Ion Pair-Directed Meta-Selective C–H Borylation of Aromatic Quaternary Ammonium Salts

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Abstract
We recently reported the use of ion pairing as a key non-covalent interaction to control regioselectivity in the iridium catalyzed C–H borylation of aromatic quaternary ammonium salts. Two classes of substrates, benzylamine- and aniline-derived ammonium salts were selectively borylated at the meta position by employing a newly developed anionic ligand for the iridium. It was proposed that the ligand interacts with the cationic substrate via an ion pairing interaction, positioning the substrate in the optimal orientation for selective activation of the meta C–H bond.

1. Introduction
Within the field of transition metal catalyzed C–H activation, iridium-catalyzed C–H borylation has emerged as a powerful strategy for arene and heteroarene functionalization. Operating under generally mild conditions, the regioselectivity of the iridium-catalyzed borylation is of particular interest in that it is primarily controlled by sterics, which sets it apart from most other arene C–H functionalization reactions typically controlled by electronics or proximity to a directing group. While this is particularly useful for the borylation of 1,3-disubstituted arenes as they afford a single product (at the 5-position), monosubstituted and 1,2-disubstituted arenes are problematic substrates leading to often inseparable mixtures of products arising from borylation at the meta and para positions.

The value of iridium catalyzed borylation in synthesis could be significantly enhanced by the development of methodology that advances beyond the simple steric control intrinsic to each substrate. Several strategies of ortho, meta, and para selective borylation have recently been reported, based on both catalyst and substrate modifications. The majority of these examples concern ortho selectivity, which has been achieved via both ‘inner sphere’ and ‘outer sphere’ directed processes. In the case of ‘inner sphere’ direction, the selectivity stems from a direct interaction between the substrate and the iridium center, and includes chelation and relay-directed borylations. In an ‘outer sphere’ directed process, most relevant to the work

Key words: ion-pairing, iridium borylation, meta-selectivity, C–H activation
discussed herein, the selectivity derives from interactions between the substrate and a ligand on the iridium, rather than the metal itself. A leading example of such a process is the *ortho*-selective borylation of Boc-protected anilines reported by Maleczka *et al.* (Figure 1). The origin of the regioselectivity in this case was proposed to be a hydrogen bonding interaction between the acidic NH in the substrate and an oxygen lone pair from one of the Bpin ligands on the active catalyst. This is consistent with experimental results and DFT calculations. The substrate scope includes 4-mono- and 3,4-disubstituted Boc-protected anilines, which afford *ortho*-borlated products in high yields and selectivities. A drop in selectivity was observed for substrates bearing a single substituent at the 3-position due to competition for borylation at the least hindered (*meta*) position.

![Figure 1](https://example.com/figure1.png)

**Figure 1** General scheme for outer-sphere borylation of NH-Boc protected anilines and the structure of the proposed transition state and general example for ortho-borylation (b) Selected examples for ortho-borylation (c) Selected examples for meta-borylation.

Compared to *ortho*-selective borylation, there are significantly fewer reports on *meta*-selective borylation of monosubstituted and 1,2-disubstituted arenes. Whilst conventional iridium-catalyzed borylation is sometimes referred to as being *meta* selective, this is generally limited to 1,3-disubstituted arene substrates where the steric preference dictates the selectivity.

A recently published example of ligand enabled *meta* selectivity is the borylation of imines generated *in situ* from benzaldehydes and primary amines, as reported by Bisht and Chattopadhyay (Figure 2). Depending on the ligand and the amine employed, *ortho* or *meta* selective borylation of the same benzaldehyde substrate could be achieved. The hemilabile ligand L2 was found to give exclusive formation of *ortho*-borlated products, when used in the presence of *tert*-butylamine. In this case, it is thought that one of the nitrogen atoms of the ligand can dissociate from the active iridium catalyst, freeing up a coordination site for activation of the substrate whilst remaining complexed to the imine, leading to *ortho* selective C–H activation.

![Figure 2](https://example.com/figure2.png)

**Figure 2** (a) General scheme for *ortho* - and *meta*-selective C–H borylation of *in situ* generated imines from benzaldehydes (b) Selected examples of substrates for ortho borylation (c) Selected examples for meta borylation.

Interestingly, *meta*-selectivity was obtained by switching the ligand to the non-hemilabile phenanthroline L3 (Figure 2). In this case, the nature of the protecting group seems to have an influence on the selectivity. While for most substrates, *tert*-butylamine led to high *meta*-selectivity, in a few cases, using the less bulky methylaniline resulted in even better selectivity (up to 100:0). Although the origin of the observed *meta* selectivity is not entirely clear, it was proposed that the reaction proceeds through one of the two transition states depicted in Figure 3. Both of them would involve an *outer sphere* interaction between a Bpin ligand on the active catalyst and the imine substrate, which is thought to direct the C–H oxidative addition to the *meta* position. The authors favoured the B–N dative interaction pathway based on experiments probing the steric effect of the imine.

![Figure 3](https://example.com/figure3.png)

**Figure 3** Hypothetical transition states that could explain the origin of *meta* selectivity in the borylation of imines.

An elegant example of ligand-directed iridium catalyzed *meta*-selective borylation was reported in 2015 by Kuninobu, Kanai *et al.* In this case, highly regioselective C–H borylation was achieved by using a novel bipyridine-derived ligand bearing a hydrogen bond donor urea moiety remote from the bipyridine ligand site (Figure 4). The urea group was envisaged to engage the acidic NH centre in close proximity to the *meta* C–H bond on the arene.
substrate (Fig 4, a). Of several ligands screened, L4 was found to give the best meta:para ratio in the borylation reaction of test substrate 1. The substrate scope was broad, including arenes possessing Lewis-basic functional groups such as amides, esters, phosphonates and phosphine oxides, as well as several examples of heteroarenes bearing amide and ester groups.13 Control experiments with methylated versions of L4 supported the hydrogen bonding hypothesis. This work is a remarkable example of the power of employing non-covalent interactions to direct transition metal catalysis.

![Figure 4](a) General reaction scheme for H-bond directed meta borylation and proposed interaction between ligand L4 with Lewis basic functionality on the substrate (b) Selected examples from substrate scope

A rare example of para-selective iridium-catalyzed borylation reported was published in 2015 by Itami et al.14 Para selectivity was achieved by employing the bulky diphosphine ligand L5 (Figure 5). The bulky active catalyst formed in situ selectively borylates certain monosubstituted benzene rings at the para position, while the ortho and meta positions are sterically blocked. For high para selectivity, a very bulky substituent is required on the substrate; changing the substituent from tert-butyl to ethyl leads to a decrease in para:meta selectivity from 90:10 to 31:68 (Figure 5).

![Figure 5](a) General scheme for Para-selective borylation of monosubstituted arenes. (b) Bulky phosphine ligand employed. (c) Selected examples from substrate scope

Musaev, Itami et al later reported an investigation into the mechanism and regioselectivity of this reaction.16 DFT calculations suggested that a complex combination of factors might be responsible for regioselectivity, such as size of substrate and ligand, a series of attractive and repulsive interactions between substrate and ligand, as well as entropic costs, all of which have to be finely balanced in order to achieve high para-selectivity.

2. Ion-pair directed meta C–H borylation

Non-covalent interactions such as hydrogen bonding or ion-pairing have been extensively employed as key interactions in catalysis to control enantioselectivity in the field of asymmetric organocatalysis.17,18 However, non-covalent interactions remain rather less explored to tackle other important selectivity aspects such as regioselectivity and site-selectivity.19,20 Within this area there are a number of leading examples of using hydrogen bonding interactions in combination with transition metals,21 but to the best of our knowledge few employing ion pairs. Ion pairing interactions have been demonstrated to be highly effective in enantioselective catalysis with transition metals22 and as such we envisaged that there should be significant potential for their application to regioselective catalysis in the field of C-H activation.

Herein, we describe in fuller detail our recent report on the use of ion pairing as a key non-covalent interaction between a functionalized ligand and an arene substrate to direct borylation to the arene meta position.24 A series of bipyridine-derived ligands were synthesized which bear an anionic sulfonate group in different orientations and distances from the pyridine rings (Figure 6). It was envisaged that an interaction between the anionic ligands and a arene-containing cationic ammonium salts could position the meta C–H bond of the substrate in close proximity to the iridium centre, thus leading to selective activation of this C-H bond. In order to find the ligand that would allow for optimal geometry in the transition state, one-carbon (L6 and L8) and two-carbon (L7 and L9) linkers between the pyridine ring and the sulfonate group were investigated.
The ligands L6-L9 were trialled on the borylation of ortho-substituted benzytrimethylammonium salt 8, alongside the standard borylation ligand dtbpy (Table 1). As there is little steric differentiation between the meta and para-positions of 8, with dtbpy an almost equimolar mixture of meta- and para-borylated products was obtained in cyclohexane, with a slight preference for the para-borylated product being observed in THF. When ligand L6 was used, an increase in the meta-selectivity to 1:1.3 was observed in THF. This was hypothesised to be due to an attractive interaction between the sulfonate and the ammonium group, which would position the meta C–H bond of the substrate in an optimal position for regioselective oxidative addition to the iridium metal centre. Ligand L6 did not perform well in cyclohexane, with less than 5% conversion observed even at higher temperature (70 °C). Extending the linker to two carbons (L7) led to full conversion of the starting material in THF but the meta:para selectivity dropped significantly, to 3:5:1. In the case of ligands where the sulfonate group extends from the 4-position of the ring (L8 and L9), the meta:para selectivity was very poor (but still noticeably different from dtbpy).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>Solvent</th>
<th>T (°C)</th>
<th>Conversion (%)</th>
<th>mp °C</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>dtbpy</td>
<td>cyclohexane</td>
<td>50</td>
<td>24</td>
<td>1:1:1</td>
</tr>
<tr>
<td>2</td>
<td>dtbpy</td>
<td>THF</td>
<td>50</td>
<td>98</td>
<td>1:2:4</td>
</tr>
<tr>
<td>3</td>
<td>L6</td>
<td>THF</td>
<td>50</td>
<td>96</td>
<td>1:1:1</td>
</tr>
<tr>
<td>4</td>
<td>L7</td>
<td>THF</td>
<td>50</td>
<td>100</td>
<td>3:5:1</td>
</tr>
<tr>
<td>5</td>
<td>L8</td>
<td>THF</td>
<td>50</td>
<td>100</td>
<td>1:8:1</td>
</tr>
<tr>
<td>6</td>
<td>L9</td>
<td>THF</td>
<td>50</td>
<td>100</td>
<td>1:1:1</td>
</tr>
<tr>
<td>7</td>
<td>L6</td>
<td>cyclohexane</td>
<td>70</td>
<td>&lt;5</td>
<td>-</td>
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</table>

*a determined by crude 1H-NMR analysis, using 1,3,5-trimethoxybenzene as internal standard

With these results in hand, the scope of this transformation was explored for both benzylamine- and aniline-derived quaternary ammonium salts; selected examples are illustrated in Figure 7. For full scope, see reference 21. For each substrate, the meta:para borylation ratio is indicated for reactions run with both ligand L6 and dtbpy in THF for comparison. A variety of substituents are tolerated in the ortho position, including halogens (10a), electron withdrawing (10f) and electron donating (10e) groups. With our current system, borylation next to substituents was not observed, apart from next to fluorine or in the case of tethered substrates.

Table 1 Ligand screening for meta C–H borylation of benzylamine-derived quaternary ammonium salt 8

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>Conversion (%)</th>
<th>m.p. °C</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>dtbpy</td>
<td>100</td>
<td>1:2:2</td>
</tr>
<tr>
<td>2</td>
<td>L6</td>
<td>100</td>
<td>59:1:1</td>
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<tr>
<td>3</td>
<td>L7</td>
<td>100</td>
<td>1:6:1</td>
</tr>
<tr>
<td>4</td>
<td>L8</td>
<td>100</td>
<td>1:6:1</td>
</tr>
<tr>
<td>5</td>
<td>L9</td>
<td>100</td>
<td>1:1:4</td>
</tr>
</tbody>
</table>

Similar results were observed with aniline-derived quaternary ammonium salt 9 (Table 2), in which there is one carbon less between the aromatic ring and the cationic ammonium functionality. Ligand L6 gave the best result of 9:5:1 meta:para borylation, while the standard dtbpy and the other three sulfonate ligands (L7-L9) led to poor selectivity (Table 2).

**Figure 6** Bipyridine-derived ligands bearing a remote anionic sulfonate group

**Figure 7** Scope of benzylamine- and aniline-derived quaternary ammonium salts (selected examples). The yields are for isolated compounds, unless in
Quaternary ammonium salts derived from heterocyclic arenes were also explored. Under standard borylation conditions, 2-substituted pyridines lead to mixtures of C5-borylated and C4,6-diborylated products, with the second borylation at C6 occurring due to an electron withdrawing group being present at the 2 position. Using ligand L6 with pyridine-derived substrates 12 and 14 resulted in excellent regioselectivity (>20:1) for C4 over C5 borylation, while with dtbpy poor regioselectivity was obtained in both cases (Figure 8).

An additional experiment carried out was addition of varying amounts of Bu4NOTs to the borylation of quarternary ammonium salt 8. Table 3 summarizes the results. The poor selectivity was not preventable and so a several-fold excess of B2pin2 was used to ensure any mono-meta conversion was not observed. The reactions were carried out in THF, except for substrate 18a, which was performed in cyclohexane. In the case of all the unsubstituted substrates, ion-pairing ligand L6 was used to ensure any mono-meta conversion was not observed. The reactions were carried out in THF, except for substrate 18a, which was performed in cyclohexane. In the case of all the unsubstituted substrates, ion-pairing ligand L6 gave excellent regioselectivity (>20:1) and superior conversions to the dimeta product, resulting in excellent isolated yields.

To further investigate this interesting effect, a variety of ligands based on the bipyridine and phenanthroline backbones (L10-
The ammonium salt products of the borylation themselves are also amenable to further functionalization and can be further functionalized in an orthogonal manner. As an example, it was demonstrated that it is possible to selectively cross couple the boronate ester, ammonium and halogen sequentially in substrate 10a (Figure 12). The ammonium group could also be cleanly removed by hydrogenation.

5. Conclusion

Using ion-pairing as a key non-covalent interaction proved to be a powerful approach for controlling the regioselectivity of iridium-catalyzed borylation of two classes of aromatic quaternary ammonium salts. This was achieved by designing a functionalized anionic ligand for the iridium which was proposed to engage into ion-pairing interactions with the charged substrates, thus directing the borylation at the desired meta position. Current studies are underway to extend this concept to control regioselectivity in other transition metal catalysed reactions.

Acknowledgments

We are grateful to AstraZeneca for a studentship (M.T.M.) through the AZ-Cambridge PhD Program and the Royal Society for a University Research Fellowship (R.J.P.). We thank Holly J. Davis for useful discussion.

References

(24) See the Supporting Information of reference 21 for full details of these experiments.