JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
pubs.acs.org/JACS
Communication

Meta Selective C−H Borylation of Sterically Biased and Unbiased Substrates Directed by Electrostatic Interaction

Jagriti Chaturvedi, Chabush Haldar, Ranjana Bisht, Gajanan Pandey, and Buddhadeb Chattopadhyay*

Cite This: J. Am. Chem. Soc. 2021, 143, 7604−7611
Read Online

ABSTRACT: An electrostatically directed meta borylation of sterically biased and unbiased substrates is described. The borylation follows an electrostatic interaction between the partially positive and negative charges between the ligand and substrate. With this strategy, it has been demonstrated that a wide number of challenging substrates, especially 4-substituted substrates, can selectively be borylated at the meta position. Moreover, unsubstituted substrates also displayed excellent meta selectivity. The reaction employs a bench-stable ligand and proceeds at a milder temperature, precluding the need to synthesize a bulky and sophisticated ligand/template.

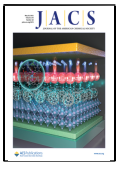
Over time, transition-metal-catalyzed C−H bond functionalization[1−5] has been recognized as one of the most important methods to construct carbon−carbon and carbon−heteroatom bonds for the synthesis of a complex molecular architecture. But, the key challenge lies in a site-selective[6−10] functionalization owing to the presence of multiple C−H bonds in organic molecules. In this context, while the last few decades have seen numerous developments in ortho selective functionalization,[11−14] the developments of meta and para functionalization[15,16] are much less compared to the ortho functionalization. Achieving the remote meta and para selectivity in an arene C−H functionalization by overcoming the steric demands is a major challenge. Consequently, the functionalization of a remote C−H bond often necessitates the attachment and detachment of a bulky directing template, which limits the practicability of this method.

In this context, among various C−H bond functionalizations, an iridium-catalyzed borylation[17−20] has been demonstrated as one of the most important synthetic tools due to the versatility of the C−B bonds.[21−24] While there are many useful methods that are now available for the ortho selective C−H borylation including the directed ortho metalations (DoM),[25,26] meta and para selective C−H borylations are still difficult to realize. Earlier only one type of meta borylation was possible via iridium catalysis from 1,3-disubstituted arenes—a seminal contribution by Smith, Maleczka, and Hartwig.[27−30] Apart from other directed meta borylations,[31,32] recently, one new paradigm of meta selective borylation has been developed by means of various noncovalent interactions[33−39] (Chart 1A). Moreover, the use of a noncovalent interaction and Lewis acid−base interaction has also been seen for para C−H borylations.[40−43]

However, despite the ingenuity of the noncovalent interaction in C−H borylation, several aspects limit its wide application. First, because of the weak nature of this interaction, a big competition is encountered for those substrates having a substituent next to the C−H borylation site. For example, the meta C−H borylation is still not possible for 4-substituted substrates. The reason behind this is solely the steric effects that hamper the noncovalent interaction next to the borylation site. Second, the requirement of customized ligands or catalysts bestows a barrier to those looking to use "standard reagents" for a practical application.[28] Herein we report a concept based on the electrostatic interaction for the meta borylation of arenes bearing $-SO_2CF_3$, $-SO_2CH_3$, $-COCF_3$, $-COCH_3$, and $-CO^tBu$ at mild reaction conditions. Moreover, we demonstrate that, with the developed concept, meta borylation can be possible with those arenes featuring a substitution at the para position with a high meta selectivity. The inspiration of this meta borylation concept is based on the recently developed electrostatically directed ortho borylation of phenols developed by Smith, Maleczka, and Singleton (Chart 1B, **TS-1**).[44] Thus, with this inspiring concept, we questioned if this strategy could be further extended toward the meta borylation of arenes.

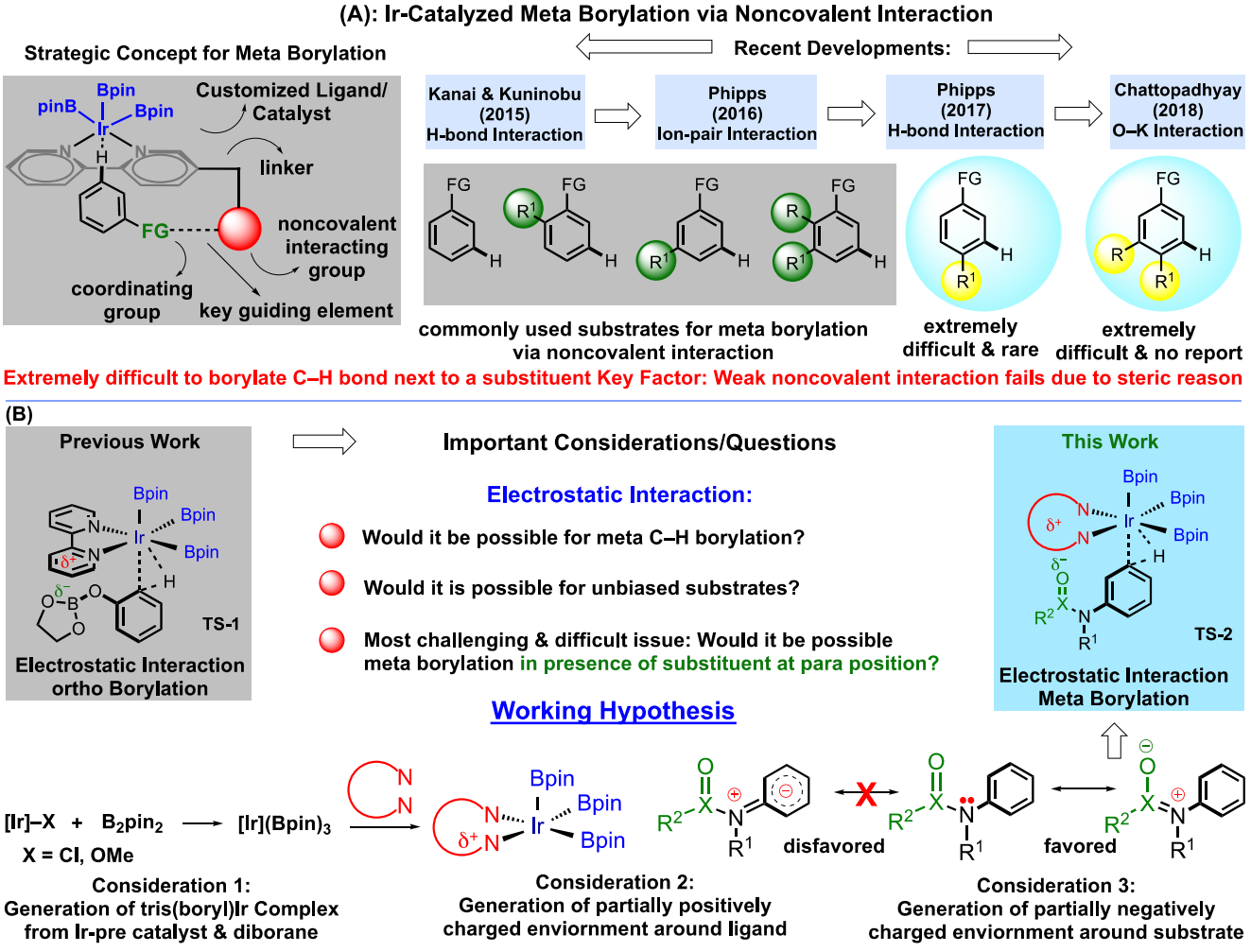
The working hypothesis of this present work is based on the following key considerations: (i) generation of the tris(boryl)(Ir) complex from Ir-precatalyst and diborane reagent, (ii) examination of commercially available bidentate nitrogen ligands instead of the customized ligands for the in situ formation of the pentacoordinated Ir complex that would likely be the partially positive charge in nature, (iii) use of such type of functionalities attached with arenes, which by virtue of resonance could develop a partial negative charge at any given heteroatom, and (iv) an appropriate electrostatic interaction between the ligand and substrate (Chart 1B, **TS-2**).

Received: February 15, 2021
Published: May 14, 2021



https://doi.org/10.1021/jacs.1c01770
J. Am. Chem. Soc. 2021, 143, 7604−7611

Chart 1. Noncovalent Catalysis for Meta Borylation: Previous and Present Work

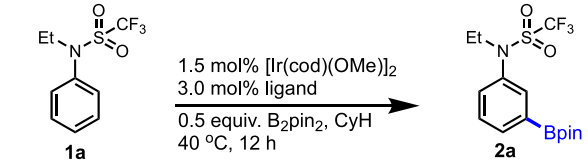


We began our studies using arene (**1a**) bearing an (Et)N–SO_2CF_3 group with the commercially available ligands (Chart 2). As per our hypothesis for an electrostatic interaction, the borylation was performed in cyclohexane using bipyridine (**L1**) at 40 °C with 1.0 equiv of bis(pinacolato)diboron (B_2pin_2) (entry 1). We observed that, while the borylation gave promising meta selectivity, it also produced significant diborylated products. Thus, to minimize the diborylation, subsequent optimizations were conducted with 0.5 equiv of the boron source (i.e., B_2pin_2). The selectivity is based on a gas chromatography/mass spectrometry (GC/MS) analysis of the reaction.

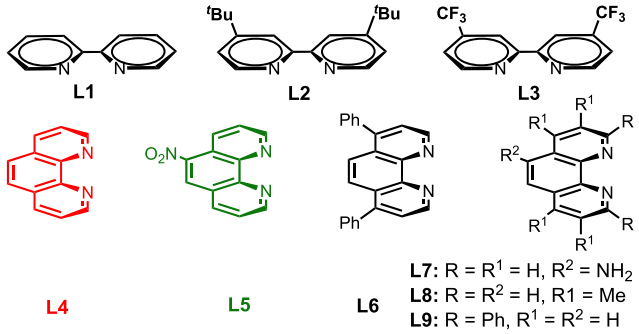
Accordingly, when the borylations were performed with bipyridine ligands (**L1**, **L2**, & **L3**) with the reduced amount of B_2pin_2 a clear trend in the enhancement of the meta selectivity was observed as the bipyridine ligands were made electron-deficient. For example, whereas bipyridine ligand (**L1**) and electron-rich bipyridine ligand (**L2**) resulted in 5.6/01 (entry 2) and 4.8/01 (entry 3) meta-to-para selectivities, respectively, an electron-deficient bipyridine ligand (**L3**) produced a much higher proportion of meta selectively (10.1/01), although with poor conversion (entry 4). From this selectivity pattern with electronically different bipyridine ligands, it may be stated that the electron-withdrawing bis-CF_3 groups attached with the bipyridine ligand (**L3**) pull the electron from the ligand system, making it more electro-positive after coordination with the iridium that interacts well with the partial negatively charged oxygen atom of the functional group of the arene via an electrostatic interaction. Next, we considered electronically different 1,10-phenanthroline ligands that are not much explored in C–H borylations.[45,46] The 1,10-phenanthroline is a rigid, planar, electron-poor heteroaromatic chelating ligand. Moreover, the two N-donor atoms point inward and are juxtaposed to each other in contrast to the bipyridine ligand. The inward inclination of N donor atoms can be disrupted by a free rotation along the single bond. Another distinctive property of the phenanthroline ligand is its π-electron deficiency, which makes it a suitable π-acceptor.[47] Thus, considering these important special properties of the phenanthroline framework, we conducted a reaction using ligand (**L4**) (entry 5). To our delight, a high meta selectivity was achieved (meta/para = 32/01) with 91% isolated borylated product (**2a**). Modification of the 1,10-phenanthroline ligand by introducing an electron-withdrawing group (**L5**) also appeared to be comparable (entry 6), although the conversion was sacrificed largely. Notably, the use of an electron-donating 3,4,7,8-tetramethylphenanthroline ligand (**L8**) and 5-amino phenanthroline ligand (**L7**) exhibited poor meta selectivity (entries 9 and 8). Moreover, we found that, while the ligand (**L6**) showed moderate meta selectivity (entry 7), the ligand (**L9**) failed completely for the borylation

https://doi.org/10.1021/jacs.1c01770
J. Am. Chem. Soc. 2021, 143, 7604–7611

Chart 2. Reaction Optimization

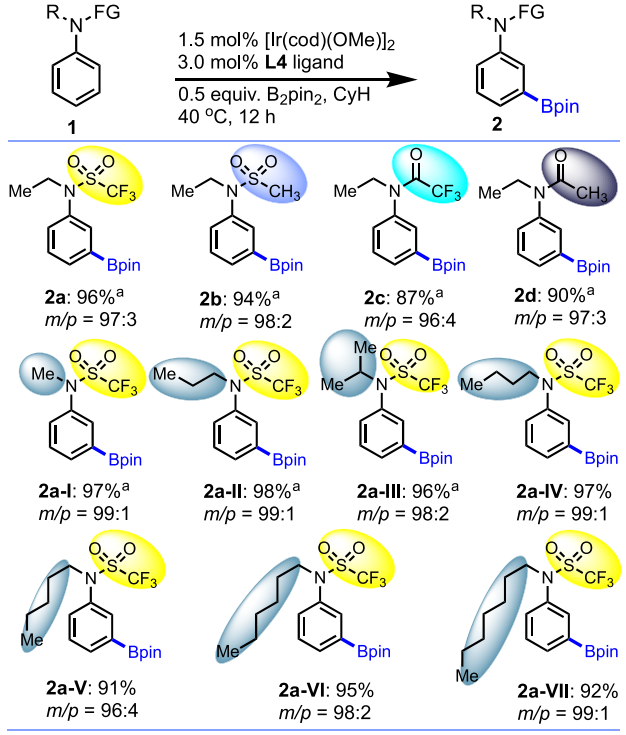


#	ligand	B_2pin_2	*meta/para*	Conv. (%)
1	L1	1.0 (equiv.)	5/1[a]	99
2	L1	0.5 (equiv.)	5.6/1	83
3	L2	0.5 (equiv.)	4.8/1	92
4	L3	0.5 (equiv.)	10.1/1	45
5	L4	0.5 (equiv.)	32/1	96 (91)
6	L5	0.5 (equiv.)	33/1	10
7	L6	0.5 (equiv.)	4/1	61
8	L7	0.5 (equiv.)	3.5/1	25
9	L8	0.5 (equiv.)	3.3/1	99
10	L9	0.5 (equiv.)	-	NR



Reactions were performed with 0.2 mmol scale. In parenthesis, Isolated yield is reported. Selectivity is based on GC/MS analysis of the reaction. [a]In addition to this meta/para isomer, significant diborylation occurred.

Chart 3. Meta Borylation of Monosubstituted Arenes



Reactions performed with 0.5 mmol scale. Isolated yields are given. [a]In these cases, very minor amount of *m,m*-diborylation occurred. But, due to the stability issue, we were unable to isolate.

(entry 10). For this failure, we reasoned that the bulky phenyl substitution at the C6 position of the ligand (**L9**) creates steric crowding that inhibited the borylation.

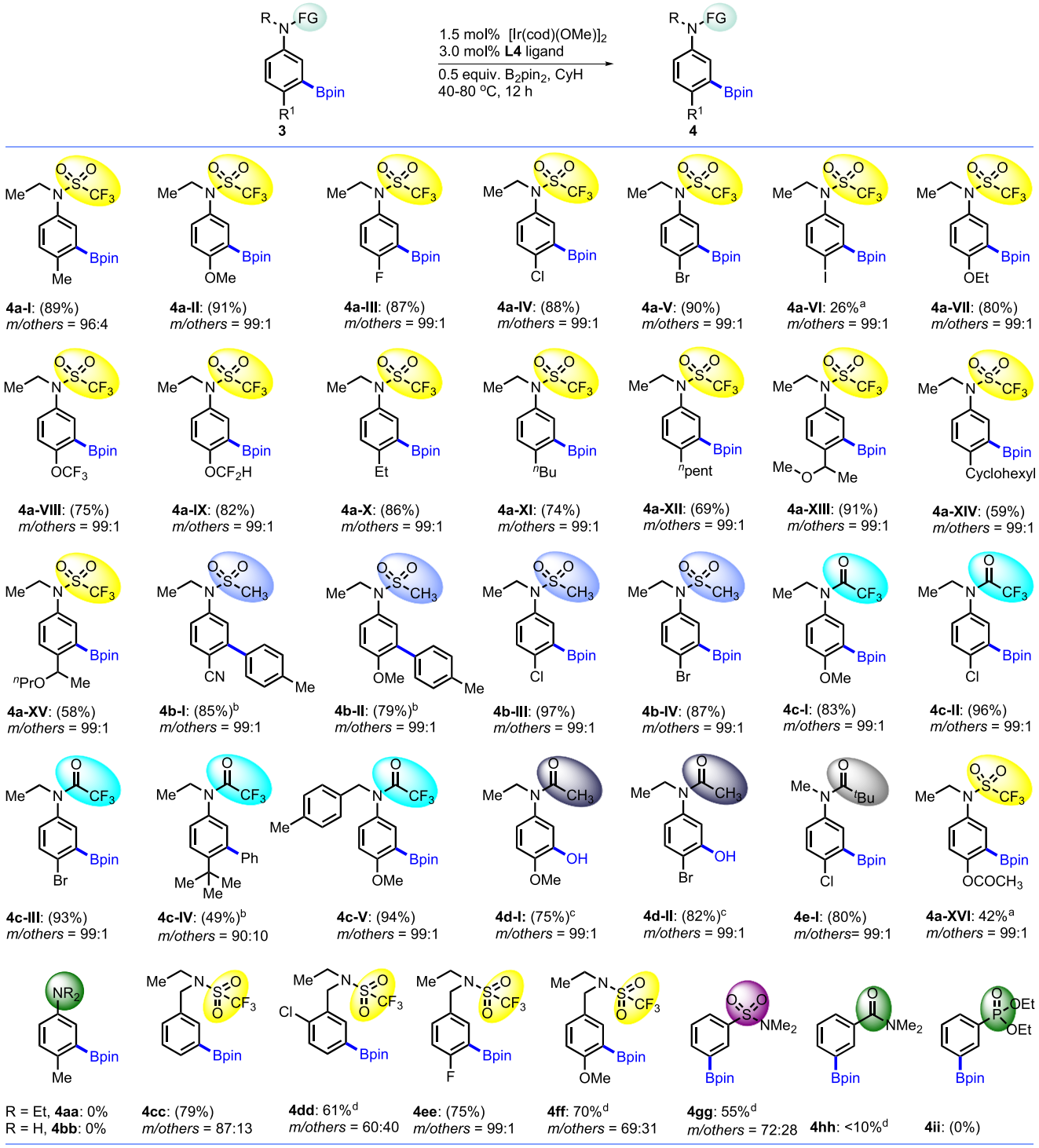
With these promising results, we then intended to test if the electrostatic interaction will be validated for other functionalities, such as Et(N)−SO_2CF_3, Et(N)−SO_2CH_3, Et(N)−$COCF_3$, and Et(N)−$COCH_3$. We found that all these functionalities exhibited a high meta selectivity (Chart 3, **2a**−**2d**). Thus, borylations were conducted with several alkyl groups containing substrates,[48] for example, methyl (**1a-I**), propyl (**1a-II**), isopropyl (**1a-III**), butyl (**1a-IV**), pentyl (**1a-V**), hexyl (**1a-VI**), heptyl (**1a-VII**), and found that an increase in chain length does not hamper the meta selectivity.

Next, we examined the scope of the meta borylation of those substrates featuring a substituent at the para position (Chart 4). To our delight, testing numerous 4-substituted substrates with five different functional groups, we found that almost all the substrates produced meta borylation products exclusively. For example, the functional groups like R(N)−SO_2CF_3, R(N)−SO_2Me, R(N)−$COCF_3$, R(N)−COMe, and R(N)−CO^{t}Bu with electronically and sterically different substituents smoothly underwent meta borylations. The bulky *tert*-butyl group at the 4-position also afforded the meta borylation (meta/para = 90/10) (entry **4c-IV**), but it was isolated via cross-coupling due to a stability issue of the borylated product. The substrate (**3c-V**) bearing a benzyl group instead of an alkyl group also selectively underwent meta borylation without disturbing the C−H bonds of the benzyl group. Importantly, conducting the borylation under the same conditions with the (**3aa**) and (**3bb**) that do not have any noncovalent interacting sites failed to undergo borylations, which demonstrates the necessity of the above-mentioned functional groups for the successful electrostatically directed meta borylation.

At this point, we were curious whether benzylamines (**3cc**−**3ff**) would be suitable substrates or not considering the greater distance compared to the anilines. Accordingly, borylation was performed with these substrates, and we found that, while unsubstituted substrate (**3cc**) and 4-fluoro substrate (**3ee**) gave good meta selectivity, 2-chloro (**3dd**) and 4-methoxy (**3ff**) provided moderate meta selectivity. This indicates that the electrostatic interaction is not strong enough for benzylamine substrates to give a high meta selectivity especially for those benzylamines bearing a substituent at the ortho or para position. For further elaboration, we attempted meta borylations with arenes bearing other functionalities. We observed that, while an arene with sulfonamide (**3gg**) exhibited good meta selectivity (m/p = 72/28), benzamide (**3hh**) and phosphonate ester (**3ii**) failed to undergo borylation—indicating the lack of an appropriate electrostatic interaction. To see the effect of other ligands (**L1** and **L2**) borylation was performed with a 4-substituted arene (**3a-II**) using (**L1** & **L2**). We found that, while (**L4**) gave a quantitative conversion, ligands (**L1**) and (**L2**) also afforded meta borylation, although with a poor conversion (49% and 53%, respectively), which suggests a significant substrate effect with the ligand (**L4**) affording

https://doi.org/10.1021/jacs.1c01770
J. Am. Chem. Soc. 2021, 143, 7604−7611

Chart 4. Substrate Scope for 4-Substituted Arenes



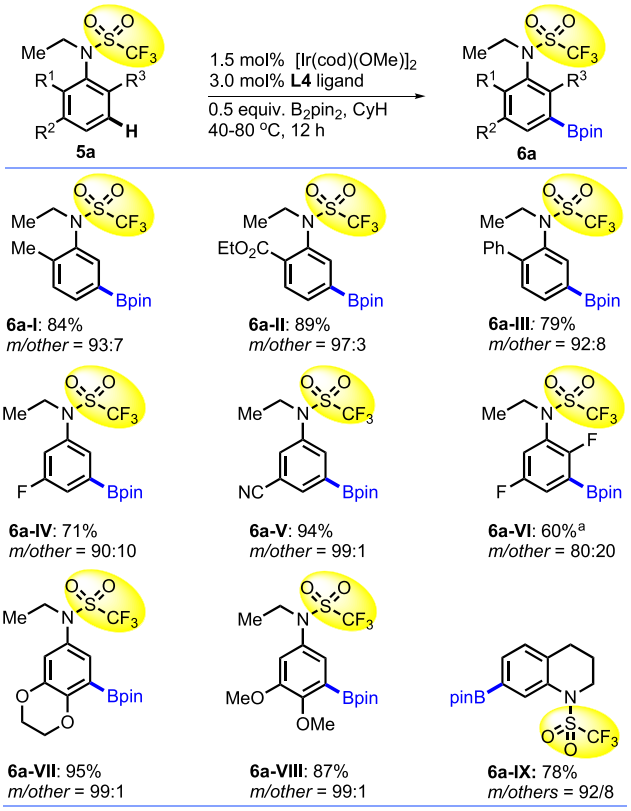
All reactions were performed with 0.5 mmol scale. Isolated yields are reported. Selectivity is based on the GC/MS analysis of the reaction. For details see, SI. [a]Crude NMR conversion is given. [b]Products were isolated after cross coupling (SI for details). [c]Products were isolated after oxidation. [d]GC/MS conversions are reported. Borylation of (**3a-II**) using **L1** and **L2** ligand afforded 49% and 53% conv. respectively.

higher efficiency. This may be attributed to the unique properties[47] of the phenanthroline ligand (**L4**).

The scope of the developed method was then evaluated for the substrates bearing substitution at the different positions of the arene (Chart 5). In all cases, a high meta selectivity was obtained with high isolated yields of the borylated products (entries **6a-I** to **6a-VIII**) including the 2,5-difluoro substrate (**6a-VI**). Notably, while the 4-F and 4-CN substrates (Chart 4) afforded a complete meta borylation (which usually gives borylation next to the F and CN group), 3-F and 3-CN substrates (Chart 5) did not give borylation completely next to these groups but, instead, resulted in a meta borylated product as the major product. This result is a further indication of an electrostatic interaction as per the proposed

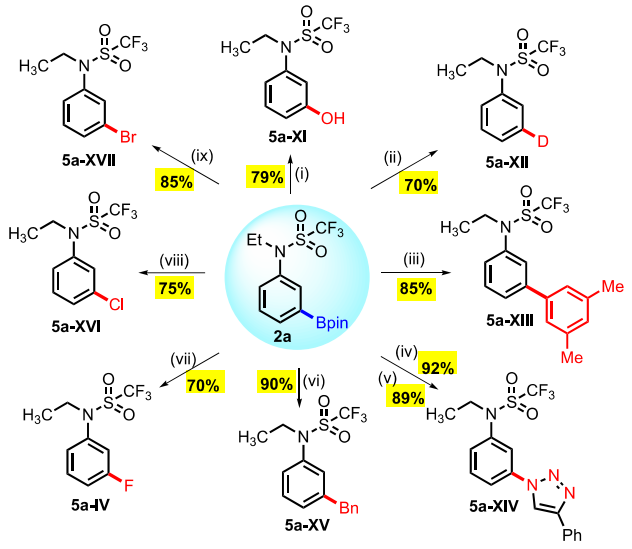
https://doi.org/10.1021/jacs.1c01770
J. Am. Chem. Soc. 2021, 143, 7604−7611

Chart 5. Substrate Scope for Substituted Arenes



Reactions were performed with 0.5 mmol scale. Isolated yields are reported. For details see: SI. [a]GC/MS conversion is reported.

Chart 6. Synthetic Transformations[a]



[a]**Conditions:** (i) 1.2 equiv of oxone, (3/1) acetone/water, 0 °C to rt, 2 h. (ii) 1.0 mol % [Ir(cyclooctadiene)OMe]$_2$, (4/1) (tetrahydrofuran/D_2O), 80 °C, 12 h. (iii) 2.5 mol % $Pd(PPh_3)_4$. 2.0 equiv of K_2CO_3, 1.1 equiv of 5-bromo-*m*-xylene, (1/1) dimethoxyethane/H_2O, 100 °C, 12 h. (iv) 10 mol % $Cu(OAc)_2$, 1.5 equiv of NaN_3, MeOH, 55 °C, under air, 24 h. (v) 1.2 equiv of phenylacetylene, 3.0 mol % sodium ascorbate, H_2O, MeOH, rt, 24 h. (vi) 1.0 mol % Pd_2(dibenzylideneacetone)$_3$.$CHCl_3$, 4.0 mol % PPh_3, 4.0 equiv of K_2CO_3, 1.2 equiv of BnBr, (10/1) tetrahydrofuran/H_2O, 100 °C, 24 h. (vii) 4.0 equiv of TFA, 2.0 equiv of $Cu(OTf)_2$, CH_3CN, 60 °C, 20 h. (viii) 3.0 equiv of $CuCl_2$, (1/1) MeOH/H_2O, 80 °C, 12 h. (ix) 3.0 equiv of $CuBr_2$, (1/1) MeOH/H_2O, 80 °C, 12 h.

hypothesis. Interestingly, we also found that the heterocyclic substrate (**5a-IX**) proceeded with the C−H borylation affording a high meta borylation.

To demonstrate the synthetic utility, we showed that the borylated compound (**2a**) can be transformed to many useful synthons employing known transformations, such as hydroxylation,[17] fluorination,[49] chlorination,[50] bromination,[50] deuteration,[51] arylation,[21] benzylation,[52] and azidation followed by cycloaddition[53] (Chart 6).

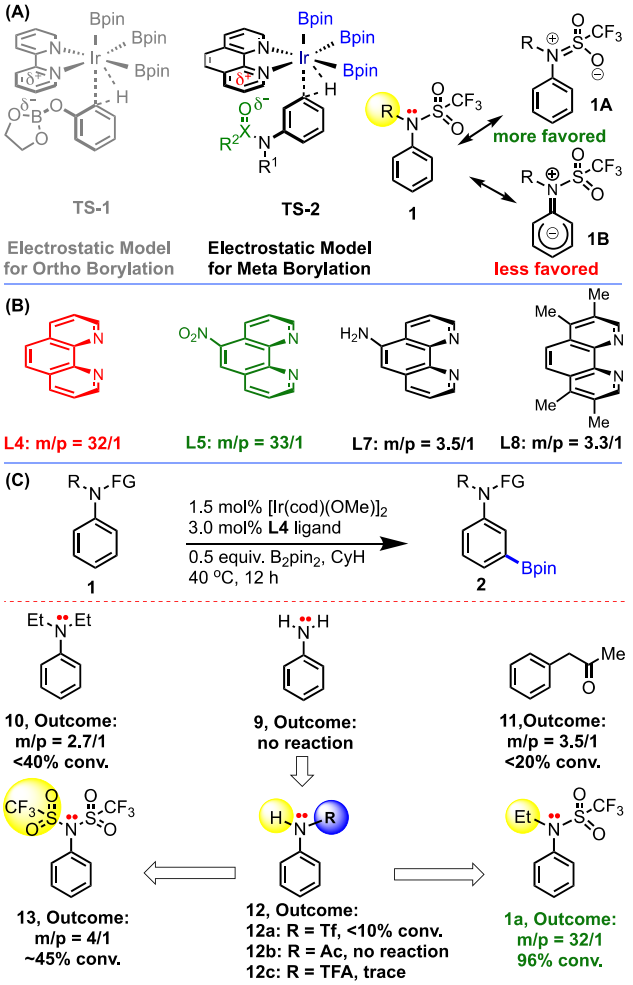
The standard reaction mechanism of the C−H borylation of arene was reported[54] earlier, and the present meta borylation possibly follows the same mechanism. But, to get an understanding of the proposed electrostatic model (Chart 7A, **TS-2**), we first analyzed the electronic effects of ligands. Earlier it has been demonstrated that, for electrostatically directed ortho borylation (**TS-1**),[44] an electronic alteration of the ligand framework affects the ortho selectivity.

Analyzing the electronic effects of the various 1,10-phenanthroline ligands,[47] we observed that the meta borylation follows the same trend (Chart 7B) that is consistent with the previous electrostatic model. For a further understanding, several control experiments were performed. As per our hypothesis, the lone-pair electrons of the nitrogen atom will be delocalized through the trifluoromethanesulfonyl group rather than the arene ring (Chart 7A) due to its strong electron-withdrawing nature, and thus the substrate (**1**) will develop a partial negative charge at the oxygen atom (**1A**) instead of the arene ring (**1B**), which would interact with the partial positive charge of the ligand. We envision that, if this hypothesis is correct, then a functional group alteration of the nitrogen atom should affect the meta selectivity. Following this hypothesis, we performed a borylation with substrates bearing several functional groups (Chart 7C) and found that substrates without suitable functional groups (**9**, **10**, & **11**) resulted in either no reaction or a nonselective borylation. Next, borylation was performed with the substrates (**12a**, R = triflate (Tf)) having a free NH unit, and it was found that the conversion was poor indicating that protection is necessary to augment the electron delocalization into the $-SO_2CF_3$ group by restricting the chelation with the catalyst. Moreover, when the R group is altered from Tf to either acetyl (Ac) (**12b**) or trifluoroacetic acid (TFA) (**12c**), almost the same trend is observed. Moreover, protection of both the H atoms of aniline (**13**) with the $-SO_2CF_3$ group afforded a regioisomeric mixture of the meta and para borylation products in statistical ratios with a moderate conversion. Thus, this finding indicates the necessity of an alkyl group as the lone pairs of N atom are delocalized over two $-SO_2CF_3$ groups and diminish the negative charge density on the carbonyl O atom. Collectively, all these control experiments are suggestive of an electrostatic model for the meta borylation.[55]

In conclusion, we have developed a method for the meta borylation of arenes via an electrostatic model. The method shows a broad substrate scope, especially for those substrates bearing a substituent adjacent to the borylation site, which was an utmost challenge. While the most iridium-catalyzed remote C−H borylations require minimum 1.0 equiv of diborane (B_2pin_2), our method requires only half of the B_2pin_2 (0.5 equiv), demonstrating the practicality of the

https://doi.org/10.1021/jacs.1c01770
J. Am. Chem. Soc. 2021, 143, 7604−7611

Chart 7. Validation of Proposed Electrostatic Model



All the reactions were conducted with 0.2 mmol scale. GC/MS ratios are given. GC/MS conversions are reported of the crude reaction.

developed method.[56] We anticipate that the method should find wide application in the context of boron-bearing small molecules for the drug discovery, natural product synthesis, and pharmaceutical industries.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.1c01770.

Full characterization, copies of all spectral data, experimental procedures (PDF)

■ AUTHOR INFORMATION

Corresponding Author

Buddhadeb Chattopadhyay − *Division of Molecular Synthesis & Drug Discovery, Center of Biomedical Research, Lucknow 226014, Uttar Pradesh, India;* orcid.org/0000-0001-8473-2695; Email: buddhadeb.c@cbmr.res.in, buddhachem12@gmail.com

Authors

Jagriti Chaturvedi − *Division of Molecular Synthesis & Drug Discovery, Center of Biomedical Research, Lucknow 226014, Uttar Pradesh, India; Department of Applied Chemistry, Babasaheb Bhimrao Ambedkar University, Lucknow 226025, Uttar Pradesh, India*

Chabush Haldar − *Division of Molecular Synthesis & Drug Discovery, Center of Biomedical Research, Lucknow 226014, Uttar Pradesh, India*

Ranjana Bisht − *Division of Molecular Synthesis & Drug Discovery, Center of Biomedical Research, Lucknow 226014, Uttar Pradesh, India*

Gajanan Pandey − *Department of Applied Chemistry, Babasaheb Bhimrao Ambedkar University, Lucknow 226025, Uttar Pradesh, India*

Complete contact information is available at: https://pubs.acs.org/10.1021/jacs.1c01770

Notes

The authors declare the following competing financial interest(s): We have filed a patent based on this work.

■ ACKNOWLEDGMENTS

This work was supported by SERB-STAR AWARD grant (STR/2019/000045), SERB-CRG grant (CRG/2018/000133), and SERB-SUPRA grant (SPR/2019/000158). J.C. thanks UGC for SRF, C.H. thanks CSIR for SRF, and R.B. thanks SERB-SUPRA for RA fellowship. B.C. thanks the SERB for the Science and Technology Award for Research. We also thank CBMR for research facilities.

■ REFERENCES

(1) Lyons, T. W.; Sanford, M. S. Palladium-Catalyzed Ligand-Directed C-H Functionalization Reactions. *Chem. Rev.* **2010**, *110*, 1147−1169.

(2) Daugulis, O.; Do, H.-Q.; Shabashov, D. Palladium- and Copper-Catalyzed Arylation of Carbon-Hydrogen Bonds. *Acc. Chem. Res.* **2009**, *42*, 1074−1086.

(3) Engle, K. M.; Mei, T.-S.; Wasa, M.; Yu, J.-Q. Weak Coordination as a Powerful Means for Developing Broadly Useful C-H Functionalization Reactions. *Acc. Chem. Res.* **2012**, *45*, 788−802.

(4) Gensch, T.; Hopkinson, M. N.; Glorius, F.; Wencel-Delord, J. Mild metal catalyzed C-H activation: examples and concepts. *Chem. Soc. Rev.* **2016**, *45*, 2900−2936.

(5) Sambiagio, C.; Schönbauer, D.; Blieck, R.; Dao-Huy, T.; Pototschnig, G.; Schaaf, P.; Wiesinger, T.; Zia, M. F.; Wencel-Delord, J.; Besset, T.; Maes, B. U. W.; Schnürch, M. A comprehensive overview of directing groups applied in metal catalysed C-H functionalisation chemistry. *Chem. Soc. Rev.* **2018**, *47*, 6603−6743.

(6) Hartwig, J. F. Catalyst-Controlled Site-Selective Bond Activation. *Acc. Chem. Res.* **2017**, *50*, 549−555.

(7) Dimakos, V.; Taylor, M. S. Site-Selective Functionalization of Hydroxyl Groups in Carbohydrate Derivatives. *Chem. Rev.* **2018**, *118*, 11457−11517.

(8) Xia, Y.; Wang, L.; Studer, A. Site-selective Radical Remote C-H Functionalization of Unactivated C-H Bonds in Amides with Sulfone Reagents. *Angew. Chem.* **2018**, *130*, 13122−13126.

(9) Kim, I.; Kang, G.; Lee, K.; Park, B.; Kang, D.; Jung, H.; He, Y. T.; Baik, M. H.; Hong, S. Site-Selective Functionalization of Pyridinium Derivatives via Visible-Light-Driven Photocatalysis with Quinolinone. *J. Am. Chem. Soc.* **2019**, *141*, 9239−9248.

(10) Ye, F.; Berger, F.; Jia, H.; Ford, J.; Wortman, A.; Börgel, J.; Genicot, C.; Ritter, T. Aryl Sulfonium Salts for Site-Selective Late-Stage Trifluoromethylation. *Angew. Chem.* **2019**, *131*, 14757−14761.

(11) Zheng, Q.; Liu, C.-F.; Chen, J.; Rao, G.-W. Functionalization of Aromatic Amides. *Adv. Synth. Catal.* **2020**, *362*, 1406−1446.

(12) Ping, L.; Chung, D. S.; Bouffard, J.; Lee, S. Transition metal-catalyzed site- and regio-divergent C-H bond functionalization. *Chem. Soc. Rev.* **2017**, *46*, 4299−4328.
(13) Huang, Z.; Lim, H. N.; Mo, F.; Young, M. C.; Dong, G. Transition metal-catalyzed ketone-directed or mediated C-H functionalization. *Chem. Soc. Rev.* **2015**, *44*, 7764−7786.
(14) Hoque, M. E.; Hassan, M. M. M.; Chattopadhyay, B. Remarkably Efficient Iridium Catalysts for Directed C(sp^2)-H and C(sp^3)-H Borylation of Diverse Classes of Substrates. *J. Am. Chem. Soc.* **2021**, *143*, 5022−5037.
(15) Yang, Y. F.; Hong, X.; Yu, J. Q.; Houk, K. N. Experimental-computational synergy for selective Pd(II)-catalyzed C-H activation of aryl and alkyl groups. *Acc. Chem. Res.* **2017**, *50*, 2853−2860.
(16) Davies, H. M. L.; Morton, D. Recent advances in C-H functionalization. *J. Org. Chem.* **2016**, *81*, 343−350.
(17) Mkhalid, I. A. I.; Barnard, J. H.; Marder, T. B.; Murphy, J. M.; Hartwig, J. F. C-H Activation for the Construction of C-B Bonds. *Chem. Rev.* **2010**, *110*, 890−931.
(18) Hartwig, J. F. Regioselectivity of the borylation of alkanes and arenes. *Chem. Soc. Rev.* **2011**, *40*, 1992−2002.
(19) Ros, A.; Fernandez, R.; Lassaletta, J. M. Functional group directed C-H borylation. *Chem. Soc. Rev.* **2014**, *43*, 3229−3243.
(20) Xu, L.; Wang, G.; Zhang, S.; Wang, H.; Wang, L.; Liu, L.; Jiao, J.; Li, P. Recent advances in catalytic C-H borylation reactions. *Tetrahedron* **2017**, *73*, 7123−7157.
(21) Suzuki, A. Cross-Coupling Reactions Of Organoboranes: An Easy Way To Construct C-C Bonds (Nobel Lecture). *Angew. Chem., Int. Ed.* **2011**, *50*, 6722−6737.
(22) Hall, D. G. *Boronic Acids: Preparation and Applications in Organic Synthesis and Medicine;* Wiley-VCH: Weinheim, Germany, 2005. DOI: 10.1002/3527606548.
(23) Neeve, E. C.; Geier, S. J.; Mkhalid, I. A. I.; Westcott, S. A.; Marder, T. B. Diboron (4) Compounds: From Structural Curiosity to Synthetic Workhorse. *Chem. Rev.* **2016**, *116*, 9091−9161.
(24) Nakamura, H.; Yasui, K.; Kanda, Y.; Baran, P. S. 11- Step Total Synthesis of Teleocidins B-1-B-4. *J. Am. Chem. Soc.* **2019**, *141*, 1494−1497.
(25) Whisler, M. C.; MacNeil, S.; Snieckus, V.; Beak, P. Beyond Thermodynamic Acidity: A Perspective on the Complex-Induced Proximity Effect (CIPE) in Deprotonation Reactions. *Angew. Chem., Int. Ed.* **2004**, *43*, 2206−2225.
(26) Hurst, T. E.; Macklin, T. K.; Becker, M.; Hartmann, E.; Kügel, W.; Parisienne-La Salle, J. C.; Batsanov, A. S.; Marder, T. B.; Snieckus, V. Iridium-Catalyzed C-H Activation versus Directed ortho Metalation: Complementary Borylation of Aromatics and Heteroaromatics. *Chem. - Eur. J.* **2010**, *16*, 8155−8161.
(27) Cho, J. Y.; Iverson, C. N.; Smith, M. R., III Steric and Chelate Directing Effects in Aromatic Borylation. *J. Am. Chem. Soc.* **2000**, *122*, 12868−12869.
(28) Ishiyama, T.; Takagi, J.; Ishida, K.; Miyaura, N.; Anastasi, N. R.; Hartwig, J. F. Mild Iridium-Catalyzed Borylation of Arenes. High Turnover Numbers, Room Temperature Reactions, and Isolation of a Potential Intermediate. *J. Am. Chem. Soc.* **2002**, *124*, 390−391.
(29) Maleczka, R. E., Jr; Shi, F.; Holmes, D.; Smith, M. R., III C-H Activation/Borylation/Oxidation: A One-Pot Unified Route to Meta-Substituted Phenols Bearing Ortho-/Para-Directing Groups. *J. Am. Chem. Soc.* **2003**, *125*, 7792−7793.
(30) Murphy, J. M.; Liao, X.; Hartwig, J. F. Meta Halogenation of 1,3-Disubstituted Arenes via Iridium-Catalyzed Arene Borylation. *J. Am. Chem. Soc.* **2007**, *129*, 15434−15435.
(31) Bisht, R.; Chattopadhyay, B. Formal Ir-Catalyzed Ligand-Enabled Ortho and Meta Borylation of Aromatic Aldehydes via in Situ-Generated Imines. *J. Am. Chem. Soc.* **2016**, *138*, 84−87.
(32) Yang, L.; Uemura, N.; Nakao, Y. meta-Selective C-H Borylation of Benzamides and Pyridines by an Iridium-Lewis Acid Bifunctional Catalyst. *J. Am. Chem. Soc.* **2019**, *141*, 7972−7979.
(33) Kuninobu, Y.; Ida, H.; Nishi, M.; Kanai, M. A. meta selective C-H borylation directed by a secondary interaction between ligand and substrate. *Nat. Chem.* **2015**, *7*, 712−717.
(34) Davis, H. J.; Mihai, M. T.; Phipps, R. J. Ion Pair-Directed Regiocontrol in Transition Metal Catalysis: A Meta-Selective C-H Borylation of Aromatic Quaternary Ammonium Salts. *J. Am. Chem. Soc.* **2016**, *138*, 12759−12762.
(35) Davis, H. J.; Genov, G. R.; Phipps, R. J. meta Selective C-H Borylation of Benzylamine-, Phenethylamine- and Phenylpropylamine-Derived Amides Enabled by a Single Anionic Ligand. *Angew. Chem., Int. Ed.* **2017**, *56*, 13351−13355.
(36) Genov, G. R.; Douthwaite, J. L.; Lahdenperä, A. S. K.; Gibson, D. C.; Phipps, R. J. Enantioselective remote C-H activation directed by a chiral cation. *Science* **2020**, *367*, 1246−1251.
(37) Bisht, R.; Hoque, Md. E.; Chattopadhyay, B. Amide Effect in C-H Activation: Noncovalent Interactions with L-Shaped Ligand for meta Borylation of Aromatic Amides. *Angew. Chem., Int. Ed.* **2018**, *57*, 15762−15766.
(38) Mihai, M. T.; Davis, H. J.; Genov, G. R.; Phipps, R. J. Ion Pair-Directed C-H Activation on Flexible Ammonium Salts: meta-Selective Borylation of Quaternized Phenethylamines and Phenylpropylamines. *ACS Catal.* **2018**, *8*, 3764−3769.
(39) Lee, B.; Mihai, M. T.; Stojalnikova, V.; Phipps, R. J. Ion Pair-Directed Borylation of Aromatic Phosphonium Salts. *J. Org. Chem.* **2019**, *84*, 13124−13134.
(40) Hoque, M. E.; Bisht, R.; Haldar, C.; Chattopadhyay, B. Noncovalent Interactions in Ir-Catalyzed C-H Activation: L-Shaped Ligand for Para-Selective Borylation of Aromatic Esters. *J. Am. Chem. Soc.* **2017**, *139*, 7745−7748.
(41) Yang, L.; Semba, K.; Nakao, Y. para-Selective C-H Borylation of (Hetero)Arenes by Cooperative Iridium/Aluminum Catalysis. *Angew. Chem., Int. Ed.* **2017**, *56*, 4853−4857.
(42) Mihai, M. T.; Williams, B. D.; Phipps, R. J. Para-Selective CH Borylation of Common Arene Building Blocks Enabled by Ion Pairing with a Bulky Counter cation. *J. Am. Chem. Soc.* **2019**, *141*, 15477−15482.
(43) 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 Phenols, Benzyl Alcohols, and Anilines Directed by Ion-Pair Electrostatic Interactions. *J. Am. Chem. Soc.* **2019**, *141*, 15483−15487.
(44) Chattopadhyay, B.; Dannatt, J. E.; Andujar-De Sanctis, I. L.; Gore, K. A.; Maleczka, R. E.; Singleton, D. A.; Smith, M. R. Ir-Catalyzed Ortho Borylation of Phenols Directed by Substrate-Ligand Electrostatic Interactions: A Combined Experimental/in Silico Strategy for Optimizing Weak Interactions. *J. Am. Chem. Soc.* **2017**, *139*, 7864−7871.
(45) Seechurn, C. C. C. J.; Sivakumar, V.; Satoskar, D.; Colacot, T. J. Iridium-Catalyzed C-H Borylation of Heterocycles Using an Overlooked 1,10-Phenanthroline Ligand: Reinventing the Catalytic Activity by Understanding the Solvent-Assisted Neutral to Cationic Switch. *Organometallics* **2014**, *33*, 3514−3522.
(46) Slack, E. D.; Colacot, T. J. Understanding the Activation of Air-Stable Ir(COD)(Phen)Cl Precatalyst for C-H Borylation of Aromatics and Heteroaromatics. *Org. Lett.* **2021**, *23*, 1561−1565.
(47) Bencini, A.; Lippolis, V. 1,10-Phenanthroline: A versatile building block for the construction of ligands for various purposes. *Coord. Chem. Rev.* **2010**, *254*, 2096−2180.
(48) Notably, in case of the substrates (**2a**−**2d** and **2a-I** to **2a-III**) we observed a minor amount of *m,m*-diborylated products under the reaction conditions. However, during the column chromatography isolation, the diborylated products perhaps decomposed and became only monoborylated products, which were isolated, and the yields are reported accordingly.
(49) Ye, Y.; Schimler, S. D.; Hanley, P. S.; Sanford, M. S. $Cu(OTf)_2$-Mediated Fluorination of Aryltrifluoroborates with Potassium Fluoride. *J. Am. Chem. Soc.* **2013**, *135*, 16292−16295.
(50) Thompson, A.; Kabalka, G.; Akula, M.; Huffman, J. The Conversion of Phenols to the Corresponding Aryl Halides Under Mild Conditions. *Synthesis* **2005**, *2005*, 547−550.
(51) Kallepalli, V. A.; Gore, K. A.; Shi, F.; Sanchez, L.; Chotana, G. A.; Miller, S. L.; Maleczka, R. E., Jr; Smith, M. R., III Harnessing C-

https://doi.org/10.1021/jacs.1c01770
J. Am. Chem. Soc. 2021, 143, 7604−7611

H Borylation/Deborylation for Selective Deuteration, Synthesis of Boronate Esters, and Late-Stage Functionalization. *J. Org. Chem.* **2015**, *80*, 8341−8353.
(52) Robbins, D. W.; Hartwig, J. F. Sterically Controlled Alkylation of Arenes through Iridium-Catalyzed C-H Borylation. *Angew. Chem., Int. Ed.* **2013**, *52*, 933−937.
(53) Dai, P. F.; Ning, X. S.; Wang, H.; Cui, X. C.; Liu, J.; Qu, J. P.; Kang, Y. B. Cleavage of C(aryl)-CH_3 Bonds in the Absence of Directing Groups under Transition Metal Free Conditions. *Angew. Chem., Int. Ed.* **2019**, *58*, 5392−5395.
(54) Boller, T. M.; Murphy, J. M.; Hapke, M.; Ishiyama, T.; Miyaura, N.; Hartwig, J. F. Mechanism of the Mild Functionalization of Arenes by Diboron Reagents Catalyzed by Iridium Complexes. Intermediacy and Chemistry of Bipyridine-Ligated Iridium Trisboryl Complexes. *J. Am. Chem. Soc.* **2005**, *127*, 14263−14278.
(55) However, we can not completely exclude the possibility of an intrinsic electronic directing effect of the sulphonamide group for the origin of the meta selectivity, which is a matter for future studies. Moreover, literature reports have revealed that the NH-R group might be considered as an activating group and that +M effect groups are found to be meta activating. For details, see: Tajuddin, H.; Harrisson, P.; Bitterlich, B.; Collings, J. C.; Sim, N.; Batsanov, A. S.; Cheung, M. S.; Kawamorita, S.; Maxwell, A. C.; Shukla, L.; Morris, J.; Lin, Z.; Marder, T. B.; Steel, P. G. Iridium-catalyzed C-H borylation of quinolines and unsymmetrical 1,2- disubstituted benzenes: insights into steric and electronic effects on selectivity. *Chem. Sci.* **2012**, *3*, 3505−3515.
(56) For B_2pin_2 0.5 mmol see: Jones, M. R.; Fast, C. D.; Schley, N. D. Iridium-Catalyzed sp^3 C-H Borylation in Hydrocarbon Solvent Enabled by 2,2′-Dipyridylarylmethane Ligands. *J. Am. Chem. Soc.* **2020**, *142*, 6488−6492.

https://doi.org/10.1021/jacs.1c01770
J. Am. Chem. Soc. 2021, 143, 7604−7611