with [Ir(dtbpy)(Bpin)$_3$(COE)] within minutes at room temperature or within a few hours at 0 °C.[81]

In 2003, Sakaki and co-workers published results of a theoretical investigation of the borylation of arenes catalyzed by a simplified model of (dtbpy)Ir intermediates.[9] Bis(ethyleneglyolato)diboron (B$_2$eg$_2$) was the model for B$_2$pin$_2$, and ethane-1,2-diylidenediamine (diim) was the model for dtbpy. From their calculations, Sakaki and co-workers concluded that a tris(boryl)iridium(III) complex was the active catalytic species, and this conclusion is in agreement with the experimental results described by Hartwig and co-workers.[81] By Sakaki's mechanism, the C−H bond of an arene undergoes oxidative addition to the Ir(diim)(Beg)$_3$ complex to form an iridium(V) intermediate that is stabilized by the electron-rich dtbpy ligand and by the strong σ-donation by the boryl ligands. Reductive elimination of arylboronate ester from the iridium(V) intermediate was calculated to be facile, and oxidative addition of a second equivalent of B$_2$eg$_2$ was then proposed to regenerate the active Ir(diim)(Beg)$_3$ intermediate.

7.9. Borylation of Arenes Catalyzed by Iridium Nanoparticles

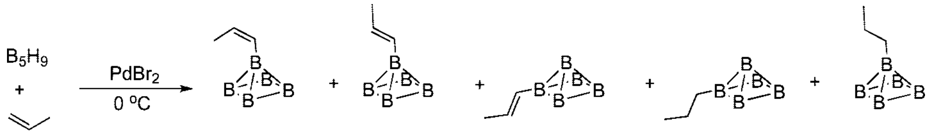
Recently, Yinghuai and co-workers described the borylation of arenes with HBpin catalyzed by iridium(0) nanoparticles (Chart 10).[115] They synthesized iridium(0) nanoparticles from the reduction of the iridacarborane complex 3,3-(Ph$_3$P)$_2$-3-H-3,1,2-IrC$_2$B$_9$H$_{11}$ in ethylene glycol under 10 bar of hydrogen. The reaction of arenes with HBpin catalyzed by the combination of Ir(0) nanoparticles and an initiator, *tetra*-2-pyridinylpyrazine (Tpy), in the ionic liquid trihexyltetradecylphosphonium methylsulfonate [THTdP][MS] under microwave irradiation (80 °C, 20 h) yielded the arylboronate ester. The arylboronate esters were hydrolyzed with HCl, and the borylation products were isolated as arylboronic

Chart 10. Arene Borylation and Hydrolysis to Arylboronic acids with Iridium(0) Nanoparticles Followed by Acidification



[a] Ten-fold excess of arene used with respect to HBpin. Isolated yield after hydrolysis and chromatography. [b] Ratio of *meta*/*para*-borylated arylboronic acids.

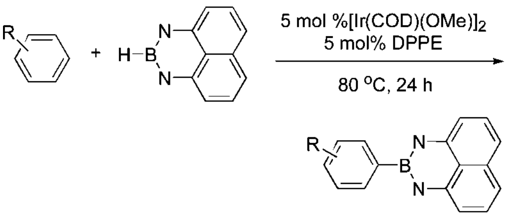
Scheme 24. PdBr$_2$-Catalyzed Dehydrogenative Borylation of Propene with Pentaborane by Sneddon and Coworkers (Note: Terminal and Bridging Hydrogens on the Boron Cluster Are Omitted for Clarity)



acids. The borylation of four arenes was studied by this method, and the products were formed in modest yields in most cases.

7.10. Iridium-Catalyzed Borylation of Arenes With 1,8-Naphthalenediaminato Borane

In all of the examples of both stoichiometric and metal-catalyzed C−H borylation reactions described in this review thus far, the only boron sources that have been used for these chemistries are HBpin and B$_2$pin$_2$. In 2009, Suginome and co-workers described the borylation of arenes with 1,8-naphthalenediaminatoborane (HBDan) catalyzed by iridium (eq 7).[116,117] They optimized the reaction of HBDan with neat benzene catalyzed by the combination of an iridium(I) precursor and a ligand, and the highest yields of ArBDan were obtained when the reactions were catalyzed by the combination of [Ir(COD)(OMe)]$_2$ and 1,2-bis(diphenylphosphino)ethane (DPPE) at 80 °C.[117] Electron-rich and electron-poor arenes as solvent were allowed to react with HBDan in the presence of [Ir(COD)(OMe)]$_2$ and DPPE to produce ArBDan in moderate to good yields. Monosubstituted arenes yielded a mixture of *meta*- and *para*-boryl products, and 1,3-disubstituted arenes yielded 1,3,5-trisubstituted products.



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7.11. Dehydrogenative Borylation of Olefins

Vinyl boronate esters (VBEs) are useful intermediates in organic chemistry. They have been employed as precursors to aldehydes and alkenyl halides and can undergo a range of metal-catalyzed reactions. Alkenylboron reagents can be synthesized by a variety of methods including hydroboration of alkynes,[118] palladium catalyzed borylation of alkenyl halides,[119] lithiation of alkenyl halides and subsequent trapping with trialkylborates,[120] hydrogenation of 1-borylalkynes,[121] hydrozirconation of 1-borylalkynes,[122] cross-metathesis of terminal olefins with pinacolvinylboronate and related alkenylboronate esters,[123−127] transmetalation of alkenyl metal reagents,[128] and transition metal-catalyzed diboration of alkynes with diboron reagents.[129−133] However, the majority of these methods involve the preactivation of the vinyl group or are unsuitable for the synthesis of β,β-disubstituted vinylboronates or cyclic vinylboronates. Thus, the dehydrogenative borylation of olefins, in which a vinylic C−H bond is replaced with a C−B bond, is an attractive alternative to these methods. It does not require the preactivation of the olefin substrates, and it can be used to form VBEs from β,β-disubstituted and cyclic olefins.

Although the data pertaining to the mechanism of C−H borylations of alkenes are scattered, two general mechanisms are likely followed. By one pathway, insertion of an alkene into a metal−boryl complex leads to a β-borylalkyl complex that undergoes β-hydrogen elimination. In this case, the C−H bond cleavage occurs by a much different mechanism than that discussed in the bulk of this revew. By a second pathway, C−H bond cleavage by a metal−boryl complex leads to a vinylmetal species that undergoes B−C bond formation.

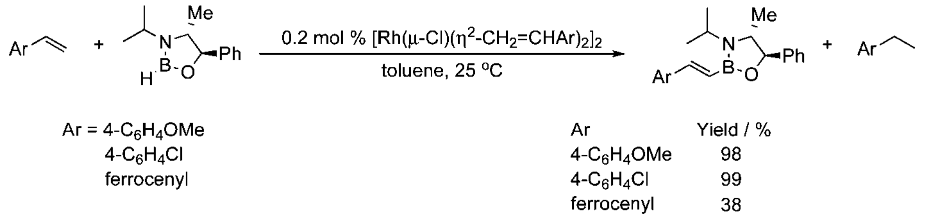
7.11.1. Dehydrogenative Borylation of Olefins Using Borane Clusters

Sneddon and co-workers reported the first dehydrogenative borylations of olefins.[134−136] The borylation of ethene, but-1-ene, and propene was reported to occur with pentaborane in the presence of PdBr$_2$ as a catalyst (Scheme 24). However, the borylation of propene led to the formation of three isomeric propenylboranes, along with two hydroboration products. This reaction also formed 50% alkane because the olefin was hydrogenated with the hydrogen that was formed in the dehydrogenative borylation process.

7.11.2. Dehydrogenative Borylation of Olefins with Concomitant Hydrogenation and/or Hydroboration

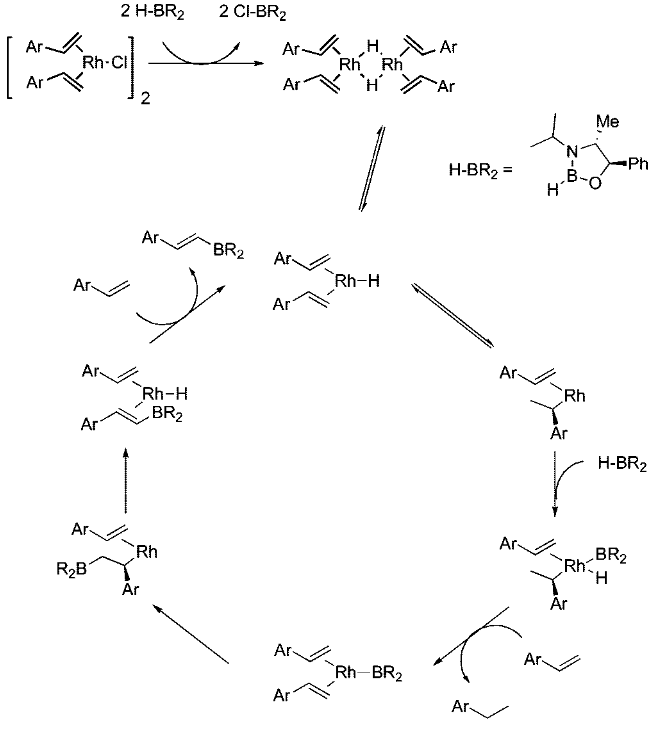
In 1992, Brown and Lloyd-Jones reported the dehydrogenative borylation of 4-vinylanisole with an oxazaborolidene in the presence of [Rh(μ-Cl)(η^2-CH$_2$=CHAr)$_2$]$_2$, (Ar = 4-MeOC$_6$H$_4$) as catalyst.[137] Reactions in toluene at room temperature gave a 1:1 mixture of VBE and hydrogenation products. In a subsequent publication by the same group, borylations of 4-vinylanisole, 4-vinylchlorobenzene, and

Scheme 25. Rhodium-Catalyzed Dehydrogenative Borylations of Vinylarenes by Brown et al



Ar	Yield / %
4-C_6H_4OMe	98
4-C_6H_4Cl	99
ferrocenyl	38

Scheme 26. Proposed Mechanism for the Rhodium-Catalyzed Dehydrogenative Borylations of Vinylarenes by Brown et al



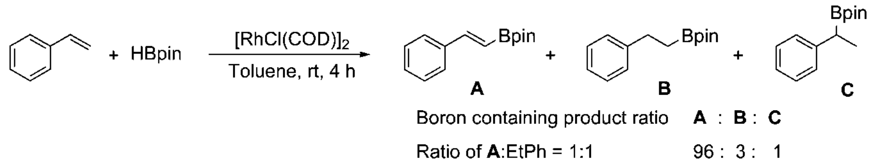
vinylferrocene with oxazaborolidene and 0.2 mol % $[\mathrm{Rh}(\mu\text{-Cl})(\eta^2\text{-CH}_2{=}\text{CHC}_6\text{H}_4\text{-4-OMe})_2]_2$ gave a 1:1 ratio of VBE and hydrogenation products.[138] No products from hydroboration were observed (Scheme 25).

The proposed mechanism of Brown's rhodium catalyzed dehydrogenative borylation of vinylarenes is detailed in Scheme 26. Initial reaction of the borane species with $[\mathrm{Rh}(\mu\text{-Cl})(\eta^2\text{-CH}_2{=}\text{CHAr})_2]_2$ is proposed to lead to the formation of a dimeric hydride complex that acts as a source of the active monomeric rhodium hydride. Reversible 1,2-insertion of one of the bound olefin ligands into the Rh−H bond then gives the 12-electron complex containing an alkene and an alkyl ligand, which oxidatively adds the oxazaborolidene B−H bond. Reductive elimination of alkane and coordination of additional olefin would then give a rhodium bisalkene boryl complex, which may insert one of the olefin ligands into the Rh−B bond to give a rhodium β-borylalkyl species. Subsequent β-hydride elimination gives a rhodium alkene vinylboronate hydride complex from which the bound VBE product is displaced by unreacted olefin to regenerate the bisalkene rhodium hydride and complete the catalytic cycle.

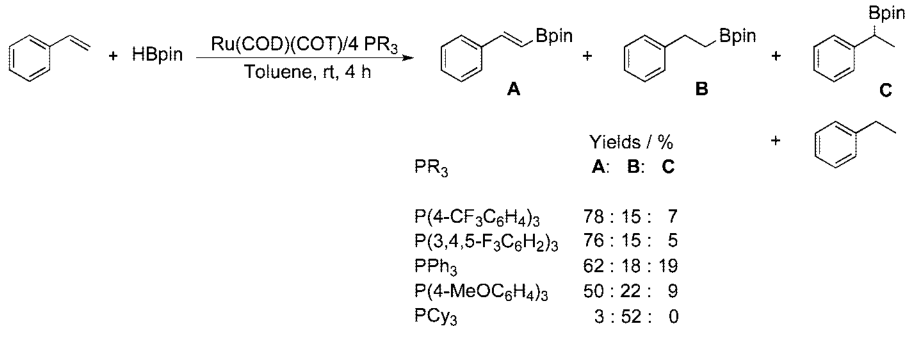
Masuda and co-workers have reported the dehydrogenative borylation of olefins with HBpin catalyzed by $[\mathrm{RhCl(COD)}]_2$ at room temperature in toluene (Scheme 27).[139] This reaction is clearly reminiscent of the reaction catalyzed by $[\mathrm{Rh}(\mu\text{-Cl})(\eta^2\text{-olefin})_2]_2$ reported by Brown and Lloyd-Jones.[137] VBE products were obtained in high yields with respect to HBpin and with selectivities as high as 96%; however, in all cases, an equal quantity of the ethylarene byproduct resulting from the sacrificial hydrogenation of the substrate was formed. In addition, Masuda and co-workers reported the synthesis of an unsymmetrical stilbene by a one-pot sequence of dehydrogenative borylation, followed by Suzuki−Miyaura cross-coupling.

Masuda and co-workers also reported dehydrogenative borylations of vinylarenes catalyzed by 1:4 mixtures of [Ru(COD)(COT)] (COD = 1,5-cyclooctadiene and COT = 1,3,5-cyclooctatriene) and monodentate phosphines to give (E)-vinylboronate products (Scheme 28).[140] These catalysts were less active than those based on rhodium. Reactions

Scheme 27. Rhodium-Catalyzed Dehydrogenative Borylation of Olefins by Masuda and Co-workers

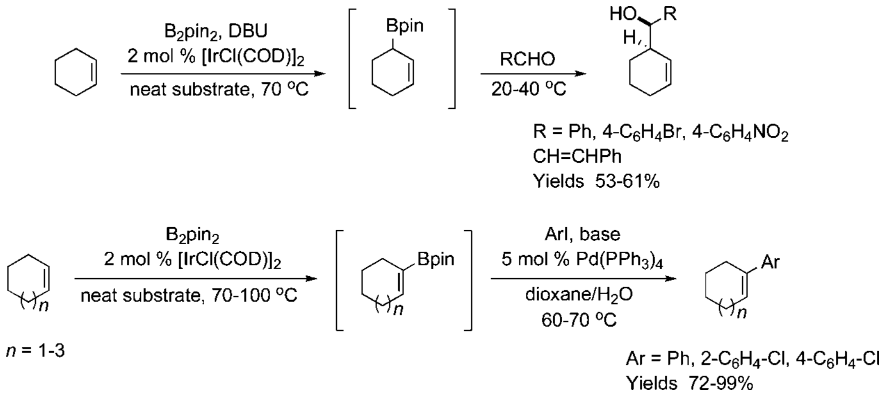


Scheme 28. Ruthenium-Catalyzed Dehydrogenative Borylation of Olefins by Masuda and Co-workers



PR_3	Yields / % A: B: C
$P(4\text{-}CF_3C_6H_4)_3$	78 : 15 : 7
$P(3,4,5\text{-}F_3C_6H_2)_3$	76 : 15 : 5
PPh_3	62 : 18 : 19
$P(4\text{-}MeOC_6H_4)_3$	50 : 22 : 9
PCy_3	3 : 52 : 0

Scheme 29. Iridium-Catalyzed Borylations of Cyclic Olefins by Szabó and Co-workers



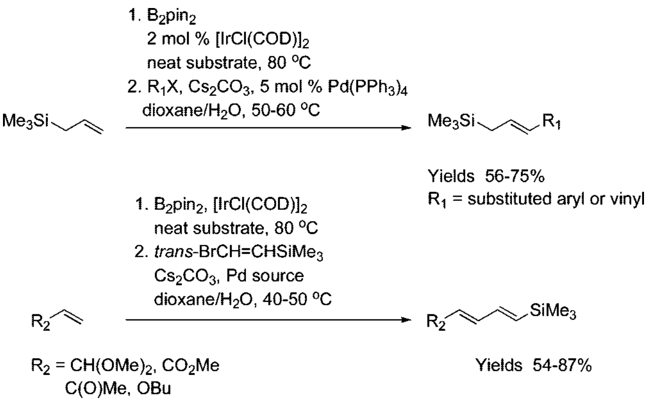
catalyzed by complexes containing phosphine ligands possessing electron-deficient aryl groups occurred with higher selectivities for dehydrogenative borylation over hydroboration, while those catalyzed by complexes of PCy_3 gave products resulting almost exclusively from hydroboration. In all cases, dehydrogenative borylation was accompanied by hydrogenation of the olefin. The proposed catalytic cycle involves the addition of two molecules of vinylarene to the ruthenium center, dehydrogenative borylation of one of the two vinylarenes and hydrogenation of the second.

Sabo-Etienne and co-workers have reported the dehydrogenative borylation of linear and cyclic olefins with HBpin in the presence of $[Ru(H)_2(H_2)_2(PCy_3)_2]$ and $[RuH\{(\mu\text{-}H)_2Bpin\}(\sigma\text{-}HBpin)(PCy_3)_2]$ as catalyst precursors.[141] The reaction of HBpin with $[Ru(H)_2(H_2)_2(PCy_3)_2]$ formed H_2 and $[RuH\{(\mu\text{-}H)_2Bpin\}(\sigma\text{-}HBpin)(PCy_3)_2]$. The reaction of this complex with ethene formed $[RuH(Bpin)(C_2H_4)(PCy_3)_2]$, and this complex was proposed to be the catalyst resting state. A range of linear and cyclic olefins underwent dehydrogenative borylation at room temperature, leading to mixtures of VBEs, hydroboration products, and alkanes from sacrificial hydrogenation of the substrates.

Szabó and co-workers reported the dehydrogenative borylation of cyclic olefins with B_2pin_2 catalyzed by $[IrCl(COD)]_2$ (Scheme 29).[142] Reactions of cyclohexene gave a 1:1 ratio of allylic and vinylic borylation products after 3 h at 70 °C, while only the vinylic borylation product was observed after 16 h. Addition of 0.5 equiv of 1,8-diazabicyclo[5.4.0]undecane (DBU) led to an increase in the ratio of allylic to vinylic products (5:1 after 3 h at 70 °C), although the proportion of the vinylic product increased with prolonged heating. At 90−100 °C, the borylation reactions gave equimolar amounts of vinylboronate esters and their saturated counterparts, with the latter resulting from sacrificial hydroboration of the substrate. The vinylboronate products were coupled in situ with aryl iodides to give cyclic trisubstituted olefins, whereas the allylic boronates were treated with aldehydes in situ to give stereodefined homoallylic alcohol products.

Szabó also reported the dehydrogenative borylation of certain linear, terminal olefins with $[IrCl(COD)]_2$ and B_2pin_2 at 80 °C to give vinylboronate esters, which were then coupled with a range of aryl and vinyl halides in a one-pot process (Scheme 30).[143] Allylsilanes and olefins substituted with carbonyl, acetal, and alkoxy substituents underwent dehydrogenative borylation to give 1:1 ratios of vinyl- and alkylboronate ester products, with the latter resulting from hydroboration by the HBpin generated by the dehydrogenative borylation with B_2pin_2. Of particular interest was the selective formation of VBEs over allylboronates from the reaction of B_2pin_2 with allyltrimethylsilane. This selectivity was attributed to a greater thermodynamic stability of the VBE product and a more favorable β-hydride elimination step.

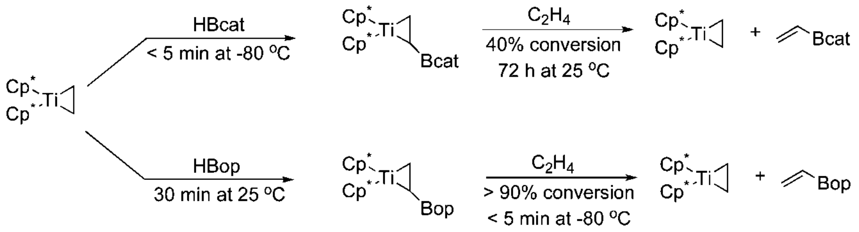
Scheme 30. Iridium-Catalyzed Dehydrogenative Borylation of Olefins and Subsequent Cross-coupling by Szabó and Co-workers



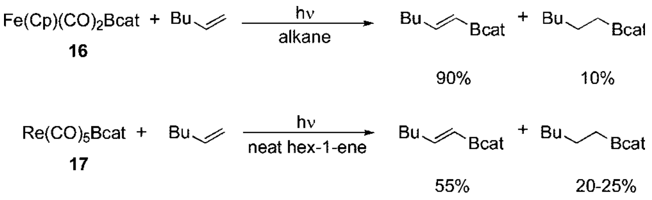
Smith and co-workers reported the reactions of ethene with monoboranes catalyzed by 3 mol % $[Cp^*_2Ti(\eta^2\text{-}CH_2{=}CH_2)]$.[144,145] The catalytic reaction using HBop (op = benzo-1,2,3-diazaborolene) gave VBE (58% yield) and ethane. In contrast, catalytic reactions conducted with HBcat gave the hydroboration product, ethylBcat, instead of the corresponding VBE. Stoichiometric addition of HBcat or HBop to $[Cp^*_2Ti(\eta^2\text{-}CH_2{=}CH_2)]$ led to the formation of boryl-substituted titanacycles, which underwent ligand exchange with additional ethene to regenerate $[Cp^*_2Ti(\eta^2\text{-}CH_2{=}CH_2)]$, and gave the VBE products. Borylation of $[Cp^*_2Ti(\eta^2\text{-}CH_2{=}CH_2)]$ with HBop to give $[Cp^*_2Ti(\eta^2\text{-}CH_2{=}CHBop)]$ was much slower than that with HBcat; however, subsequent displacement of the VBE by ethene was much faster for the Bop analogue $[Cp^*_2Ti(\eta^2\text{-}CH_2{=}CHBop)]$ than for the Bcat compound $[Cp^*_2Ti(\eta^2\text{-}CH_2{=}CHBcat)]$ (Scheme 31).

Zirconocene and hafnocene complexes of butadiene were shown to react stoichiometrically with excess 9-BBN (9-BBN = 9-borabicyclo[3.3.1]nonane) at 100 °C to give the analogous complexes of 1-boryl-butadiene by an as-yet-unknown mechanism.[146] In an interesting related reaction, $Cp_2Zr(\eta^2\text{-}RCH{=}CH_2)(PPh_2Me)$ complexes in which R = Et, Ph were shown to react with 2 equiv of $[HB(C_6F_5)_2]_n$ to release 1 equiv of the phosphine−borane adduct $Ph_2MeP\cdot HB(C_6F_5)_2$ and to form the unusual zwitterionic complex $Cp_2Zr\{\eta^3\text{-}[CH(R)CH_2BH(C_6F_5)_2]\}$.[147] Although C−H activation did not take place, the product demonstrates an

Scheme 31. Stoichiometric Reactions of [$Cp^*_2Ti(\eta^2\text{-}CH_2{=}CH_2)$] with Boranes and Ethene by Smith and Co-workers



Scheme 32. Photochemically Induced Dehydrogenative Borylation of Olefins by Hartwig and Co-workers



interesting transformation in which an early transition metal alkene complex reacts with a borane and may well be relevant to the above-mentioned results of Smith and co-workers with titanocene complexes.

7.11.3. Photochemically Induced Stoichiometric Dehydrogenative Olefin Borylation

During the course of initial studies on stoichiometric C−H activation reactions, Hartwig and co-workers reported the photolysis of [$CpFe(CO)_2(Bcat)$] and [$Re(CO)_5(Bcat)$] in the presence of terminal and internal olefins (Scheme 32).[148,149] The reaction of [$CpFe(CO)_2(Bcat)$] with hex-1-ene led to the formation of the terminal hexenylboronate ester in 90% yield, along with 10% of hexyl-Bcat. The reaction of [$Re(CO)_5(Bcat)$] with hex-1-ene gave 55% of the terminal, *trans*-VBE product by NMR spectroscopy, with the majority of the remaining material (20−25%) consisting of the alkylboronate, presumably formed by metal-catalyzed hydroboration. Reactions of [$Re(CO)_5(Bcat)$] with internal olefins were less selective; the reaction of 4-octene gave the VBE product, along with at least 3 isomeric vinylboronates and octyl-Bcat from hydroboration. Photolysis of [$Re(CO)_5(Bcat)$] in the presence of norbornene gave a single VBE product, along with two isomeric hydroboration products, whereas the reaction with cyclohexene formed products other than vinylboronate esters. The formation of the VBE products was proposed to occur via photochemically induced dissociation of CO, followed by coordination of the olefin. Direct C−H bond cleavage, followed by B−C bond-forming reductive elimination, would then yield the observed product.

7.11.4. Dehydrogenative Borylation of Olefins under Hydroboration Conditions

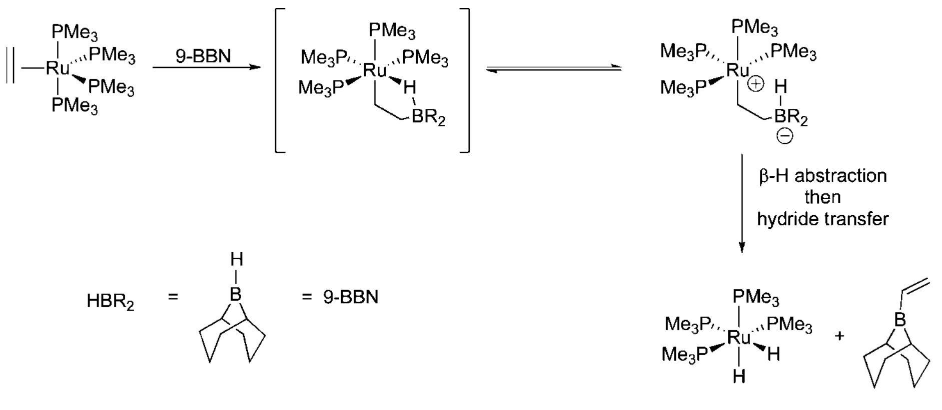
Marder, Baker, and co-workers observed the formation of vinylboranes in the stoichiometric reactions of [$Ru(\eta^2\text{-}C_2H_4)(PMe_3)_4$] with 9-borabicyclo-[3.3.1]-nonane (9-BBN).[150] Addition of the boryl group to the bound olefin formed a cyclic alkyl borohydride species, which is in equilibrium with a zwitterionic ruthenium β-borylalkyl complex, from which β-hydride elimination and hydride transfer gave the vinylborane product and [$Ru(H)_2(PMe_3)_4$] (Scheme 33).

The same group observed the formation of VBE products in their study of the stoichiometric insertion of olefins into Rh−B bonds.[151] Analysis of the reaction of [$RhCl(Bcat)_2(PPh_3)_2$] with 2 equiv of 4-vinylanisole in CD_2Cl_2 by ^1H NMR spectroscopy showed the formation of VBE, 1,2-bis(boronate ester) (1,2-BBE), and internal hydroboration products in a 2:3:2 ratio, as well as trace amounts of the terminal hydroboration product. VBEs were observed as side products in the catalytic diborations of olefins with B_2cat_2 and 1 mol % of [$RhCl(PPh_3)_3$] as catalyst precursor at room temperature[152] and in the catalytic hydroborations of certain allyl silyl ethers with HBcat in the presence of [$RhCl(PPh_3)_3$] as catalyst.[153]

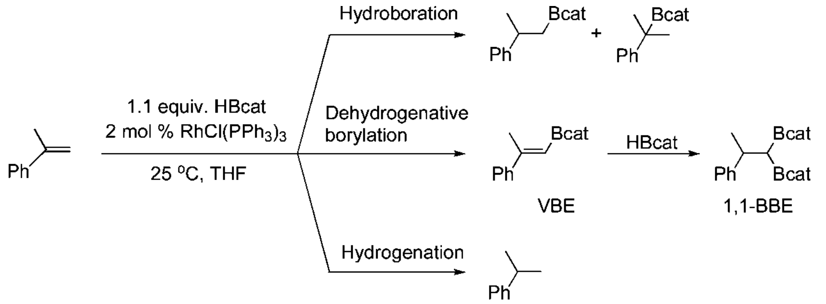
7.11.5. Dehydrogenative Borylation of Olefins without Sacrificial Hydrogenation

Marder, Baker, and co-workers reported the first example of catalytic dehydrogenative borylation of olefins without significant hydrogenation of the substrate.[154] In addition, they reported the dehydrogenative borylation of 1,1-disubstituted olefins. The reaction of α-methylstyrene with 1.1 equiv of HBcat in the presence of 2 mol % of [$RhCl(PPh_3)_3$] as a catalyst precursor in THF at room temperature gave VBE and 1,1-BBE (derived from the hydroboration of the VBE product) with a combined selectivity of 80% (53% for

Scheme 33. Stoichiometric Ru-Mediated Formation of Vinylboranes Reported by Marder, Baker, and Co-workers



Scheme 34. Borylation of α-Methylstyrene with HBcat Catalyzed by [RhCl(PPh$_3$)$_3$] (Wilkinson's Catalyst)



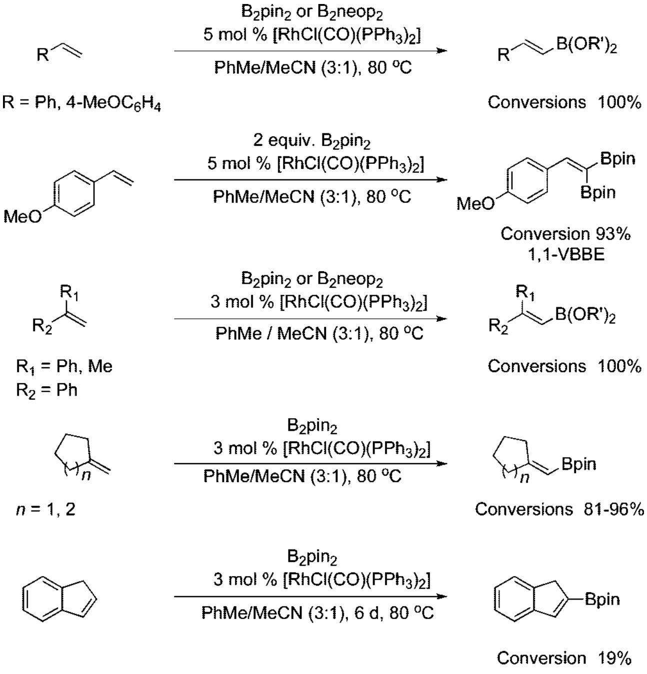
VBE and 27% for 1,1-BBE), along with 17% hydroboration and 3% hydrogenation. The pathways are summarized in Scheme 34.

Westcott and co-workers reported several systems for the dehydrogenative borylation of olefins. They showed that the dehydrogenative borylation of aminopropyl vinyl ethers in the presence of [RhCl(PPh$_3$)$_3$] as a catalyst precursor formed VBE as the sole boron containing product,[155] although the issue of whether sacrificial hydrogenation of the substrate occurred was not explicitly addressed.

In 2003, Marder and co-workers reported the dehydrogenative borylation of olefins with B$_2$pin$_2$ or B$_2$neop$_2$ (neop = neopentaneglycolate = OCH$_2$CMe$_2$CH$_2$O) in the presence of 3 mol % of the catalyst precursor *trans*-[RhCl(CO)(PPh$_3$)$_2$], at 80 °C without sacrificial hydrogenation of an equivalent of the substrate.[156] Vinylarenes, such as 4-vinylanisole, along with 1,1-disubstituted olefins, such as α-methylstyrene, diphenylethylene, methylenecyclopentane, and methylenecyclohexane, underwent dehydrogenative borylation in the presence of *trans*-[RhCl(CO)(PPh$_3$)$_2$] as the catalyst precursor. The selectivity depended on the solvent. Reactions conducted in THF, toluene, and 1,4-dioxane yielded complex mixtures of VBEs, hydroboration products, hydrogenation, vinyl bis(boronate ester)s (VBBEs), and saturated bis(boronate ester)s (BBEs) with 4-vinylanisole as substrate. In contrast, reactions conducted in neat CH$_3$CN selectively formed VBEs, but these reactions were slow. Reactions performed in a 3:1 mixture of toluene to CH$_3$CN selectively formed VBEs with acceptable rates. Reactions conducted with substoichiometric amounts of B$_2$pin$_2$ (0.67 equiv) occurred with up to 100% conversion, showing that both boron moieties of B$_2$pin$_2$ can be incorporated into the VBE products with some substrates.

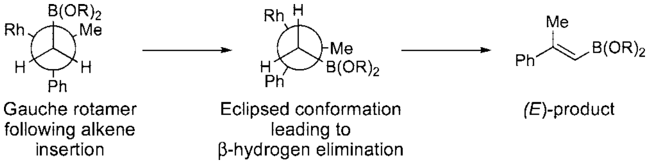
In subsequent work, Marder and co-workers extended the scope of the dehydrogenative borylations catalyzed by *trans*-[RhCl(CO)(PPh$_3$)$_2$] (Scheme 35).[157] In addition to reactions conducted with the diboron reagents B$_2$pin$_2$ and B$_2$neop$_2$, they found that reactions conducted with HBpin occurred, although they were slower than those with B$_2$pin$_2$ or B$_2$neop$_2$. One equiv of B$_2$neop$_2$ is required to effect complete conversions because only one of the two boron moieties can be readily incorporated. This is presumably due to the instability of HBneop formed under the reactions conditions. The reaction of 4-vinylanisole with 2 equiv of B$_2$pin$_2$ and an increased catalyst loading from 3 to 5 mol % led to the formation of the 1,1-vinyl bis(boronate ester) (1,1-VBBE), i.e., the replacement of both geminal hydrogen atoms on the =CH$_2$ group with boronate moieties, in a single catalytic reaction (up to 93% selectivity). The range of substrates was expanded from the vinyl arenes and 1,1-disubstituted olefins previously studied to include 1-octene and indene. The reaction of 1-octene was rapid, but led to mixtures of the VBBE and VBE in a 2:1 ratio with the VBBE product consisting of several isomers, presumably resulting from double bond isomerization. Of the VBBEs formed, the major component is the 1,1-VBBE isomer (66%), indicating that both geminal olefin hydrogens were replaced. In contrast, the borylation of indene with B$_2$pin$_2$ led to selective formation of the VBE, with borylation occurring at the 2-position, but only 19% conversion was observed after 6 days at 80 °C. The slow reaction of indene was attributed to an unfavorable β-hydride elimination step due to the difficulty of achieving coplanarity of the Rh and β-hydride moieties, although it is possible that this substrate is borylated via a different mechanism from other olefins. No reaction was observed with 2-methyl-2-butene or 3,4,4-trimethyl-2-pentene, suggesting that the system is not effective for dehydrogenative borylation of 1,1,2-trisubstituted olefins.

Scheme 35. Rhodium-Catalyzed Dehydrogenative Borylations of Olefins by Marder and Co-workers



The reactions were also conducted at 150 °C in sealed tubes in a microwave reactor giving, in general, fairly similar product distributions to those obtained by conventional heating at 80 °C, but with much shorter reaction periods (minutes vs days). For 1,1-disubstituted styrenes, conversions were improved when the amount of B$_2$pin$_2$ was increased from 0.67 equiv to 1.0 or 2.0 equiv. In general, the rate enhancements observed in the microwave reactions were consistent with that expected from the higher temperature employed and, thus, do not appear to reflect any special

Scheme 36. Eclipsed Conformation Leading to (*R*)-Hydrogen Elimination



microwave enhancement, although catalyst lifetimes were somewhat reduced at the higher temperatures.

The origin of the selectivity for VBE formation over diboration/hydroboration and the origins of the beneficial role of MeCN solvent in achieving the highest selectivities remain unclear. Certainly, the system promotes rapid β-hydride elimination following olefin insertion into a Rh−B bond, which must be faster than competing processes that would result in saturated products.

The observed selectivity for the formation of (*E*)-vinyl boronate products was proposed to result from diastereoselective β-hydride elimination from a rhodium β-borylalkyl intermediate. For α-methylstyrene, highly selective borylation of the C−H bond *cis* to the Me group gives rise to a 1,1-disubstituted product that cannot be prepared by alkyne hydroboration. Following a *syn* addition of Rh and boryl groups to the olefin, either of the two diastereotopic β-hydrogens may be transferred to Rh. Because β-hydride elimination requires a *syn* disposition of rhodium and hydride moieties, rotation around the C−C bond is required. Elimination from the least-hindered rotamer (as illustrated for the α-methylstyrene case in Scheme 36) would, therefore, lead to the observed (*E*)-product. The direction of the insertion of the styrenic substrates into the Rh−B bond generates the more-hindered insertion product, placing the large groups α to the metal center. This is presumably a direct consequence of the nucleophilicity of the boryl ligands,[35−39] which prefer to attack the terminal carbon of the styrenes during the olefin insertion step, and the ability of the electron-withdrawing phenyl group to stabilize the Rh−C bond.

Westcott and co-workers reported dehydrogenative borylations of a range of vinylarenes in the presence of bulky rhodium diimine complexes as catalysts.[158] The reactions of HBcat, B$_2$cat$_2$ and HBpin with vinylarenes catalyzed by the three rhodium complexes shown in Figure 3 gave complex mixtures of products, but reactions with B$_2$pin$_2$ gave predominantly *trans*-VBE products. The borylation of 4-fluorostyrene with B$_2$pin$_2$ and an unspecified catalytic amount of the zwitterionic diimine rhodium Bcat$_2$ π-complex in toluene at 80 °C gave a 98% yield of the VBE product along with trace hydrogenation products.

Miyaura and co-workers reported the borylation of vinyl C−H bonds in cyclic vinyl ethers by B$_2$pin$_2$ catalyzed by [Ir(OMe)COD]$_2$ and dtbpy (Table 11).[159,160] This catalyst has been used widely for the borylation of aromatic C−H bonds, vide supra. Borylation of 1,4-dioxene with 0.5 equiv of B$_2$pin$_2$ at room temperature in hexane gave the VBE product in 81% yield. Borylations of dihydropyran and dihydrofuran gave mixtures of α- and β-borylated products in ratios of 75:25 and 49:51, respectively. Substrates containing substituents at the γ-position in dihydropyrans reacted with higher regioselectivity; borylation occurred solely at the α-position. Borylation of dihydrofurans was less selective; even γ, γ-disubstituted substrates gave products resulting from both α- and β-borylation. In addition, the borylation of 1*H*-isochromene occurred solely α to oxygen, even in the presence of unhindered aromatic C−H bonds.

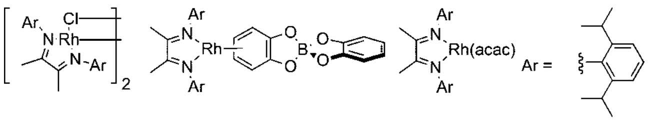
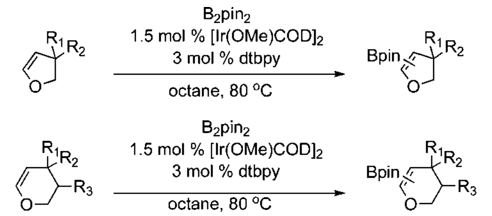
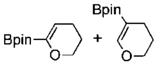
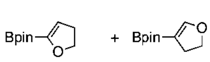
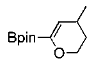
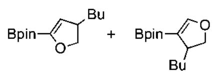
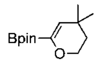
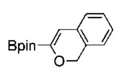
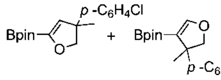


Figure 3. Bulky rhodium diimine catalysts for dehydrogenative borylation of olefins by Westcott and co-workers.

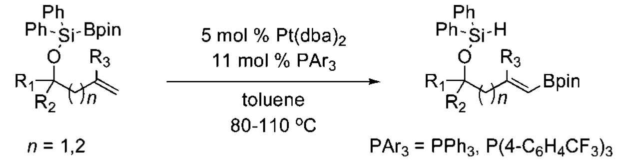
Table 11. Iridium-Catalyzed Dehydrogenative Borylation of Cyclic Vinyl Ethers by Miyaura and Co-workers[a]



product	GC yield / %	product	GC yield / %
	64 (75:25)		75 (49:51)
	61		71 (86:14)
	65		
	81		73 (95:5)

[a] All reactions were carried out at 80 °C for 8 h using B$_2$pin$_2$ (1.0 mmol), substrate (3.0 mmol), [Ir(OMe)COD]$_2$ (0.015 mmol), and dtbpy (0.03 mmol) in octane in a sealed tube. GC yields are based on boron moieties in B$_2$pin$_2$.

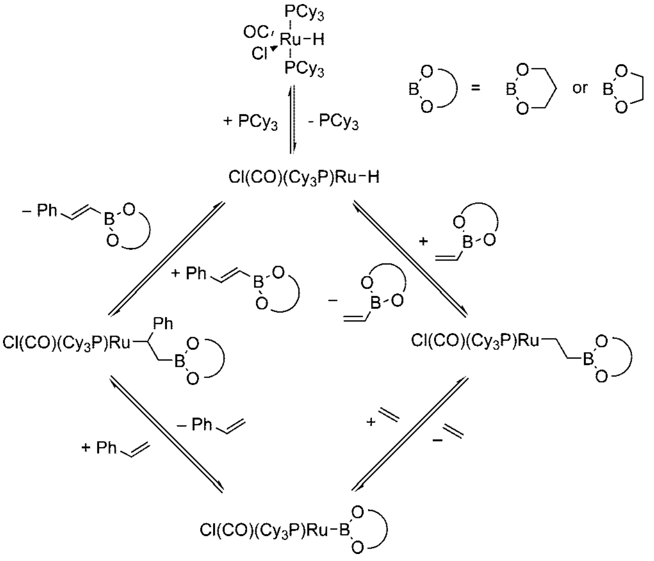
Scheme 37. Dehydrogenative Borylation of 1,2-Disubstituted Alkenes by Suginome and Co-workers



Suginome and co-workers have reported a platinum-catalyzed dehydrogenative borylation of 1,2-disubstituted olefins tethered to silylboronate groups to give (*E*)-VBEs in which Si−B and olefinic C−H bonds are transformed into Si−H and C−B bonds, respectively (Table 11).[161] Silylboronates were synthesized from their corresponding alcohols[162] by reaction with ClPh$_2$SiBpin, and these materials were converted to the VBE products in moderate to high yields in toluene at 80−100 °C in the presence of 5 mol % Pt(dba)$_2$ and 11 mol % PAr$_3$. No products arising from intramolecular alkene silylboration[163] were observed. A mechanism was proposed in which oxidative addition of the Si−B bond to the Pt^0 center would give a Pt^{II} (boryl)(silyl) species. Subsequent intramolecular 1,2-insertion of the olefin into the Pt−B bond, followed by β-hydride elimination, would give the VBE product and a platinum hydride, which could reductively eliminate Si−H to regenerate the Pt^0 species.

This work is closely related to that in an earlier report by Gerdin and Moberg[164] on Ni-catalyzed addition of silylbo-

Scheme 38. Ruthenium Catalyzed Transfer Borylation of Vinylarenes by Marciniec and Co-workers



ranes to 1,3-dienes in toluene at 80 °C. Gerdin and Moberg observed that Ni^0, formed by DIBALH (DIBALH = diisobutylaluminum hydride) reduction of $Ni(acac)_2$, in the presence of 2 equiv of PEt_3, catalyzed the reaction of Me_2PhSi-Bpin with 1,3-dienes, such as (*E*,*E*)-5,7-dodecadiene or (*E*,*E*)-2,4-hexadiene, to give 1:1 mixtures of allylsilanes and dienyl-1-boronate esters by a disproportionation process. A deuterium-labeling study supported a mechanism in which oxidative addition of the silylborane to Ni^0 to cleave the B−Si bond is followed by regioselective insertion of the diene into the resulting Ni−B bond. Because β-hydride elimination is much faster than C−Si reductive elimination, the dienylboronate ester and a nickel silyl hydride complex form. The latter reacts with a second equivalent of diene to give the allylsilane product. Thus, 2 equiv of diene are required to give 1 equiv of dienylboronate; the second equivalent is consumed in the hydrosilylation process. This sequence is reminiscent of that in early studies of rhodium- or ruthenium- catalyzed dehydrogenative borylation of styrenes using, for example, oxazaborolidines or HBpin (section 7.11.2). In these previous studies, 1 equiv of alkene was converted to the alkenylboron compound, while a second equivalent of alkene served as the sacrificial hydrogen acceptor.

7.11.6. Boryl Transfer Reactions and β-Boryl Elimination

Marciniec and co-workers reported a boryl transfer reaction between two olefins using $[Ru(H)(Cl)(PCy_3)_2(CO)]$ as the catalyst and 2-vinyl-1,3,2-dioxaborolane, (vinyl-Beg), or 2-vinyl-1,3,2-dioxaborinane as sources of a boryl group.[165] A range of styrenic and vinyl ether substrates were borylated in moderate to high yields, with reactions performed at 80 °C in benzene using a 5:1 ratio of olefin to vinylboronate to limit background reactions. A mechanism was proposed (Scheme 38) in which $[Ru(H)(Cl)(PCy_3)_2(CO)]$ dissociates PCy_3 to give the active species $[Ru(H)(Cl)(PCy_3)(CO)]$. By this mechanism, migratory insertion of vinylboronate then occurs into the Ru−H bond of $[Ru(H)(Cl)(PCy_3)(CO)]$ to give the β-borylalkyl species $[Ru\{CH_2CH_2B(OR)_2\}(Cl)(PCy_3)(CO)]$, which would undergo β-boryl elimination to give $[Ru\{B(OR)_2\}(Cl)(PCy_3)(CO)]$. Insertion of styrene into the Ru−B bond to give $[Ru\{CHPhCH_2B(OR)_2\}(Cl)(PCy_3)(CO)]$, followed by β-hydride elimination, would yield the VBE product and regenerate $[Ru(H)(Cl)(PCy_3)(CO)]$. The insertion of vinyl-Bcat into the Ru−H bond of $[Ru(H)(Cl)(PCy_3)_2(CO)]$ and subsequent extrusion of ethene to give $[Ru(Bcat)(Cl)(PCy_3)_2(CO)]$ was demonstrated in stoichiometric experiments, as was the reaction of $[Ru(Bcat)(Cl)(PCy_3)_2(CO)]$ and styrene to give VBE and $[Ru(H)(Cl)(PCy_3)_2(CO)]$. The possibility of an olefin cross-metathesis pathway was eliminated by deuterium labeling studies.

The mechanism of the above process was also examined by DFT calculations.[166] The energetics of the reversibility of the boryl ligand migration (olefin insertion into a metal−boryl bond) was explored, and the β-boryl elimination process was calculated to have a low barrier. It was concluded that the *p*-orbital on boron of the boryl ligand was not important in either the boryl migration or β-boryl elimination processes, but that the high nucleophilicity of the Ru−boryl σ-bond promotes the boryl migration.

8. Applications of Metal-Catalyzed Borylation of Arenes and Alkanes

The high selectivity and high yields of metal-catalyzed borylation of arenes and alkanes have been exploited to prepare functionalized materials, such as modified polyolefins, and small molecules that would be difficult to functionalize selectively by other methods. This section first describes the rhodium-catalyzed functionalization of polyolefins and, second, the iridium-catalyzed functionalization of small molecules.

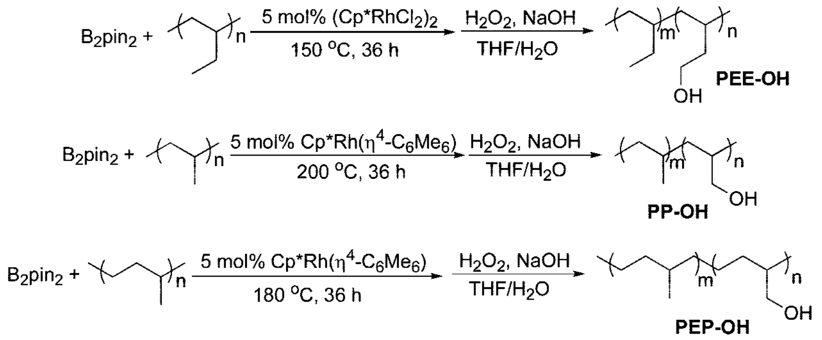
8.1. Functionalization of Polyolefins

The ability to prepare polyolefins containing varying degrees of polar functional groups would expand the potential applications of materials derived from olefins. The incorporation of polar functionality is predicted to improve adhesion to metal and glass surfaces and permeability to gases among other properties.[167−170] Thus, a major goal for the synthesis of polyolefins has been the development of methods to generate materials containing functional groups, such as alcohols, amines, and carbonyl groups. One approach to the synthesis of such materials is the selective C−H bond functionalization of polyolefins.

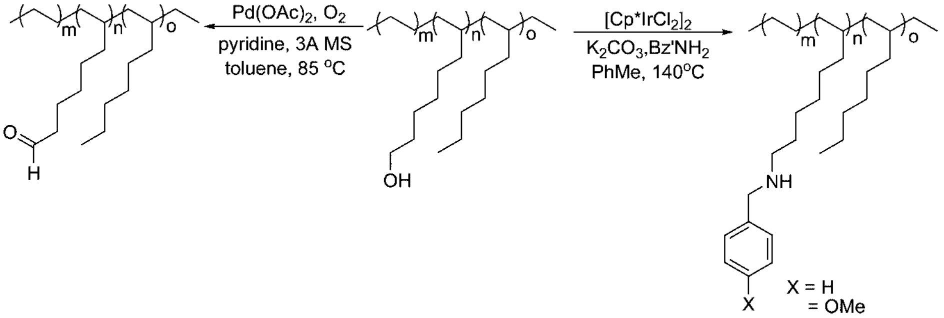
There are two main approaches to the functionalization of polyolefins: the polymerization of monomers containing functional groups and the direct functionalization of preformed polymers. The copolymerization of functionalized and unfunctionalized α-olefins is challenging because of the incompatibility of polar functionality with common polyolefin polymerization catalysts.[171] The postfunctionalization of polyolefins has been investigated, but most methods rely on radical-based functionalizations that typically alter the molecular weights and polydispersity indices (PDIs) of the starting polymers by chain scissions, chain transfers, and coupling reactions.[172−174] Also, such functionalizations by radical mechanisms typically occur at tertiary C−H bonds, which are contained in the polymer backbone, rather than the polymer side chains.[175]

Thus, Hartwig and Hillmyer sought to use the borylation of C−H bonds to functionalize polyolefins at the termini of side chains without altering the PDI. In a series of publications, Hartwig, Hillmyer, and co-workers reported the synthesis of hydroxylated polymers by the Cp*Rh-catalyzed

Scheme 39. Hydroxylation of Alkyl Polymers



Scheme 40. Functionalization of Hydroxylated Alkyl Polymers



borylation and subsequent oxidation[176−178] of various polymers, such as polyethylethylene (PEE), polypropylene (PP), and polyethylene (PE)/octene copolymers. Hartwig, Hillmyer, and co-workers investigated the reactions of polyolefins with B_2pin_2 catalyzed by Cp*Rh complexes, such as $[Cp^*RhCl_2]_2$ and $Cp^*Rh(\eta^4\text{-}C_6Me_6)$ in the polymer melt, followed by oxidation of the borylated polymers with basic H_2O_2. In general, these reactions formed polymers possessing functional groups at the termini of the side chains, and the PDI and molecular weight of the polymers were unaltered by the functionalization process. Thus, the functionalization of macromolecular hydrocarbons occurs to form products that are similar to those of low-molecular-weight alkanes.

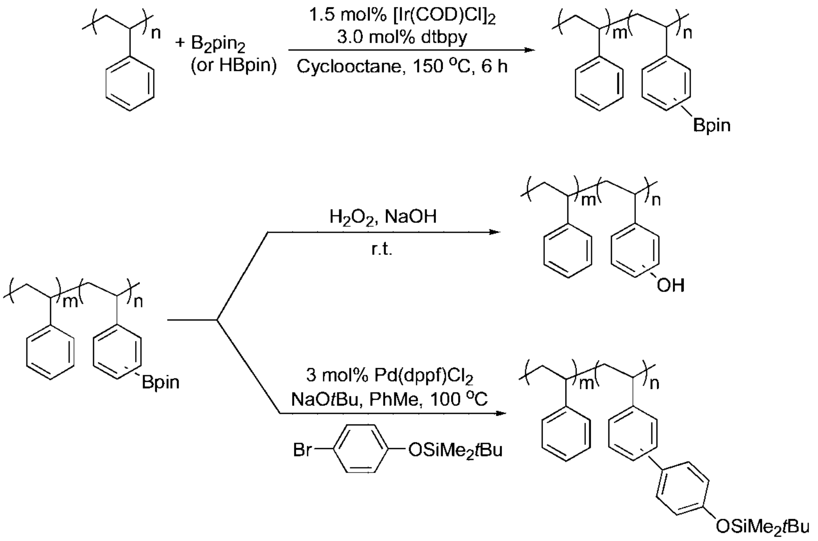
Hartwig, Hillmyer, and co-workers first studied the borylation of polyethylethylene (PEE) with B_2pin_2 catalyzed by 5 mol % $[Cp^*RhCl_2]_2$, followed by oxidation of the borylated polymer with hydrogen peroxide and sodium hydroxide in a THF and water mixture.[176] PEE with a molecular weight of $M_n = 1.7$ kg/mol (M_n = number-average molecular weight) underwent borylation and hydroxylation, and approximately 7% of the side chains were functionalized when a ratio of 0.07 B_2pin_2 to monomer was used. The borylation and oxidation of PEE conducted with a ratio of 0.3 B_2pin_2 to monomer provided hydroxylated PEE in which 13% of the side chains were functionalized, and the borylation and oxidation of PEE conducted with a 1:1 ratio of B_2pin_2 to monomer provided hydroxylated PEE in which 19% of the side chains were functionalized.

Hartwig, Hillmyer, and co-workers also reported the borylation and the subsequent oxidation of poly(ethylene-*alt*-propylene) (PEP), atactic or isotactic polypropylene (PP), and linear low-density polyethylene (LLPE) (Scheme 39).[177] In all cases, they observed exclusive terminal functionalization of the polymer chains without significant alteration of the M_n or PDI of the functionalized polymers. Also, the tacticity of the polymers did not affect the degree of functionalization of the polyolefins. The same groups investigated the reaction of PEP with B_2pin_2 in the presence of 2.5 mol % $[Cp^*RhCl_2]_2$ at 150 °C for 60 h, and the oxidation of the resulting PEP-Bpin by basic H_2O_2 gave hydroxylated PEP in 60% yield with 1.4% hydroxylated side chains. The reaction of polypropylene with B_2pin_2 catalyzed by 5 mol % $Cp^*Rh(\eta^4\text{-}C_6Me_6)$ at 200 °C for 24−30 h and subsequent oxidation of the borylated polymer with basic H_2O_2 gave functionalized, atactic PP containing 1.3% hydroxylated side chains in 75−90% yield, and isotactic PP containing 1−1.5% hydroxylated side chains was isolated in 97% yield. The borylation of LLPE with B_2pin_2 catalyzed by 5 mol % $Cp^*Rh(\eta^4\text{-}C_6Me_6)$ at 150 °C yielded polymer containing approximately 20% hydroxylated side chains.

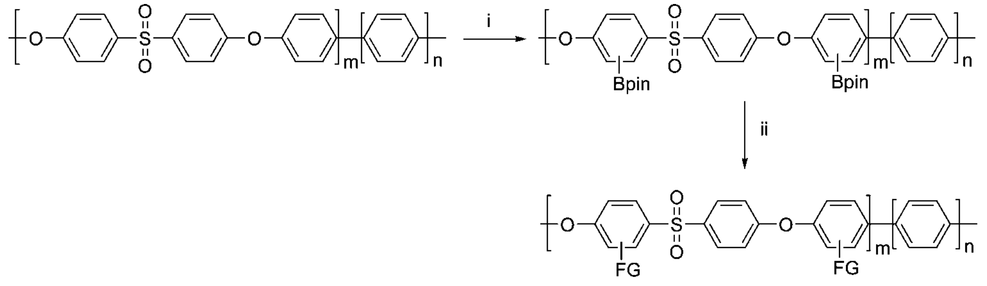
These research groups demonstrated that the hydroxylated polymers synthesized by the borylation and oxidation of polyolefins could be further functionalized.[178] In one case, the corresponding polymer containing formyl groups at the termini of the side chains was prepared by oxidation of the hydroxylated LLPE with O_2 in the presence of $Pd(OAc)_2$.[179] In a second case, the corresponding polymer containing *N*-benzylamino groups at the side chains was produced by reaction of the hydroxylated LLPE with benzylamine catalyzed by $[Cp^*IrCl_2]_2$ (Scheme 40).[180]

In addition to the borylation of alkyl C−H bonds, the borylation of aryl C−H bonds has been used to functionalize polymers. In 2007, Bae and co-workers reported the borylation of syndiotactic, isotactic, and atatic polystyrenes (Scheme 41).[181] The reaction of polystyrene with B_2pin_2 catalyzed by 1.5 mol % $[Ir(COD)Cl]_2$ and 3 mol % dtbpy in cyclooctane at 150 °C yielded a material in which 42% of of the styrene units had undergone borylation. The reaction of polystyrene with HBpin in the presence of 1.5 mol % $[Ir(COD)Cl]_2$ and 3 mol % dtbpy in cyclooctane at 150 °C yielded a material in which 10% of the styrene units had undergone borylation. The tacticity of polystyrene did not affect the borylation reaction. Also, Bae and co-workers did not observe any change in M_n or PDI of the polystyrene after borylation. To demonstrate the utility of the borylation of polystyrene, they further functionalized the polymers by

Scheme 41. Ir-Catalyzed Borylation of Polystyrene



Scheme 42. Functionalization of Polysulfones (Conditions: (i) B_2pin_2, 1.5 mol % $[Ir(COD)Cl]_2$, 3 mol % dtbpy, THF, 80 °C, 12 h; (ii) *p*-BrPh-FG, 3 mol % $Pd(PPh_3)_4$, 3 equiv of K_2CO_3, THF/H_2O (10:1), 80 °C, 6 h)



FG = C(O)Me, NMe_2, NHC(O)O*t*Bu, CH_2OH, C(O)H

oxidizing the boronic esters to hydroxyl groups with basic H_2O_2 and by performing a Suzuki−Miyaura cross-coupling reaction with an aryl halide (Scheme 41). In 2009, they also functionalized aryl groups of a polysulfone[182] by iridium-catalyzed borylation followed by Suzuki−Miyaura cross-coupling reactions (Scheme 42).

8.2. One-Pot Syntheses of Organic Compounds

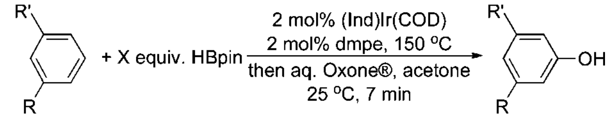
Iridium-catalyzed borylation of arenes provides access to aromatic compounds that would be difficult to synthesize by other methodologies. For example, the synthesis of 3,5-disubstituted aryl halides, phenols, and anilines can be lengthy if the parent arene contains *ortho*/*para*-directing groups. Typical functionalizations of a 1,3-disubstituted arene containing *ortho*/*para*-directors provides 1,2,4-trisubstituted products because of electronic factors, and further synthetic manipulations are needed to obtain a 1,3,5-trisubstituted arene. The regiochemistry of iridium-catalyzed borylation, however, is controlled by steric factors. Therefore, iridium-catalyzed borylation of 1,3-disubstituted arenes yields, in most cases, 1,3,5-trisubstituted arenes, regardless of the electronic properties and directing effects of the substituents on the arene. Several research groups have taken advantage of the selectivity of iridium-catalyzed borylation of arenes to develop methodologies for the synthesis of arenes with substitution patterns less accessible by conventional methodology.

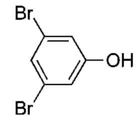
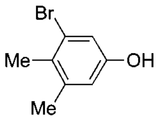
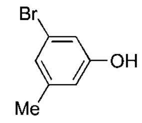
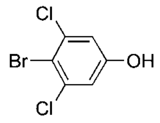
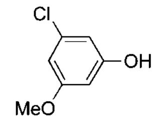
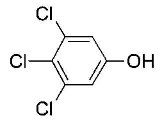
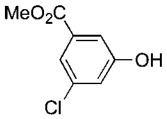
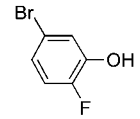
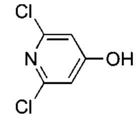
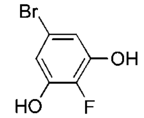
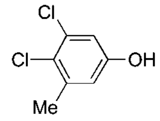
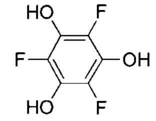
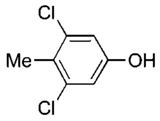
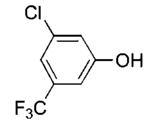
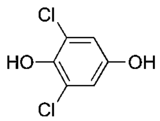
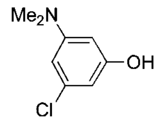
8.2.1. One-Pot Syntheses of Phenols and Arylamines

Maleczka, Smith, and co-workers developed a one-pot procedure for the synthesis of 3,5-disubstituted phenols.[183] Arylboronate esters were prepared from the reaction of arenes with HBpin catalyzed by 2 mol % (Ind)Ir(COD) and 2 mol % dmpe.[183] The crude arylboronate esters from the iridium-catalyzed borylation were then converted to the corresponding phenols by reaction with Oxone. Webb and Levy reported the oxidation of arylboronate esters with a buffered solution of Oxone and base.[184] By omitting the base and buffer components of the original oxidation protocol and conducting the oxidation with an aqueous Oxone solution with the substrate in organic solvents, Maleczka, Smith, and co-workers reproducibly converted arylboronate esters to the corresponding phenols. This procedure converted both electron-rich and electron-poor arenes to the corresponding phenols and was tolerant of ester, ether, and halogen functionalities (Table 12). They also showed that the reactions could be conducted with aryl iodides if the borylation step was conducted with the catalyst based on $[Ir(COD)(OMe)]_2$ and dtbpy because reactions with this catalyst can be conducted at lower temperatures.

Aminoarylboronate esters have also been synthesized by iridium-catalyzed borylation of arenes. In 2006, Smith, Maleczka, and co-workers published the synthesis of a variety of aminoarylboronate esters using a one-pot sequence of iridium- and palladium-catalyzed reactions. A series of *meta*- and *para*-substituted aryl halides were converted to their corresponding arylboronate esters with an iridium

Table 12. One-Pot Conversion of Arenes to Phenols Using Ir-Catalyzed Borylation



HBpin equiv	borylation time (h)	phenol product	Yield[a]	HBpin equiv	borylation time (h)	phenol product	Yield[a]
2.0	18		87%	2.5	50		72%
1.5	12		81%	2.0	3.5		80%
2.0	18		79%	1.8	3		89%
1.5	3		70%	0.25	3.5		68%
1.5	3		64%	4.5	53		74%
2.0	12		85%	5.0	63		51%
2.0	12		88%	1.5	3.5		80%
2.5	16		68%	2.0	18		79%

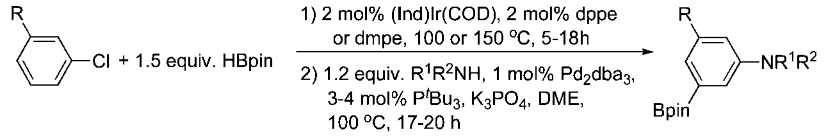
catalyst, and the halogenated arylboronate esters underwent Buchwald–Hartwig coupling with amines in the presence of a palladium catalyst to yield amino-substituted arylboronate esters (Table 13).[185] The highest yields of aminoarylboronate esters were obtained with 1 mol % $Pd_2(dba)_3$, 3–4 mol % P*t*Bu_3, and dried K_3PO_4 in anhydrous DME. This tandem borylation and amination method formed the desired products with aryl halides containing alkyl, ester, alkoxy, and amino groups to form the corresponding aminoaryl boronic esters in moderate to good yields.[185]

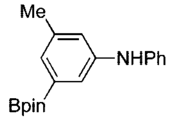
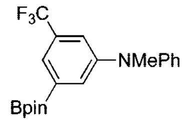
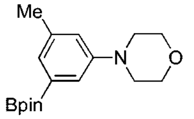
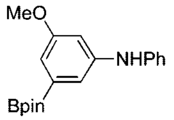
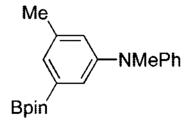
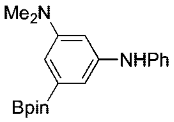
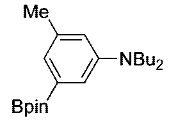
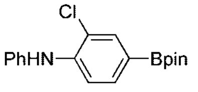
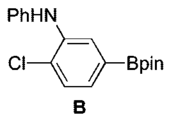
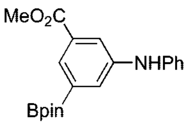
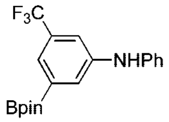
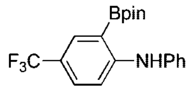
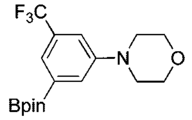
Smith and co-workers also developed a procedure for the synthesis of 5-substituted-3-aminophenols by a three-step synthetic sequence.[186] The first step of this sequence is the reaction of a 3-substituted bromoarene with HBpin catalyzed by the combination of either (Ind)Ir(COD) and dmpe or $[Ir(COD)(OMe)]_2$ and dtbpy. The second step is the coupling of the crude arylboronate ester with a nitrogen nucleophile selectively at the C–Br bond in the presence of $Pd_2(dba)_3$ and Xantphos.[187–189] The final step is the oxidation of the resulting arylboronate to the corresponding phenol, and this step required purification of the crude material through a small plug of silica gel prior to performing the oxidation of the arylboronate ester to the phenol by exposure to a solution of Oxone in acetone. A variety of 5-substituted-3-aminophenols were synthesized by this method in moderate to high yields (Table 14).[186]

8.2.2. One-Pot Syntheses of Aryl Bromides and Aryl Chlorides

Hartwig and co-workers have sought to increase the scope and utility of the borylation of arenes by conversion of the arylboronate esters to products that typically have been less accessible from these reagents than phenols. For example, they have reported one-pot sequences for the conversion of arenes to aryl halides, arylamines, aryl ethers, and enantioenriched arylmethylamines. In these cases, one challenge has been the extension of chemistry of arylboronic acids to the reactions of the arylboronate esters that are formed from the C–H borylation chemistry. Thus, in parallel, methods

Table 13. Tandem Borylation and Cross-Coupling of Aryl Chlorides to Produce Borylated Aryl Amines



amine	product	% yield[a]	amine	product	% yield[a]
$PhNH_2$		75 63 (X= Br)	PhMeNH		65
Morpholine		73	$PhNH_2$		61
PhMeNH		83	$PhNH_2$		73
Bu_2NH		50	$PhNH_2$	 A  B	46 (19:1 A:B)
$PhNH_2$		47			
$PhNH_2$		71	$PhNH_2$		45
Morpholine		49			

[a] Isolated yields based on two runs. [b] A 19:1 ratio of A/B was isolated when 1,2-dichlorobenzene was the starting arene.

have been developed to use the C—H borylation to form the more reactive arylboronic acids and aryl trifluoroborates from arenes by one-pot procedures. These processes are described in this subsection.

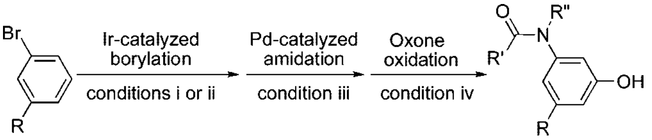
Hartwig and co-workers synthesized aryl halides from arenes by C—H borylation, followed by reaction with copper(II) halide salts as the source of halogen (Table 15).[190] To develop this method, a route to aryl bromides from the crude arylboronate esters was needed. Several methods that had been described previously were tested, such as the use of dibromodimethylhydantoin or the combination of Chloramine T and sodium bromide, but these methods led to low yields or gave high yields with a limited set of arylboronates. In contrast, the reaction of the crude arylboronates with an excess of $CuBr_2$ in a mixture of methanol and water produced the aryl bromide in good yield with a variety of arylboronate esters. The related reaction of arylboronate esters with $CuCl_2$ to form aryl chlorides occurred in good yield with a similar range of arylboronate esters (Table 16).

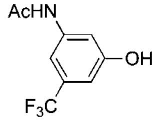
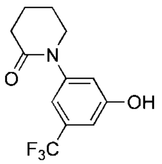
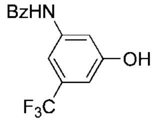
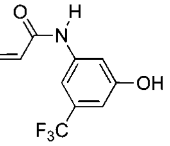
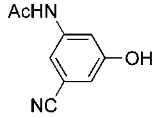
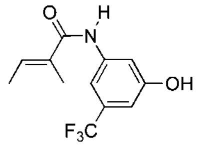
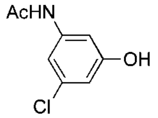
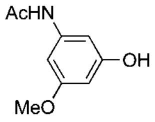
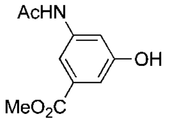
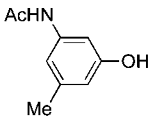
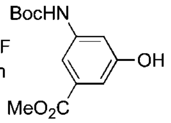
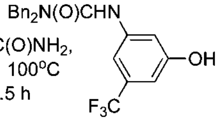
The scope of the conversion of arenes to aryl bromides by iridium-catalyzed arene borylation and subsequent bromination is summarized in Table 15. This two-step process occurred in moderate to good yields and tolerated alkoxy, alkyl, halide, nitrile, ester, amide, pivaloyl, and TIPS-protected hydroxyl functionalities. The corresponding conversion of arenes to aryl chlorides provided this class of aryl halide with yields and substrate scope that were comparable to those for the conversions of arenes to aryl bromides (Table 16).

8.2.3. One-Pot Syntheses of Arylamines and Aryl Ethers

In 2007, Hartwig and co-workers reported the conversion of arenes to arylamines and aryl ethers by a sequence of arene borylation, followed by copper mediated Chan—Lam amination or Chan—Lam—Evans etherification.[191] Thus, arylamines were synthesized from the reaction of the crude arylboronates that were generated by Ir-catalyzed arene borylation (Scheme 43). Reaction of this crude product with 2 equiv of alkylamine, 1 equiv of potassium fluoride, and powdered molecular sieves in the presence of 10—20 mol % $Cu(OAc)_2 \cdot H_2O$ in acetonitrile at 80 °C led to the arylamine. Arylboronate esters were not successfully coupled with substituted anilines, but diarylamines were synthesized

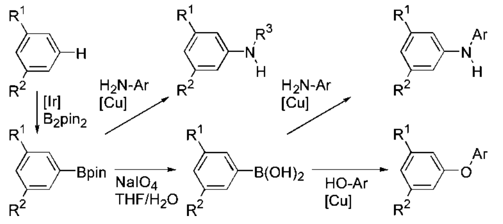
Table 14. Synthesis of 3-Aminophenols Utilizing Ir-Catalyzed Arene Borylation[d]



borylation conditions	amidation conditions	product[a]	borylation conditions	amidation conditions	product[a]
HBpin (1.8 equiv.) Conditions i, neat, 4 h	$AcNH_2$, THF 80°C, 4 h	 63%	HBpin (1.8 equiv.) Conditions i, neat, 4 h	δ-valerolactam 100 °C, THF, 2 h	 46%[b]
HBpin (1.8 equiv.) Conditions i, neat, 4 h	$BzNH_2$, THF 80°C, 4 h	 82%	HBpin (1.8 equiv.) Conditions i, neat, 4 h	acrylamide 100 °C, THF, 2 h	 37%
HBpin (1.6 equiv.) Conditions ii, hexane, 4 h	$AcNH_2$, THF 80°C, 3 h	 68%	HBpin (1.7 equiv.) Conditions i, hexane, 3.5 h	tiglic amide 100 °C, THF 1.5 h	 66%
HBpin (1.6 equiv.) Conditions ii, hexane, 4 h	$AcNH_2$, THF 80°C, 3 h	 75%	HBpin (2.0 equiv.) Conditions i, neat, 10 h	$AcNH_2$, DME 120°C, 4 h	 33%[c]
HBpin (2.0 equiv.) Conditions ii, hexane,18 h	$AcNH_2$, THF 100°C, 2 h	 60%	HBpin (2.0 equiv.) Conditions i, neat, 12 h	$AcNH_2$, DME 120°C, 3 h	 40%[c]
HBpin (2.0 equiv.) Conditions ii, hexane, 18 h	$BocNH_2$, THF 100°C, 2.5 h	 46%[b]			
HBpin (1.8 equiv.) Conditions i, neat, 4 h	$Bn_2NC(O)NH_2$, THF, 100°C 1.5 h	 55%			

[a] Average isolated yield. [b] Suzuki–Miyaura byproducts also observed. [c] Proteodeborylation also observed. [d] Borylation conditions: (i) ArH (2 mmol scale), HBpin, 2 mol % (Ind)Ir(COD)-dmpe, 150 °C; removal of volatiles under vacuum; (ii) HBin, 1.5 mol % $[Ir(COD)(OMe)]_2$, 3 mol % dbtpy, r.t.; removal of volatiles under vacuum.

Scheme 43. Synthesis of Arylamines and Aryl Ethers Using Ir-Catalyzed Arene Borylation

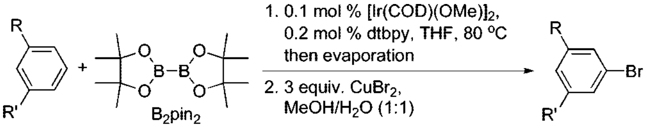


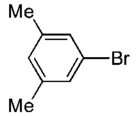
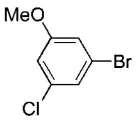
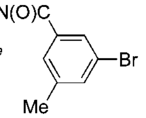
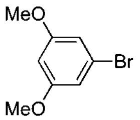
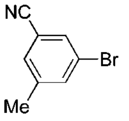
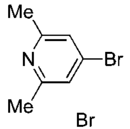
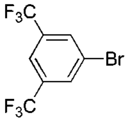
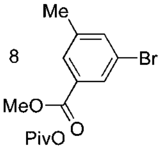
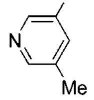
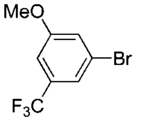
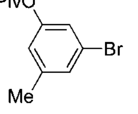
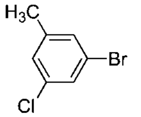
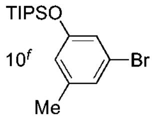
by the coupling of arylboronic acids, which were generated by the one-pot conversion of arenes to arylboronic acids,[192] with anilines in the presence of 10 mol % $Cu(OAc)_2$ and 10 mol % decanoic acid in toluene at room temperature.[191,193] Aryl ethers were synthesized by the reaction of phenols with the same arylboronic acids in the presence of 1 equiv of $Cu(OAc)_2$, 5 equiv of NEt_3, and molecular sieves in methylene chloride.

8.2.4. Conversion of Arenes to Arylboronic Acids and Potassium Aryltrifluoroborates

Hartwig and co-workers have described one-pot procedures for the conversion of arenes to arylboronic acids and potassium aryltrifluoroborates.[192] Several groups have previously reported the conversion of arylboronate esters to the corresponding arylboronic acids by hydrolysis with added $NaIO_4$ to oxidize the resulting pinacol to acetone,[194,195] and Hartwig and co-workers investigated whether the iridium byproducts from the catalytic borylation of arenes would interfere with the

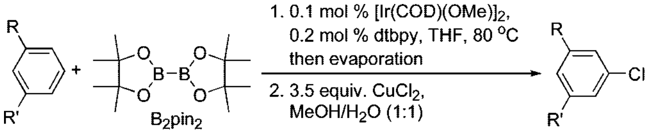
Table 15. Conversion of Arenes to Aryl Bromides Using Ir-Catalyzed Arene Borylation

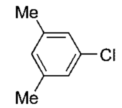
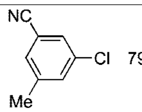
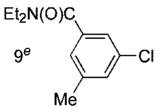
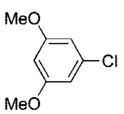
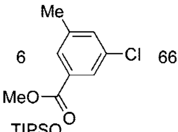
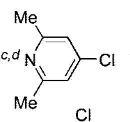
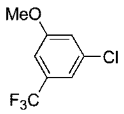
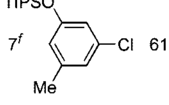
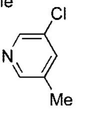
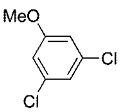
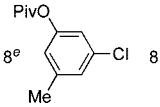


entry	product	yield[a]	entry	product	yield[a]	entry	product	yield[a]
1[b]		61%	6		75%	11[e]		80%
2		65%	7		65%	12[c,d]		72%
3		62%	8		68%	13[c,d]		51%
4		75%	9[e]		74%			
5		59%	10[f]		57%			

[a] Average isolated yield from two experiments. All reactions were run on a 2.0 mmol scale. [b] 0.5 mol % **1** and 1.0 mol % **2** used. [c] Contained 2% pinacol by ^{1}H NMR spectroscopy. [d] 3.0 mol % **1** and 6.0 mol % **2** used. [e] 1.0 mol % **1** and 2.0 mol % **2** used. [f] 2.0 mol % **1** and 4.0 mol % **2** used.

Table 16. Conversion of Arenes to Aryl Chlorides Utilizing Ir-Catalyzed Arene Borylation



entry	product	yield[a]	entry	product	yield[a]	entry	product	yield[a]
1[b]		61%	5		79%	9[e]		65%
2		55%	6		66%	10[c,d]		72%
3		77%	7[f]		61%	11[c,d]		46%
4		54%	8[e]		81%			

[a] Average isolated yield from two experiments. All reactions were run on a 2.0 mmol scale. [b] 0.5 mol % **1** and 1.0 mol % **2** were used. [c] Contained 2% pinacol by 1H-NMR spectroscopy. [d] 3.0 mol % **1** and 6.0 mol % **2** used. [e] 1.0 mol % **1** and 2.0 mol % **2** used. [f] 2.0 mol % **1** and 4.0 mol % **2** used.

hydrolysis of the pinacolate ester with NaIO$_4$. Crude arylboronate esters and NaIO$_4$ reacted in a mixture of THF and water in the presence of the iridium byproducts from the borylation procedure to form arylboronic acids.

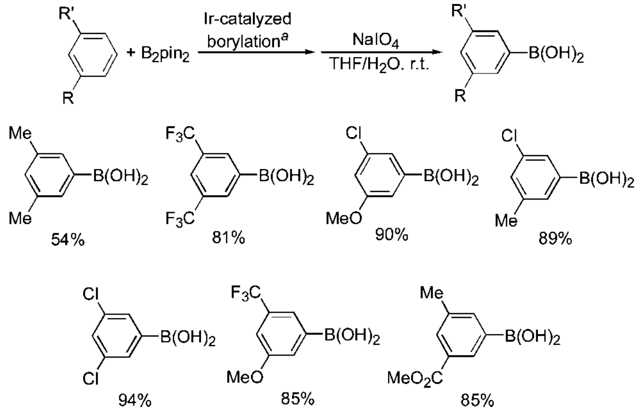
Thus, a one-pot procedure was developed involving C—H borylation, followed by oxidative hydrolysis of the crude boronic ester to the corresponding boronic acid. The C—H borylation step was conducted with B$_2$pin$_2$ and a combination of only 0.1 mol % [Ir(COD)(OMe)]$_2$ and 0.2 mol % dtbpy in THF. Reaction of the resulting boronic ester with NaIO$_4$ and water at room temperature, followed by quenching with aqueous HCl, formed the arylboronic acids in moderate to excellent yields. This one-pot process produced boronic acids from both electron-rich and electron-poor arenes that contained halide, alkyl, alkoxide, and ester functionalities (Table 17).

One limitation of the one-pot methodology for the conversion of arenes to arylboronic acids was the low yields of heteroaryl boronic acids from heteroarenes. The C—H borylation occurred in high yield, but the oxidative hydrolysis step occurred in low yield. In contrast, the conversion of several types of heteroarylboronate esters to potassium heteroaryltrifluoroborates with potassium hydrogen difluoride occurred in good yield. Thus, to overcome the limitations of the oxidative hydrolysis procedure, Hartwig and co-workers also developed the conversion of arenes and heteroarenes to potassium trifluoroborates as a one-pot procedure. This process was shown to occur with electron-rich and electron-poor arenes containing alkyl, alkoxide, ester, and halide functionalities (Table 18).[192]

8.2.5. One-Pot Synthesis of Chiral Arylmethylamines

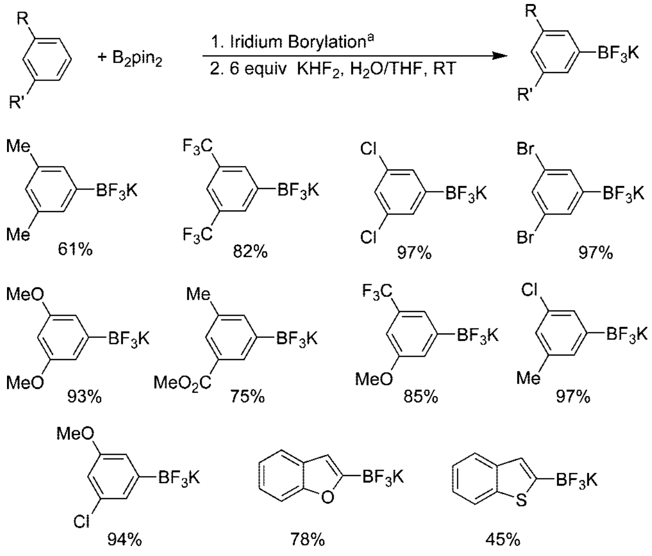
Rhodium-catalyzed additions of boronic acids to imines to form chiral arylmethylamines are known, and these

Table 17. One-Pot Conversion of Arenes to Arylboronic Acids



[a] Borylation of arene was carried out on a 10 mmol scale using 0.1% $[Ir(COD)Cl]_2$ and 0.2% dtbpy in THF at 80 °C. $NaIO_4$ (15.0 mmol) was added to 5 mmol of crude ArBpin in a 4:1 THF/H_2O mixture. [b] Isolated yields on a 5 mmol scale of arene. Yields are the average of two reactions.

Table 18. One-Pot Conversion of Arenes to Potassium Aryltrifluoroborates



[a] Borylation of arene was carried out on a 10 mmol scale using 0.1% $[Ir(COD)Cl]_2$ and 0.2% dtbpy in THF at 80 °C. KHF_2 (5.7 mmol) was added to 5 mmol of crude ArBpin in a 4:1 THF/H_2O mixture. Isolated yields on a 5 mmol scale of arene.

reactions can be conducted diastereoselectively to form enantioenriched diarylmethylamines from *tert*-butylsulfinimines.[196,197] Thus, Hartwig and Boebel sought to develop a sequence involving C−H borylation, followed by rhodium-catalyzed addition of the boronic ester to the imine to convert arenes to enantioenriched diarylmethylamines (Scheme 44).[198] As part of this work, they demonstrated that this sequence to convert arenes into enantioenriched α,α-diaryl methylamines could be conducted as a one-pot procedure.

8.2.6. One-Pot C−H Borylation—Suzuki−Miyaura Cross-Coupling

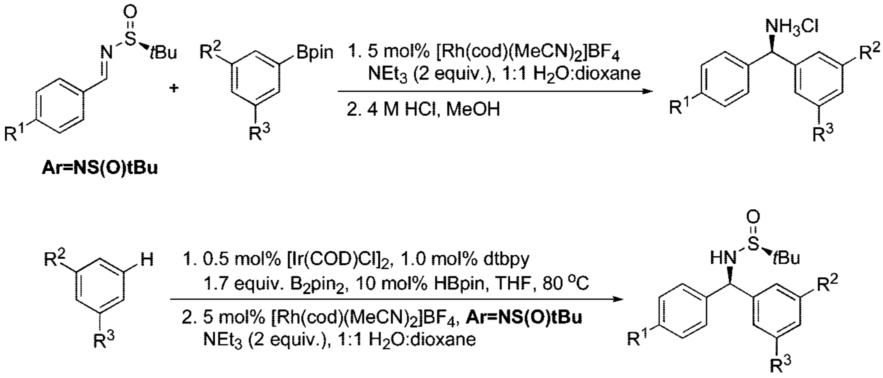
Several groups have reported one-pot sequences involving arene or heteroarene C−H borylation, followed by Suzuki−Miyaura cross-coupling. For example, Smith and co-workers[75] reported the borylation of 3,5-dichlorobenzene with HBpin catalyzed by 2 mol % of the combination of [Ir(indenyl)(COD)] and dppe at 100 °C, followed by the coupling of the resulting 1,3,5-$C_6H_3Cl_2$(Bpin) with 3-bromotoluene catalyzed by $Pd(PPh_3)_4$ in DME to give the corresponding biaryl in 80% yield. Similarly, Ishiyama, Nobuta, Hartwig, and Miyaura reported the borylation of 1,3-dichlorobenzene catalyzed by the combination of $[Ir(COD)(OMe)]_2$ and dtbpy in hexane at 25 °C, followed by cross-coupling of the resulting boronic ester with 4-$MeO_2C-C_6H_4-Br$ catalyzed by $Pd(dppf)Cl_2$ in DMF.[199] Marder and co-workers later reported one-pot combinations of C−H borylation and Suzuki−Miyaura cross-coupling for the synthesis of 4- and 5-(1′-naphthyl)-2-phenylpyridine from 2-phenylpyridine, vide supra. Also, as noted above, diborylation of dtbpy at the 6,6′ positions, followed by removal of the hexane solvent and palladium-catalyzed cross-coupling in dry DMF solvent, formed either 6-Ph- or 6,6′-Ph_2-dtbpy depending on the amount of PhI and $K_3PO_4 \cdot 2H_2O$ added.[200] Similarly, 2,3-dimethylpyrazine underwent borylation and cross-coupling of the resulting heteroarylboronate with 2-bromothiophene in a one-pot procedure to give the unusual bisheterocycle, 2,3-Me_2-5-(2-thienyl)pyrazine.

To avoid the changes in solvent in these sequences, Yamamoto, Ishiyama, and Miyaura have recently reported a one-pot borylation−cross-coupling procedure,[201] in which the borylation of 1,3-dichlorobenzene with either HBpin or B_2pin_2 was conducted in hexane in the presence of the $[Ir(COD)(OMe)]_2$/dtbpy catalyst system, followed by addition of the aryl bromide, $[Pd(dppf)Cl_2]$ as catalyst, $K_3PO_4 \cdot nH_2O$, and DMF, directly into the previous reaction mixture. Most recently, Steel, Marder, and co-workers[202] showed that both steps of this sequence could be conducted in MTBE (MTBE = MeO*t*Bu), giving excellent yields of unsymmetric biaryls. The use of this solvent eliminates the need to change solvents or to add a second, high-boiling, polar solvent. In addition, they have also shown that the one-pot, single-solvent process can be effected using microwave irradiation.[203] The use of microwave heating resulted in considerable acceleration of both steps in the sequence. The aryl and heteroaryl C−H borylation step took place at 80 °C, giving excellent yields of the aryl and heteroarylboronates, typically in minutes, using the $[Ir(COD)(OMe)]_2$/dtbpy catalyst system in MTBE. For example, *N*-Boc protected pyrrole underwent the borylation process in only 3 min using 1.5 mol % $[Ir(COD)(OMe)]_2$ and 3 mol % dtbpy and B_2pin_2 to give 3-Bpin-*N*-Boc-pyrrole in 98% isolated yield. In a 2-step process, *N*-Boc protected pyrrole underwent borylation, followed by cross-coupling with methyl-4-iodobenzoate, using 5 min of microwave irradiation at 80 °C for each step to give a 95% isolated yield of the cross-coupled *N*-Boc-3-(C_6H_4-4-CO_2Me)pyrrole product. These irradiation times are significantly shorter than the 1 h irradiation time employed by Gaunt and co-workers[204] for the microwave-assisted borylation of *N*-Boc protected pyrrole in the presence of 2 mol % $[Ir(COD)Cl]_2$ and 4 mol % dtbpy in hexane at 100 °C. Such a one-pot, single-solvent, microwave-assisted process in MTBE represents a powerful method for the synthesis of compound libraries.

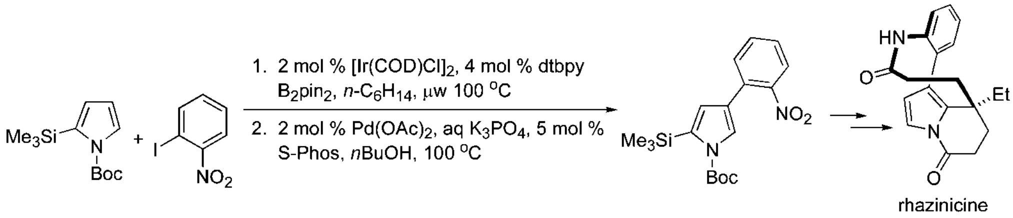
8.2.7. Applications of the Sequence of C−H Borylation and Cross-Coupling

Recently, Gaunt and co-workers reported a total synthesis of rhazinicine in which the iridium-catalyzed borylation of heteroarenes was the first step.[204] They

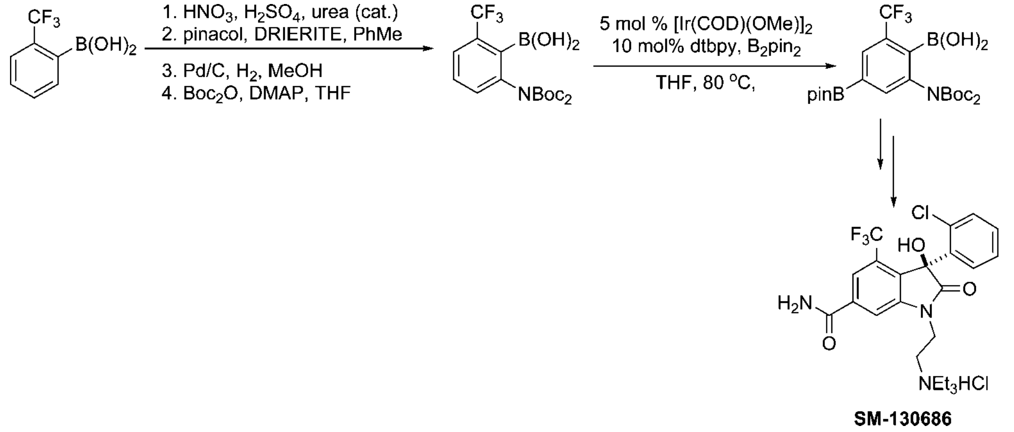
Scheme 44. Rh-Catalyzed Addition of Arylboronate Esters to *tert*-Butylsulfinimines and the One-Pot Procedure for the Conversion of Arenes to Chiral α,α-Diaryl Methyl Amines



Scheme 45. Synthesis of Rhazinicine



Scheme 46. Synthesis of SM-130686 Using Iridium-Catalyzed C−H Borylation



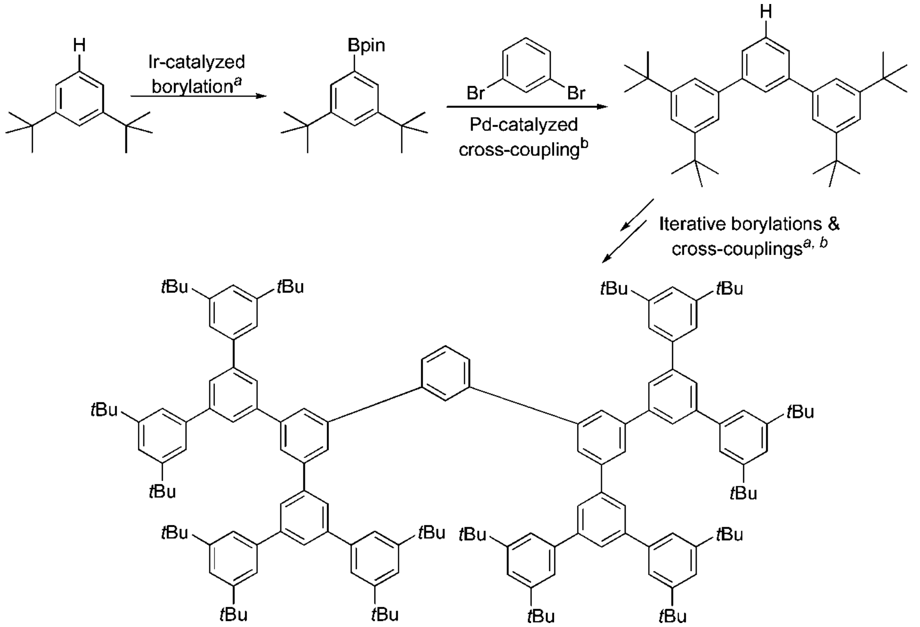
performed the reaction of *N*-Boc-protected 2-trimethylsilylpyrrole with B_2pin_2 catalyzed by $[Ir(COD)Cl]_2$ and dtbpy to functionalize selectively the 3-position of the pyrrole. The resulting heteroarylboronate ester was then coupled with 2-iodonitrobenzene (Scheme 45).

Tomita, Shibasaki, and co-workers reported a recent application of iridium-catalyzed borylation of arenes toward the synthesis of SM-130686, a growth hormone secretagogue (Scheme 46).[205] One key step of the synthesis was a CuF-catalyzed asymmetric arylation.[206] However, a second key step was iridium-catalyzed arene borylation. The benzamide functionality in the final product was derived from an aryl boronic ester unit, which was installed by the borylation of arenes catalyzed by the combination of $[Ir(COD)(OMe)]_2$ and dtbpy.

Finke and Moore reported the sequence of C−H borylation, followed by cross-coupling, for the synthesis of macromolecules (Scheme 47).[207] They synthesized 1,3,5-polyphenylene dendrons by an iterative sequence of iridium-catalyzed borylation of arenes, followed by palladium catalyzed Suzuki−Miyaura cross-coupling. The reaction of 1,3-di-*tert*-butylbenzene with B_2pin_2 catalyzed by the combination of $[Ir(COD)(OMe)]_2$ and dtbpy yielded 3,5-di-*tert*-butylphenylboronic ester. This 3,5-di-*tert*-butylphenylboronate ester was coupled with 1,3-dibromobenzene in the presence of 5 mol % $Pd(OAc)_2$ and 10 mol % S-Phos (2-dicyclohexylphosphino-2′,6′-dimethoxybiphenyl). The first-generation dendron was then converted to the next-generation boronic ester with B_2pin_2 in the presence of catalytic amounts of $[Ir(COD)(OMe)]_2$ and dtbpy. The resulting borylated oligoarene was allowed to react with 1,3-dibromobenzene in the presence of $Pd(OAc)_2$ and S-Phos to form the next-generation dendron. By this iterative sequence of iridium-catalyzed borylations and Suzuki−Miyaura cross-couplings, 1,3,5-polyphenylene dendrons were prepared in high yields.

Wagenknecht and co-workers[208] recently used the compound pyrene-2-Bpin, initially prepared by Marder and co-workers[107] in the synthesis of 5-(2-pyrenyl)-2′-deoxyuridine, as a new thymidine analogue. In this case, they prepared pyrene-2-Bpin from pyrene in 37% yield by borylation using an in situ catalyst system prepared by suspending $[Ir(COD)Cl]_2$ in cyclohexane, treating with NaOMe, and then adding a cyclohexane solution of the pyrene substrate, B_2pin_2, and the dtbpy ligand. This yield is lower than the 68% yield obtained by Marder and co-workers, using an alternative protocol. The pyrene-2-Bpin was subsequently cross-coupled

Scheme 47. Synthesis of a 1,3,5-Polyphenylene Dendron via One-Pot C−H Borylation and Suzuki−Miyaura Cross-Coupling Reactions



[a] Conditions: 3 mol % $[Ir(COD)(OMe)]_2$, 6 mol % dtbpy, 1 equiv of B_2pin_2, cyclohexane, 80 °C, 4 h. [b] Conditions: 5 mol % $Pd(OAc)_2$, 10 mol % S-Phos, aq. NaOH, THF, 60 °C, 2 h.

with 5-iodo-2′-deoxyuridine using $Pd(dppf)Cl_2$ and NaOMe (65 °C, 60 h) to give 5-(2-pyrenyl)-2′-deoxyuridine (2PydU) in 62% isolated yield. Importantly, 2PydU and 2PydU-modified DNA are useful systems in that they showed only weak electronic coupling between the pyrenyl and uridine aromatic π-systems. Thus, and in contrast to the 1PydU isomer, the 2PydU chromophore displays optical properties similar to those of pyrene, demonstrating the utility of the borylation chemistry in accessing otherwise difficult to obtain isomeric derivatives of aromatic compounds.

Finally, Odom and co-workers have used this C−H borylation and cross-coupling sequence to prepare ligands for transition metal complexes.[209] They reported the borylation of 1,3-$i$$Pr_2C_6H_4$ catalyzed by (Ind)Ir(COD) and dmpe at 130 °C as the initial step in their multistep synthesis of 6-(3,3-Me_2-pent-4-enyl)-2,4-$i$$Pr_2$-aniline. This ligand was then used to prepare a tethered molybdenum alkylidene−imine−bis(alkoxide) catalyst for olefin metathesis.

9. Conclusion

C−H activation is an area that is actively being investigated by a number of research groups, and many researchers have postulated that future synthetic advances will result from the selective functionalization of C−H bonds. Direct C−H functionalization allows synthetic chemistry to be conducted without the typical need for all reagents to contain functional groups. However, few current C−H functionalization methods can compete with existing synthetic methods, and many current C−H functionalization methods require harsh reaction conditions and are limited in substrate scope. In contrast to many of these methods, the borylation of aryl C−H bonds occurs under mild conditions, with high turnover numbers, and with a broad tolerance for functional groups. In addition, the metal-catalyzed borylation of alkanes was the first and remains the only process that provides products from terminal functionalization of alkyl chains regardless of the length of or presence of heteroatoms in the chain. It is remarkable that only about a decade separates the initial observation of stoichiometric functionalization of arenes and alkanes with metal−boryl complexes in high yield and the development of catalysts for the borylation of arenes that are now widely used and that have been shown to functionalize arenes with greater than 24 000 turnovers.[18,40]

Nevertheless, the utility of C−H borylation could be increased with further developments. A system that catalyzes the reaction of alkanes and arenes with boron sources other than B_2pin_2, HBpin, and HBdan would increase the synthetic utility of the boronic esters obtained. For example, the boronic esters of catechol and neopentyl glycol are commonly employed as reagents in a number of reactions, such as cross-couplings. The development of a catalyst for the borylation of alkanes at temperatures lower than 150 °C would also likely lead to an improved substrate scope. Considering the rapid development of this C−H borylation chemistry, one can anticipate that further advances will lead to C−H bond functionalizations with main group reagents that will lead, in turn, to additional, widely used synthetic methods.

10. Note Added in Proof

Smith and Maleczka reported the borylation of Bocprotected azoles: 1. Kallepalli, V. A.; Shi, F.; Paul, S.; Onyeozili, E. N.; Maleczka, R. E.; Smith, M. R. III, *J. Org. Chem.* **2009** ASAP, DOI: 10.1021/jo901822b.

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