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Control of *meta*-selectivity in the Ir-catalyzed aromatic C-H borylation directed by hydrogen bond interaction: A combined computational and experimental study

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ABSTRACT

The origin of regioselectivity in *meta*-selective C-H borylation of benzamides directed by hydrogen bond interaction between ligand and substrate is elucidated through combined computational and experimental studies. We discover that a non-directed pathway, in which the urea moiety in ligand recognizes the O atom in Bpin instead of substrate, competes with the directed pathway and erodes the *meta*-selectivity. The non-directed pathway is sensitive to steric repulsion between Bpin and urea, and thus can be impeded by introducing a bulky substituent into the urea moiety. Accordingly, we optimize the ligand and improve the *meta*-selectivity in the Ir-catalyzed C-H borylation of some previously reported unsuccessful arenes.

Regioselective C–H bond activation of arenes provides an efficient approach for obtaining functionalized aromatics in organic synthesis [1–3]. The directed *ortho*-selective C–H functionalization of arenes is well established through transition-metal catalysis [4–7]. Compared with proximal *ortho*-C-H bonds, the *meta*- and *para*-C-H bonds are away from the directing group but are adjacent to each other, leading to more difficulties in achieving the high regioselectivity [8,9]. In recent years, quite a few elegant methods are developed to control remote selective C–H activation, such as σ-bond activation-assisted functionalization [10–13], template strategy [14–22], noncovalent interaction direction [23–33], Pd(II)/norbornene cooperative catalysis [34–36], traceless directing group strategy [37], and catalyst or reagent controlled strategy [38–43]. Recently, noncovalent interaction directed iridium-catalyzed borylation becomes a robust approach [44–47] because the borylated products can be served as versatile synthetic building blocks in chemical and industrial synthesis [48–51].

In 2015, Kanai and coworkers reported a *meta*-selective C–H borylation of arenes using a bipyridine-derived ligand with a urea moiety [23]. Aromatic amides, phosphonates and phosphine oxides are suitable for this reaction, but the ratios of *meta*-selectivity highly depend on the substrates, ranging from 30:1 to 0.5:1. The authors claimed that hydrogen bond interaction between ligand and substrate placed the iridium center in close proximity to the *meta*-C-H bond of substrates and controlled the regioselectivity (Fig. 1A). The mechanism of Ir-catalyzed C–H borylation of arenes has been established by Sakaki [52], Hartwig [53], Houk [54] and Ke [55] groups, in which the rate-determining step is C–H bond oxidative addition (Fig. 1B). Sunoj and coworkers reported a computational study on Kanai's work, and they also proved that the aromatic C–H activation is the regioselectivity-determining step. In addition, they demonstrated that the observed high *meta*-selectivity was predominantly attributed to a good number of noncovalent interactions between catalyst/ligand and substrate [56]. However, through a combined computational and experimental study, we found that the origin of *meta*-selectivity is much more complex than expected.

We first explored the electronic effect of substituents in the urea moiety of ligand to validate the important role of hydrogen bond interaction in controlling regioselectivity. We used 2,2′-bipyridine (bpy) as ligand to evaluate the intrinsic borylation selectivity of benzamide **1a**, which gave a *meta* to *para* ratio of 0.7:1 (Fig. 2). Meanwhile, ligands **L1**-**L5** were synthesized and tested in the iridium-catalyzed borylation of benzamide **1a**. As shown in Fig. 2, for **L1** and **L2**, with electron-donating groups (OMe and Me), the ratios of *meta* to *para* were 2.9:1 and 3.2:1, respectively. For ligand **L3**, a slightly increased *meta*-selectivity (3.9:1) was observed. However, ligands **L4** and **L5** with electron-withdrawing groups (Cl

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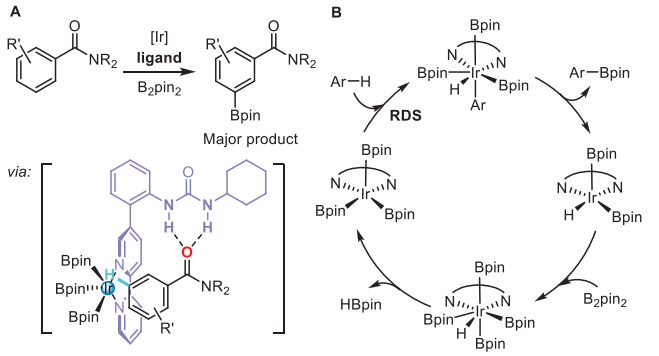


Fig. 1. (A) Hydrogen bond interaction directed *meta*-selective C-H borylation proposed by Kanai and coworkers. (B) Catalytic cycle for the Ir-catalyzed borylation of arenes using B_2pin_2.

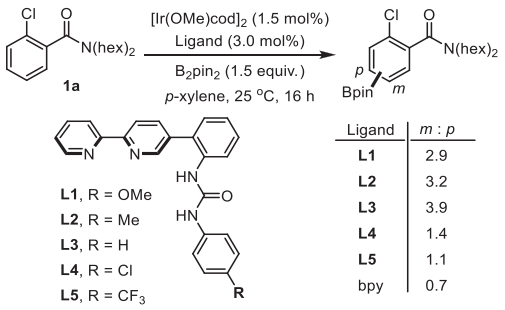
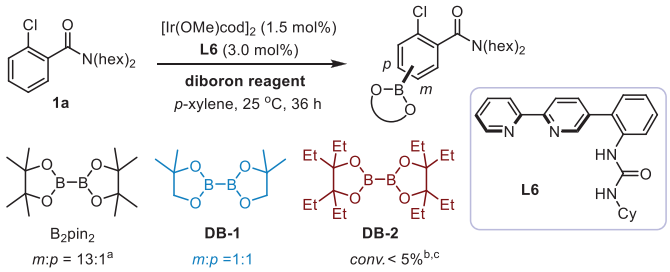


Fig. 2. The electronic effect of substituents in the urea moiety of ligand on the regioselectivity.

and CF_3) exhibited even lower *meta*-selectivities (1.4:1 and 1.1:1). Especially for **L5**, the selectivity of borylated products was very close to that using bpy ligand without hydrogen bond interaction. It is well known that ureas bearing electron-withdrawing groups are better hydrogen bond donors than those with electron-donating groups, and it should enhance the hydrogen bond interaction between ligand and substrate [57]. With stronger hydrogen bonds, the *meta*-selectivity would have been further improved, rather than becoming much worse. What is the deeper reason behind this unusual experimental phenomenon?

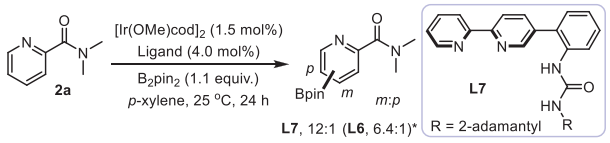
To answer this question, DFT calculations were conducted using **L5** as ligand (Fig. 3). According to Kanai's hydrogen bond recognition model shown in Fig. 1A, we located the *meta*- and *para*-C-H activation transition states **TS1-meta** and **TS1-para** directed by hydrogen bond interaction. Computational results showed that the free energy of **TS1-meta** is 3.6 kcal/mol lower than that of **TS1-para**, implying that **L5** favors *meta*-selectivity greatly. This result was obviously inconsistent with our experimental data, in which only 1.1:1 of *meta* to *para* selectivity was obtained. We then conducted extensive conformational search and discovered another two non-directed transition states **TS1-meta-ND** and **TS1-para-ND** with even lower energies, which were not reported in previous study by Sunoj and coworkers [56]. In the non-directed pathway, the urea moiety in ligand recognizes the O atom in Bpin bound to iridium center *via* N–H···O hydrogen bonding, rather than the C=O group in substrate. Taking these four transition states into account (Fig. 3), it is now clear that the non-directed **TS1-meta-ND** and **TS1-para-ND** control the ratio of the *meta*- and *para*-borylated products. As their free energy difference is only 0.6 kcal/mol, predicting an approximate 1:1 mixture of *meta*- and *para*-borylated products, this is in good agreement with the experimental result (**L5**, m:p = 1.1, Fig. 2). These calculations indicated that the previously overlooked non-directed pathway played a critical role in determining regioselectivity, even overriding the directed pathway.



Scheme 1. Influence of diboron reagents on regioselectivity. [a] data from Ref. [23]. [b] Conversion of **1a**. [c] At 50 °C, m:p = 0.5:1, 90% conversion of **1a**.

As shown in Scheme 1, Kanai and coworkers reported that, in the presence of B_2pin_2, the borylation of **1a** gave a 13:1 ratio of *meta* to *para* using ligand **L6** [23]. We speculated that the non-directed pathway would also exist in this case, and that it would become predominant when the B_2pin_2 was replaced by a smaller diboron reagent, which favors the hydrogen bond interaction between the boron group and the urea moiety of ligand, leading to deteriorated *meta*-selectivity. To test the steric effect of the boron group, DFT calculations were carried out using the less bulky diboron reagent **DB-1** (Scheme 1), and four transition states were located (Fig. 4). As expected, both non-directed transition states **TS2-meta-ND** and **TS2-para-ND** had lower free energies than two directed transition states **TS2-meta** and **TS2-para**, indicating that the regioselectivity was again determined by the non-directed pathway. The negligible energy difference of 0.2 kcal/mol predicted a poor regioselectivity. To confirm this prediction, **DB-1** was synthesized and tested using the same ligand **L6**. Indeed, it delivered *meta*- and *para*-borylated products as a 1:1 isomeric mixture (Scheme 1). On the other hand, the diboron reagent with bulkier substituent was also investigated. B_2Epin_2 (**DB-2**), a more stable boronic ester than B_2pin_2, was synthesized *via* two steps from 3-pentanone according to a known procedure [58]. Unfortunately, B_2Epin_2 exhibited poor reactivity in the borylation of **1a** using **L6** (conv. < 5%). Therefore, ligand evolution may be a more promising approach to improve the *meta*-selectivity.

With the computational and experimental results in hand, we then focus on how to utilize our findings to improve the previously reported suboptimal results. Kanai and coworkers reported the borylation of heteroaromatic amide **2a** using **L6** as ligand, which gave a moderate regioselectivity (m:p = 6.4:1, Scheme 2). We located the *meta*- and *para*-C-H activation transition states of this reaction (Fig. 5A). Among them, **TS3-meta** and **TS3-para-ND** were responsible for generating the *meta*- and *para*-borylated product. The preference of *meta*- over *para*-C-H borylation is 1.2 kcal/mol, in accordance with the reported selectivity (m:p = 6.4:1). Due to its more electron-withdrawing aromatic ring, amide **2a** is a poorer hydrogen bond acceptor than benzamide. As a result, its carbonyl group has less advantage against the O atom of Bpin to interact with the urea moiety of ligand, further favoring the non-directed pathway. We envisioned that, through increasing the steric repulsion be-



Scheme 2. Steric effect of ligands on the *meta*-selective borylation of **2a**. * data from Ref. [23].

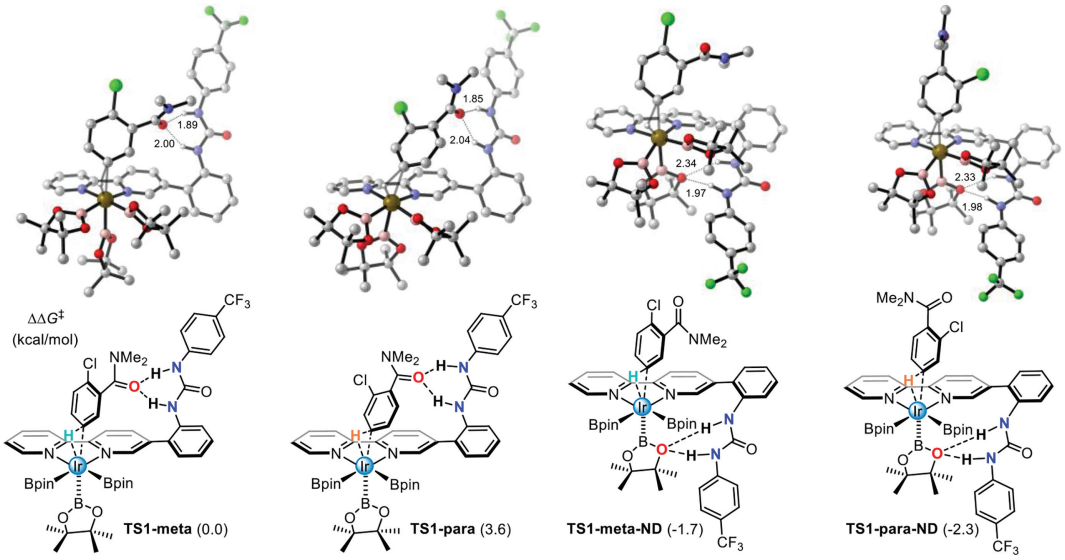


Fig. 3. DFT-computed geometries and Gibbs free energies for the C-H activation transition states of **1a-Me** using B_2pin_2 and **L5** as ligand, computed with SMD(*p*-xylene)-ωB97X-D/6–311+G(d,p)[SDD for Ir]//M06/6–31G(d)[SDD for Ir]. For improved clarity, most hydrogen atoms are omitted. All distances are in Å.

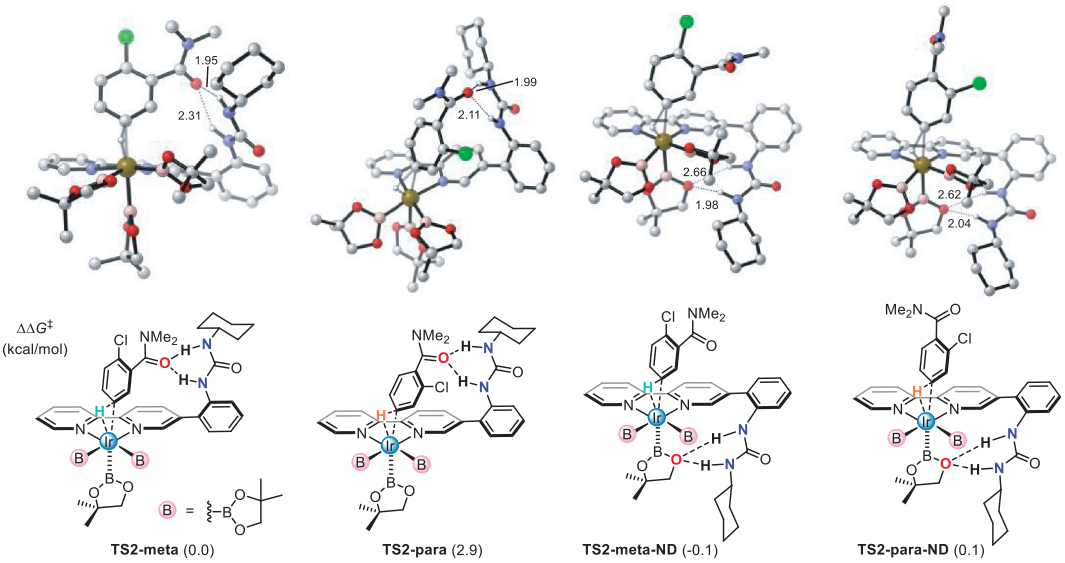


Fig. 4. DFT-computed geometries and Gibbs free energies for the C–H activation transition states of **1a-Me** using **DB-1** and **L6** as ligand, computed with SMD(*p*-xylene)-ωB97X-D/6–311+G(d,p)[SDD for Ir]//M06/6–31G(d)[SDD for Ir]. For improved clarity, most hydrogen atoms are omitted. All distances are in Å.

tween the urea moiety of ligand and the Bpin group bound to iridium center, the non-directed pathway would be inhibited. Therefore, we changed the cyclohexyl to a much bulkier 2-adamantyl and designed ligand **L7**. Further DFT calculations showed that the steric repulsion between the urea moiety and Bpin increased the energies of non-directed transiton states **TS4-meta-ND** and **TS4-para-ND** by 3–5 kcal/mol, impeding the non-directed pathway effectively (Fig. 5B). Meanwhile, as the free energy of directed transition state **TS4-meta** is much lower than those of three other transition states, a higher *meta*-selectivity is anticipated. When the 2-adamantyl-bearing ligand **L7** was synthesized and used in the C–H borylation reaction, it indeed gave a higher selectivity (m:p = 12:1, Scheme 2). This realized the control of *meta*-selectivity through inhibiting the non-directed *para*-C-H borylation by inceasing the size of substituent on the urea moiety.

Encouraged by this positive result, ligand **L7** was used for the substrates with poor *meta*-selectivities in Kanai's work (Scheme 3) [23]. In the borylation of benzamide **3a**, a 6.9:1 ratio of *meta* to *para* was reported by using **L6**, while an enhanced selectivity (m:p = 12:1) was obtained by using our ligand **L7**. Previously, *N*-methylisoindolin-1-one **4a** showed a *meta*-regioselectivity of only 3.3:1. This selectivity was as high as 15:1 when **L7** was used as ligand. Finally, for aryl phosphonate **5a**, the *para*-borylated product was generated as major product (m:p = 0.5:1) using **L6**, which was similar to the result using dtbpy, a typical ligand exhibiting intrinsic selectivity of substrates in the Ir-catalyzed borylation [59,60]. Significantly, our ligand **L7** enabled the *meta*-selective borylation of **5a**, delivering the desired *meta*-product with a high selectivity (m:p = 12:1).

In summary, this work combines calculations and experiments to elucidate the origin of regioselectivity in hydrogen bond interaction directed *meta*-selective C–H borylation of benzamides. The non-directed pathway, in which the ligand recognizes Bpin instead of substrate, is disclosed. We find that the non-directed *para*-borylation pathway plays an important role in controlling regioselectivity through competing with the *meta*-borylation path-

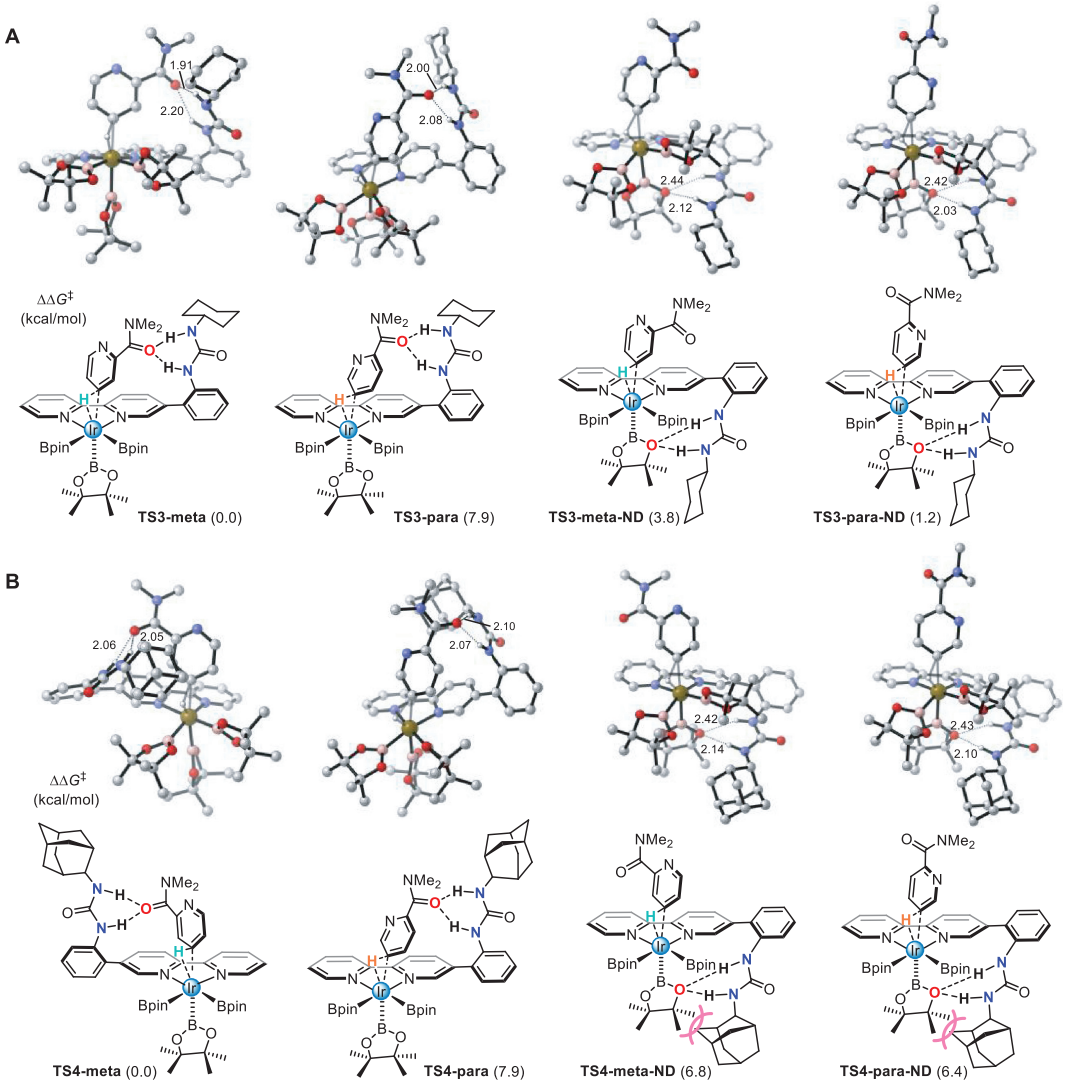
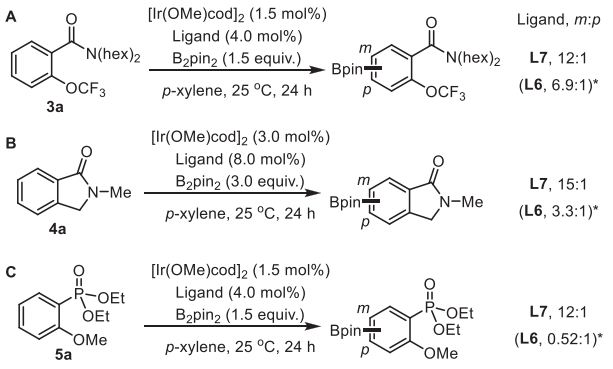


Fig. 5. DFT-computed geometries and Gibbs free energies for the C–H activation transition states of **2a** using B_2pin_2 and **L6** or **L7** as ligand, computed with SMD(*p*-xylene)-*ω*B97X-D/6–311+G(d,p)[SDD for Ir]//M06/6–31G(d)[SDD for Ir]. For improved clarity, most hydrogen atoms are omitted. All distances are in Å.



Scheme 3. The comparison of *meta*-selectivity in the C–H borylation of arenes by using ligands **L6** and **L7**. * data from Ref. [23].

ways. This study demonstrates that the electronic and steric effects of ligand and the size of diboron reagent affect the regioselectivity by tuning the barriers of directed and non-directed pathways. Based on these findings, the ligand is improved and applied into some previously reported unsuccessful arenes, giving excellent performance. This work is a cornerstone of our ligand design in the remote C–H activation, which leads to the tunable *meta*- and *para*-selective C–H borylation of arenes bearing a variety of multi-transformable directing groups [61,62].

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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