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A *meta*-selective C–H borylation directed by a secondary interaction between ligand and substrate

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Regioselective C–H bond transformations are potentially the most efficient method for the synthesis of organic molecules. However, the presence of many C–H bonds in organic molecules and the high activation barrier for these reactions make these transformations difficult. Directing groups in the reaction substrate are often used to control regioselectivity, which has been especially successful for the *ortho*-selective functionalization of aromatic substrates. Here, we describe an iridium-catalysed *meta*-selective C–H borylation of aromatic compounds using a newly designed catalytic system. The bipyridine-derived ligand that binds iridium contains a pendant urea moiety. A secondary interaction between this urea and a hydrogen-bond acceptor in the substrate places the iridium in close proximity to the *meta*-C–H bond and thus controls the regioselectivity. ^{1}H NMR studies and control experiments support the participation of hydrogen bonds in inducing regioselectivity. Reversible direction of the catalyst through hydrogen bonds is a versatile concept for regioselective C–H transformations.

Regioselective transformations are important for efficient syntheses. Regioselectivity can be achieved by introducing activated functional groups such as halogens and triflates, but bypassing this step would be attractive. For this reason, C–H transformations have recently received increasing attention as efficient and ideal alternative reactions. C–H transformations require fewer reaction steps to attain the target molecule and generate less waste than conventional methods involving preactivation processes. However, it is usually difficult to realize regioselective C–H transformations except with special substrates bearing only one possible reaction site and/or a directing group. In the case of C(sp^2)–H transformations of aromatic rings, the use of directing groups generally produces only *ortho*-selective reactions[1–6]. The development of *meta*-selective transformations is very difficult, but synthetically useful[7]. Several pioneering examples of *meta*-selective transformations have been reported recently. First, iridium-catalysed C(sp^2)–H borylation and silylation afford a mixture of *meta*- and *para*-borylated and silylated products, respectively (Fig. 1a shows borylation)[8–14]. In the case of 1,3-disubstituted aromatic compounds, only *meta*-borylated (or silylated) products are obtained. In these reactions, the steric effects of substituents at the 1 and 3 positions control regioselectivity. Second, palladium-catalysed oxidative C(sp^2)–H alkenylation produces *meta*-alkenylated products (Fig. 1b)[15–17]. The regioselectivity is controlled by electronic effects, and aromatic compounds with electron-withdrawing group(s) and pyridines are used as substrates. Third, ruthenium-catalysed *meta*-selective C(sp^2)–H sulfonation[18] and alkylation[19] have been reported (Fig. 1c shows alkylation). These reactions proceed via the formation of an *ortho*-arylruthenium intermediate directed by the pyridyl group, followed by remote electrophilic aromatic substitution assisted by a strong *para*-directing effect from the ruthenium centre. Fourth, hypervalent iodine-mediated arylation affords *meta*-arylated products from aromatic amides and α-aryl carbonyl compounds (Fig. 1d)[20,21]. In Fig. 1b–d, regioselectivity is controlled by electronic effects. Fifth, palladium-catalysed oxidative alkenylation provides *meta*-selective alkenylated products (Fig. 1e)[22–24]. Regioselectivity is thus controlled by a well-designed directing group connected to the aromatic ring through a special long linker. Here, we report an iridium-catalysed *meta*-selective C–H borylation of aromatic amides, esters, phosphonates, phosphonic diamide and phosphine oxides controlled by hydrogen bonds, in which the hydrogen-bonding donor site of the ligand recognizes the hydrogen-bonding acceptor site of the substrate and orients the *meta*-C–H bond of the substrates to the catalytic site (Fig. 2)[25]. The directing group-controlled reaction (Fig. 1e) and the present hydrogen-bond-controlled reaction (Fig. 2b) are related: the directing group is covalently bound to the substrate in Fig. 1e, whereas the hydrogen-bonding ligand, required only in a catalytic amount, interacts reversibly with the substrate in Fig. 2b.

Results and discussion

To overcome the problems described above (Fig. 1a–e), we designed a new catalytic system in which a hydrogen-bond donor was appended to a metal-binding ligand such that a secondary interaction between this donor and a suitable hydrogen-bond acceptor in the substrate would place the metal centre of the catalyst in close proximity to the desired C–H group (Fig. 2b). We hypothesized that hydrogen bonding would be suitable for controlling the relative positions of the catalyst and the reaction site of the substrates because it has both the appropriate strength (not so strong that it would prevent catalyst turnover) and the directionality required.

To validate the catalytic system, we selected iridium-catalysed C(sp^2)–H borylation[9]. We used a bipyridine core as a ligand for C–H borylation[9] and a urea moiety as a hydrogen-bonding donor for the carbonyl groups[26] (Fig. 2b). To achieve high *meta*-selectivity, selection of the appropriate linker between the ligand for the transition metal and hydrogen-bonding site is important. Molecular

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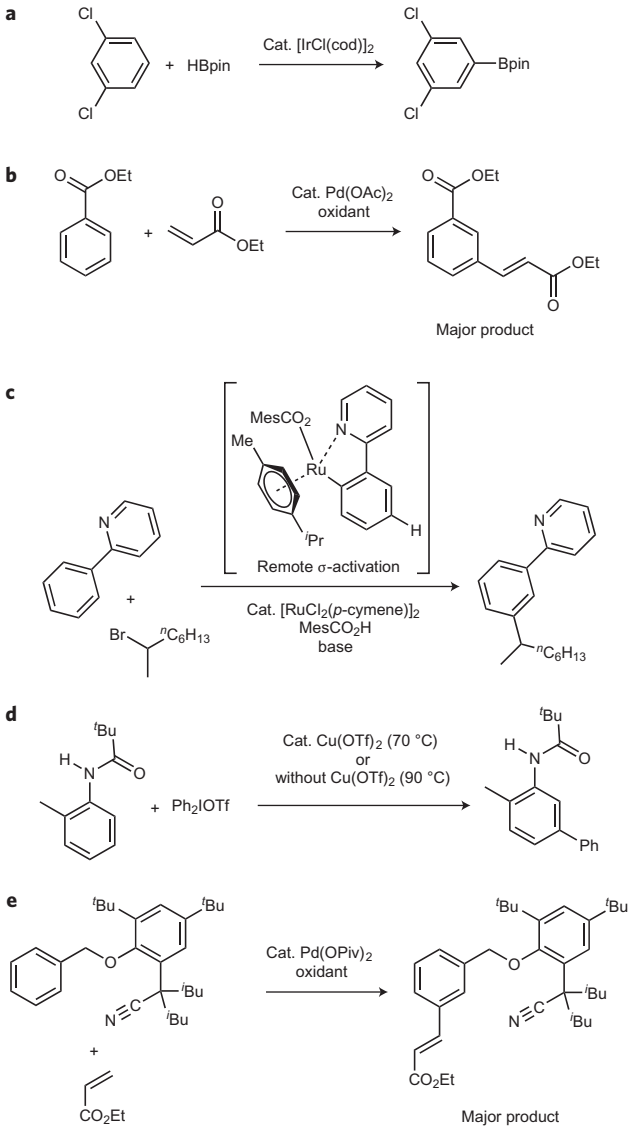


Figure 1 | *meta*-Selective C–H transformations. Regioselectivity is controlled by: **a**, steric effects; **b**, electronic effects; **c**, a strong para-directing effect from the ruthenium centre (electronic effects); **d**, electronic effects in hypervalent iodine-mediated arylation; **e**, a directing group.

modelling studies suggested that *ortho*-phenylene was a suitable linker. Based on this design, the catalytically active iridium centre should be placed in close proximity to a C–H bond at the *meta*-position of aromatic substrates.

We first investigated several known and designed ligands for iridium-catalysed C–H borylation (Table 1). Treatment of aromatic amide **1a** with bis(pinacolato)diboron (B_2pin_2, **2a**) in the presence of catalytic amounts of $[Ir(OMe)(cod)]_2$ (cod = cyclooctadiene) and a reported ligand (4,4′-di-*tert*-butyl-2,2′-bipyridine [dtbpy] or $(MeO)_2$bpy) gave a mixture of *meta*- and *para*-borylated products **6a** in moderate yield with low regioselectivity (*meta*/*para* = 1.9 and 1.4, entries 1 and 2). In a previous study, an iridium-catalysed reaction using *N*,*N*-diethylbenzamide as a substrate afforded a mixture of *ortho*-, *meta*- and *para*-borylated products with the *ortho*-borylated form as the major product[27]. The *meta*-selectivity was markedly higher when designed ligand **3a** was used (50% yield, *meta*/*para* = 8.3, entry 3). In this case, however, the *ortho*-borylated product was not detected by ^{1}H NMR and gas chromatography (GC) analyses of a crude mixture. Compared with **3a**, other substituents on the urea moiety (ligands **3b**–**3f**) did not improve the *meta*/*para* ratio (entries 4–8). The borylation reaction did not proceed using ligand **3g** (bearing a thiourea moiety, entry 9). When ligand **3a** in *p*-xylene solvent was used, the *meta*/*para* ratio increased to 27, whereas the yield of **6a** slightly decreased (entry 10). The *ortho*-phenylene linker is important for high *meta*-selectivity. When using a methylene or phenylethynylene linker (ligands **4** and **5**), the *meta*/*para* ratio was low or the borylation reaction did not proceed (entries 11 and 12). When the amounts of diboron **2a**, $[Ir(OMe)(cod)]_2$ and **3a** were increased, the yield of **6a** also increased, but the *meta*/*para* ratio decreased (entry 13). The borylation reaction did not proceed in the absence of **3a**.

We then investigated the substrate scope of the borylation reaction (Table 2). In all cases of *ortho*-mono-substituted aromatic amides **1b**–**1j**, regioselectivity was greatly improved by **3a** (condition A; upper row) compared with dtbpy (condition B; lower row) and the corresponding *meta*-mono-borylated products **6b**–**6j** were obtained in moderate to excellent yields. The borylation reaction exhibited high functional group tolerance with methoxy, bromo, chloro, fluoro, trifluoromethyl, trifluoromethoxy and methoxycarbonyl groups, which remained unchanged during the reaction. The *meta*-selective borylation reaction also proceeded when the substituents on the amide nitrogen atom were changed (**1k**–**1n**). Interestingly, the yield of product **6m** was drastically increased by **3a** compared with dtbpy. Although product **6o** was obtained when bis(hexylene glycolato)diboron (**2b**) was used as a borylation reagent, the yield and regioselectivity were decreased compared to when **2a** was used. In the case of *meta*-mono-substituted aromatic amides **1p**–**1s** and *ortho*- and *meta*-disubstituted aromatic amides **1t**–**1u**, only single products **6p**–**6u** were formed with both ligands **3a** and dtbpy. The borylation of heteroaromatic amides **1v**–**1z** proceeded regioselectively to afford **6v**–**6z** and, in some cases, **3a** improved regioselectivity compared with dtbpy. Because regioselective borylation proceeded from both six- and

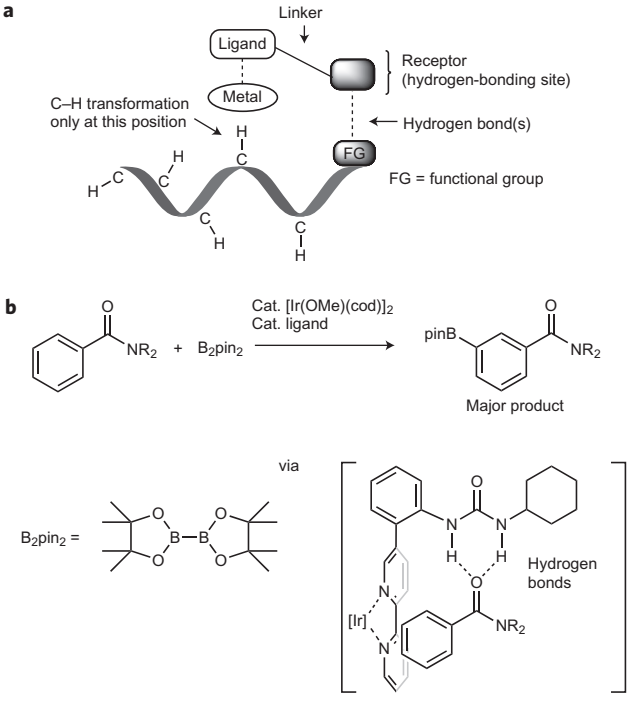
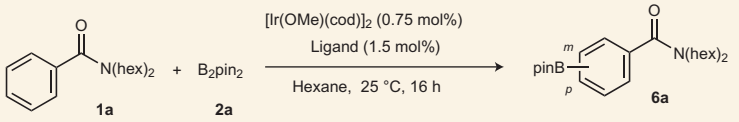


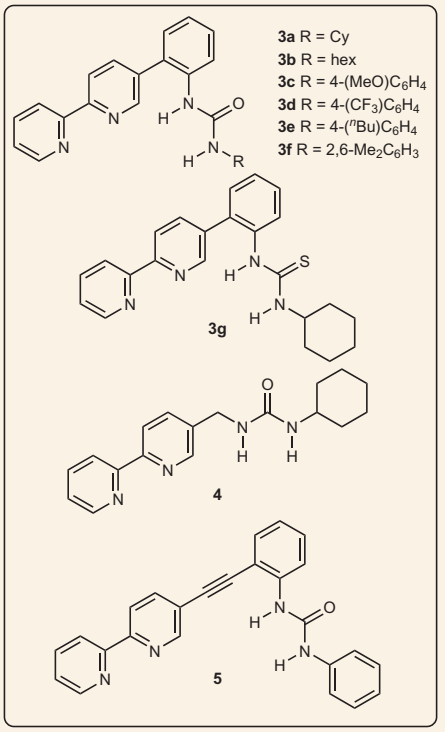
Figure 2 | Concept of regioselective C–H transformations controlled by a hydrogen-bonding secondary interaction between ligand and substrate. **a**, Design of catalytic systems for regioselective C–H transformations. **b**, Hydrogen-bond-controlled *meta*-selective C–H borylation as a possible proof of concept (this work).

Table 1 | Structures of new ligands for *meta*-selective C–H transformations and their application to iridium-catalysed borylation.



1a 2a 6a

Entry	Ligand	Yield (%)* (mono)	Ratio of *meta* to *para**	Yield (%)* (di)†	Recovery of 1a (%)*
1‡	dtbpy§	67	1.9	3	30
2	$(MeO)_2$bpy‖	52	1.4	4	44
3	**3a**	50	8.3	3	47
4	**3b**	31	7.4	0	69
5	**3c**	22	1.4	1	77
6	**3d**	31	7.2	1	66
7	**3e**	40	3.9	4	56
8	**3f**	32	3.6	0	68
9	**3g**	0	–	0	>99
10‡	**3a**	44	27	10	45
11‡	**4**	47	2.0	3	50
12‡	**5**	0	–	0	>99
13‡,¶	**3a**	51 (48)#	17 (19)**	22 (17)#	27



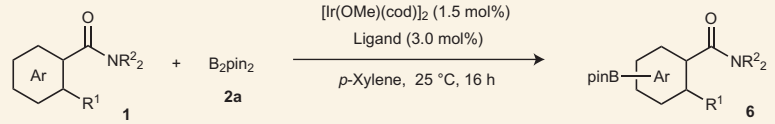
2a (0.75 equiv). *Determined by ^{1}H NMR using 1,1,2,2-tetrachloroethane as an internal standard. †*N,N*-Dihexyl-3,5-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide. ‡*p*-Xylene was used as a solvent. §dtbpy = 4,4′-di-*tert*-butyl-2,2′-bipyridine. ‖$(MeO)_2$bpy = 4,4′-dimethoxy-2,2′-bipyridine. ¶**2a** (1.0 equiv), [Ir(OMe)(cod)]$_2$ (1.5 mol%), **3a** (3.0 mol%). #Isolated yield. **Ratio of *meta* to *para* in the isolated product.

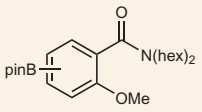
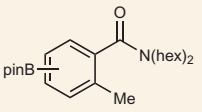
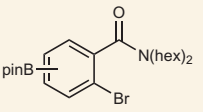
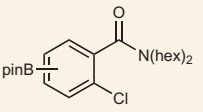
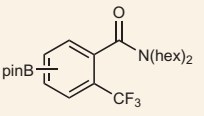
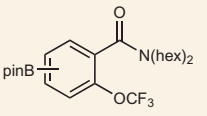
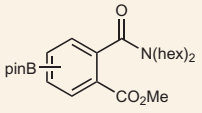
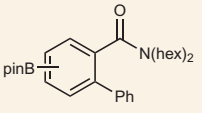
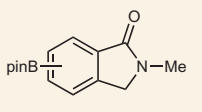
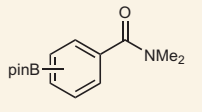
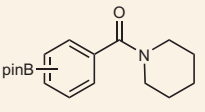
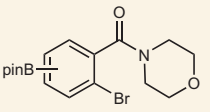
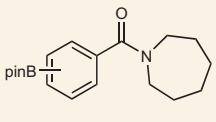
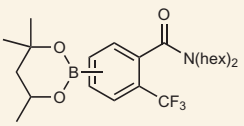
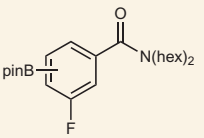
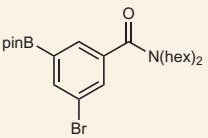
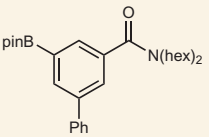
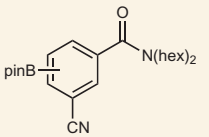
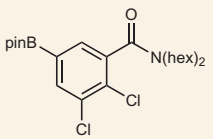
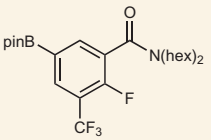
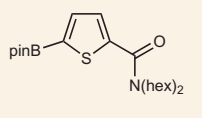
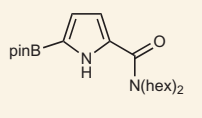
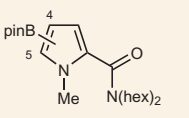
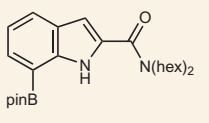
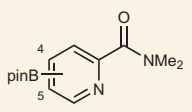
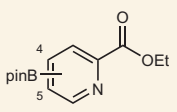
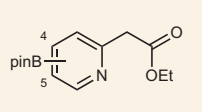
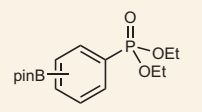
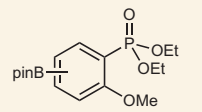
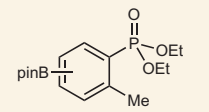
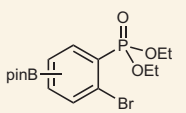
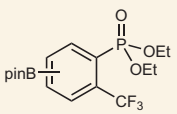
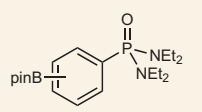
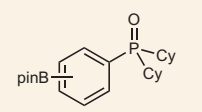
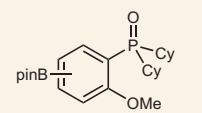
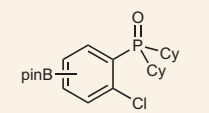
five-membered (hetero)aromatic amides, ligand **3a** must have the flexibility to accept several substrate types. Regioselective borylation also proceeded using aromatic esters **1A** and **1B**. In these reactions, the CF_3 group-substituted ligand **3d** led to higher regioselectivity than **3a** (**6A**, 98% yield [*meta*/*para* = 3.7]; **6B**, 94% yield [*meta*/*para* = 0.59]). C–H borylation also proceeded using aromatic phosphorus compounds, such as aryl phosphonates **1C**–**1G**, phosphonic diamide **1H** and phosphine oxides **1I**–**1K**, and the corresponding borylated products **6C**–**6K** were obtained with high *meta*-selectivity. In most entries, the total percentages of the yields of borylated products and recovered starting materials were almost quantitative. *N*,*N*-Dihexyl-2-naphthamide, *N*,*N*-dihexyl-2-(methylthio)benzamide and *N*,*N*-dihexyl-4-(trifluoromethyl)benzamide did not give the borylated products. In addition, the borylated products were not obtained using benzaldehyde, acetophenone and nitrobenzene.

The reaction mechanism of the iridium-catalysed borylation has been reported previously[28] and the present reaction probably proceeds via the same pathway. To confirm the importance of hydrogen bonding between the substrates and the urea moiety of ligand **3a** for the high regioselectivity, we conducted the following experiments. First, significant lower field shifts of the urea N–H protons of ligand **3a** were observed by ^{1}H NMR in the presence of substrate **1a** (Fig. 3a, entries 1–3)[29,30]. This finding strongly supports our notion that a hydrogen-bonding interaction occurs between **3a** and amide substrates. Second, borylation reactions were carried out using control ligands **3a-Me$_1$** and **3a-Me$_2$**, with the nitrogen atom(s) of the urea moiety protected by methyl group(s) (Fig. 3b). As a result, the *meta*/*para* ratio of the borylated products dramatically decreased compared with the use of **3a** and the ratio was almost the same as when using the dtbpy ligand. Consistent with this result, ^{1}H NMR revealed no significant chemical shift changes of the N–H proton of **3a-Me$_1$** in the presence of **1a** (Fig. 3a, entries 4–6). The regioselectivity was also low (*meta*/*para* = 1.0) when the reaction was carried out using another control ligand **3h**, which has the urea moiety at the *para*-position of the phenylene linker (Fig. 3b). This result indicates that the spatial arrangement of the bipyridine and urea moieties is crucial to furnish the high *meta*-selectivity. In addition, covalently connecting the bipyridine and urea moieties is indispensable for the high *meta*-selectivity. Thus, when a mixture of cyclohexylphenylurea and 2,2′-bipyridine was used, the *meta*/*para* ratio was comparable to that when using dtbpy (Fig. 3b, 2,2′-bipyridine + urea). This finding indicates that the intramolecularity of the bipyridine and urea moieties is important to bring the position of the iridium centre close to the *meta*-position of the substrate. Third, a high *meta*/*para* ratio was observed in nonpolar solvents (hexane, 60% yield, *meta*/*para* = 6.9; cyclohexane, 43% yield, *meta*/*para* = 29; *p*-xylene, 42% yield, *meta*/*para* ≥ 30; THF, 27% yield, *meta*/*para* = 3.5; *N*-methylpyrrolidone, 15% yield, *meta*/*para* = 2.8 for reactions of **1a** using **3a**), at a lower reaction temperature and under a higher concentration. These findings are consistent with the notion that hydrogen bonds between the amide group of substrates and the urea moiety of the ligand are key to controlling regioselectivity.

To demonstrate the utility of this reaction, we performed two experiments. The first involved a reaction that is practical and can be performed on a gram scale. Treatment of 1.00 g **1f** with **2a** produced 1.23 g **6f** in 90% yield (*meta*/*para* ≥ 30). The yield of **6f** in the gram-scale reaction was comparable to that shown in Table 2 (**1f**: 89.4 mg scale). In the second experiment, we performed a competition reaction between an amide and an ester using ligand **3a** or dtbpy. Treatment of a 1:1 mixture of amide **1k** and methyl benzoate and **2a** (1.5 equiv.) with catalytic amounts of [Ir(OMe)(cod)]$_2$ (1.5 mol%) and **3a** (3.0 mol%) in *p*-xylene at 25 °C for 16 h gave borylated-amide (**6k**) and -ester in 44% yield (*meta*/*para* = 21) and 16% yield (*meta*/*para* = 1.0), respectively. On the other hand, when catalytic amounts of [Ir(OMe)(cod)]$_2$ (1.5 mol%) and dtbpy (3.0 mol%) were used, borylated-amide (**6k**) and -ester were obtained in 7% yield (*meta*/*para* = 2.5) and 45% yield (*meta*/*para* = 1.0),

Table 2 | Regioselective aromatic C–H borylation controlled by hydrogen bonding.



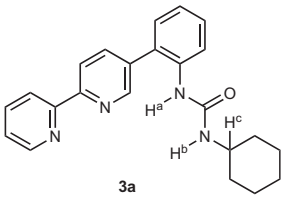
 **6b** A: 59% (7.8) B: 40% (0.46)	 **6c** A: 35% (12) B: 39% (0.72)	 **6d** A: 96% (7.5) B: 97% (0.46)	 **6e** A: >99% (13) B: >99% (0.61)	 **6f** A: >99% (>30) B: >99% (0.86)	 **6g** A: >99% (6.9) B: >99% (0.25)
 **6h** A: >99% (>30) B: >99% (2.1)	 **6i** A: 26% (>30) B: 32% (3.9)	 **6j*** A: 51% (3.3) B: 54% (1.1)	 **6k†** A: 44% (27) B: 49% (1.5)	 **6l†** A: 46% (>30) B: 40% (1.5)	 **6m** A: 95% (3.3) B: 5% (0.67)
 **6n†** A: 46% (17) B: 45% (2.3)	 **6o‡** A: 77% (5.0) B: 56% (1.1)	 **6p** A: >99% (9.1) B: >99% (1.0)	 **6q** A: 85% B: >99%	 **6r** A: >99% B: >99%	 **6s** A: 92% (20) B: 75% (12)
 **6t** A: >99% B: >99%	 **6u** A: >99% B: >99%	 **6v** A: 86% B: 90%	 **6w** A: 94% B: 96%	 **6x§** A: 84% (6.6) B: 95% (2.3)	 **6y‖** A: 86% (>30) B: 89% (>30)
 **6z¶** A: 86% (6.4) B: 88% (1.9)	 **6aa§,#** A: >99% (4.3) B: 92% (1.3)	 **6bb§,#** A: 99% (1.5) B: 89% (0.48)	 **6cc**** A: 52% (16) B: 61% (1.5)	 **6dd††** A: 82% (0.52) B: >99% (0.28)	 **6ee††** A: 85% (7.5) B: >99% (0.59)
 **6ff††** A: 99% (13) B: >99% (0.32)	 **6gg††** A: 44% (>30) B: 99% (0.55)	 **6hh**** A: 46% (>30) B: 61% (1.3)	 **6ii**** A: 44% (>30) B: 53% (1.9)	 **6jj** A: >99% (>30) B: 86% (0.42)	 **6kk** A: >99% (>30) B: >99% (0.14)

2a (1.5 equiv.) was used unless otherwise noted. A: ^{1}H NMR yield of *mono*-borylated products (as a mixture of *meta*- and *para*-products) using **3a** as a ligand with the *meta*/*para* ratio described in parentheses. B: ^{1}H NMR yield of *mono*-borylated products using dtbpy as a ligand with the *meta*/*para* ratio described in parentheses. See Supplementary Fig. 1 for details. *35 °C, 24 h. †**2a** (1.0 equiv). ‡Bis(hexylene glycolato)diboron (**2b**) was used as a borylation reagent. §Ratio of 5-position/4-position. ‖[Ir(OMe)(cod)]$_2$ (2.0 mol%), **3a** (4.0 mol%), 24 h. ¶Ratio of 4-position/5-position. #**3d** was used as a ligand. **2a** (1.0 equiv.), 40 °C, 6 h. ††40 °C.

respectively. The contrasting substrate preference using either **3a** or dtbpy is probably due to hydrogen bonding between **3a** and **1k**, whereas the inherent substrate reactivity (that is, electronic factor) underlies the ester preference when using dtbpy. These findings indicate that both regio- and chemoselectivity can be controlled by the use of ligand **3a** with its hydrogen-bonding ability.

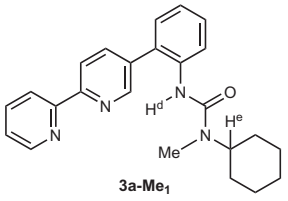
In summary, we have successfully developed a regioselective aromatic C–H borylation using a designed iridium catalyst comprising a bipyridine moiety, with a pendant hydrogen-bond donor. This is the first reported catalyst-controlled regioselective C–H borylation of aromatic compounds. The important aspect of this reaction is that hydrogen bonding between the substrates and the catalyst controls the regioselectivity of a C–H bond transformation. The present catalytic system has the following merits: (1) it has a wide substrate scope; (2) common functional groups are used for catalyst direction; and (3) the ligands are easily accessed. We believe that the present

a



Entry	3a (mM)	1a (mM)	3a/1a	H^a (ppm)	H^b (ppm)	H^c (ppm)
1	2.5	0	1/0	5.65	3.60	3.63
2	2.5	2.5	1/1	5.78	3.74	3.65
3	2.5	160	1/64	7.00–7.50*	5.88	3.89

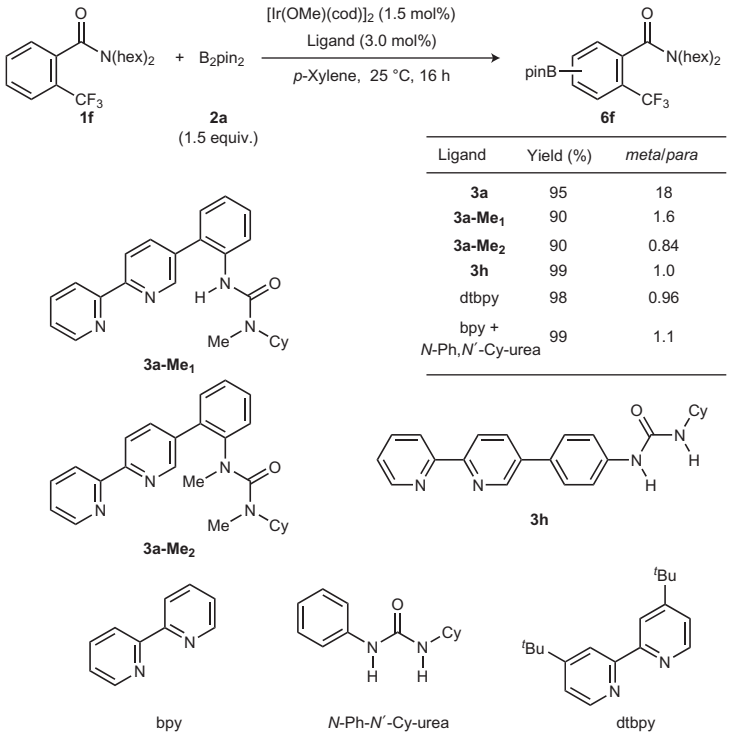
^{1}H NMR spectra were measured using benzene-d_6.



Entry	3a-Me$_1$ (mM)	1a (mM)	3a-Me$_1$/1a	H^d (ppm)	H^e (ppm)
4	2.5	0	1/0	6.26	3.91
5	2.5	2.5	1/1	6.26	3.91
6	2.5	160	1/64	6.37	3.92

^{1}H NMR spectra were measured using benzene-d_6.

b



Ligand	Yield (%)	*meta*/*para*
3a	95	18
3a-Me$_1$	90	1.6
3a-Me$_2$	90	0.84
3h	99	1.0
dtbpy	98	0.96
bpy + *N*-Ph,*N*′-Cy-urea	99	1.1

Figure 3 | Mechanistic support for the importance of hydrogen bonding between the catalyst and substrates in controlling regioselectivity. a, ^{1}H NMR chemical shift changes caused by interaction between ligand **3a** and amide **1a** or **3a-Me$_1$** and **1a**. **b**, Comparison of product *meta*/*para* ratios using **3a**, **3a-Me$_1$**, **3a-Me$_2$**, **3h**, dtbpy and a mixture of bpy and a urea derivative. *Because the signal overlapped with aromatic signals, the value of the chemical shift could not be determined.

concept will give a general solution for controlling the regioselectivity of C–H bond transformations and other reactions, without the need for directing groups.

Methods

Full experimental details and characterization of the compounds can be found in the Supplementary Information.

General procedure for *meta*-selective C(sp^2)–H borylation. A mixture of [Ir(OMe)(cod)]$_2$ (2.5 mg, 3.8 μmol, 1.5 mol%), ligand **3a** (2.8 mg, 7.5 μmol, 3.0 mol%) and bis(pinacolato)diboron (**2a**) (95.2 mg, 0.375 mmol, 1.50 equiv.) was added to a solution of a benzamide derivative (0.250 mmol, 1.0 equiv.) in *p*-xylene (1.5 ml). The mixture was then stirred at 25 °C for 16 h. The product was isolated by recycling preparative HPLC to give a *meta*/*para* mixture of borylated products (or only a *meta*-borylated product).

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Acknowledgements

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Author contributions

Y.K. conceived and designed the experiments and ligands, and prepared the manuscript. H.I. and M.N. performed the experiments. Y.K. and M.K. directed the project. All authors discussed the results and commented on the manuscript.

Additional information

Supplementary information and chemical compound information are available in the online version of the paper. Reprints and permissions information is available online at www.nature.com/reprints. Correspondence and requests for materials should be addressed to Y.K. and M.K.

Competing financial interests

The authors declare no competing financial interests.