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Mechanistic Origins of Regioselectivity in Cobalt-Catalyzed C(sp²)-H Borylation of Benzoate Esters and Arylboronate Esters



Most strategies to selectively activate and functionalize a specific C–H bond in an organic molecule rely upon carefully engineered spatial interactions between a substrate and a transition metal catalyst. Here, we report a conceptually distinct alternative strategy, whereby a cobalt catalyst distinguishes between subtly different $C(sp^2)$ -H sites of an arene based on electronics rather than sterics. Mechanistic studies elucidated the origins of substrate-controlled regioselectivity in the $C(sp^2)$ -H borylation of benzoate esters and arylboronate esters.



Tyler P. Pabst, Linda Quach, Kaitlyn T. MacMillan, Paul J. Chirik

pchirik@princeton.edu

HIGHLIGHTS

Electronically derived regioselectivity in cobaltcatalyzed C(sp²)-H borylation

Reversible C–H oxidative addition of aryl esters in a Curtin-Hammett regime

Arylboronate borylation under kinetic control of C(sp²)-H oxidative addition

Sufficiently electron-deficient arylboronates undergo reversible oxidative addition

Pabst et al., Chem 7, 237–254 January 14, 2021 © 2020 Elsevier Inc. https://doi.org/10.1016/j.chempr.2020.11.017

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Mechanistic Origins of Regioselectivity in Cobalt-Catalyzed C(sp²)-H Borylation of Benzoate Esters and Arylboronate Esters

Tyler P. Pabst,¹ Linda Quach,¹ Kaitlyn T. MacMillan,¹ and Paul J. Chirik^{1,2,*}

SUMMARY

Synthetic and mechanistic investigations into the C(sp²)-H borylation of various electronically diverse arenes catalyzed by bis(phosphine)pyridine (^{iPr}PNP) cobalt complexes are reported. Borylation of various benzoate esters and arylboronate esters gave remarkably high selectivities for the position para to the functional group; in both cases, this regioselectivity was found to override the orthoto-fluorine regioselectivity, previously reported for (^{iPr}PNP)Co borylation catalysts, which arises from thermodynamic control of C(sp²)-H oxidative addition. Mechanistic studies support pathways that result in para-to-ester and para-to-boronate ester selectivity by kinetic control of B-H and C(sp²-H) oxidative addition, respectively. Borylation of a particularly electron-deficient fluorinated arylboronate ester resulted in acceleration of C(sp²)-H oxidative addition and concomitant inversion of regioselectivity, demonstrating that subtle changes in the relative rates of individual steps of the catalytic cycle can enable unique and switchable site selectivities.

INTRODUCTION

The site-selective functionalization of $C(sp^2)$ -H bonds is a powerful approach for the construction and diversification of small molecules.^{1–5} Typically, site selectivity in metal-catalyzed C–H functionalization reactions is achieved with directing groups that form discrete metal-ligand bonds during the catalytic cycle and distinguish the various C–H bonds by proximity. While widely applied, this approach relies on specific, predisposed functional groups, limiting its synthetic utility. An alternative strategy exploiting electronically controlled regioselectivity, whereby catalysts distinguish between possible sites of activation by their electronic properties, is appealing due to its potentially broad utility and reliance on the inherent properties of the substrate. In practice, however, such a relationship between site electronics and regioselectivity in metal-catalyzed C–H functionalization has neither been demonstrated nor rigorously understood.

Of the numerous known transformations for the functionalization of C–H bonds, borylation is among the most attractive due to the number of synthetic applications of the readily handled arylboronate ester products.^{6,7} Catalytic C(sp²)-H borylations typically employ iridium precatalysts such as [Ir(COD)OMe]₂ (COD = 1,5-cyclooctadiene) in combination with 4,4'-di-*tert*-butyl-2,2'-bipyridine (dtbpy) or a related substituted bipyridine ligand. Using either B₂Pin₂ or HBPin (Pin = pinacolato) as the boron source, high turnover numbers are achieved in many cases, and

The Bigger Picture

Carbon-hydrogen (C-H) bonds are ubiquitous in organic molecules, and methods for their selective functionalization to more reactive functional groups is a long-standing goal in catalysis, as applied to organic synthesis. Of the established methods involving transition metal catalysts, many employ carefully engineered substrate-catalyst interactions, placing the targeted C-H bond proximal to the metal catalyst, resulting in activation and subsequent functionalization. Here, we report mechanistic investigations describing a conceptual alternative to this approach whereby a cobalt-based borylation catalyst differentiates between subtle electronic differences in C(sp²)-H bonds of benzoate esters and arylboronate esters. These advances motivate studies of catalysts that rely on inherent differences in C-H bond electronics to distinguish chemically inequivalent sites, providing a new tool for organic synthesis.







remarkable chemoselectivity for C(sp²)-H borylation is observed even in the presence of more polar carbon-halogen bonds.^{8,9}

Selectivity in iridium-catalyzed C(sp²)-H, borylation is principally sterically driven.^{8–10} Arene C-H bonds ortho to bulky (CH₃ or larger) substituents are inaccessible to the C-H activating Ir-tris(boryl) intermediate, and no or minimal borylation occurs at these sites; the remaining, accessible C(sp²)-H bonds are typically functionalized to generate approximately statistical mixtures of products (e.g., toluene affords a 2:1 mixture of meta- and para-borylated products, Scheme 1A). Experimental and computational studies have provided insight into the origin of the sterically derived regioselectivity.^{11,12} For all substrates examined experimentally, irreversible C(sp²)-H oxidative addition to Irtris(boryl) has been invoked as the turnover-limiting step. Density functional theory calculations of the oxidative addition revealed late transition states with fully formed iridium-carbon bonds, and a distortion/interaction model was applied in an attempt to rationalize the observed regioselectivity of the borylation of various arenes.¹³ The transition state interaction energy between the iridium catalyst and the substrate at each sterically accessible C(sp²)-H bond served as the most effective predictor of the experimentally observed selectivities. This model was constructed using the assumption that C(sp²)-H oxidative addition was turnover limiting for all substrates examined, and that it proved to be an effective predictor of regioselectivity suggests that the mechanism of iridium-catalyzed borylation is consistent over a wide range of arenes despite differences in substrate electronic properties.

Established strategies to bias precious metal borylation catalysts away from statistical, sterically derived regioselectivity depends upon carefully engineered steric or electrostatic interactions. Numerous Lewis basic directing groups have been employed to affect ortho-directed borylation.¹⁴⁻²² More elaborate approaches involving secondary interactions between catalyst and substrate have been required to achieve meta-selective borylation; such interactions involve hydrogen bonding,²³ Lewis acid-base pairing,²⁴ and ion pairing.^{25–30} Selective borylation at the site para to a substituent has proven particularly challenging, with limited strategies for this outcome (Scheme 1B) including the use of exceptionally large phosphine ligands or Lewis acid co-catalysts.^{31–33} An example of *para*-selective borylation of benzoate esters employed a unique quinolyl-substituted bipyridine ligand engaged in a secondary-substrate interaction involving a bridging alkali metal.³⁴ Recently, the laboratories of Smith and Phipps independently introduced a strategy utilizing tight substrate anion-ammonium ion pairs as a means of blocking most of the sterically accessible C(sp²)-H bonds on the substrate to favor borylation para to a given substituent. 35,36

In comparison to the strategies that rely upon steric or electrostatic interactions, regioselective borylation methodologies resulting from inherent oxidative addition preferences of the metal catalyst at a given site, e.g., electronically driven site selectivity, are exceedingly rare. It has been demonstrated that the iridium/bipyridine catalysts fail to distinguish between the electronically distinct $C(sp^2)$ -H bonds in 3-substituted fluoroarenes and provide approximately statistical product distributions in borylation of these substrates.³⁷ Platinum catalysts supported by either *N*-heterocyclic carbenes or a [PSiN] pincer ligand were shown to borylate fluorinated arenes with improved regioselectivity for the position *ortho* to the fluorine substituent albeit under harsh conditions and by an unknown mechanism.^{38,39}

Our laboratory has reported that bis(phosphino)pyridine (iPr PNP) cobalt complexes are active catalysts for the C(sp²)-H borylation of various arenes and

²Lead Contact

¹Department of Chemistry, Princeton University, Princeton, Princeton, NJ 08544, USA

^{*}Correspondence: pchirik@princeton.edu https://doi.org/10.1016/j.chempr.2020.11.017





Scheme 1. The Selectivity of Metal-Catalyzed C(sp²)-H Borylation in the Absence of Traditional Directing Groups

(A) Statistical selectivity in the borylation of toluene, representative of selectivities often observed in standard iridium-catalyzed C(sp²)-H borylation reactions.

(B) Known strategies to affect *para*-selective C(sp²)-H borylation using specialized catalytic systems.

(C) Substrate-controlled para selective cobalt-catalyzed $C(sp^2)$ -H borylation, where the selectivity responds to substrate electronics (this work).

heterocycles;^{40–42} moreover, these catalysts have demonstrated high regioselectivity for borylation *ortho*-to-fluorine substituents.³⁷ A comprehensive mechanistic study established that fluoroarene borylation by the cobalt catalysts occurs by a mechanism in which $C(sp^2)$ -H oxidative addition to a Co(I)-boryl species is fast and reversible.⁴³ Oxidative addition of the arene substrate is, therefore, under thermodynamic control; metalation at the *ortho* site is favored due to the thermodynamic ortho fluorine effect, whereby metal–aryl complexes with ortho fluorine substituents form stronger M–C bonds.^{44–46} The ability of cobalt catalysts to distinguish subtle electronic differences in arene $C(sp^2)$ -H bonds motivated studies beyond fluorine substituents. An improved understanding of electronically driven site selectivity and its mechanistic origins would enable new synthetically useful, site-selective borylation methods that rely on the inherent properties of the substrate rather than preinstalled directing groups or statistical, sterically driven selectivity.

Here we describe the discovery and mechanistic interrogation of cobalt-catalyzed borylation reactions wherein regioselectivity outcomes were found to be dictated by the electronic properties of the arene substrate (Scheme 1C). The presence of an ester or boronate ester functional group resulted in a strong preference for borylation at the position *para* to this substituent subsubstitutent a selectivity which overrode the previously observed thermodynamic *ortho*-to-fluorine regioselectivity. This phenomenon was then leveraged toward the synthesis of *para*-disubstituted arenes containing ester and boronate functional groups or two chemically distinct boronate substituents. Mechanistic investigations revealed that benzoate ester





substrates undergo catalytic $C(sp^2)$ –H borylation by a mechanism involving fast $C(sp^2)$ –H oxidative addition and which is similar to that which has been determined to result in *ortho* to fluorine regioselectivity for fluorinated (non-ester) arenes; however, the regioselectivity in the case of benzoate ester borylation appears to arise from a kinetic phenomenon rather than metal–carbon and carbon–hydrogen bond thermodynamics. In contrast, mechanistic studies of arylboronate ester borylation revealed a distinct mechanism in which $C(sp^2)$ -H oxidative addition is turnover limiting and likely under kinetic control. Subtle substrate modification resulted in acceleration of $C(sp^2)$ -H oxidative addition and inversion of regioselectivity to result in selective borylation *ortho* to a fluorine substituent rather than *para* to the boronate substituent, as a result of thermodynamic control, establishing the relationship between reaction regioselectivity and the identity of the operative mechanism.

RESULTS AND DISCUSSION

Borylation of Electronically Diverse Arenes

The unique, electronically derived site selectivity observed in fluoroarene borylation with [(^{iPr}PNP)Co] catalysts inspired evaluation of the influences of various substituents on the regioselectivity of the reaction. Studies commenced with the borylation of various monosubstituted difluorinated arenes using the air-stable cobalt precatalyst³⁷ 1-(OPiv)₂ (Scheme 2). These substrates were selected for their high activity toward C-H borylation as well as the ease of product characterization by ¹⁹F NMR spectroscopy. Most importantly, this class of substrates allowed for rapid assessment of ring substituent effects in the site selectivity of the reactions. Borylation occurred efficiently at room temperature over the course of 24 h in THF with B₂Pin₂ as the borylating agent and 5 mol % 1-(OPiv)2 with 20 mol % of HBPin as the activator. In each case, high yields of the borylated product(s) were obtained. While the borylation of 2,5-difluorotoluene (2a) proceeded with marginal selectivity for the position para to the methyl substituent, the analogous trifluoromethyl-substituted compound 2b was functionalized with 73:27 selectivity for the para product, illuminating the influence of the [CF₃] substituent on the site preference for the reaction. Anisole (2c) and the N-acetyl-protected aniline (2d) derivatives were borylated primarily at the meta position, though the selectivity for the meta product was greater (85:15 versus 60:40) for the former. Ester substituents were found to enforce a significant preference for para-selective functionalization, as the reaction of a 2,5-difluorobenzoate ester (2e) afforded a 96:4 mixture of products favoring that arising from borylation para to the ester group. Strikingly, borylation of the 2,6-difluorinated isomer (2f) of this substrate likewise afforded predominantly the para-to-ester functionalized product in an 80:20 ratio, demonstrating that the para influence of the ester overrode the previously described *ortho*-to-fluorine site selectivity with (^{iPr}PNP)Co catalysts. Borylation of trimethylsilyl-substituted 2g resulted in a 65:35 ratio of the para- and meta-functionalized products, respectively. Notably, when 2,5-difluorophenyl pinacolboronate ester 2h was subjected to the reaction conditions, the para-diborylated product was obtained with almost exclusive selectivity. The reaction of the analogous [BDan]-substituted (Dan = 1, 8-diaminonaphthyl) arene 2i likewise afforded predominantly the mixed para-diborylarene product, albeit with slightly diminished (93:7) selectivity. Attempts to borylate the MIDA (N-methylimidodiacetic boronic acid ester) and trifluoroborate derivatives of 2h and 2j resulted in no detectable amounts of borylation products, likely due to unfavorable solubility properties and unwanted side reactivity, respectively.

The observation of high *para* selectivity for the borylation of arylboronate esters 2h and 2i and the apparent large size of the boronate ester substituents raised questions as to the origin of this unique site selectivity. To decouple the influences of steric and electronic factors on the high selectivities of these reactions, an





Scheme 2. Borylation of Various Substituted Difluoroarenes with $\mathsf{B}_2\mathsf{Pin}_2$ Using 1-(OPiv)_2 as Precatalyst

^aThe values in the table are the ratios of arylboronate products resulting from borylation of the substrate drawn. All reactions reached >90% conversion unless otherwise noted.

^bReaction conducted at 60°C.

^cReaction reached 60% conversion.

approximately isosteric acetal-substituted arene (2j) was prepared and borylated under standard catalytic conditions. While 2h was borylated preferentially at the *para* position, the modest 69:31 selectivity observed was significantly less than the nearexclusive *para* selectivity observed for the reaction of 2h. The superior *para* selectivity with 2h (99:1 versus 69:31) indicates that, while sterics may influence the selectivity of the reaction to some extent, the electronics of the boryl substituent are crucial to the high regioselectivity.

The borylation of 2,6-difluoroaryl boronate esters was pursued to determine whether the observed *para* directing effect of the boronate ester persisted in the presence of different $C(sp^2)$ -H bonds *ortho*-to-fluorine substituents. Cobalt-cata-lyzed borylation of 2,6-difluorophenylBPin (2k) with 1 equiv of B₂Pin₂ afforded predominantly the *para*-borylated product with a 91:9 selectivity over the *meta* isomer.



Remarkably, the borylation proceeded with >9:1 selectivity for functionalization *para* to the initial BPin substituent despite the presence of sterically accessible C–H bonds *ortho*-to-fluorine substituents. Likewise, the reaction of [BDan]-substituted **2I** proceeded with 92:8 selectivity in favor of borylation at the *para* position.

Scope of Benzoate Ester and Arylboronate Ester Borylation

With the rare observation of para selectivity in C-H functionalization without the aid of steric directing groups, cobalt-catalyzed C(sp²)-H borylation of various benzoate esters and arylboronate esters was explored. Notably, the observed para selectivity is orthogonal to that expected from classical electrophilic aromatic substitution reactions, and such methods are reported to yield mixtures of regioisomers favoring the meta-functionalized product when either benzoate esters or arylboronic acids are employed as the substrate.⁴⁷ Given the motivation to explore electronically derived regiocontrol in C(sp²)-H activation reactions, only arene substrates with multiple sterically accessible but electronically differentiated C(sp²)-H bonds were selected for these studies. Namely, all substrates examined have at least two distinct $C(sp^2)$ -H bonds that are not ortho to a sterically demanding substituent (CH₃ or larger). Using 5 mol % of the well-defined dihydride boryl precatalyst 1-(H)₂BPin and 1 equiv of B₂Pin₂, various substituted benzoate ester substrates were borylated in excellent yield to selectively generate the corresponding 4-borylbenzoate esters (Scheme 3). Two 2,5-difluorinated benzoate esters bearing methyl and tert-butyl substituents on the O-bound portion of the ester were subjected to the reaction conditions to afford the corresponding para-borylated products 3e and 3m with essentially identical regioselectivities, indicating that the steric profile at this position has little impact upon the outcome. Borylation of a trifluorinated ester afforded predominantly the para-functionalized product 3n in a 92:8 ratio over the minor, meta-borylated product, while a 2,3-difluorinated substrate gave exclusively the para-borylated product 30. In two cases where para-to-ester selectivity proved to override the previously described ortho-to-fluorine selectivity, 3f and 3p were obtained from the reaction of the corresponding benzoate esters. Borylation of these two substrates occurred with approximately 80:20 regioselectivity in favor of the product arising from $C(sp^2)$ -H borylation of the position para to the ester substituent, with the selectivity for 3f improving to 95:5 upon purification by flash column chromatography. Borylation of 2-trifluoromethylbenzoate methyl ester (2q) afforded 3q and 3q'in a 70:30 ratio.

The synthesis of 1,4-diborylsubstituted arenes with one [BPin] and one [BDan] substituent was also pursued due to the well-demonstrated differential reactivity of the two boron substituents, for example, in Suzuki-Miyaura cross-coupling.^{48–50} Under identical reaction conditions to those employed for the borylation of benzoate esters, a selection of [BDan]-substituted arenes were borylated to generate the corresponding mixed diborylarenes (Scheme 3).

Borylation of arylboronate ester substrates with multiple aryl fluoride substituents proceeded efficiently at room temperature and with high regioselectivity for borylation *para* to the [BDan] substituent. The products of these reactions were readily isolated by filtration of the crude reaction mixtures through a thin pad of silica followed by solvent removal and washing the resulting solid with a portion of cold pentane. The products arising from borylation of 2,5-difluorophenylBDan were isolated in 89% yield and with a 98:2 ratio of the *para*- and *meta*-borylated products **3i** and **3i**'. Borylation of 2,6-difluorophenylBDan(2l) and 2,3,6-trifluorophenylBDan(2r) on a larger than one-gram scale afforded the corresponding products **3I** and **3r** in



Scheme 3. Scope of the para-Selective $\mathsf{C}(\mathsf{sp}^2)\text{-}\mathsf{H}$ Borylation of Benzoate Esters and Arylboronate Esters Catalyzed by $1\text{-}(\mathsf{H})_2\mathsf{BPin}$

Scope of the borylation of arylBDan compounds to generate mixed 1,4-diborylarenes. ^aAll reactions were run on 0.50 mmol scale at 23°C for 24 h unless otherwise noted. Isolated yields are shown unless otherwise noted.

^b3.5 mmol scale.

^c4.0 mmol scale.

^d2.0 mmol scale.

^eReaction conducted at 60°C.

^fYield determined by ¹H NMR spectroscopy.

80% yield (96:4 regioselectivity) and 83% yield (>99:1), respectively. Borylation of 2,3-difluorinated **2s** and difluorinated anisole derivative **2t** also proceeded with high yield and excellent selectivity to generate **3s** and **3t** with near exclusivity in both cases. For comparison to previously established catalytic systems, the borylation of **2l** was also carried out with [Ir(COD)OMe]₂ and dtbpy; this reaction produced a complex mixture of organoboron products due to multiple borylations of the diaminonapthyl substituent in addition to the arene ring (see Supplemental Information for details). This result demonstrates that the superior activity of the iridium catalysts is detrimental to regioselectivity as an uncontrolled borylation results when multiple aromatic rings with different electronic properties are present. Iridium-catalyzed

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borylation of the analogous BPin-substituted compound (2k) generated *para*-diborylated 3k as the major product, but with a significant amount of the triborylated product arising from initial borylation *meta* to the boryl substituent of the substrate. Considering the high regioselectivity observed in the borylation of 2k by the (PNP) Co catalyst, this result demonstrates the heightened sensitivity of the cobalt system to the electronics of the distinct sites of the arene substrate.

Application of the cobalt-catalyzed method to arenes bearing substituents other than or in addition to fluorine maintained the high regioselectivity for para-diborylarenes, though some substrates bearing fewer fluorine substituents displayed lower activity. Increased temperatures (see Scheme 3) were necessary for synthetically useful yields in many of these cases, and column chromatography was required for isolation of the products (see Supplemental Information for details). Monofluorinated aryIBDan substrates bearing methoxy (2v) and methyl (2w) substituents underwent catalytic C(sp²)-H borylation with 89:11 regioselectivity or greater for the position para to [BDan]. An ethoxybenzene derivative (2x) was borylated with 87:13 selectivity favoring the 1,4-diborylarene product 3x despite the presence of a different $C(sp^2)$ -H bond ortho to a fluorine substituent. Borylation of sulfonamide (2y) and trifluoromethyl-substituted (2z) substrates without aryl fluoride substituents also proceeded, albeit with reduced regioselectivity and activity. Curiously, the borylation of 2-fluoro-6-trifluoromethylphenylBDan (2aa) yielded predominantly the meta-diborylarene product 3aa'. This anomalous regioselectivity will be discussed in detail later in the text.

While the cobalt-catalyzed C(sp²)-H borylations of many of the substrates discussed above (see Scheme 3) proceed efficiently and with high regioselectivites, next-generation catalysts are required to expand the scope and overall activity. Substrates containing aryl chloride and bromide moieties were found to be unsuitable for borylation with the cobalt catalysts; this is consistent with previously published results indicating that (^{iPr}PNP)Co catalysts are intolerant of aryl halide substituents other than fluoride (see the Supplemental Information for details).³⁷ Other substrates were found to be incompatible with the method due to insufficient activation, including PhBDan and its 2-methoxy-substituted derivative. While the successful reactions described above demonstrate the electronic sensitivity of the cobalt catalysts with superior activity and functional group tolerance is necessary in order to extend the utility of this method to the borylation of more electron-rich arene substrates as well as those with more diverse functionality.

Mechanistic Investigations of Benzoate Ester Borylation

The high *para*-to-functional group regioselectivity observed in borylation of select benzoate esters and arylboronates raised questions about the origins of this rare regioselectivity and the mechanism operative in the catalytic reactions for each substrate class. For all mechanistic studies, the well-defined cobalt precatalyst, **1**-(H)₂BPin was used to eliminate any complications associated with activation of **1**-(OPiv)₂.⁵¹ First, substrate **2f** was used for investigations into benzoate ester borylation because of the orthogonal selectivity to that observed from the *ortho*-to-fluorine cases reported previously.³⁷ Variable time normalization analysis (VTNA), as described by Burés, was applied to determine the overall rate law of this reaction using trials with varying initial concentrations of **1**-(H)₂BPin, arene **2f**, and B₂Pin₂ (Scheme 4A).⁵² Using this procedure, the rate law described by Equation 1 was obtained.

Scheme 4. Mechanistic Investigations for the 1-(H)_2BPin-Catalyzed C(sp 2)-H Borylation of Benzoate Esters

(A) Borylation of **2f** with **1-(H)₂BPin** and the experimentally determined rate law.

(B) Parallel deuterium kinetic isotope effect experiments for the borylation of **2ab**.

(C) Cobalt resting states were observed in situ by $^{19}{\rm F}$ and $^{31}{\rm P}$ NMR spectroscopy for the borylation of **2ab**.

(D) Competition kinetic isotope effect experiments for the borylation of **2ab**.

(Equation 1)

As in our previous studies of fluoroarene borylation catalyzed by (^{'Pr}PNP)Co complexes, the order in arene substrate was determined to be zero, indicating saturation behavior. This result is consistent with a reaction mechanism whereby C(sp²)-H oxidative addition is fast relative to subsequent steps of the catalytic cycle. In light of the orthogonal regioselectivity of the borylation of **2f** compared to previous fluorinated arenes examined, further mechanistic experiments were pursued. For





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deuterium kinetic isotope effect (KIE) studies, 2,6-difluorobenzoate *tert*-butyl ester (2ab) and its deuterated variant 2ab-d₃ were employed, as the hydrogen isotope exchange procedure employed for the synthesis of the deuterated substrate does not tolerate methyl esters.⁵³ Upon measurement of the initial rates of 1-(H)₂BPin-cata-lyzed C(sp²)-H borylation of 2ab and 2ab-d₃ in the presence of 1.75 equiv of B₂Pin₂ in two separate vessels, a value of 3.3(1) was determined for the ratio of k_H/k_D at 23°C (Scheme 4B). Notably, previous mechanistic investigations on the ortho-selective borylation of fluorinated arenes gave k_H/k_D values close to unity, suggesting that C–H bond cleavage did not occur during the rate-determining step of these reactions.⁴³ The proposed origins of the observed KIEs will be discussed at length later in this section.

Monitoring the catalytic borylation *in situ* by ¹⁹F and ³¹P NMR spectroscopy revealed the presence of two Co(I)-aryl species accessible by $C(sp^2)$ -H oxidative addition to 2f followed by reductive elimination of HBPin. In contrast to previous studies on fluoroarene borylation, where only the *ortho*-fluorinated Co(I)-aryl species was observed spectroscopically during the catalytic reaction, the two species *para*- and *meta*-4f were present in an approximately 2:1 ratio.⁴³ A significant amount of the Co(I)-boryl species 1-BPin⁴¹ was simultaneously observed by ³¹P NMR spectroscopy. These three species were observed at the beginning of the time course, but all three decreased in relative concentration as the reaction progressed, and 1-(H)₂BPin became the only Co species observed in significant amounts as conversion increased. This behavior has been described previously and is attributed to the increasing concentration of HBPin, the stoichiometric by-product of the reaction, which pulls the cobalt catalyst off-cycle when present in large concentration.⁴³

Temperature effects for the borylation of 2f were also investigated (see the Supplemental Information for details). In contrast to the previous mechanistic studies with fluorinated arenes, where regioselectivity remained constant independent of the temperature of the reaction,³⁷ the preference for borylation of 2f at the *para* position eroded slightly but significantly at higher temperatures and improved to 83:17 when the reaction was performed at 4°C.

The relatively large, normal deuterium KIE determined for the borylation of 2f is in contrast to the near-unity values previously obtained for ortho-to-fluorine selective borylation using the same catalyst; additionally, this data might appear to conflict with the rate law determined for this reaction, which indicates that the rate of the transformation is independent of the initial concentration of 2ab. This zeroth-order in 2ab combined with the spectroscopic identification of Co(I)-aryl species paraand *meta*-4f strongly suggest that the C(sp²)-H activation step precedes the turnover-limiting step of this catalytic reaction. Another possibility that reconciles all available data is that the apparent C-H/C-D KIE arises instead from the rate-determining cleavage of a B–H (or B–D) bond. Indeed, the mechanism that we have previously proposed for fluoroarene borylation catalyzed by 1-(H)₂Bpin involves the reaction of the Co(I)-aryl species with HBPin to generate a Co(III) intermediate, which then undergoes reductive elimination of the arylboronate product. When $2f - d_3$ is employed as the substrate, DBPin (rather than HBPin) is expected to undergo oxidative addition with the Co(I)-aryl species; as such, the $k_{\rm H}/k_{\rm D}$ value of 3.3(1) observed when reactions were performed in separate vessels (vide supra) is not necessarily derived from the relative rates of C-H and C-D bond cleavage. To assess this possibility, a competition KIE experiment was performed; notably, parallel and competition KIE experiments can yield different values for the same



catalytic reaction, offering valuable insights into the operative mechanism.⁵⁴ Catalytic borylation at 23°C of an equimolar mixture of 2ab and 2ab-d₃ in the presence of 1 equiv of B₂Pin₂ as well as 5 mol % of 1-(H)₂BPin (Scheme 4D, top) afforded a value of 1.5 for k_H/k_D . The erosion of this value compared with that observed in the parallel KIE experiments may be attributed to the presence of both HBPin and DBPin in the reaction mixture, as each is proposed to arise from the initial C-H (or C-D) oxidative addition of 2ab or 2ab-d₃ to 1-BPin followed by reductive elimination of the corresponding borane. To further investigate the possibility that the observed KIEs are associated with a mechanism involving slow B-H oxidative addition, a similar competition experiment was performed in the presence of 5.0 equiv of HBPin. Under these conditions, the concentration of HBPin in the reaction mixture is much higher than that of DBPin at any given time, and no rate difference should be expected for the formation of 3ab versus $3ab-d_2$; in this experiment, a $k_{\rm H}/k_{\rm D}$ value of 1.1 was determined, demonstrating essentially complete erosion of the preference for borylation of 2ab over 2ab-d₃ and providing additional support for a B-H bond cleavage event as the slow step of the catalytic reaction.

Given all of the available experimental data, a mechanism for the 1-(H)₂BPin-catalyzed C(sp²)-H borylation of benzoate esters is proposed wherein the fundamental steps resemble those previously implicated in the ortho-selectivity borylation of fluorinated arenes, but where differences in the rates of these steps relative to one another result in selective functionalization para to the ester substituent. The cobalt precatalyst 1- $(H)_2$ BPin eliminates H₂ by a multi-step sequence⁵⁵ to generate the C–H activating boryl species, 1-BPin. The species then undergoes C(sp²)-H oxidative addition to generate a Co(III)-aryl-hydride-boryl intermediate with mutually cis boryl and hydride ligands, and this species then reductively eliminates HBPin to generate Co(I)-aryl species para- and meta-4f. In contrast to previous studies⁴³ in which only one isomer of the Co(I)-aryl species of (^{'Pr}PNP) was observed in situ, isomers metalated at both the major and minor sites of functionalization were observed, indicating that both of these species are kinetically accessible during catalysis and are generated in comparable amounts. As suggested by the KIE experiments, subsequent addition of HBPin to either Co(I)-aryl species to generate the corresponding Co(III) species with mutually cis aryl and boryl ligands is proposed to be the turnover-limiting step. Reductive elimination of the arylboronate ester product follows, and the resulting hydride species 1-H can then react with either B₂Pin₂ (to regenerate 1-BPin) or HBPin (to regenerate 1-(H)₂BPin).

With knowledge of the mechanism for the *para*-selective borylation of benzoate esters in hand, one may rationalize the origins of the observed regioselectivity. Considering that the rate of the reaction is independent of the concentration of arene 2f, and the two Co(I)-aryl species *para*- and *meta*-4f are present and observable by ¹⁹F and ³¹P NMR spectroscopy during the reaction, it appears that the C(sp²)-H oxidative addition is fast and reversible and culminates in rapid interconversion between *para*- and *meta*-4f. This rapid interconversion of the two Co(I)-aryl species followed by turnover-limiting oxidative addition of HBPin constitute a Curtin-Hammett scenario⁵⁶ wherein the selectivity of the reaction is determined by the relative rates of the reaction of HBPin with either *para*-4f to give the major *para*-borylated product or *meta*-4f to give the minor product.

Various subtle but significant pieces of data distinguish the mechanism implicated in the selective *ortho*-borylation of fluorinated arenes from that proposed in this study by which benzoate esters are preferentially *para*-borylated. In both cases, a zeroth-order dependence on the concentration of the arene substrate was demonstrated, and *in situ* analysis



of the resting states of the reaction revealed the formation of Co(I)-aryl species. However, in the ortho-to-fluorine case, only the ortho-fluorinated Co(I)-aryl species was observed, indicating that the regioselectivity of the reaction is determined prior to the formation of this species. In the para-to-ester case, both possible isomers of the Co(I)aryl complex are formed with a slight (approximately 2:1) preference for para-4f over meta-4f, and this ratio is inferior to that of the eventual arylboronate product distribution, suggesting that the Co(I)-aryl intermediates may have comparable thermodynamic stability while a subsequent step of the reaction favors the production of the para-borylated product. In terms of temperature effects, the regioselectivity in borylation of simple fluorinated arenes previously examined remained constant as a function of reaction temperature. In contrast, borylation of 2f at various temperatures revealed that the para-toester selectivity improves slightly at low temperatures and slowly erodes as reaction temperature is increased, supporting kinetically controlled regioselectivity. Finally, parallel KIE experiments for a catalytic borylation, which gave ortho-to-fluorine regioselectivity, afforded a k_H/k_D value of 1.1(1) that stands in clear contrast to the value of 3.3(1) obtained in the present para-to-ester case, ostensibly arising from a turnover-limiting oxidative addition of HBPin (or DBPin) to a Co(I)-aryl species (vide supra). This raises questions related to the lack of a KIE in the previously examined ortho-to-fluorine case. It is worthwhile to note that, in a comprehensive computational study concerning the mechanism of the C(sp²)-H borylation of benzene by (^{iPr}PNP)Co complexes, DFT calculations using the ω B97XD functional predict oxidative addition of HBPin to the Co(I)aryl to be the turnover-limiting step for this substrate.⁵⁵ Moreover, the subsequent reductive elimination of arylboronate product from the resulting complex was found to occur with a kinetic barrier of 14.8 kcal/mol compared with a barrier of 17.2 kcal/ mol required for the slow step. It is anticipated that the relative barriers to these two slowest steps of the catalytic cycle may change as a function of the arene substituents and substitution pattern, and these variations can, in turn, result in a change in the turnover-limiting step. For a reaction in which C-B reductive elimination is turnover limiting, the value of $k_{\rm H}/k_{\rm D}$ is expected to be near unity, while reactions with turnover-limiting B-H oxidative addition to Co(I)-aryl should afford normal, primary KIE values such as the value of 3.3(1) observed in the borylation of 2ab and 2ab-d₃.

Mechanistic Investigations of Arylboronate Ester Borylation

We next turned our attention to experimental mechanistic studies of arylboronate borylation that also results in regioselective functionalization at the *para* position. For these investigations, 2,6-difluorinated substrate 2k was selected due to its structural similarity to 2f and because of the pronounced *para*-to-boronate selectivity observed despite the presence of different arene sites *ortho*-to-fluorine substruturents. VTNA was applied for the catalytic C(sp²)-H borylation of 2k and the rate law expressed in Equation 2 was obtained.

Rate =
$$k[1-(H)_2BPin]^1[2k]^1[B_2Pin_2]^0$$
 (Equation 2)

A first-order dependence on both the cobalt precatalyst and the arene substrate was observed, supporting a pathway whereby $C(sp^2)$ -H oxidative addition is turnover limiting. To further assess this possibility, the deuterated arene $2k-d_3$ was prepared (see the Supplemental Information) and the deuterium KIE was determined. In two separate vessels, 2k and $2k-d_3$ were each borylated in the presence of 5 mol % 1-(H)₂BPin and 1.75 equiv of B₂Pin₂, and a value of 2.0(1) was measured for k_H/k_D ratio at 23°C. A normal value of this magnitude is consistent with turnover-limiting C–H bond cleavage (Scheme 5B). In addition, *in situ* monitoring of the borylation reaction by ¹H and ³¹P NMR spectroscopy established that the cobalt(I)-boryl, 1-BPin,⁴¹ is the



k_D (23 °C) (<1 half-life) H_3 BPin H F₃C F₃C 5 mol % 1-(H)2BPin B₂Pin₂ THF, 23 °C, time - DBPin BPin 1-(H)₂BPin

Scheme 5. Mechanistic Investigations for the 1-(H)₂BPin-Catalyzed C(sp²)-H Borylation of Arylboronate Esters 2k and 2ac

(A) Borylation of 2k with 1-(H)₂BPin and the experimentally determined rate law.

(B) Parallel deuterium kinetic isotope effect experiments for the borylation of 2k.

(C) Cobalt resting state observed in situ by 31 P NMR spectroscopy for the borylation of 2k.

(D) Borylation of 2ac with $1-(H)_2BPin$ and the experimentally determined rate law. (E) Parallel deuterium kinetic isotope effect experiments for the borylation of 2ac.

(F) Cobalt resting state observed in situ by ¹⁹F and ³¹P NMR spectroscopy for the borylation of **2ac**.



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catalyst resting state consistent with slow C–H oxidative addition of the arene 2k (Scheme 5C).

All of the experimental data obtained for the borylation of 2k are consistent with turnover-limiting $C(sp^2)$ -H oxidative addition, establishing a change in mechanism compared with our previous reports of *ortho*-to-fluorine selective borylation with 1-(H)₂BPin. These previous studies demonstrated that fast and reversible $C(sp^2)$ -H oxidative addition under thermodynamic control resulted in the observed selectivity for borylation *ortho*-to-fluorine substituents, a consequence of forming the strongest Co–C bond. It is apparent from the change in the mechanism that the introduction of an inductively donating boronate ester substituent effectively slows $C(sp^2)$ -H oxidative addition relative to the subsequent steps of the reaction.

That the turnover-limiting step of the borylation of 2k was found to be distinct from other previously studied fluoroarene substrates prompted consideration of the possible origins of the observed para-to-boron selectivity. As in the case of iridium-catalyzed borylation, turnover-limiting C(sp²)-H oxidative addition implies that this step is irreversible and, therefore, selectivity-determining, where the selectivity results from the different kinetic barriers for C-H bond cleavage. In the case of the borylation of 2k, the C(sp²)-H bonds ortho to fluorine are stronger than the C(sp²)-H bond para to the boronate ester substituent due to the established ortho stabilizing effect of fluorine.⁴⁶ The observed selectivity for borylation of the sites para to the [BPin] substituent is, therefore, consistent with kinetically controlled selectivity, as the reaction favors activation of the weakest available arene C-H bond. It should be noted that, while the regioselectivities for both iridium- and cobalt-catalyzed borylation of this substrate are presumed to result from kinetically controlled oxidative addition, the selectivity of the cobalt-catalyzed reaction for the position para to the boronate substituent is superior under the conditions examined. The fundamental difference between C(sp²)-H oxidative addition at the two metals that causes the distinct selectivities is likely a result of the greater ionicity of the forming metal-carbon bonds with cobalt compared to the analogous bonds with iridium.⁴⁶ Development of a more complete explanation for the superior electronic control observed with cobalt and associated computational investigations are ongoing. In previous studies of ortho-selective fluoroarene borylation, the observed product ratios remained constant when the reaction temperature was varied, consistent with a reaction under thermodynamic control.³⁷ In the borylation of 2k, varying the reaction temperature from 4°C to 80°C resulted in a gradual erosion of the regioselectivity, as the temperature increased (see the Supplemental Information for details). While the ratio of products improved to 94:6 at 4°C, activity decreased significantly, reaching only 59% conversion after 1 week. Conversely, heating to 80°C resulted in a rapid borylation but produced a diminished 81:19 selectivity in favor of the para-diborylated product. The observed temperature effects further support a kinetically controlled regioselectivity for the borylation of 2k.

Observation of kinetically controlled *para*-to-boronate ester selectivity in the cobalt-catalyzed $C(sp^2)$ -H borylation of 2k that overrides the previously reported *ortho*-to-fluorine selectivity inspired other means of enabling substrate-controlled regioselectivity. Of particular interest were arenes with both fluorine and boronate ester substituents that were sufficiently electron deficient to accelerate $C(sp^2)$ -H oxidative addition and enable thermodynamic rather than kinetic control. Replacement of one fluorine in 2k with a more electron-withdrawing trifluoromethyl substituent affords arene 2ac, which is anticipated to be more activated toward $C(sp^2)$ -H oxidative addition than is 2k. Borylation of 2ac with 1 equiv of B₂Pin₂ in the presence of 5 mol % 1-(H)₂BPin at 23°C generated predominantly



the product of borylation *ortho* to the fluorine substituent in a 77:23 ratio, with the minor product arising from borylation of the other sterically accessible $C(sp^2)$ -H bond (*para* to the BPin substituent) (Scheme 5D).

The observed *ortho*-to-fluorine regioselectivity observed with 2ac prompted an investigation of the mechanism and kinetic behavior of this reaction. Using VTNA, the rate law for the C(sp²)-H borylation of 2ac with 1-(H)₂BPin was determined (Equation 3).

$Rate = k[1-(H)_2BPin]^1[2ac]^0[B_2Pin_2]^0$ (Equation 3)

In contrast to the rate law in Equation 2 for the borylation of 2k, a zeroth-order dependence in arene substrate was observed for the borylation of 2ac, indicating saturation behavior, which is consistent with fast and reversible $C(sp^2)$ -H oxidative addition. This result was corroborated by deuterium kinetic isotope experiments; in two separate vessels, borylation of 2ac and 2ac-d₂ with 5 mol % 1-(H)₂BPin provided a k_H/k_D value of 1.2(2) at 23°C, indicating that neither C–H bond cleavage nor B–H bond cleavage occurs in the turnover-limiting step of the reaction (Scheme 5E). *In situ* monitoring of the catalytic reaction by ¹⁹F and ³¹P NMR spectroscopy established the cobalt(I)-aryl complex, *ortho*-4ac, as the initial resting state (Scheme 5F), and the minor Co(I)-aryl isomer was not observed by ¹⁹F NMR spectroscopy at any point in the time course. These data are consistent with fast and reversible C(sp²)-H oxidative addition of the substrate, as previously reported for the borylation of fluorinated arenes. In addition, the selectivity of the borylation reaction was unchanged from 23°C to 80°C (see the Supplemental Information for details).

In summary, the subtle electronic differences in arene substitution between 2f, 2k, and 2ac were sufficient to change the selectivity-determining phenomena in the catalytic borylation of these substrates with 1-(H)₂BPin (Scheme 6). In the reaction of benzoate ester substrates such as 2f, it is proposed that C(sp²)-H oxidative addition and subsequent reductive elimination of HBPin reversibly generate Co(I)-aryl species, of which multiple regioisomers are kinetically accessible; the observed parato-ester regioselectivity of the catalytic reaction is then derived from a kinetic preference for the reaction of HBPin with the para-activated Co(I)-aryl intermediate over the analogous reaction with the meta-activated isomer. With 2k, slow C(sp²)-H oxidative addition is under kinetic control and favors borylation at the position para to the boronate ester, while oxidative addition of 2ac proceeds reversibly to preferentially generate thermodynamically favored ortho-fluorinated cobalt aryl intermediates in a non-Curtin-Hammett regime resulting predominantly in borylation ortho to the fluorine substituent. Importantly, the presence or absence of a Curtin-Hammett selectivity-determining scenario is dependent upon the disparity between the rate of interconversion of the relevant equilibrating intermediates and the rate of the subsequent turnover-limiting step.⁵⁶ Detailed understanding of the relative rates of fundamental steps in the catalytic cycles investigated in this study enables substrate-controlled regioselectivity derived from the electronic properties of chemically inequivalent C(sp²)-H sites, a concept which promises to empower rational advances in regioselective C-H activation methodology.

EXPERIMENTAL PROCEDURES

Resource Availability

Lead Contact

Further information and requests for resources and reagents should be directed to and will be fulfilled by the Lead Contact, Paul J. Chirik (pchirik@princeton.edu).







Scheme 6. Mechanistic Explanation for Substrate-Controlled Selectivity as a Result of Arene Electronics

(A) Experimentally determined rate laws for catalytic borylation and predominant site of $C(sp^2)$ -H borylation for arene substrates examined in this work.

(B) Explanation for observed regioselectivity in cobalt-catalyzed borylation as a consequence of the relative rates of $C(sp^2)$ -H oxidative addition.

Materials Availability

All unique reagents generated in this study are available from the Lead Contact without restriction.

Data and Code Availability

All datasets generated within these investigations are available in the Supplemental Information.

SUPPLEMENTAL INFORMATION

Supplemental Information can be found online at https://doi.org/10.1016/j.chempr. 2020.11.017.

ACKNOWLEDGMENTS

Financial support was provided by the NIH (5R01GM121441). T.P.P. thanks Amgen for financial support as well as Princeton University for an Edward C. Taylor Fellowship. L.Q. acknowledges support from the Alfried Krupp von Bohlen und Halbach Foundation. We also thank AllyChem for a gift of B₂Pin₂.





AUTHOR CONTRIBUTIONS

T.P.P., L.Q., and K.T.M. performed the experiments and analyzed the data. P.J.C. supervised the research and assisted with experimental design and data analysis. All authors contributed to the preparation and revision of the manuscript.

DECLARATION OF INTERESTS

The authors declare no competing interests.

Received: April 21, 2020 Revised: August 8, 2020 Accepted: November 14, 2020 Published: December 9, 2020

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