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

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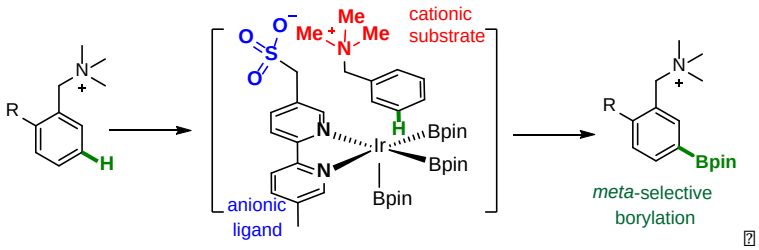

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Abstract

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.

Key words ion-pairing iridium borylation *meta*-selectivity C-H activation

Robert Phipps obtained his undergraduate degree from Imperial College, London in 2006 before moving to the University of Cambridge where he completed his PhD studies with Prof. Matthew Gaunt in 2010. He spent two years working with Prof. F. Dean Toste at UC Berkeley as a Marie Curie Postdoctoral Fellow. In 2013, he returned to Cambridge where he commenced independent research from 2014 as a Royal Society University Research Fellow. He has been the recipient of the Reaxys PhD prize (2010) and more recently a Thieme Chemistry Journal Award (2016). His research group is interested in applying non-covalent interactions to control regioselectivity and site selectivity in catalysis.

Madalina Mihai obtained her MSci degree from the University of Birmingham in 2014. During her final year, she investigated organocatalytic reactions of triketopiperazines under the supervision of Prof. Nigel Simpkins. She is currently pursuing her PhD in the group of Dr. Robert Phipps at the University of Cambridge. Her current research focusses on regioselective iridium-catalyzed C–H borylation of charged arenes and heteroarenes.

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.[1] 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.[1,2] 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.[1,2]

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*-,[3–11] *meta*-[12,13] and *para*-[14] 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-[8,15] and relay-directed[4] borylations. In an 'outer sphere' directed process, most relevant to the work

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).[3] 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.[3] The substrate scope includes 4-monosubstituted and 3,4-disubstituted Boc-protected anilines, which afford *ortho*-borylated 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.

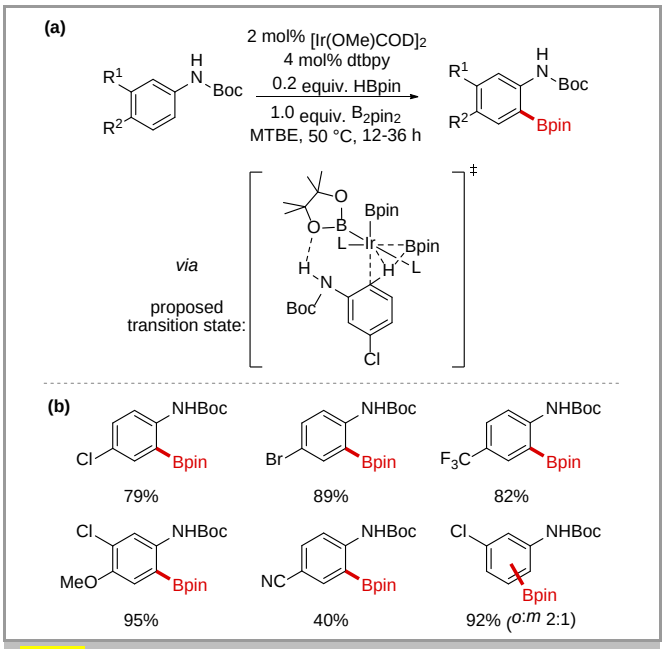


Figure 1 (a) General scheme for outer-sphere borylation of NH-Boc protected anilines and the structure of the proposed transition state (b) Selected examples for *ortho* borylation; dtbpy = 4,4′-Di-tert-butyl-2,2′-dipyridyl **L1**

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).[12] Depending on the ligand and the amine employed, either *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*-borylated products, when used in the presence of *tert*-butyl amine. 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.

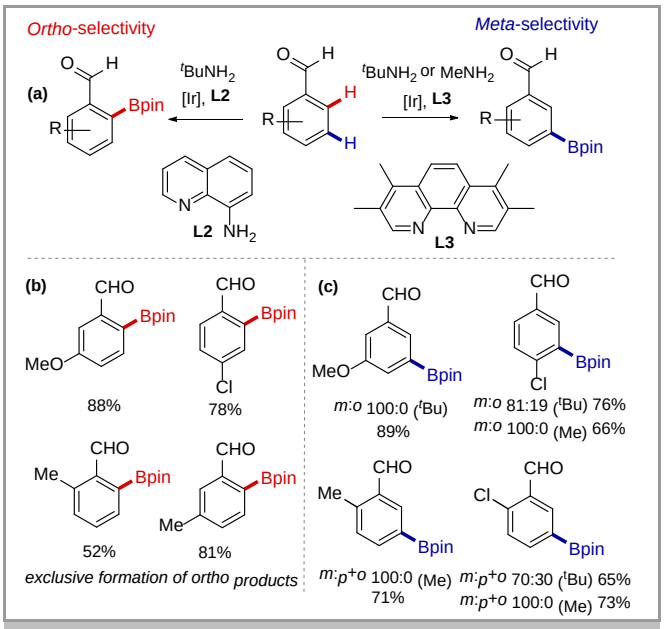


Figure 2 (a) General scheme for *ortho*- and *meta*-selective C–H borylation of *in situ* generated imines from benzaldehydes[12] (b) Selected examples of substrates for *ortho* borylation (c) Selected examples for *meta* borylation

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 methylamine 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.

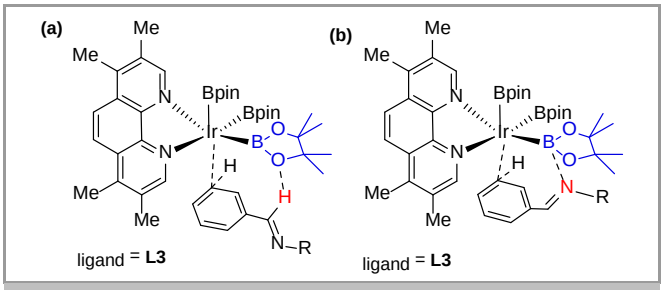


Figure 3 Hypothetical transition states that could explain the origin of *meta* selectivity in the borylation of imines[12]

An elegant example of ligand-directed iridium catalyzed *meta*-selective borylation was reported in 2015 by Kuninobu, Kanai *et al.*[13] 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 into a hydrogen bonding interaction with a Lewis basic functional group on the substrate, thus positioning the iridium 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.

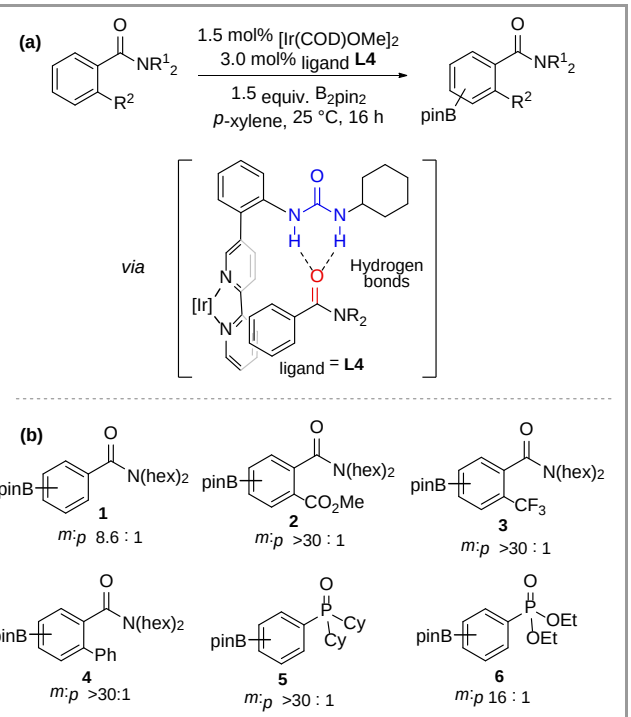


Figure 4 (a) General reaction scheme for H-bond directed *meta* borylation and proposed interaction between ligand **L4** with Lewis basic functionality on the substrate (b) Selected examples from substrate scope

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).

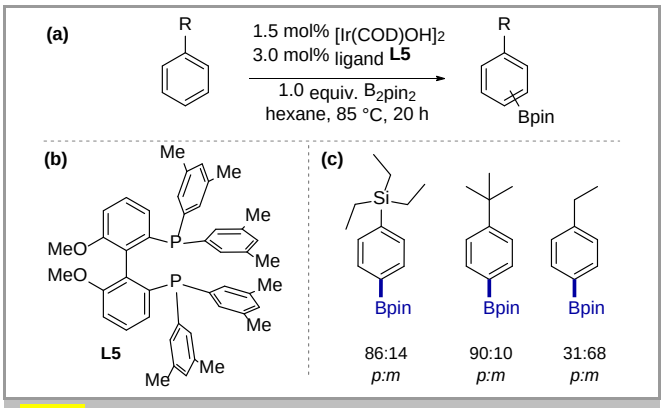


Figure 5 (a) General scheme for *Para*-selective borylation of monosubstituted arenes.[14] (b) Bulky phosphine ligand employed. (c) Selected examples from substrate scope

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,[19] 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 metals[18] 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.[21] 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.

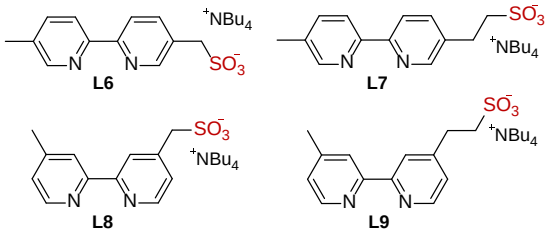
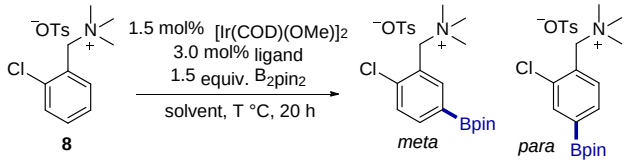


Figure 6 Bipyridine-derived ligands bearing a remote anionic sulfonate group

The ligands **L6**-**L9** were trialled on the borylation of *ortho*-substituted benzyltrimethylammonium 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 11:1 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 1 Ligand screening for *meta* C–H borylation of benzylamine-derived quaternary ammonium salt **8**

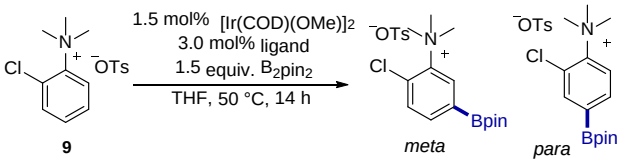


Entry	Ligand	Solvent	T (°C)	Conversion (%)[a]	*m*:*p*[a]
1	**dtbpy**	cyclohexane	50	24	1.1:1
2	**dtbpy**	THF	50	98	1:2.4
3	**L6**	THF	50	96	11:1
4	**L7**	THF	50	100	3.5:1
5	**L8**	THF	50	100	1.8:1
6	**L9**	THF	50	100	1.1:1
7	**L6**	cyclohexane	70	<5	-

[a] determined by crude ^{1}H-NMR analysis, using 1,3,5-trimethoxybenzene as internal standard

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 8.5:1 *meta*:*para* borylation, while the standard **dtbpy** and the other three sulfonate ligands (**L7**-**L9**) led to poor selectivity (Table 2).

Table 2 Ligand screening for *meta* C–H borylation of aniline-derived quaternary ammonium salt **9**



Entry	Ligand	Conversion (%)[a]	*m*:*p*[a,b]
1	**dtbpy**	100	1:2.2
2	**L6**	100	8.5:1
3	**L7**	100	1.6:1
4	**L8**	100	1.6:1
5	**L9**	100	1:1.4

[a] determined by crude ^{1}H-NMR analysis, using 1,3,5-trimethoxybenzene as internal standard; [b] *meta* consists of mixture of mono- and di-*meta*

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. Fr 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.

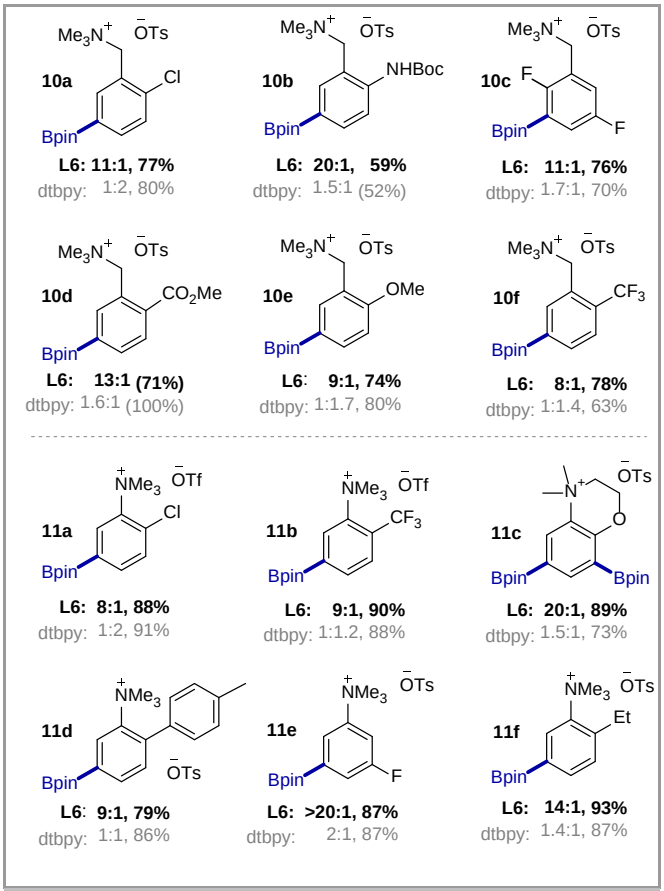


Figure 7 Scope of benzylamine- and aniline-derived quaternary ammonium salts (Selected examples). The yields are for isolated compounds, unless in

brackets, in which case NMR yields are reported. Reactions run on a 0.25 mmol scale. Typical reaction conditions: 1.5 mol% $[Ir(COD)(OMe)]_2$, 3.0 mol% ligand (**L6** or **dtbpy**), 1.5 equiv. B_2pin_2 in THF (0.2 M) at 50 °C for 20 hours.

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.[22,23] 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).

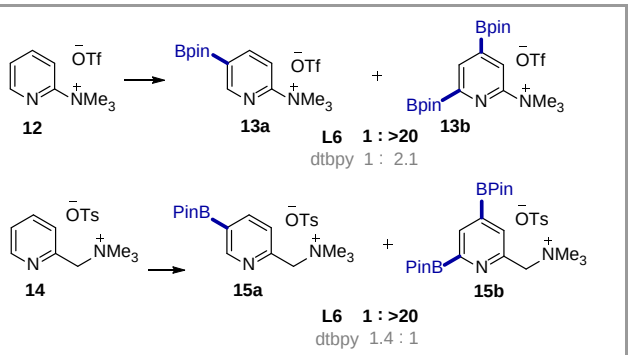


Figure 8 Borylation of heteroarene substrates (Selected examples).

3. Control experiments

In order to test the ion-pairing hypothesis, neutral substrates **16** and **17** were submitted to borylation using charged ligand **L6** (Figure 9). Substrate **17** was chosen due to its steric similarity to **8** and the fact that it is not charged. The poor selectivity obtained with both these substrates provides some support for the ion-pairing as the key interaction that directs the borylation at the *meta* position in **8**.

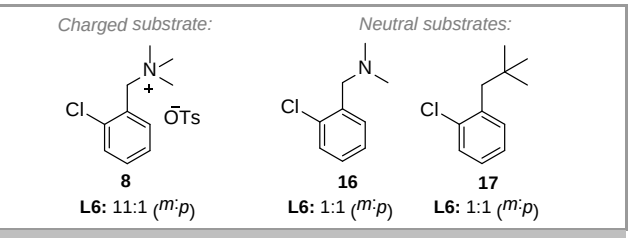
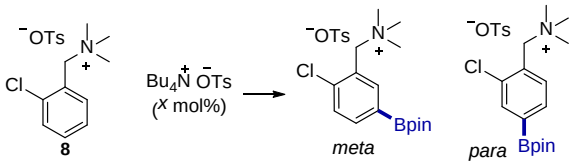


Figure 9 Borylation of cationic compound **8** vs neutral substrates **16** and **17** using anionic ligand **L6** in THF

An additional experiment carried out was addition of extraneous Bu_4NOTs to the borylation of test substrate **8** (Table 3). A decrease in *meta* selectivity was observed with increasing amounts of salt being present, possibly due to the competition between excess NBu_4 cation and substrate as counterions of the anionic ligand. This further supports an ion-pairing interaction as key for high *meta* selectivity.

Table 3 Control experiment: Addition of varying amounts of Bu_4NOTs to the borylation of quarternary ammonium salt **8.**



Entry	x mol%	Conversion (%)[a]	*m*:*p*[a,b]
1	0	89	10.1 : 1
2	50	86	7.6 : 1
3	100	82	5.3 : 1
4	200	82	4.9 : 1
5	300	86	5.1 : 1
6	400	79	4.6 : 1

[a] determined by crude ^{1}H-NMR analysis, using 1,3,5-trimethoxybenzene as internal standard; [b] *meta* consists of mixture of mono- and di-*meta*

4. Unexpected selectivity with dtbpy in cyclohexane

While exploring the scope of this reaction, a series of interesting results were obtained with substrates bearing no substituents on the arene portion.[24] For this class of substrates, diborylation was not preventable and so a several-fold excess of B_2pin_2 was used to ensure any mono-*meta* was converted all the way to the di-*meta*. Intriguingly, when the reactions were carried out with the standard **dtbpy** ligand in cyclohexane, unusually high *meta* selectivity was observed for several unsubstituted benzylamine- and aniline-derived substrates (Figure 10). In the case of substrate **18a**, the *meta* selectivity was observed to increase from 3.2:1 in THF, to 7.3:1 in MTBE, to 13:1 in cyclohexane, indicating a dependency on solvent polarity. In cyclohexane, the substrates generally had very poor solubility, but low to moderate conversions were still observed, commonly to a mixture of mono and di*meta* borylated products. Notably, in the case of all the unsubstituted substrates, ion-pairing ligand **L6** in THF gave excellent regioselectivity (>20:1) and superior conversions to the di*meta* product, resulting in excellent isolated yields.

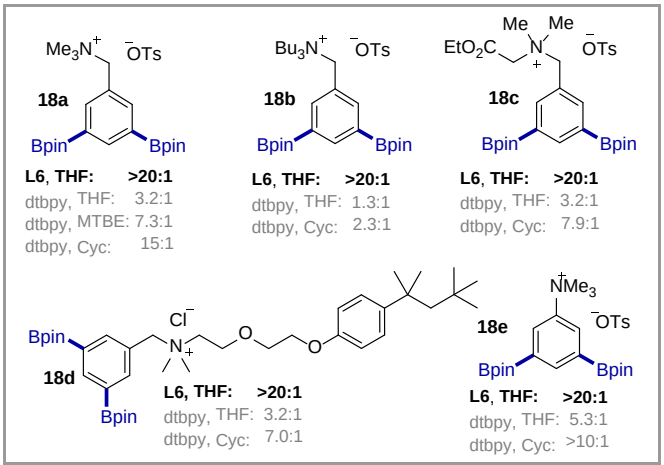
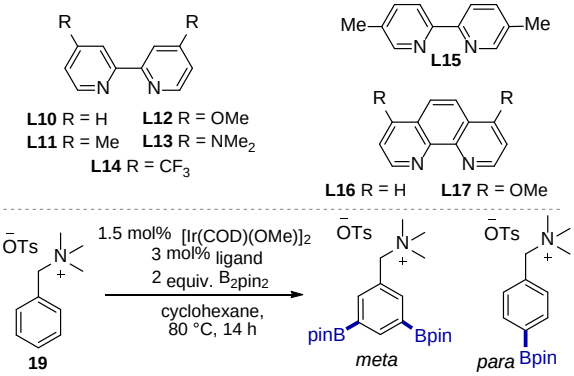


Figure 10 Borylation of unsubstituted substrates with **L6 (in THF)** and **dtbpy** (in THF and cyclohexane). Ratio shown is *meta*:*para* of crude reaction mixture. *Meta* figure refers to a mixture of mono and di*meta*.

To further investigate this interesting effect, a variety of ligands based on the bipyridine and phenanthroline backbones (**L10-**

L17) were tested on the unsubstituted substrate **19** using cyclohexane as solvent (Table 4). Apart from **dtbpy** (13:1 *m*:*p*) and **L12** (5.5:1 *m*:*p*), no other ligands gave significant *meta*:*para* selectivity. From the results in Table 4, no electronic trend was obvious and the origin of the high selectivity with **dtbpy** in cyclohexane remains unclear at this stage.

Table 4 Screening of ligands for unsubstituted substrates



Entry	Ligand	Conversion (%)[a]	*m*:*p*[a]
1	**L10**	0	-
2	**L11**	69	2.9:1
3	**dtbpy**	45	13:1
4	**L12**	83	5.5:1
5	**L13**	41	3.1:1
6	**L14**	0	-
7	**L15**	31	3.4:1
8	**L16**	24	3.5:1
9	**L17**	46	4.2:1
10	**L3**	88	2.5:1

[a] determined by crude ^{1}H-NMR analysis, using 1,3,5-trimethoxybenzene as internal standard. *Meta* figure refers to a mixture of *mono* and di*meta*.

This intriguing selectivity with **dtbpy** in cyclohexene is, however, not general. On the introduction of an *ortho* substituent, the reaction becomes non-selective. All substrates were examined under these conditions and found to be non-selective. Selected examples are illustrated in Figure 11.[24]

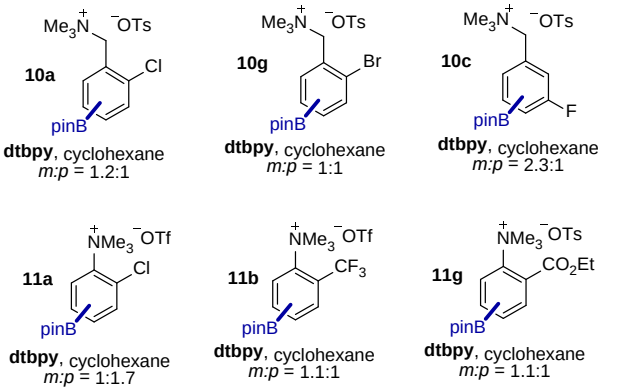


Figure 11 Borylation of *ortho*-substituted quaternary ammonium salts with dtbpy in cyclohexane universally resulted in poor selectivity.

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.

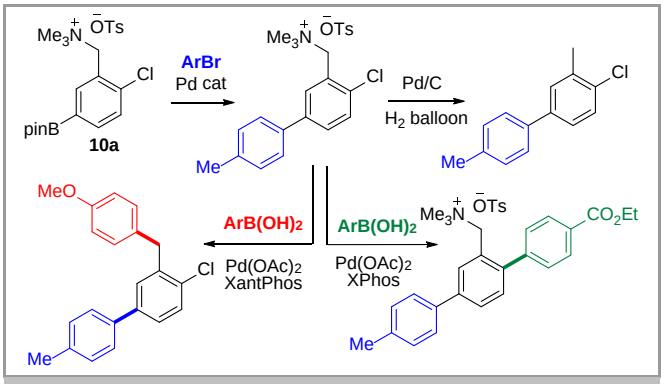


Figure 12 Cross-coupling of borylation product **10a**

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

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