Communication

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J. Am. Chem. Soc., **Just Accepted Manuscript** • DOI: 10.1021/jacs.5b11683 • Publication Date (Web): 21 Dec 2015

Formal Ir-Catalyzed Ligand-Enabled ortho- and meta-Borylation of Aromatic Aldehydes via in situ Generated Imines

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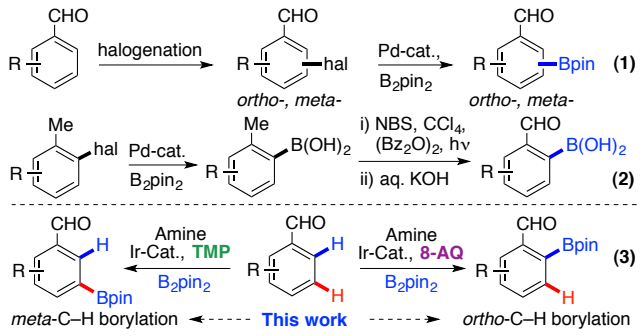
Supporting Information Placeholder

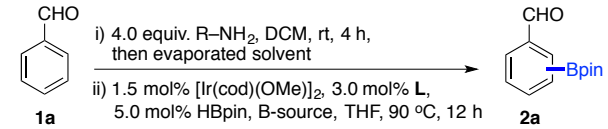
ABSTRACT: Ligand-enabled development of ortho and meta C–H borylation of aromatic aldehydes is reported. It was envisaged that while ortho-borylation could be achieved using *tert*-butylamine as the traceless protecting/directing group, meta-borylation proceeds via an electrostatic interaction and a secondary interaction between the ligand of the catalyst and the substrate. These ligand/substrate electrostatic interaction and secondary B–N interaction provide an unprecedented controlling factor for meta selective C–H activation/borylation.

Over the past decade, C–H bond functionalizations have attracted extensive attention as competent and ideal reactions.[1] In this perspective, the C–H bond borylation has shown potential because of the synthetic versatility for which B–C bonds are well-known. A major challenge in C–H borylations is how to control the selectivity. Generally, steric effects often govern the regioselectivity of aromatics,[2] which makes the C–H borylations complementary to widely used directed ortho metalations (DoMs).[3] However, the inherent functional group restriction and practical limitations of DoMs, (for example, groups like esters are incompatible with DoM and require low temperature) have strengthened efforts to develop efficient method for ortho C–H borylations. In this context, few methods for the functional group[4] directed ortho borylations[5] have been developed.

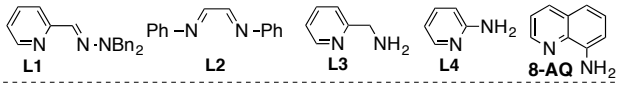


On the other hand, meta selective C–H bond borylation of arenes remains a great challenge. Development of strategy for meta selective C–H bond borylation is very difficult. Literature reports revealed that only one type of meta C–H borylation is available by Smith-Maleczka[6] and Hartwig[7] from 1,3-disubstituted arenes. The regiochemistry of this meta borylation results mainly from sterics.[8] Despite the broad utility of this sterically-controlled meta borylation, the chemistry is limited mostly to 1,3-disubstituted arenes. Moreover, the arenes bearing reactive functional groups such as aldehydes, ketones etc. are not well tolerated.[9] Notably, when this manuscript was in preparation, a paper describing a novel concept of a meta selective C–H borylation by a secondary interaction between ligand and substrate has appeared.[10] Unarguably, this method is one of the most efficient approaches towards meta borylation. However, there are many unsolved problems for the meta borylation. Thus, a critical challenge in developing these catalytic processes is the selective ortho and meta borylation of benzaldehydes. Traditionally, ortho and meta borylated benzaldehydes were prepared via a combined halogenation of benzaldehydes followed by a Miyaura cross-coupling reaction with bis(pinacolato)diborane (eq. 1 & eq. 2).[11,12] Herein, we report the discovery of a one-pot unified strategy for the ortho and meta selective C–H borylation of benzaldehydes using ligand enabled iridium-catalyzed C–H activation (eq. 3).

Table 1. Evaluation and Optimization of Reaction Conditions[a]



#	R	Ligand (L)	B-source	Ratio (o/m/p)[b]	Yield (%)
1	Me	L1	B_2pin_2 (0.7 eq.)	–	0
2	^{i}Pr	L1	B_2pin_2 (0.7 eq.)	–	0
3	^{t}Bu	L1	HBpin (1.5 eq.)	33/37/30	53
4	^{t}Bu	L1	B_2pin_2 (0.7 eq.)	86/8/6	57[c]
5	^{t}Bu	8-AQ	HBpin (1.5 eq.)	–	0
6	^{t}Bu	8-AQ	B_2pin_2 (0.7 eq.)	100/0/0	87[d]
7	Me	8-AQ	B_2pin_2 (0.7 eq.)	100/0/0	7
8	^{t}Bu	L2	B_2pin_2 (0.7 eq.)	100/0/0	66[e]
9	^{t}Bu	L3	B_2pin_2 (0.7 eq.)	95/3/2	72[f]
10	^{t}Bu	L4	B_2pin_2 (0.7 eq.)	97/2/1	62[g]

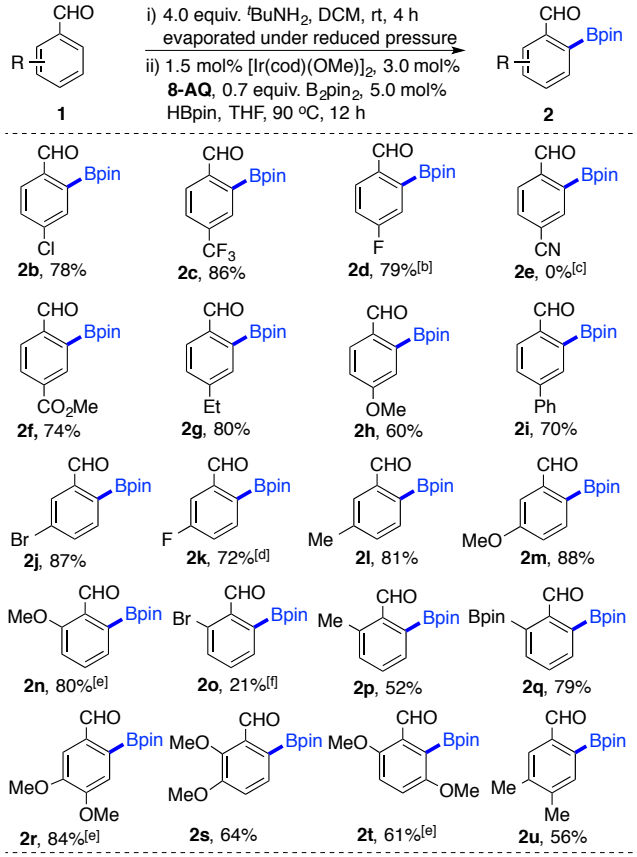


[a]Reactions were run with 1.0 mmol substrate, yields are for isolated ortho-isomer after column chromatography. [b]Ratios are calculated by GC-FID analysis from crude reaction mixture; in GC/MS no imine borylated products were found, only aldehyde borylated products were observed. [c]Mono/*o,o*-di = 90/10. [d]Mono/*o,o*-di = 89/11. [e]Mono/*o,o*-di = 80/20. [f]Mono/*o,o*-di = 87/13. [g]Mono/*o,o*-di = 85/15.

Recently, Fernández-Lassaletta[13] Sawamura,[14] and Ishiyama[15] disclosed an elegant nitrogen-directed ortho borylation of 2-phenylpyridines and hydrazones. Inspired by these results, we hypothesized that imines may serve as an easily removable directing groups[16] for ortho borylation of benzaldehydes. To test this hypothesis, benzaldehyde-derived imines were treated

with B_2pin_2 under the standard borylation conditions using hydrazone-derived ligand (**L1**) developed[13a] by Fernández and Lassaletta (entry 1, Table 1). While no borylation was observed for methyl and isopropyl imines, the *tert*-butyl imine gave good ortho selectivity (86%, entry 4).[17] Notably, when the crude reaction mixtures were monitored by GC/MS, the products appeared as aldehyde borylated products.[18] Gratifyingly, the combination of *tert*-butylamine, 8-AQ and B_2pin_2 was found to be the best borylation conditions having 100% ortho selectivity with excellent isolated yield (87%, entry 6). Notably, methylamine provided only 7% yield using 8-AQ as ligand system (entry 7), presumably methylimine is incapable to open a vacant coordination site in order to undergo the ortho borylation due to the less sterics compared to the *tert*-butylimine.[19] Other ligand systems such as **L2**, **L3** and **L4** were less effective than 8-AQ ligand system and the results are summarized in Table 1 (entries 8-10).

Table 2. Ortho-Borylation of Substituted Benzaldehydes[a]

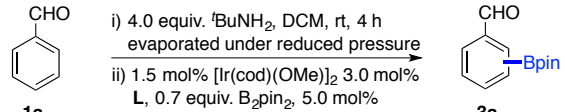


[a]Reactions were run with 1.0 mmol substrate, yields are for isolated aldehyde borylated products after column chromatography. [b]Ortho/meta = 93/07. [c]No reaction occurred even with ligand **L1**. [d]*o-o* di = 75/25. [e]Reactions were conducted using **L1** ligand. [f]21% conversion, failed to isolate due to rapid protodeborylation.

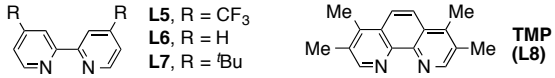
With these promising results in hand, borylations for a range of aldehydes were executed and the results are shown in Table 2. The reactions were conducted under identical conditions, and the reaction times were not optimized. It was found that diverse substituents such as halogens (Cl, F, Br), alkyl groups (Me, Et, CF_3), phenyl, methoxy were tolerated well under these borylation conditions. Irrespective of the substituent present in the aryl ring, 4-substituted benzaldehydes smoothly underwent C–H borylations to afford the ortho-directed products in good to excellent yields without any diborylations (entries 2b–2d & 2f-2i), except entry 2d, which resulted 7% meta isomer. However, 4-cyanobenzaldehyde failed to undergo C–H borylation (entry 2e). Employment of other ligand systems such as **L1**, **L2**, **L3** and **L4** were also unsuccessful (see SI for details). Remarkably, for 4-phenylbenzaldehyde borylation, the Ph C–H bonds are unperturbed under borylation conditions producing exclusively ortho directed product (entry 2i). Notably, meta-substituted benzaldehydes (entries 2j-2m) reacted regioselectively at the sterically less impeded C–H site. In the case of 3-fluorobenzaldehyde, though the expected borylation position is the most acidic proton flanked in between CHO and F, didn't undergo borylation exclusively (25% borylation) under these reaction conditions (entry 2k), instead it underwent ortho borylation, which is less acidic compared to the another ortho proton. Next, we studied the scope of 2-substituted substrates. It was found that both electron-rich and electron-poor substituents are very efficient in these C–H borylations giving exclusively ortho products (entries 2n, 2p & 2q). However, 2-bromobenzaldehyde borylation was not good (21% conversion, entry 2o). Furthermore, we have shown that these borylations could be successfully employed to a range of highly electron-rich and differently substituted benzaldehydes (entries 2r-2u).

Next, we focused on the ligand screening for the meta selective C–H activation/borylation. We chose benzaldehyde as our model system and borylation was performed with bipyridines **L5-L7**. As shown in Table 3, there is a clear indication for increasing meta selectivity as the bipyridine ligand is made more electron rich (entries 1-3). Encouraged by these initial results, we next attempted borylation using TMP ligand (**L8**). To our delight, improved meta selectivity (66% meta-borylated aldehyde product) was observed with excellent conversion (entry 4). To find out the origin of the increased selectivity, we hypothesized that two important factors might be playing significant role, such as i) an electrostatic interaction,[20] which is arising due to the encapsulation[21] between the iridium trisboryl complex attached with electron rich ligand and imine substrate, and ii) the secondary interaction of the substrate via either H-bonding[22] between the imine hydrogen atom and boryl oxygen atom of the catalyst (Chart 1, **TS-1**), or the interaction between the imine N atom and boryl B atom of the catalyst (**TS-2**).

Table 3. Ligand Screening for meta-Borylation[a]



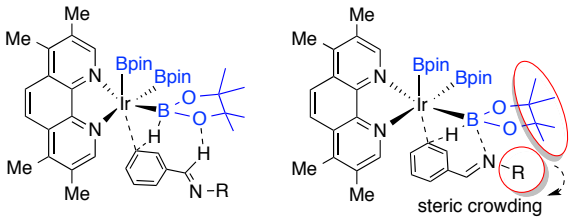
#	L	(meta/para/ortho)[b]	mono/di	Conversion (%)[c]
1	**L5**	11/61/28	89/11	63
2	**L6**	33/46/21	82/18	83
3	**L7**	47/37/16	88/12	88
4	**L8**	66/23/11	97/03	93 (67)[d]



[a]Reactions were run with 1.0 mmol substrate. [b]GC ratios. [c]GC conversion was measured using dodecane as internal standard. [d]In parentheses isolated yield for aldehyde meta-borylated product.

As the electrostatic interaction is present in both cases (**TS-1** & **TS-2**) which is enhancing the meta selectivity, question remains which **TS** (**TS-1** or **TS-2**) is actually controlling the meta selectivity? In case of H-bond directed approach (**TS-1**), the imine substituent (R) is far away from the reaction centre and thus, the outcome of the meta borylation should not be dependent on the size of the R group. On the other hand, in case of **TS-2**, the outcome should be affected by the size of the R group, because of the close proximity of the R group and the boryl group of the catalyst. Thus, we hypothesized that steric alteration of the imine substituent (R) from ^{t}Bu→^{i}Pr→Me, meta selectivity should be enhanced further.

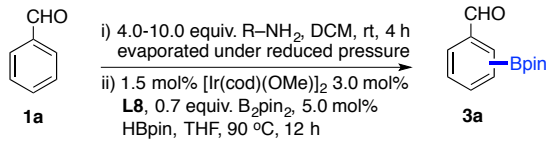
Chart 1. Hypothesis for the Origin of meta-Selectivity



TS-1: H Bond Directed **Ts-2: B–N Bond Directed**

To test this hypothesis, borylations were performed with isopropyl imine and methyl imine of the benzaldehyde. Remarkably, a clear trend for the enhancement of the meta selectivity was observed as the imine substituent (R) is made small (Table 4). We reasoned that the enhanced meta selectivity (100% for R = Me) results at the expense of reduced steric crowding, which facilitates the seconday interaction through the imine N atom and boryl B atom of the catalyst (**TS-2**). However, the question of mechanism is open to debate and the detailed mechanism of each step remains to be ascertained.

Table 4. Effect of Imine Substituent: Proof of Hypothesis for meta-Borylation[a]



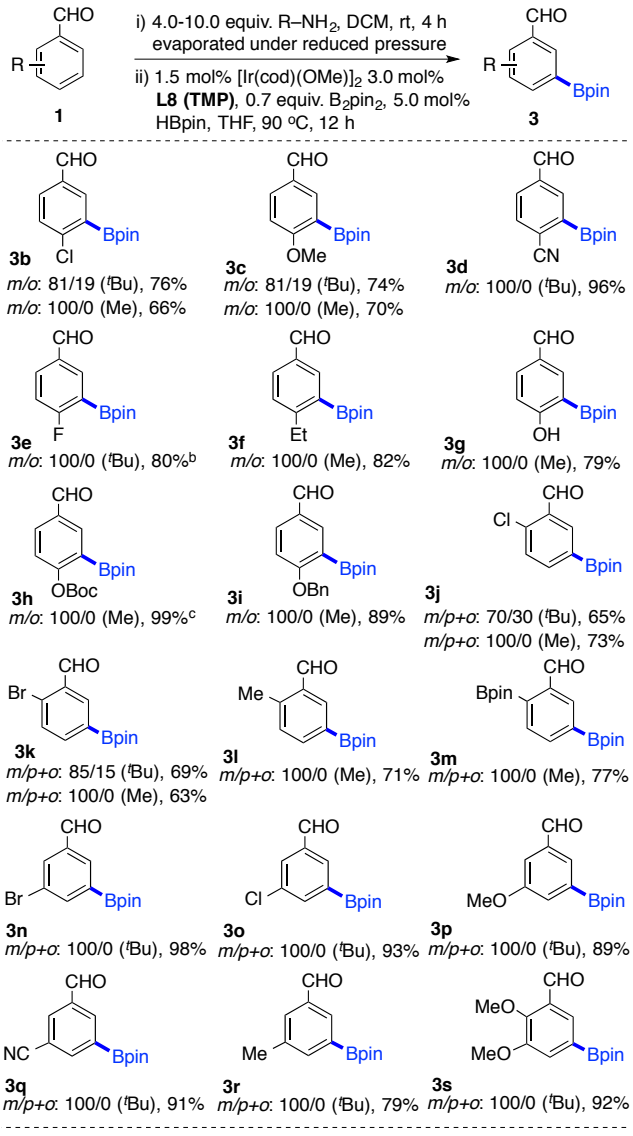
1a **3a**

#	R	meta/(para+ortho)[b]	mono/di	Conversion (%)[c]
1	**^{t}Bu**	66/34	93/07	78 (57)
2	**^{i}Pr**	84/16	90/10	73
3	**Me**	97/03	97/03	80 (73)[d]

[a]Reactions were run with 1.0 mmol substrate, see SI for details. [b]GC ratios. [c]GC conversion; in GC/MS no imine borylated products were found, only aldehyde borylated products were observed. [d]In parentheses isolated yield of the aldehyde borylated product.

Next, we explored the substrates scope for the meta borylations and the results are summarized in Table 5. A wide range of substituents were well tolerated under the borylation conditions affording excellent meta selectivity with excellent isolated yields. For example, while 4-chlorobenzaldehyde gave 81/19 meta/ortho selectivity (**entry 3b**) using *tert*-butylamine, it afforded 100% meta selectivity with methylamine as the protecting/directing group. 4-Methoxybenzaldehyde gave 81/19 and 100/0 meta/ortho selectivity by the employment of *tert*-butylamine and methylamine respectively. (entry **3c**). Likewise, 4-cyano-, 4-fluoro-, 4-ethyl-, 4-hydroxybenzaldehydes, resulted meta isomer as the sole products (entry 3d-3g). It deserves mentioning that even use of very bulky substituents at the 4-position of the benzaldehyde such as OBoc[23] and OBn group (entries 3h & 3i) afforded complete meta selectivity. Thus, these observations are consistent with the notion that an electrostatic interaction and secondary interaction between the imine N atom and the boryl B atom of the catalyst.

Table 5. Meta-Borylation of Substituted Benzaldehydes[a]



[a]Reactions were run with 1.0 mmol substrate, for details see SI, yields are for isolated aldehyde meta-borylated products after column chromatography. [b]2.0 mmol substrate was used. [c]99% conversion.

On the other hand, 2-substituted substrates proved to be challenging because of several open reactive sites for C–H activation/borylation. For example, 2-Bpin-, 2-bromo-, 2-chloro-, and 2-methyl-benzaldehydes could give mixture of isomers. To our delight, they resulted complete meta selectivity (entry 3j-3m). For meta-substituted benzaldehydes, as expected borylations occurred at the meta position and no other borylations were observed (entries 3n-3r). Moreover, highly electron-rich 2,3-dimethoxybenzaldehyde proved to be an excellent meta borylating substrate giving excellent yield (entry 3s).

In summary, we have developed two complementary methods for the ortho and meta selective C–H bond activation/borylation of aromatic aldehydes that cannot be obtained with DoM, or any other methodology. While the ortho borylation proceeds through directed C–H activation/borylation using *tert*-butylamine as the traceless protecting/directing group, the meta borylation undergoes through an electrostatic interaction and a secondary interaction between the ligand of the catalyst and the substrate. Both methods have shown very broad substrate scope and functional group tolerance. However, at this stage, we are not entirely certain about the working hypothesis for meta selective C–H activation/borylation and further studies are underway, which will be reported in due course.

ASSOCIATED CONTENT

Supporting Information Available: Full characterization, copies of all spectral data, experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

Thanks to Professor Milton R. Smith III (Michigan State University, USA) for helpful suggestions. BC thanks DST, New Delhi for Ramanujan Faculty Award and RB for JRF (Sanction No: SB/S2/RJN-45/2013). We are thankful to Dr. Bikash Baishya and Mr. Ajay Verma for helpful discussion on NMR analysis and Mr. Durga Prasad and Mr. Prasant for HRMS. We are also thankful to the reviewers for helpful suggestions. We thank the Director, CBMR for research facilities.

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(17) The *o*-$BpinC_6H_4CHO$ can easily be distinguished by the ~ 0.6 ppm downfield shift of its CHO resonance in ^1H NMR spectra due to hydrogen bonding to a Bpin O.

(18) The imine borylated products can be seen in the crude proton NMR (see SI for details). We assumed that in the GC/MS, the imine borylated products are hydrolyzed. Likewise, during silica gel column chromatography, the products are hydrolyzed.

(19) The mechanism of the ortho C–H bond activation/borylation of aldehydes via in situ generated imines is related to the analogous ortho borylation of hydrazones as reported by Fernández-Lassaletta.[13a]

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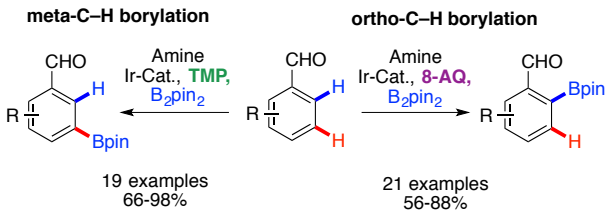
(23) Isolation of the 3h was failed due to the elimination of the Boc group during silica gel column chromatography, it was isolated as 3g.

TOC Graphic


meta-C–H borylation
ortho-C–H borylation
CHO
R
H
Bpin
Amine
Ir-Cat., TMP,
B2pin2
Amine
Ir-Cat., 8-AQ,
B2pin2
19 examples
66-98%
21 examples
56-88%