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Ion Pair-Directed Regiocontrol in Transition-Metal Catalysis: A Meta-Selective C−H Borylation of Aromatic Quaternary Ammonium Salts

Holly J. Davis, Madalina T. Mihai, and Robert J. Phipps*

Department of Chemistry, University of Cambridge, Lensfield Road, Cambridge CB2 1EW, United Kingdom

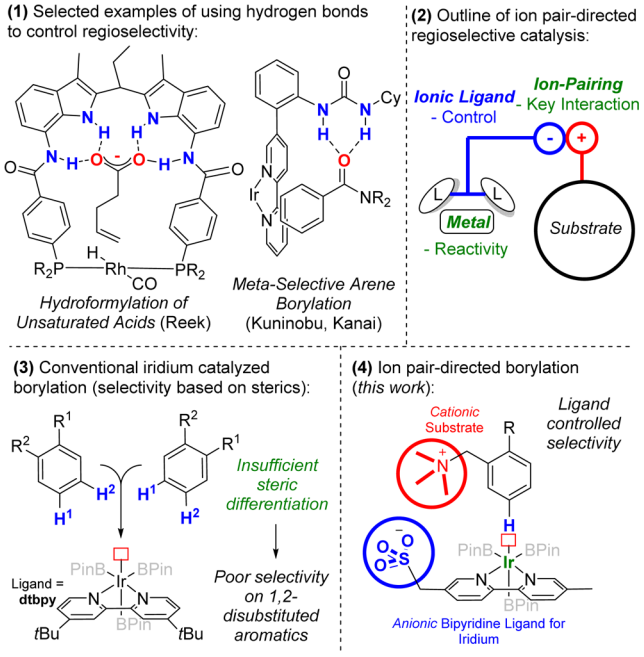
Supporting Information

ABSTRACT: The use of noncovalent interactions to direct transition-metal catalysis is a potentially powerful yet relatively underexplored strategy, with most investigations thus far focusing on using hydrogen bonds as the controlling element. We have developed an ion pair-directed approach to controlling regioselectivity in the iridium-catalyzed borylation of two classes of aromatic quaternary ammonium salts, leading to versatile meta-borylated products. By examining a range of substituted substrates, this provides complex, functionalized aromatic scaffolds amenable to rapid diversification and more broadly demonstrates the viability of ion-pairing for control of regiochemistry in transition-metal catalysis.

The use of noncovalent interactions to direct transition-metal catalysis is a potentially powerful yet relatively underexplored strategy, particularly for addressing issues of regioselectivity in synthetic chemistry. Alongside hydrogen bonds, ion-pairing interactions have emerged as a powerful tool for control of enantioselectivity,[1] but an equally important aspect in which careful control is required is regioselectivity. Important advances have demonstrated that multiple hydrogen bonds are able to provide precise molecular recognition in particular situations,[2] delivering regioselectivity in reactions such as site-selective oxygenation of sp^3 C−H bonds,[3] regioselective hydroformylation of unsaturated carboxylic acids,[4] and most recently, regioselective arene borylation,[5] among others (Chart 1, eq 1).[6] In contrast to this, ion-pairing interactions have not been explored in the context of addressing regioselectivity challenges. If, however, a single electrostatic interaction could be successfully employed to position a reactive metal center via dynamic ion exchange, this could help to reduce the need for a synthetically elaborate "receptor" portion of the catalyst, potentially increasing both practicality and generality (Chart 1, eq 2). It is possible that the perceived lack of directionality of ion pairs when compared with single and particularly multiple hydrogen bonds has inhibited their investigation thus far. Here, we demonstrate ion-pairing to be a viable approach to address issues of regiocontrol in the iridium-catalyzed borylation of aromatic C−H bonds.

Arguably the most common problem of regioselectivity is encountered in functionalization of arenes, making this an ideal forum to test our ion-pairing approach. Iridium-catalyzed C−H borylation stands apart in that regioselectivity is largely controlled by sterics, as opposed to electronics or proximity.[7] Consequently, it is very powerful for functionalization of 1,3-disubstituted arenes. However, monosubstituted or 1,2-disubstituted arenes generally give inseparable mixtures of isomers (Chart 1, eq 3), unless a particular substituent can direct either ortho[6c,8] or meta,[9] or a bulky ligand favor para.[10,11] In particular, accessing the meta position is desirable due to the relative paucity of methods to access this position, despite recent interest.[5,9,12] To address this, we sought to investigate cationic arene substrates in iridium-catalyzed borylation, anticipating that the charged center would be able to ion pair with an anionic bifunctional ligand (Chart 1, eq 4). Quaternary ammonium salts are readily accessed, and many methods exist for their elaboration in sp^2, sp^3, and heteroatom cross coupling,[13] reduction,[14] conversion to boronate esters,[13d,15] partners for C−H activation,[16] displacement with ^{18}F,[17] and [1,2] and [2,3] rearrangement chemistry[18] among others. In approaching the design of a suitable ion-pairing ligand, we began by elaborating an example of the basic transition state for iridium-catalyzed borylation, as calculated by Singleton, Maleczka, Smith et al.[6c,19] By modifying the structure to append a sulfonate-bearing tether onto the bipyridine back-

Chart 1



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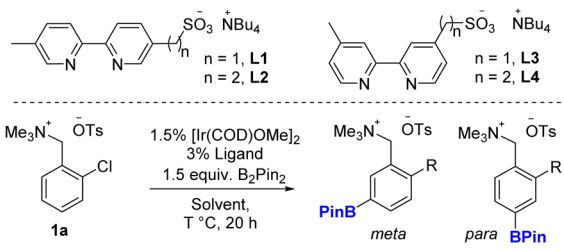
bone, a productive ion-pairing interaction appears plausible with a quaternized benzylamine substrate undergoing C−H oxidative addition at the meta-position. On alkylammonium salts, the positive charge is spread over the methyl/methylene units directly adjacent to the nitrogen,[20] and thus it is possible that less conventional interactions such as C−H−O hydrogen bonds could provide directionality at close proximity.[21] We synthesized anionic bipyridine ligand **L1** in only two steps from inexpensive, commercial material.[22] Using quaternized 2-chlorobenzylamine (**1a**) as a test substrate, conventional ligand **dtbpy** gave poor levels of selectivity in both THF and cyclohexane (Table 1, entries 1 and 2), although in THF, a

Table 1. Evaluation of Ligands on Substrate 1a

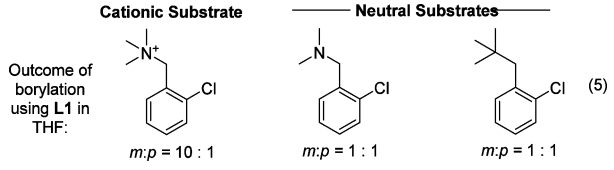


entry	solvent	ligand	T	conv.[a]	meta:para[a]
1	cyclohexane	**dtbpy**	50	24	1.1:1
2	THF	**dtbpy**	50	98	1:2.4
3	THF	**L1**	50	96	10:1
4	THF	**L2**	50	100	3.5:1
5	THF	**L3**	50	100	1.8:1
6	THF	**L4**	50	100	1.1:1
7	cyclohexane	**L1**	70	<5	–

[a]Determined by ^{1}H NMR analysis with reference to an internal standard.

small preference for the para position was observed. Pleasingly, using **L1** instead of **dtbpy** gave 10:1 selectivity for the meta position (entry 3). A ligand with a longer linker (**L2**) and isomers where the linker extends from the 4-position (**L3** and **L4**) all gave poorer selectivity (entries 4 to 6), and **L1** gave very low conversion in cyclohexane, even at 70 °C (entry 7).

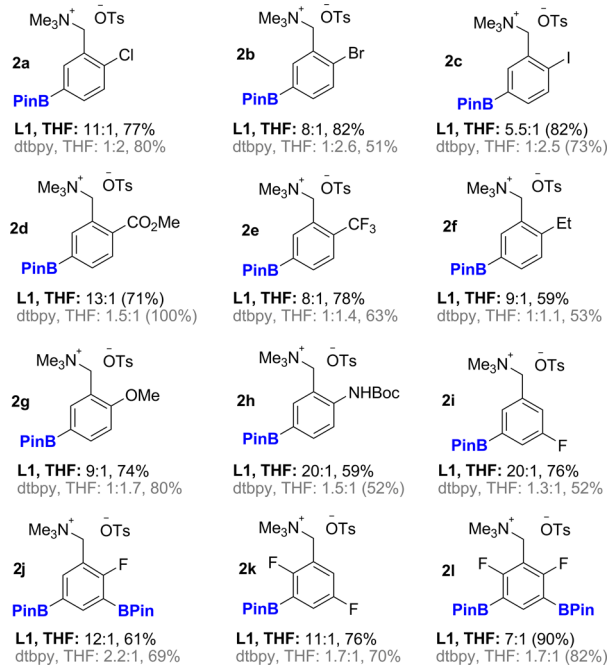
Control experiments with two neutral surrogates for **1a** gave poor selectivity with **L1**, demonstrating the importance of the positive charge on the substrate and supporting the ion pairing hypothesis (eq 5).[22] Also, the addition of varying amounts of



Bu_4NOTs to the borylation of **1a** using **L1** led to some decrease in the meta-selectivity, potentially due to the excess Bu_4N^+ displacing the substrate as ligand counterion and a subsequent increase in nondirected borylation.[22]

With regard to scope of the transformation (Scheme 1), a variety of substituents are tolerated in the ortho position including halogens (**2a**−**2c**), electron-withdrawing (**2d** and **2e**) and electron-donating (**2f** and **2g**) groups. A Boc-protected amine is also compatible (**2h**). Meta-fluoro substrate **2i** gives high selectivity with **L1**, and an ortho-fluoro results in diborylation via initial borylation at the 5-position (**2j**).

Scheme 1. Substrate Scope for Ion Pair-Directed Borylation of Quaternized Benzylamine Derivatives[a]



[a]Typically: Substrate (0.25 mmol), B_2Pin_2 (0.375 mmol), [Ir(COD)-OMe]$_2$ (1.5 mol %), ligand (3 mol %), solvent (0.2 M), 50−70 °C (see SI for details). Yields shown are isolated except where shown in parentheses (NMR yields with reference to internal standard). Isomeric ratios are meta:para taken from analysis of crude ^{1}H NMR spectra.

Substrates **2k** and **2l** demonstrate that our ion-pairing ligand is able to "reach past" ortho-fluoro substituents in both cases to impart high selectivity in the first borylation. Indeed, in **2l** borylation occurs preferentially adjacent to the fluorine (meta) rather than in the less hindered para-position. In all cases, poor selectivity was observed with standard borylation ligand **dtbpy**. The products were isolated by precipitation from ether, except in several cases where the products decomposed upon isolation; in these few cases, yields were determined by NMR with reference to an internal standard.

We next investigated whether aniline-derived quaternary ammonium salts may exhibit similar trends (Scheme 2). While we were concerned that moving the arene one carbon closer to the ammonium group could disrupt the selectivity, basic modeling suggested that this substrate class also looked viable according to our hypothesis, since there are a number of different ways in which the cationic substrate and anionic ligand can plausibly associate. In the event, anionic ligand **L1** again proved to be a powerful meta-director and provided good to excellent selectivity in most cases, far superior to analogues **L2**−**L4**.[22] As before, the scope was found to be broad with respect to functionality tolerated with electron-withdrawing (**4a**−**4c**), -donating (**4d**−**4f**), halogens (**4a**), and aromatic groups (**4g**).[23] Heterocyclic substrates (**4h** and **4i**) had a propensity for diborylation due to the reduced steric demand of the aliphatic ring, although **4h** could be stopped at the mono. Several fluorine-containing substrates underwent selective borylation using **L1** (**4j** and **4k**). Furthermore, borylation to give **4a** could be carried out efficiently on gram scale. We also investigated aromatic heterocyclic substrates (Scheme 3). 2-

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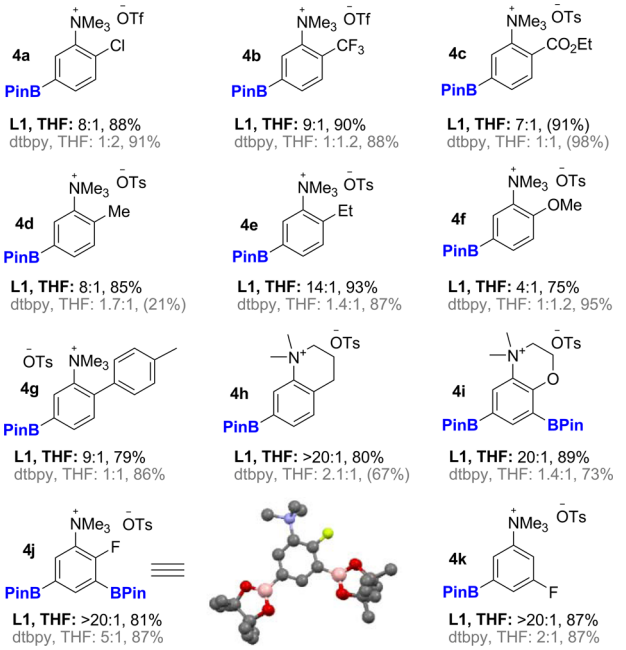
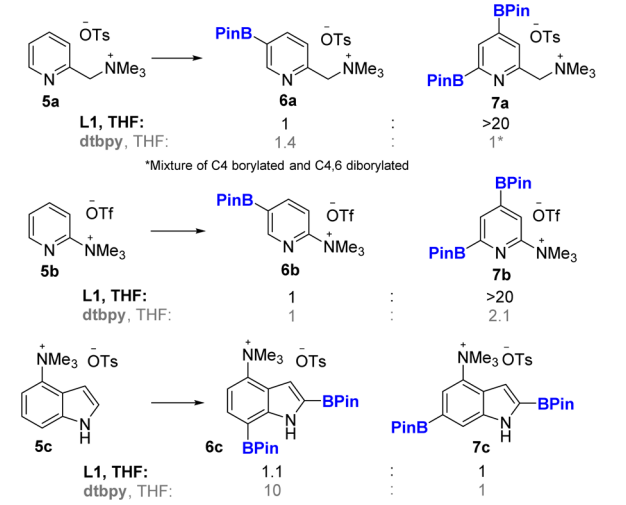
Scheme 2. Substrate Scope for Ion Pair-Directed Borylation of Quaternized Aniline Derivatives



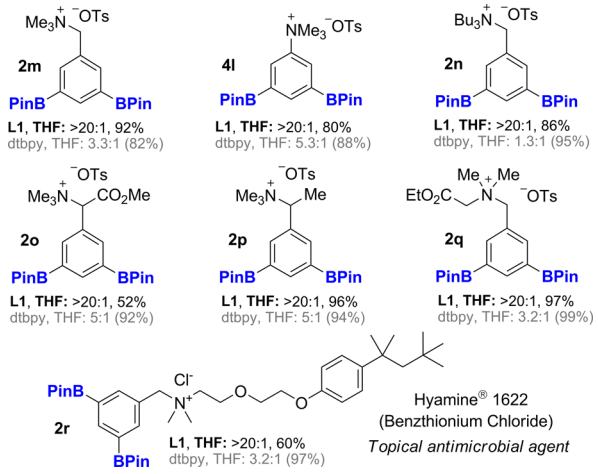
Scheme 3. Borylation of Aromatic Heterocycles



Substituted pyridines generally give mixtures upon borylation and with **dtbpy** pyridyl ammonium salts **5a** and **5b** gave nonselective 5- and 4,6-diborylation.[24] In the latter case, borylation at C4 occurs initially but is followed by a facile second borylation at C6.[24b] Using **L1** in both cases leads to very high selectivity for the 4,6-diborylated product, indicating high levels of regiocontrol over C4 vs C5 borylation. Free NH indoles are established to undergo initial borylation at the 2-position, followed by a second directed borylation at the C7 position due to a directing effect of the N-heteroatom.[24a,25] On substrate **5c**, the 2,7 diborylated isomer was the predominant product with **dtbpy**. Despite the innate substrate direction to C7, **L1** was able to significantly affect the regiochemical outcome, and roughly equal amounts of C2,6 and C2,7 diborylated isomers were obtained.

We examined a selection of derivatives without arene substituents, which resulted in symmetrical diborylation with >20:1 selectivity in all cases using **L1** (Scheme 4).[26] As well as unsubstituted versions of earlier substrates (**2m** and **4l**), this

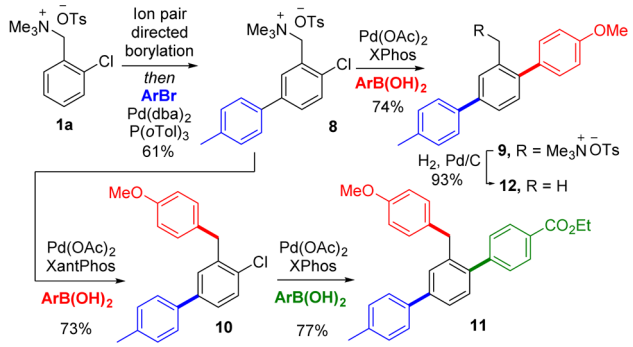
Scheme 4. Diborylation of Unsubstituted Arenes



includes a substrate quaternized with butyl groups (**2n**), benzylammonium salts with α-substitution (**2o** and **2p**), and a glycine-derived ammonium salt (**2q**). We also demonstrate application to the meta-selective diborylation of the antimicrobial surfactant benzthionium chloride (**2r**).

To demonstrate the utility of our products, which contain up to three orthogonal handles for cross-coupling, we carried out a borylation/Suzuki coupling of **1a** and used this as the basis for two subsequent palladium-catalyzed cross couplings in an iterative manner (Scheme 5). Notably, we discovered that in

Scheme 5. Application to Iterative Cross-Coupling



compound **8**, the ammonium functionality can be selectively coupled with a boronic acid in the presence of the chloride, using $Pd(OAc)_2$/Xantphos (**8** to **10**). Conversely, using XPhos selectively couples the chloride and leaves the ammonium untouched (**8** to **9**). This ligand-controlled chemoselectivity using palladium catalysis is significant, as previously only nickel catalysis has been used in coupling of benzyl ammonium salts with boronic acids, a protocol not tolerant of halide functionality, limiting application to sequential couplings.[13f] This discovery, together with the extensive cross-coupling literature,[13] provides ample opportunity for rapid diversification of the versatile aromatic structures accessible using this ligand-directed approach to borylation. Furthermore, the ammonium handle can be readily cleaved by hydrogenation, if desired (**9** to **12**).

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We have developed a readily accessed, anionic ligand that engages in a substrate−catalyst ion-pairing interaction to enable meta-selective borylation of two distinct classes of aromatic quaternary ammonium salts. The use of noncovalent interactions to control regioselectivity in transition-metal catalysis is an area of great potential. This study demonstrates the viability of ion-pairing as a powerful tool for the development of new regioselective transformations.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b08164.

Crystallographic data (CIF)

Experimental procedures and spectral data (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*rjp71@cam.ac.uk

Notes

The authors declare no competing financial interest.

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(26) Interestingly, several of these substrates gave higher than expected meta selectivity with **dtbpy** in THF (**2o**, **2p**, and **4l**). Switching to cyclohexane with **dtbpy** as ligand gave unexpectedly high meta selectivity for these compounds, albeit in generally low conversion to mixtures of mono and diborylated compounds. The substrates in Schemes 1−3 were found to give poor selectivity using dtbpy/cyclohexane, demonstrating that this unusual effect was not general and restricted to substrates with no arene substituents. For further details and screening of **1a** and **1m** against a range of bipyridine ligands in cyclohexane to probe this, see SI.

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