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Para-Selective C−H Borylation of Common Arene Building Blocks Enabled by Ion-Pairing with a Bulky Countercation

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Supporting Information

ABSTRACT: The selective functionalization of C−H bonds at the arene *para* position is highly challenging using transition metal catalysis. Iridium-catalyzed borylation has emerged as a leading technique for arene functionalization, but there are only a handful of strategies for *para*-selective borylation, which operate on specific substrate classes and use bespoke ligands or catalysts. We describe a remarkably general protocol which results in *para*-selectivity on some of the most common arene building blocks (anilines, benzylamines, phenols, benzyl alcohols) and uses standard borylation ligands. Our strategy hinges upon the facile conversion of the substrates into sulfate or sulfamate salts, wherein the anionic arene component is paired with a tetrabutylammonium cation. We hypothesize that the bulk of this cation disfavors *meta*-C−H borylation, thereby promoting the challenging *para*-selective reaction.

Use of transition metals to catalytically functionalize arene C−H bonds has undergone tremendous development. While most advances have dealt with *ortho*-selective functionalization, the past decade has seen many advances in *meta*-selective reactions.[1] Many of these approaches have been based on templates or ligands with extended architectures, or on strategies which proceed via metalation at the *ortho* position. Considering this, it is not surprising that methods to direct transition metals to the *para* position remain rather fewer, given the greater distance from existing functionality.[2] Although S_EAr mechanisms give the *para* isomer when electrophiles react with electron rich arenes, it is uncommon for transition metals to perform C−H bond functionalization via S_EAr mechanisms.[3] Exceptions are several examples using gold catalysis[4] and a smaller number of examples using high-valent copper[5] or palladium.[6] Yet such selectively metalated intermediates are extremely versatile and new methods to access them are urgently required.[7,8]

Iridium-catalyzed borylation has emerged to become one of the most versatile and intensively used of modern arene functionalization methods.[9,10] While regioselectivity is typically determined by steric considerations, numerous modifications can direct borylation to the *ortho* position[11] and, to a lesser extent, the *meta* position.[12] In contrast, there are only three instances where *para*-selective iridium catalyzed C−H borylation has been achieved (Figure 1a).[13,14] Saito, Segawa and Itami used a bulky, chiral phosphine ligand to create a highly sterically congested environment at iridium.[15] However, high *para*-selectivity was limited to substrates possessing a very bulky substituent, and 1,2-disubstituted arenes were unselective. Nakao and co-workers used a bulky Lewis acid catalyst to complex aromatic amides, both activating the substrate and forcing borylation to occur at the most remote position due to steric interactions.[16] Most recently, Chattopadhyay and co-

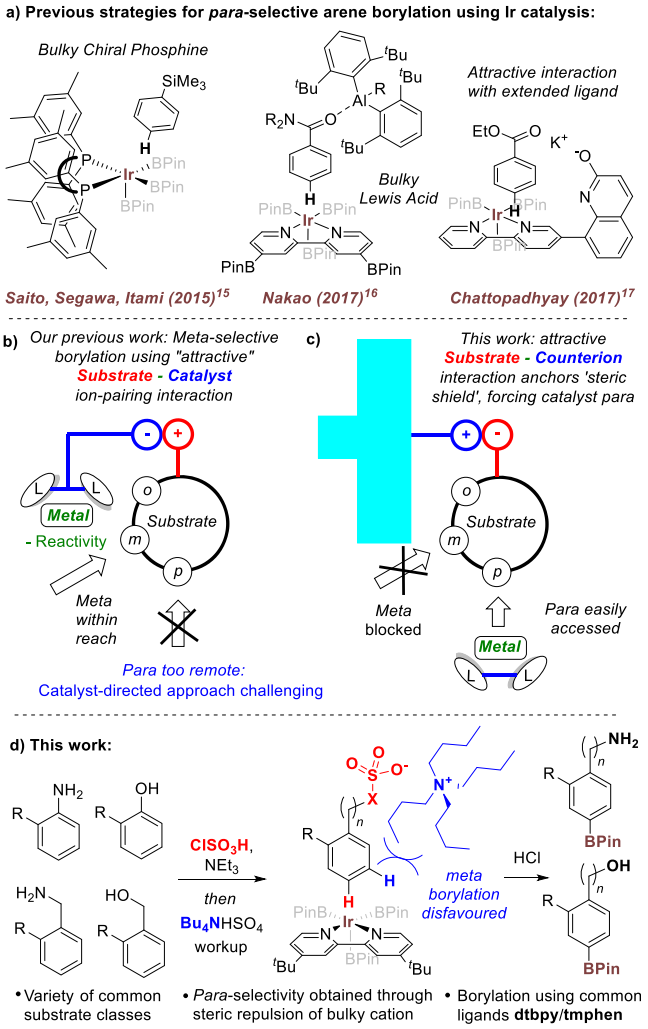

Figure 1. Previous *para*-selective Ir-catalyzed borylation approaches and that taken in this work.

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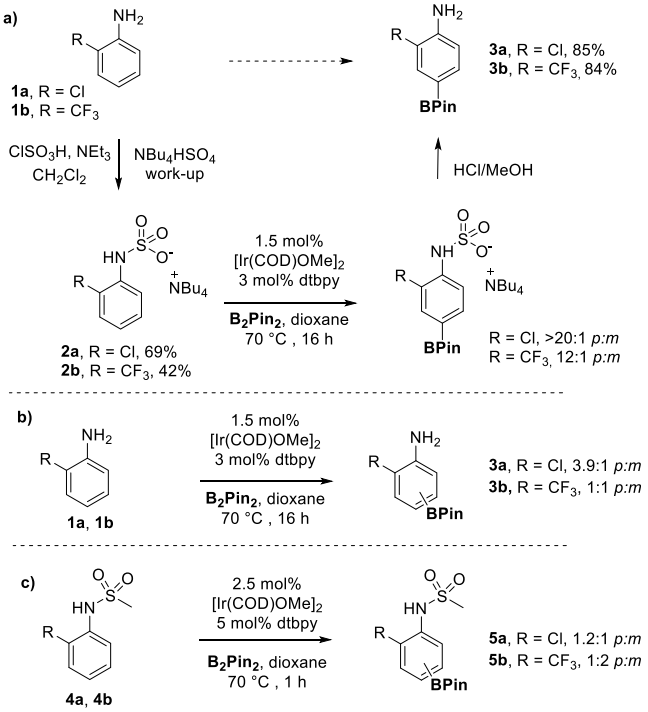
workers disclosed an "L-shaped" bipyridine ligand proposed to direct borylation to the *para* position by virtue of interaction between the potassium salt of the ligand and an ester in the substrate.[17]

Despite the inventiveness of these approaches, two aspects limit wider application. First, they are restricted to relatively narrow substrate classes. Second, they require bespoke or noncommercially available ligands or catalysts, presenting a barrier to those looking to use "off-the-shelf" reagents, such as end-users in the pharmaceutical industry. At the outset of this work, we sought to develop a general and practical strategy that would enable *para*-selective borylation of a range of common substrate classes using readily available catalysts and ligands. We have previously utilized attractive ion-pairing interactions between catalyst and substrate to direct the iridium metal to the arene *meta* position (Figure 1b).[12c,f,h] We were concerned that adopting a similar strategy to target the *para* isomer would be very challenging due to the distance that the ligand would be required to reach. A design able to achieve this would likely have a complex, extended structure necessitating lengthy synthesis and reduced practical utility. We envisaged an alternative ion-pairing strategy in which the counterion of the substrate does not deliver the reactive catalyst, but is unfunctionalized and bulky, acting as a "steric shield" to obstruct borylation at the *meta* position, thereby resulting in *para*-selectivity with standard "off-the-shelf" borylation catalysts (Figure 1c).

We envisaged that the ubiquitous tetrabutylammonium cation may consitute an ideal "steric shield"; the alkyl chains project outward at all angles from the tetrahedral nitrogen, occupying a large area. This bulky cation could be paired with a variety of common arene building blocks (anilines, benzylamines, phenols, benzyl alcohols) which can all be rendered temporarily anionic in a single simple step through conversion to the corresponding sulfate (X = O) or sulfamate (X = N) salts (Figure 1d). Herein, we demonstrate the realization of this approach, which we believe represents the most general strategy for *para*-selective borylation developed to date and indeed provides complementarity to existing strategies. In contrast to our earlier work, the key ion-pairing interaction in this system is not being exploited in an attractive sense between substrate and catalyst, but rather to temporarily anchor the "steric shield" to the substrate. The resulting repulsive steric interactions with the incoming catalyst thereby guide the latter to the remote position that would be the most challenging to reach using a strategy invoking attractive catalyst-substrate interactions.

We began by converting 2-chloroaniline (**1a**) to the corresponding tetrabutylammonium sulfamate salt **2a** by treatment with chlorosulfonic acid followed by cation exchange using Bu_4NHSO_4 (Scheme 1a). To our delight, iridium-catalyzed borylation of **2a** under standard conditions with 4,4′-di-*tert*-butyl-2,2′-dipyridyl (dtbpy) as a ligand resulted in >20:1 selectivity for the *para* isomer. Simply treating the crude reaction mixture with HCl in methanol revealed the parent aniline, which give 85% yield of *para*-borylated aniline **3a** over two steps and only a single purification procedure. A similar outcome was achieved for the electronically different 2-trifluoromethylaniline (Scheme 1a, **1b** to **3b**). In contrast, direct borylation of parent anilines **1a** and **1b** results in *m*:*p* ratios of 1:3.9 and 1:1, respectively (Scheme 1b). The moderate *para*-selectivity in direct borylation of **1a** echoes a similar observation made by Krska, Maleczka, Smith and co-

Scheme 1. (a) Initial Results; (b, c) Control Reactions



workers, the origins of which are not obvious.[18] Accordingly, we examined **4a** and **4b**, control substrates much closer in electronic nature to **2a** and **2b**, and found both of these give poor selectivity (Scheme 1c). This outcome suggests that the high *para*-selectivity obtained with sulfamate salts **2a** and **2b** does not have electronic origins and that the salt formation and association with the tetrabutylammonium cation are crucial factors.

With these initial results in hand, we next examined a selection of 2-substituted anilines and were pleased to find that the high levels of *para*-selectivity were observed for a range of useful building blocks (Scheme 2A). Bromide and iodide substituents were well tolerated (**3c**, **3d**), both giving >20:1 *para*-selectivity. The latter is notable given the incompatibility of many other C−H activation methods with iodide substituents. Arenes bearing trifluoromethoxy (**3e**) and difluoromethoxy (**3g**) substituents are also compatible, as is the difluorinated **3h**. Interestingly, the *para*-selectivity was slightly reduced with a resonance withdrawing substituent (2-CN, **3f**), in-line with the precedent that this substituent has a small *para*-directing (relative to itself) electronic effect in borylation.[19] Substrates bearing electron-donating substituents (isopropyl, methoxy) gave low conversion, albeit with excellent *para*-selectivity (see SI).

Given the ubiquity of benzylamines as aromatic building blocks, we next sought to test our strategy on benzylamine-derived sulfamates. As with the aniline variant, these tetrabutylammonium salts are easily synthesized from cheap materials. This class proved highly amenable, in most cases giving >20:1 regioselectivity (Scheme 2B). A range of useful halide substituents was tolerated, including Cl (**7a**), Br (**7b**), I (**7c**) and F (**7g**). Trifluoromethyl (**7d**), trifluoromethoxy (**7e**) and difluoromethoxy (**7f**) substituted variants also performed well. A methoxy-substituted variant gave excellent selectivity but with poor conversion (**7h**). It was necessary to derivatize the free amine products to enable purification on silica;

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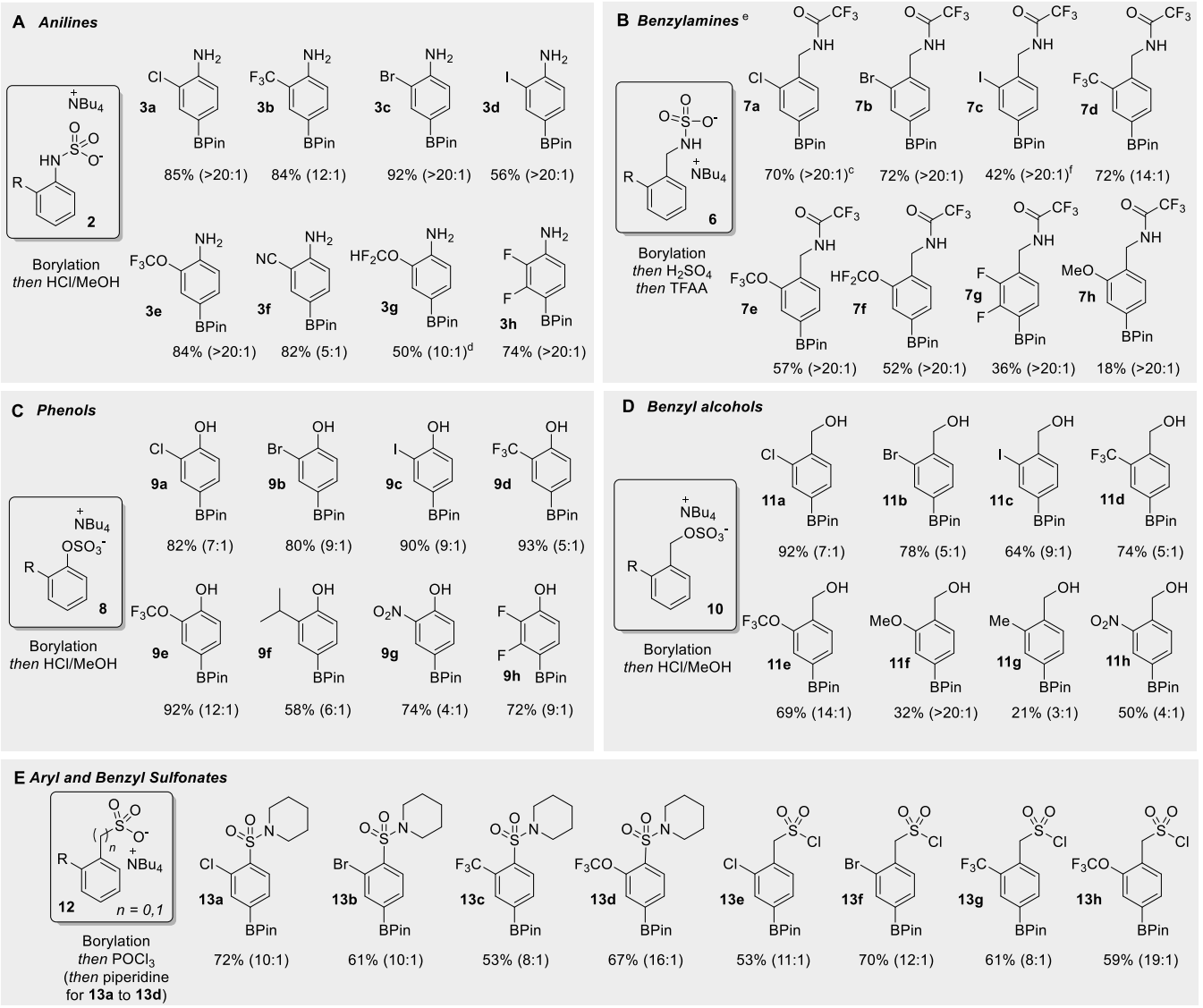
Scheme 2. Scope of *para* C−H Borylation of Aniline (A), Benzylamine (B), Phenol (C) and Benzyl Alcohol (D) Derivatives, and Aryl and Benzylsulfonates (E)[a,b]



[a]Typically: substrate (0.25 mmol), B_2Pin_2 (0.25−0.5 mmol), $[Ir(COD)OMe]_2$ (1.5−2.5 mol %), dtbpy (3−5 mol %), 1,4-dioxane (0.33−0.5 M), 70 °C (see SI for full details). [b]Isomeric ratios are *para*:*meta* taken from analysis of crude ^{1}H NMR spectra after borylation, unless otherwise stated. Yields shown are isolated and typically include *meta* and *para* isomers which are generally inseparable. [c]Selectivity assessed after HCl step. [d]Selectivity assessed after trifluoroacetate protection step. [e]3,4,7,8-Tetramethyl-1,10-phenanthroline used instead of dtbpy. [f]Oxidized to corresponding phenol for isolation.

isolated yields are following borylation/hydrolysis/trifluoroacetylation.

Encouraged by the effectiveness of the strategy thus far, we next extrapolated this to the ubiquitous oxygen-containing building blocks, phenols and benzyl alcohols.[20] The tetrabutylammonium sulfate salts of these compounds are also easily obtained and cleaved. Gratifyingly, high *para*-selectivity was observed for a number of *ortho*-substituted phenol-derived sulfate salts, encompassing Cl (**9a**), Br (**9b**), I (**9c**), CF_3 (**9d**), OCF_3 (**9e**), *i*Pr (**9f**) and a difluorinated analogue (**9h**) (Scheme 2C). Control borylations on 2-chlorophenol and on a 2-chlorophenol sulfate ester gave poor selectivity.[21] Interestingly, selectivity (by crude ^{1}H nuclear magnetic resonance (NMR) analysis following borylation) was somewhat reduced compared with the aniline-derived sulfamates. Particularly, substrates possessing conjugatively withdrawing groups such as nitro (**9g**) exhibited only moderate *para*-selectivity. This is likely due to the substituent electronic influence on the desired *para*-selectivity (*vide supra*).

Remarkably, the extension to a fourth common substrate class, benzyl alcohols, was well tolerated (Scheme 2D, **11a**−**11h**). As in the phenol-derived sulfates, regioselectivity was adversely affected by resonance withdrawing groups (**11h**), but positively reinforced by resonance donors (**11f**). These results suggest that in substrate classes when the *para*-directing influence from the associated cation is weaker, substituents electronic effects can have greater impact on selectivity.

Finally, to further reinforce the generality and practicality of our strategy for the selective synthesis of complex, multifunctional building blocks, we targeted aryl sulfonates and benzyl sulfonates, substrates which inherently bear a negative charge (Scheme 2E). The former are readily accessed from

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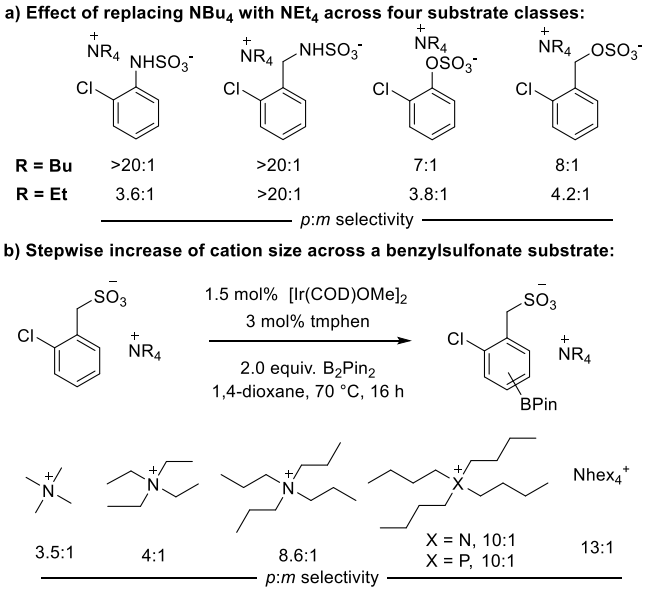
commercially available aryl sulfonyl chlorides by treatment with tetrabutylammonium hydroxide, and the latter by the action of sodium sulfite on benzyl halides, followed by cation exchange. Furthermore, through treatment with $POCl_3$, both sulfonates can be easily converted to sulfonyl chlorides, valuable precursors to sulfonamides. Both of these substrate classes result in *para*-selective borylation, in line with our hypothesis. Aryl sulfonates bearing *ortho* Cl (**13a**), Br (**13b**), CF_3 (**13c**) and OCF_3 (**13d**) gave excellent *para*-selectivity, as did the analogously substituted benzyl sulfonates (**13e**−**13h**). Following borylation, the crude borylated sulfonates were either converted through to the corresponding piperidine sulfonamides (**13a**−**13d**) or were isolated as sulfonyl chlorides (**13e**−**13h**).

At the outset, we advanced the tentative hypothesis that the bulk of the associated tetrabutylammonium cation may occupy sufficient space around the arene such that borylation at the normally accessible *meta* positions becomes disfavored (Figure 1C). To probe this hypothesis, we synthesized the 2-Cl member of the first four substrate classes with the smaller tetraethylammonium cation (synthesis of the tetramethyl variant for all members proved problematic) to gauge the impact on selectivity (Scheme 3a). These experiments showed

Scheme 3. Experiments To Probe Origin of Selectivity



that for three of the four classes, *para*-selectivity was significantly reduced, in line with our hypothesis (in the fourth, selectivity remained excellent at >20:1). We next selected the benzyl sulfonate substrate class to carry out a complete evaluation of sequential modulation of cation size on a single substrate. These experiments showed a clear and consistent trend to higher *para*-selectivity as the cation grows larger (Scheme 3b).

Finally, in order to visualize the steric effect of the associated tetrabutylammonium cation, we were able to obtain X-ray structures of the starting materials for three substrate classes (Figure 2). These give a visual impression of the bulk provided by the cation and support our central tenet that it could feasibly act as a noncovalent "shield" to block the arene *meta*-position. Accordingly, one might expect that removal of the *ortho* substituent incorporated into all substrates thus far may

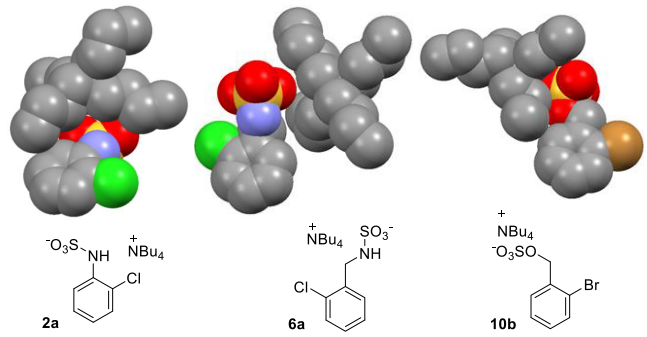


Figure 2. X-ray crystal structures of starting materials allowing visualization of the bulk of the tetrabutylammonium cation.

reduce *para*-selectivity as both *meta* positions would be open to borylation and the cation would not be able to block both at any one time. Indeed, this is the case; the *para*-selectivity was drastically reduced for all unsubstituted variants providing further support for our hypothesis.[21] We also extended the chain length of all three classes of substrate as the 2-Cl variant but found that with two methylenes between the arene and the anionic group, selectivity was reduced to around 3:1 *p*:*m*, presumably due to the much greater flexibility.[21]

In conclusion, we have developed a general method for the *para*-selective C−H borylation of a broad range of the most useful arene building blocks encompassing anilines, benzylamines, phenols and benzyl alcohols as well as several classes of arenesulfonate, valuable precursors to sulfonamides.[22] Our method produces a variety of complex trisubstituted arene cores often with three functional handles for further elaboration that in many cases would require numerous steps to obtain by other methods. We provide evidence to suggest that this is due to ion-pairing of a bulky tetrabutylammonium cation with the substrate, which is rendered temporarily anionic. The bulky cation blocks the *meta* position, promoting borylation at the most remote and typically most challenging *para* position. Our approach provides a practical and general solution to the challenge of *para*-selective C−H borylation and demonstrates a new strategy for the utilization of ion-pairing interactions in catalysis.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.9b07267.

Experimental procedures and spectral data (PDF)

Crystallographic data for **2a** (CIF)

Crystallographic data for **10b** (CIF)

Crystallographic data for **6a** (CIF)

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Notes

The authors declare no competing financial interest.

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(21) See Supporting Information for full details.

(22) After submission of our work, we became aware that the groups of Maleczka and Smith had developed a similar approach to *para*-selective borylation. We are grateful to them for agreeing to publish their results in a back-to-back fashion with our own: Montero Bastidas, J. R.; Oleskey, T. J; Miller, S. L.; Smith, M. R.; Maleczka, R. E. Para-Selective, Iridium-Catalyzed C−H Borylations of Sulfated. *J. Am. Chem. Soc.* **2019**.

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