ORGANIC CHEMISTRY FRONTIERS

HIGHLIGHT

View Article Online
View Journal

Cite this: DOI: 10.1039/d1qo00452b

Noncovalent interactions in Ir-catalyzed remote C–H borylation: a recent update

Saikat Pandit, Sudip Maiti and Debabrata Maiti*

Received 23rd March 2021,
Accepted 1st May 2021

DOI: 10.1039/d1qo00452b

rsc.li/frontiers-organic

Iridium catalyzed direct C–H borylation has provided a powerful strategy to construct a complex molecular architecture in a relatively straightforward way. Controlling regioselectivity is one of the most challenging issues in these transformations. Enormous efforts of the synthetic community have helped to overcome the selectivity issue in the case of proximal C–H borylation by introducing a directing group concept along with noncovalent interaction. However, selectively targeting a remote C–H bond is a formidable challenge and often requires special designing of the directing template. In this highlight, we aim to provide a recent update on noncovalent interaction enabled Ir-catalyzed remote C–H borylation, with a special emphasis on the corresponding enantioselective variant.

Over the past decades, attractive noncovalent interactions, specifically hydrogen bonding and ion-pairing, have emerged as a key component for controlling selectivity in the realm of enzymatic catalysis and asymmetric organocatalysis.[1] Despite substantial advances, the utilization of attractive noncovalent interactions to engineer substrate–ligand orientation towards the transition metal-catalyzed regioselective activation of the remote C–H bond of arenes still remains a significant challenge.[2]

Iridium catalyzed direct C–H borylation is of unique importance because the C–B bond can act as a lynchpin to access *ipso* C–C and C–heteroatom bonds.[3] But the major challenge associated with it is regioselectivity, which is mostly governed by steric effects. For example, the regioselective C–H borylation of 1,3-disubstituted arenes **1** is advantageous compared to mono or 1,2-disubstituted arenes **3**, which generally produces an inseparable mixture of isomers **4a** and **4b** unless there are any other effects such as the influence of the bulky ligand[4,5] or the presence of a particular substituent to direct a specific position[6,7] (Fig. 1a). The mechanism of this conventional iridium-catalyzed borylation[8] involves the *in situ* generation of tris-boryl complex **5**, which then undergoes a rapid and reversible dissociation of cyclooctene (COE) to form another active 16-electron tris-boryl complex **6**. This 16-electron complex then undergoes C–H bond cleavage due to the lower energy barrier for C–H bond cleavage compared to the barrier for the elimination of B_2pin_2; as a consequence, the arene reacts with an Ir (III) boryl complex, not with an Ir(I) boryl complex. Now, the mechanism for C–H bond cleavage by a metal boryl complex

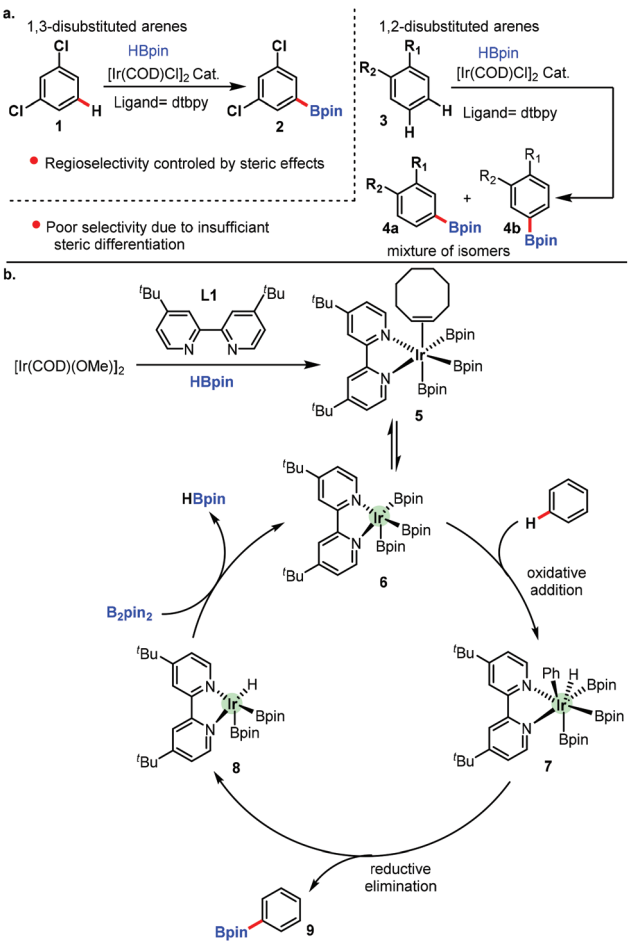


Fig. 1 (a) Regioselectivity issues in iridium-catalyzed borylation and (b) the proposed mechanistic cycle for conventional iridium-catalyzed borylation.

Department of Chemistry, Indian Institute of Technology Bombay, Powai, Mumbai-400076, India. E-mail: dmaiti@iitb.ac.in

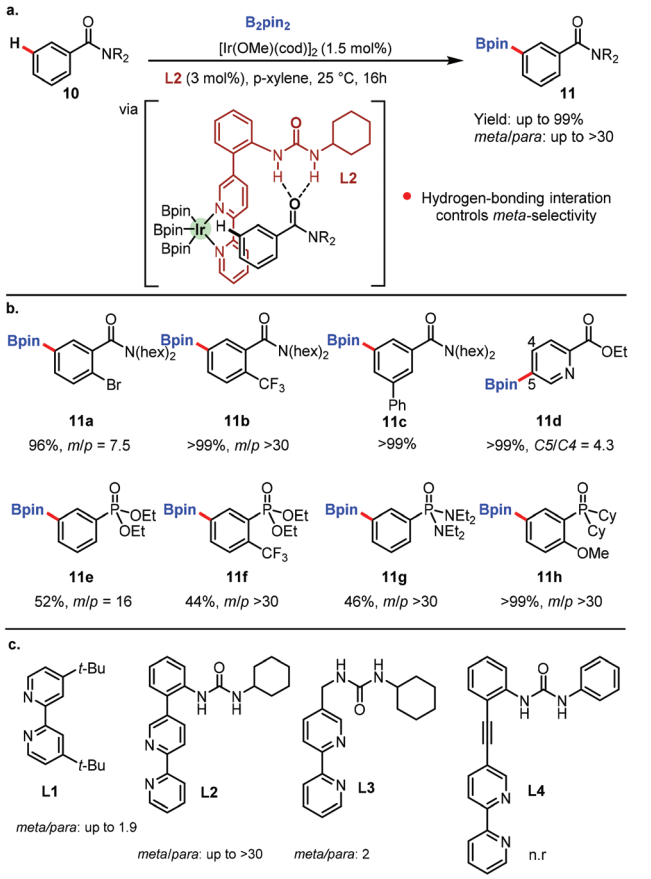
can proceed either *via* the oxidative addition pathway or *via* the σ-bond metathesis process.[8] Recent computational studies concluded that C–H bond cleavage by the iridium tris-boryl complex **6** occurs *via* oxidative addition of the arene C–H bond followed by reductive elimination to generate the arene C–B bond (Fig. 1b).[8,9]

Therefore, achieving regioselectivity in arene C–H borylation by overriding the steric demands of the substituents is a major challenge. Several directed metalation approaches where the native functional group can direct the active catalyst have been employed to achieve *ortho*-C–H borylation,[10,11] whereas selectively targeting a remote C–H bond often requires the attachment and detachment of a bulky directing template which limits the practicability of this strategy. However, the development of an efficient strategy for the construction of the remote regioselective C–B bond by using noncovalent interactions in conjunction with transition metal catalysis is of immense interest.[12]

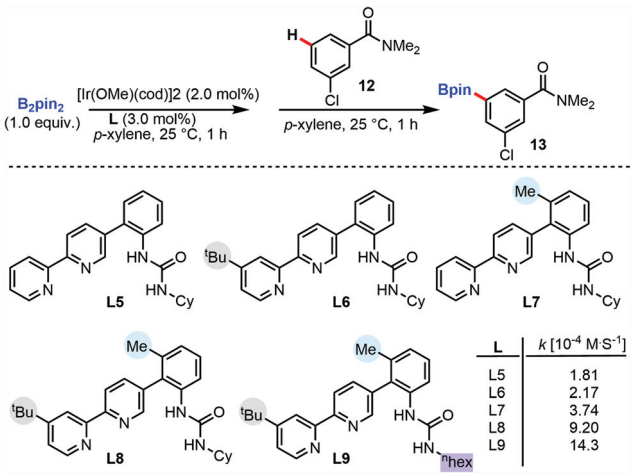
In this highlight article, we aim to provide the readers a concise overview of noncovalent interaction enabled Ir-catalyzed remote C–H borylation. This highlight also emphasizes the latest contributions in noncovalent interaction-mediated enantioselective remote C–H borylation.

In 2015, Kanai *et al.* first demonstrated iridium-catalysed remote C–H functionalization through hydrogen-bonding interaction by the implementation of a suitable L-shaped template **L2** containing a urea moiety as a hydrogen bond donor tethered to a bipyridyl motif for substrate anchoring and thereby bring the *meta*-C–H bond close to the catalytic site (Scheme 1a).[13] In this report, a library of aromatic amides, esters, phosphonates, phosphonic diamides and phosphine oxides undergo borylation with good yields and excellent *meta*-selectivity (Scheme 1b). The low regioselectivity and mixture of isomers were obtained by using a standard borylation ligand, 4,4′-di-*tert*-butyl-2,2′-bipyridine (dtbbpy) **L1** (Scheme 1c),[13] which again proves that the hydrogen bonding between the substrate and the newly designed template is the key controlling factor in achieving regioselectivity. Moreover, the length of the *ortho*-phenylene linker is also an essential factor for achieving high *meta*-selectivity (Scheme 1c).

Furthermore, the Kanai group demonstrated that the H-bonding mediated *meta*-selective C–H borylation can be accelerated by tuning the electronic and steric properties of the urea-containing bipyridine ligand **L5**.[14] Their molecular modelling study suggested that the reactivity could be accelerated by increasing the electronic density of the bipyridine moiety, twisting the plane of *ortho*-phenylene and bipyridyl components through the introduction of a functional group in the *ortho*-phenylene ring, and also by changing the substituents in the urea moiety. When they introduced an electron-donating *tert*-butyl group in the bipyridine moiety **L6** and a methyl group in the *ortho*-phenylene ring **L7** and both in the same ligand **L8**, in all cases, the rate increased gradually compared to the rate obtained by using ligand **L5** (Scheme 2). The rate is further increased by introducing an *n*-hexyl group in place of the cyclohexyl group in the urea moiety **L9**. In addition, they also expressed the functional group and substrate specificity by performing different intermolecular and intramolecular competition reactions using urea-containing bipyridine ligands.[14]



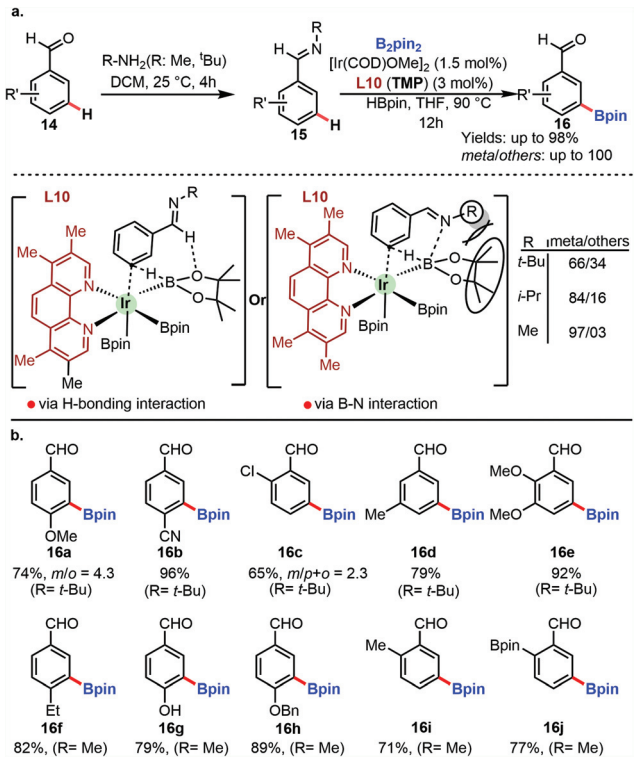
Scheme 1 a) Hydrogen-bonding interaction to control the *meta*-selectivity; (b) scope of *meta*-selective C–H borylation with various substrates and (c) exact design of the ligand to achieve high regioselectivity.



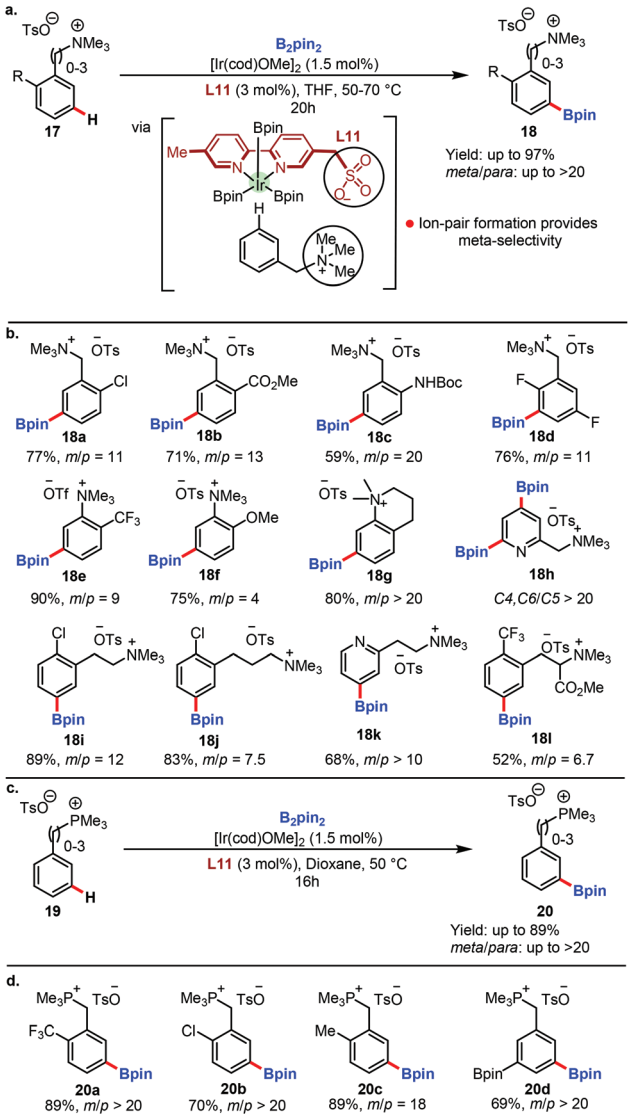
Scheme 2 Variation of the initial reaction rate constant (*k*) of C–H borylation with different urea-containing bipyridine ligands.

At the same time, the Chattopadhyay group illustrated an approach of *meta*-selective borylation of aromatic aldehyde *via in situ* generated imines **15**. They hypothesized that the electrostatic interaction as well as a secondary B–N interaction between the substrate and the metal catalyst could play a pivotal role in achieving the close proximity of the iridium catalyst to the *meta*-C–H bond (Scheme 3a).[7] Several control experiments showed that the regioselectivity mainly depends on the bulkiness of the R group of imines. With increasing steric crowding between the R group and the boryl group of the catalyst, the *meta*-selectivity decreases significantly, which indicates that the regioselectivity is governed by the secondary interaction between the B atom of the iridium tris-boryl catalyst and the N atom of imines. A wide range of aldehydes were well tolerated in this borylation method with excellent *meta*-selectivity and yields (Scheme 3b).

After these pioneering examples, in 2016, the Phipps group introduced a new concept of noncovalent interaction, namely, the ion-pair directed approach in order to address the regioselectivity issue. The interaction between cationic aromatic quaternary ammonium salt **17** and the anionic sulfonate tethered to a bipyridyl motif **L11** is the key point to achieve regioselectivity, which brings the *meta*-C–H bond to the close proximity of the active catalyst (Scheme 4a).[15] A variety of quaternized benzylamine and quaternized aniline derivatives and aromatic heterocycles were well compatible in this borylation protocol with good yields and excellent regioselectivity (Scheme 4b).



Scheme 3 a) Secondary B–N interaction to control the regioselectivity and (b) scope of *meta*-selective borylation with various benzaldehydes.



Scheme 4 a) Ion-pair interaction for the *meta*-C–H borylation of an aromatic quaternary ammonium salt; (b) substrate scope with various aromatic and heteroaromatic quaternary ammonium salts containing different chain lengths; (c) ion-pair interaction to achieve the *meta*-selective C–H borylation of phosphonium salts and (d) substrate scope with different aromatic phosphonium salts.

In 2018, Phipps *et al.* also illustrated that the same ligand **L11** is also efficient for the *meta*-selective C–H borylation of a more flexible system such as quaternized phenylamine and phenylpropylamine, although the selectivity decreases with increasing chain length.[16] This pioneering strategy of ion-pair interaction was also successfully employed for the *meta*-C–H borylation of phosphonium salts **19** using the same anionic bipyridine ligand **L11** (Scheme 4c).[17]

In 2017, Phipps and co-workers also found that the same anionic bipyridine ligand **L11** containing a sulfonate scaffold was also proficient as a hydrogen bond acceptor to control the regioselectivity for the borylation of amide containing aromatic substrate **21**, which acts as a hydrogen bond donor in an

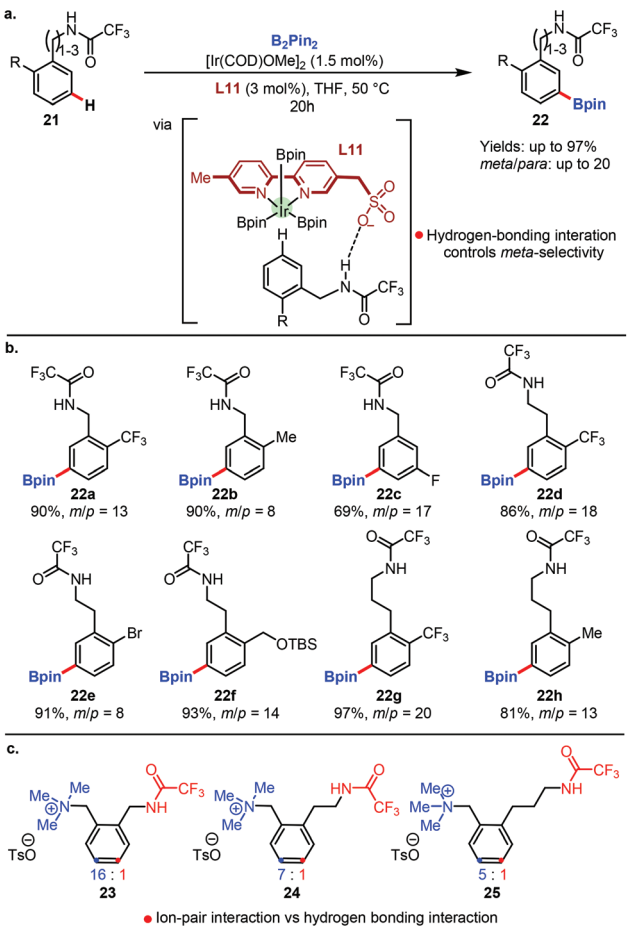
electronically inverted strategy to that of the Kanai group methodology,[13] providing a complementary substrate scope (Scheme 5a).[18] This method was applied to various amides derived from benzylamines, phenethylamines and phenylpropylamines, which have great applications in pharmaceuticals and materials chemistry, and the borylated products were obtained with good to excellent yields and regioselectivity (Scheme 5b).

The capability of this single ligand by both ion-pair and hydrogen-bonding interactions further encourages the conduction of an experiment to compete these two types of noncovalent interactions in a single molecular context. For this, the authors incorporated both the quaternary ammonium ion and the amide functionality with different chain lengths in benzene **23**, **24** and **25** and noted that the ion-pair interaction dominates over the hydrogen-bonding interaction to give the *meta*-selective borylation with respect to their position (Scheme 5c).[16]

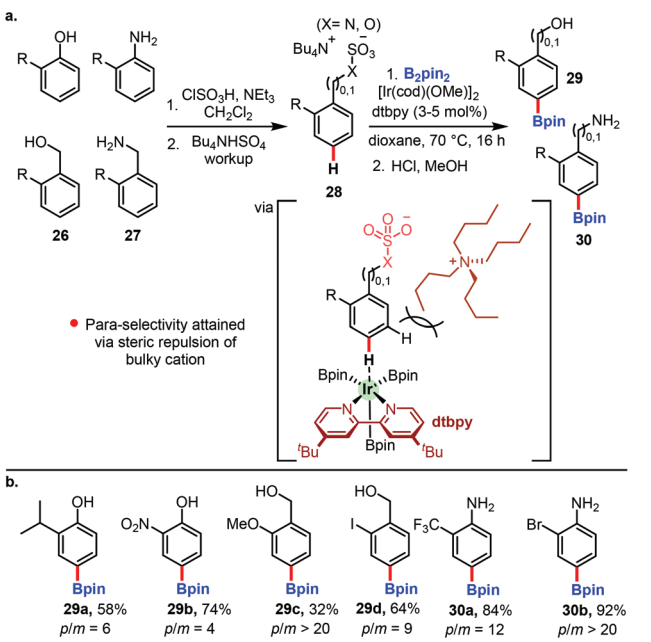
Furthermore, in 2019, Phipps and co-workers discovered a very general and practical methodology for the *para*-selective C–H borylation of a range of common substrate classes **26** and **27** by using commercially available ligands and catalysts.[19] Herein, they employed the same ion-pairing strategy in an alternate way using a bulky counter cation to provide a "steric shield" around the *ortho*- and *meta*-positions leading to *para*-borylated products under standard borylation conditions (Scheme 6a). A large class of substrates including anilines, benzylamines, phenols and benzyl alcohols were borylated using this methodology with excellent regioselectivity and yields (Scheme 6b). In addition, they also performed some control studies on the bulkiness of the counter cation to probe the selectivity and reached a conclusion that the bulky counter cation is actually playing the major role in site selectivity, not the electronic factor of the substrate.[19]

At the same time, the Smith and Maleczka group also reported the *para*-selective C–H borylation of sulfates and sulfamates using the same concept of ion-pair electrostatic interaction between the substrate and the bulky counter cation under conventional borylation conditions (Scheme 7a).[20] Like the previous work of the Phipps group, they also hypothesized that the alkyl chain of the counter cation provides a steric bulk to restrict the *meta* position, allowing the reactive iridium catalyst to come in the close proximity of the *para*-position. A range of sulfates derived from phenol and benzyl alcohols, and sulfamides derived from anilines were also well tolerated under their borylation conditions (Scheme 7b).

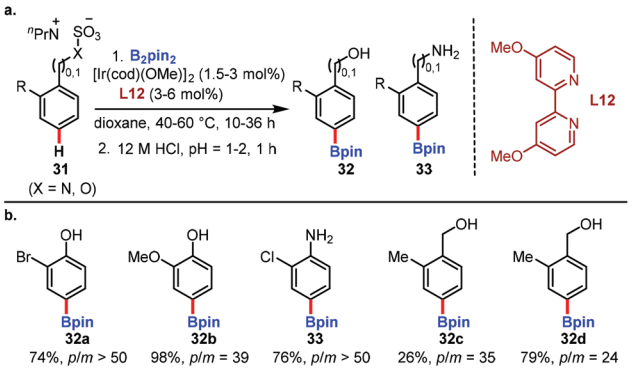
Meanwhile, in 2017, the Chattopadhyay group developed a new catalytic system for the *para*-selective borylation of aromatic ester **34** through metal coordination. They designed the L-shaped ligand **L13** by attaching a 2-hydroxyquinoline moiety with the bipyridine motif, which *in situ* generates O–M (M: Li,



Scheme 5 a) An anionic sulfonate-based bipyridine ligand is also capable of achieving *meta*-selectivity *via* H-bonding interaction; (b) substrate scope of *meta*-C–H borylation with various amide derivatives and (c) ion-pair interaction dominates over H-bonding interaction.



Scheme 6 a) Steric shield of the bulky counter cation controls the *para*-selectivity and (b) broad substrate scope with various anilines, phenols and benzyl alcohols.



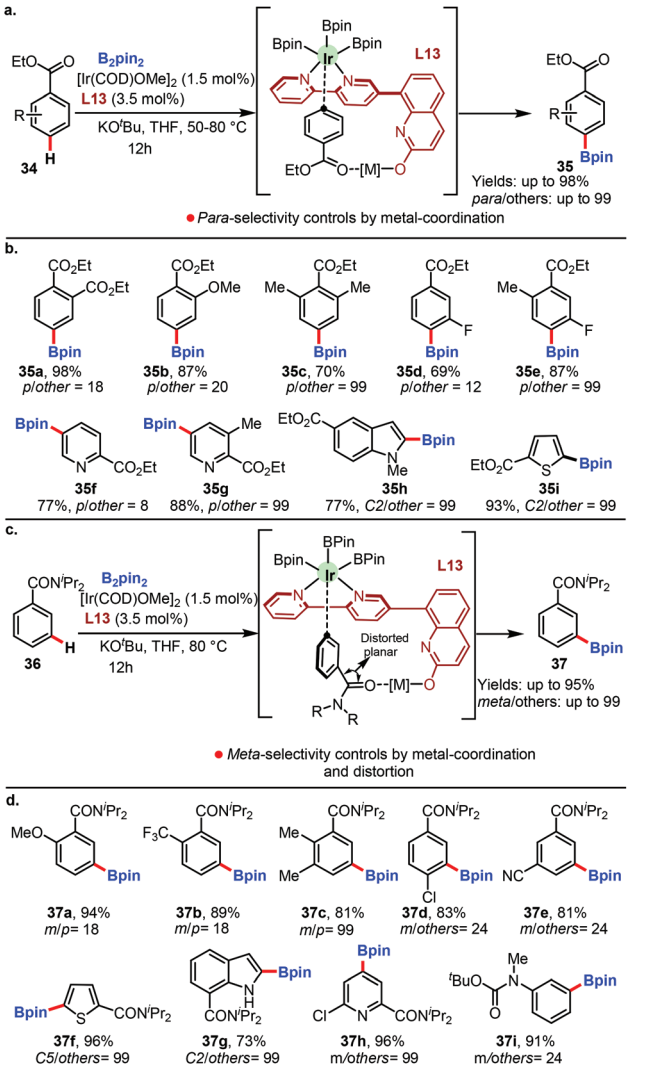
Scheme 7 a) Steric shield of the bulky counter cation controls the *para*-selectivity and (b) broad substrate scope with different sulfates and sulfamates derived from common substrate classes.

Na, and K), would interact with the carbonyl oxygen of the ester through noncovalent interaction and directs the active iridium catalyst to the close proximity of the *para*-C–H bond (Scheme 8a).[21] Here, the selectivity is highly dependent on the choice of the metal ion, and it is investigated that from $Li^+ \rightarrow Na^+ \rightarrow K^+$ there is an extreme variation of regioselectivity, and great success was achieved in the presence of potassium. A series of aromatic and heteroaromatic esters were borylated with great functional group tolerance and excellent *para*-selectivity (Scheme 8b).

One year later, Chattopadhyay *et al.* employed the same L-shaped bifunctional ligand **L13** for aromatic amides **36**, affording excellent *meta*-selectivity through O···K noncovalent interaction. The *meta*-selectivity was achieved due to the distortion of the arene ring from the carbonyl plane by appropriate *N*-substitution, bringing the *meta*-C–H bond close to the active catalyst (Scheme 8c).[22] A range of aromatic amides, heterocycles and anilides were borylated with exclusive *meta*-selectivity by this strategy compared to the classical borylating ligand dtbbpy (Scheme 8d).

In 2017, the Nakao group employed the concept of cooperative iridium/Lewis acid catalysis to achieve the *para*-selective C–H borylation of benzamide and pyridine derivatives **38** and **39**. Here, they designed a complex bulky aluminium Lewis acid which forms complexation with the basic functional unit of the substrate. The regioselectivity is mainly achieved by the steric repulsion between the bulky aluminium Lewis acid (MAD) coordinated to the substrate and the iridium catalyst (Scheme 9a).[23] A wide range of substrates were borylated under these reaction conditions with good regioselectivity and yields (Scheme 9b).

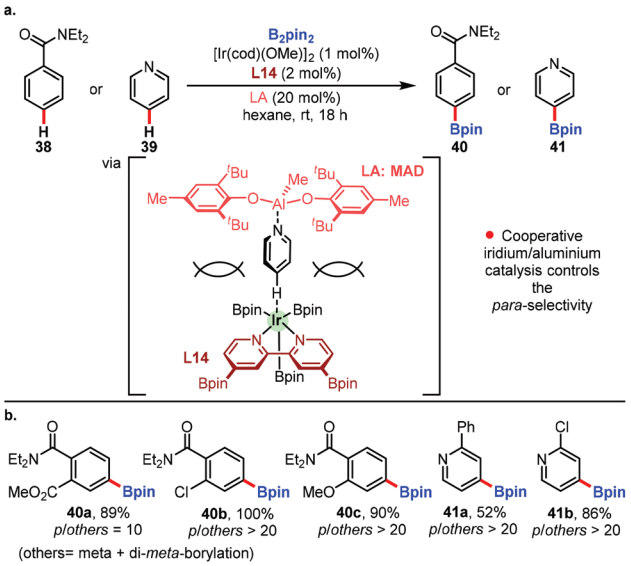
Recently, using a similar Lewis acid–base concept, Nakao *et al.* developed a bifunctional template containing Lewis acidic sites **L15** and **L16** to anchor the substrate containing a Lewis basic functionality for *meta*-selective borylation. Inspired by their previous work on *para*-borylation of benzamides and pyridines by cooperative Ir–Al catalysis,[23] they designed a rigid aluminium-biphenoxide tethered bipyridine motif and a borane-containing phenanthroline motif to recognize benza-



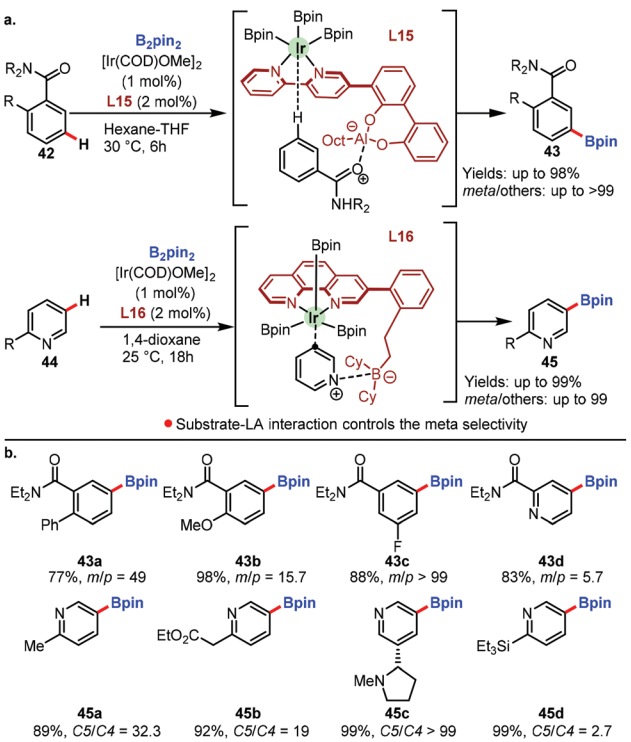
Scheme 8 a) Regioselectivity achieved *via* perfect substrate anchoring through metal coordination; (b) scope of the *para*-selective borylation of aromatic and heteroaromatic esters; (c) distortion of the arene ring to achieve the *meta*-selectivity and (d) substrate scope of the *meta*-selective borylation of aromatic and heteroaromatic amides and anilides.

mides and pyridines, respectively, bringing the *meta*-C–H bond close to the region of the iridium catalyst (Scheme 10a).[24] They demonstrated that this novel concept has broad functionality tolerance including the Lewis basic group affording excellent yields with exclusive regioselectivity (Scheme 10b).

However, these approaches are mainly designed to overcome regioselectivity issues. In contrast, the remote control of enantioselectivity by using these attractive noncovalent interactions is a great challenge and until recently, no efficient organometallic catalyst design strategy was available.[25] In 2020, Phipps and co-workers described an iridium-catalyzed method for the enantioselective *meta*-C–H borylation of the geminal diaryl motif by virtue of ion-pair interaction enabled long-range asymmetric induction (Fig. 2).[26]



Scheme 9 a) *para*-Selective C–H borylation is achieved *via* cooperative iridium/Lewis acid catalysis and (b) substrate scope with different benzamides and pyridine derivatives.



Scheme 10 a) Perfect design of the ligand to achieve the regioselectivity *via* LA–LB interaction and (b) substrate scope with various benzamide and pyridine derivatives.

The authors hypothesized that the exchange of the achiral tetrabutyl ammonium counterion of the anionic ligand scaffold by a chiral cation could pave the way for enantioselective desymmetrization of the prochiral geminal diaryl

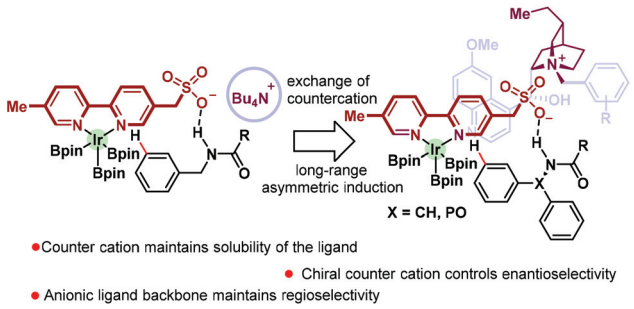
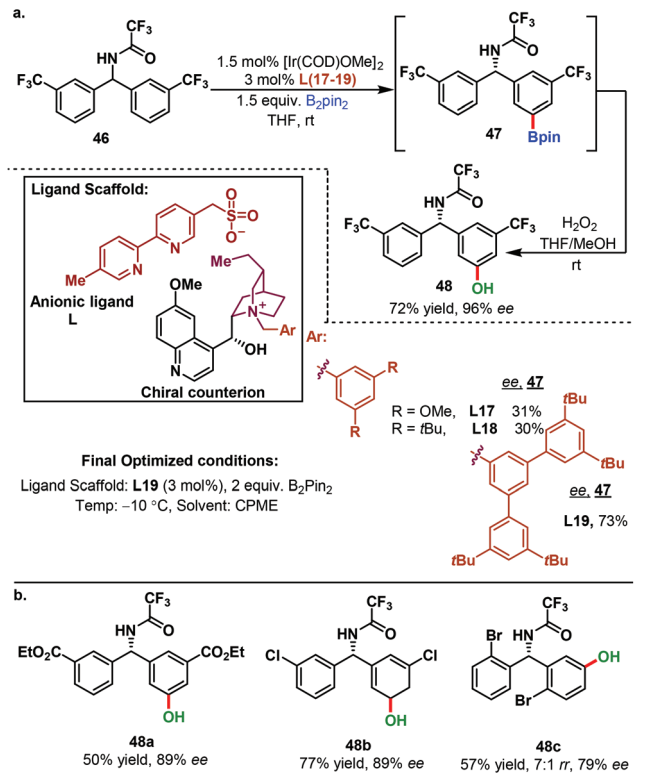


Fig. 2 Combination of hydrogen-bonding and ion-pair interactions to achieve enantioselectivity.



Scheme 11 a) Reaction optimization using the model substrate **46** and (b) scope of enantioselective C–H borylation with benzhydrylamide derivatives (rr, regioisomeric ratio).

motif resulting in the formation of C-center and P-center chiral compounds.[27]

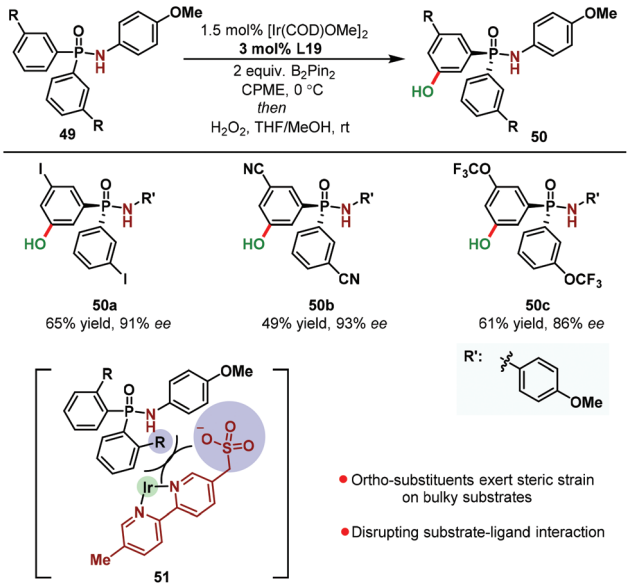
The Phipps group introduced various ion-paired ligands bearing a chiral counter cation, obtained from *N*-benzyl substituted dihydroquinine (DHQ) derivatives (Scheme 11). Initially, they performed the reaction of symmetrical benzhydrylamide **46** under the typical conditions of C–H borylation in tetrahydrofuran at room temperature using ligands [**L17** and **L18**] with 3,5-dimethoxy and 3,5-di-*tert*-butyl substituted benzyl groups on the quaternized nitrogen atom, which resulted in 31% and 30% enantiomeric excess, respectively. It is worth mentioning here that they converted the resulting borylated

product to the corresponding alcohol by treating it with H_2O_2 for ease of purification.

Further screening of several substituted aryl groups at the 3- and 5-positions of the *N*-benzyl group of the counter cation revealed that *tert*-butyl substituted **L19** significantly improves enantioselectivity (73% ee). Subsequently, they optimized other reaction parameters with **L19**, which shed light on the fact that in the presence of cyclopentyl methyl ether (CPME) as the solvent, the reaction temperature can be reduced to −10 °C without hampering the reactivity. Importantly, under these conditions, with a low loading of ligand **L19** (3 mol%), *meta*-C–H borylation proceeded with 96% ee and 72% isolated yield. Notably, the other variants of **L19** with either the methyl protected quinine hydroxyl group or the stereochemically inverted hydroxyl group were found to be detrimental under the optimal reaction conditions, providing 72% and 11% ee, respectively. Surprisingly, the ligand system bearing a Maruoka-type chiral cation was completely ineffective to impart a chiral environment which resulted in the formation of a racemic product (0% ee). The trifluoroacetyl protecting group on benzhydrylamine was found to be beneficial for providing an excellent yield and enantioselectivity. The scope of the reaction was quite broad in terms of benzhydrylamide derivatives. The electron-withdrawing substituents including halogens, trifluoromethoxy, esters, and nitriles at the 3-position of the substrates were well tolerated under the reaction conditions to provide moderate to good yields and excellent enantioselectivity (Scheme 11b). In contrast, electron-donating substituents afforded the desired product at room temperature, albeit with moderate enantioselectivity. Furthermore, various electron-withdrawing substituents at the *ortho*-position of benzhydrylamide were found to be compatible, providing excellent regio- and enantioselectivity (Scheme 11b). It is noteworthy that the reaction of these *ortho*-substituted benzhydrylamides with the conventional dtbpy ligand afforded a regioisomeric product (1.6 : 1, *m*/*p*), which proves that the sulfonated bipyridine ligand scaffold **L19** is able to control both of these selectivity issues.

In addition to the large scope of benzhydrylamide derivatives, a broad variety of symmetrical diarylphosphinamides were compatible under the reaction conditions. Different useful electron-withdrawing functional groups at the 3-position of the aromatic ring of diarylphosphinamide bearing a *para*-methoxy phenyl group on the nitrogen atom were well tolerated to give the desired product with excellent enantioselectivity (Scheme 12). The resulting P-chiral compounds[28] are an important structural motif in enantioselective catalysis and in medicinal chemistry.[29] Interestingly, the substitution at the *ortho*-position resulted in the loss of both regioselectivity and enantioselectivity. The authors speculated that both the *ortho*-substituents and bulky quaternary phosphorous center could provide sufficient steric bulk to destroy the conformational orientation for crucial substrate–ligand interactions (**51**).

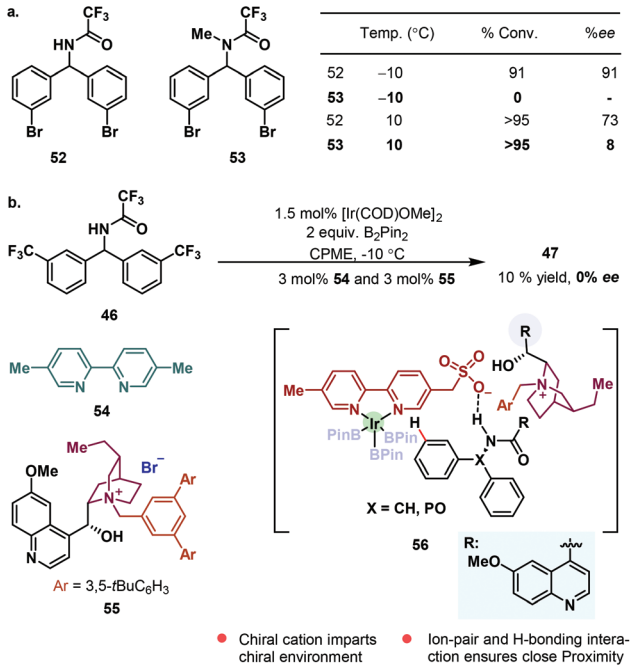
To show the further utility of this protocol, Phipps and coworkers demonstrated various regioselective transformations



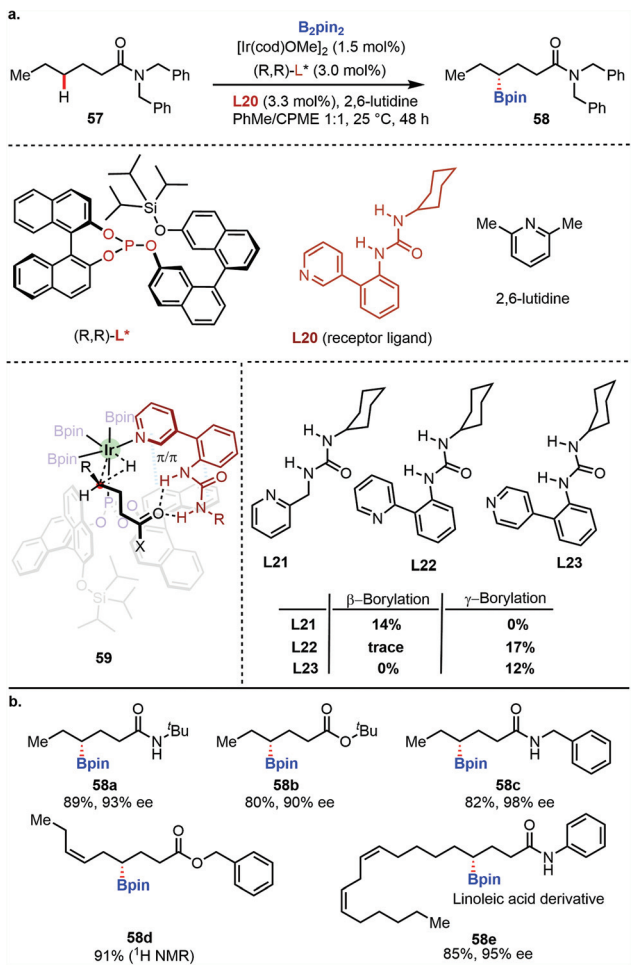
Scheme 12 Representative scope of enantioselective C–H borylation with diarylphosphinamide derivatives.

by virtue of electronic differentiation of the aromatic ring. Several control experiments provided insight into the mechanistic hypothesis. First, the reaction was conducted with an *N*-methyl protected substrate under the optimized conditions at −10 °C, resulting in 0% conversion, while the desired product formation was observed at an elevated temperature (10 °C) with 8% ee, which suggests that hydrogen-bonding interaction plays a crucial role in improving both reactivity and selectivity (Scheme 13a). Second, the reaction was carried out together with the neutral ligand **54** and the bromide salt of chiral cation **55**, leading to the formation of a racemized product (Scheme 13b). These observations prove the role of the ligand scaffold, where the anionic ligand is associated with the chiral cation through ion-pair interaction for enantioinduction (**56**).

Very recently, the Sawamura group discovered an excellent approach for highly enantioselective remote C(sp^3)–H borylation of aliphatic carboxylic acid amides and esters through the combination of urea–pyridine receptor ligand **L20** with the chiral-monophosphite ligand **L*** to generate the active chiral Ir-catalyst (Scheme 14a).[30] From the computational data, they proposed that this urea–pyridine receptor ligand plays a dual role of anchoring the substrate *via* hydrogen-bonding interaction between the two NH hydrogen of urea and the carbonyl oxygen of the substrate and binding the Ir catalyst *via* the pyridine moiety. This geometrical orientation brings the γ-C-(sp^3)–H bond to the close proximity of the Ir center for functionalization. A highly enantioselective γ-C-(sp^3)–H borylation to produce **58** was achieved using this strategy which is mainly due to the various noncovalent interactions between the substrate and the catalyst, including π/π interaction between the receptor–ligand and the naphthalene ring of the phosphite chiral ligand and C(sp^3)–H···O hydrogen bonds, leading to the



Scheme 13 a and b) Control experiments.



Scheme 14 a) Enantioselective γ-C–H borylation and (b) representative examples of enantioselective γ-C–H borylation.

preference for one enantiotopic C(sp^3)–H bond over others (**59**). They showed that when the temperature of the reaction increased from 25 °C to 80 °C, both the reactivity and enantioselectivity diminished, which again supported the statement of substrate binding with the urea–pyridine ligand *via* hydrogen-bonding interaction. They also reported that the changes in the receptor ligand structure affect the selectivity of borylation and the yield of the γ-C(sp^3)–H borylated product, *i.e.* from **L21** to **L23** the β-borylation is diminished, although in the case of **L23** the yield of γ-borylation is less. A wide range of aliphatic amides and esters with the variation of different aliphatic chains are well tolerated in this strategy and giving the γ-bolylated product with a high yield and excellent enantioselectivity (Scheme 14b).

Conclusions

In this highlight, we have emphasized to provide the recent developments on various remote C–H borylation techniques based on noncovalent interactions and their implementation to address both regio- and enantio-selectivity issues. In the current scenario, the utilization of noncovalent interactions in remote C–H functionalizations is emerging as a straightforward route for developing regio- and enantio-selective transformations, and thereby holds special attention in both academia and industry. Regioselectivity is achieved *via* the noncovalent interaction between the substrate and the bipyridine-based ligand bearing a suitable receptor group, whereas stereoselectivity is achieved mainly by the use of a chiral ligand, which can interact with the substrate and the Ir-bound catalytic ligand scaffold *via* noncovalent interaction, providing a chiral atmosphere around the catalyst to differentiate one enantiomer from the other. The noncovalent interactions which are discussed in this highlight article are hydrogen-bonding interaction, ion-pair interaction, Lewis acid–Lewis base interaction, π/π interaction and O–K···O═C noncovalent interaction to attain both regioselectivity and stereoselectivity. However, several other weak noncovalent interactions such as cation–pi, anion–pi or π/π stacking are yet to be discovered in this context of Ir-catalyzed C–H borylation to achieve both site selectivity and stereoselectivity. Also, this Ir-catalyzed borylation in the aliphatic system is less known compared to the aromatic system. The recent discovery by the Sawamura group to achieve C(sp^3)–H borylation using noncovalent interaction will expand the scope of this field in aliphatic systems. There is no doubt that the development made by Kanai, Phipps and other groups on the weak noncovalent approach will show a new path of diversification in remote C–H functionalization. Although until now only Ir-catalyzed borylation was reported based on these noncovalent interactions, we believe that these elegant discoveries will inspire chemists to diversify the scope of this interaction for different new transformations. In addition, the enantioselective synthesis by using this mild noncovalent approach will improve the synthetic method-

ologies for the synthesis of various drug molecules, agrochemicals and complex useful materials.

Author contributions

S. P. collected all the literature. S. P. and S. M. wrote the manuscript. D.M. supervised the work.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

We thank the Science and Engineering Research Board India (CRG/2018/003951) for the financial support. Fellowship from the UGC, India (SM) is greatly acknowledged.

Notes and references

1 For selected reviews, see: (*a*) R. R. Knowles and E. N. Jacobsen, Attractive noncovalent interactions in asymmetric catalysis: Links between enzymes and small molecule catalysts, *Proc. Natl. Acad. Sci. U. S. A.*, 2010, **107**, 20678; (*b*) K. Brak and E. N. Jacobsen, Asymmetric ion–pairing catalysis, *Angew. Chem., Int. Ed.*, 2013, **52**, 534; (*c*) S. E. Wheeler, T. J. Seguin, Y. Guan and A. C. Doney, Noncovalent interactions in organocatalysis and the prospect of computational catalyst design, *Acc. Chem. Res.*, 2016, **49**, 1061; (*d*) F. D. Toste, M. S. Sigman and S. J. Miller, Pursuit of noncovalent interactions for strategic site-selective catalysis, *Acc. Chem. Res.*, 2017, **50**, 609.

2 For reviews on remote C–H activation, see: (*a*) M. T. Mihai, G. R. Genov and R. J. Phipps, Access to the *meta* position of arenes through transition metal catalysed C–H bond functionalisation: a focus on metals other than palladium, *Chem. Soc. Rev.*, 2018, **47**, 149; (*b*) A. Dey, S. K. Sinha, T. K. Achar and D. Maiti, Accessing remote *meta*– and *para*–C(sp^2)–H bonds with covalently attached directing groups, *Angew. Chem., Int. Ed.*, 2019, **58**, 10820; (*c*) S. Govaerts, A. Nyuchev and T. Noel, Pushing the boundaries of C–H bond functionalization chemistry using flow technology, *J. Flow Chem.*, 2020, **10**, 13.

3 *Boronic Acids: Preparation and applications in organic synthesis, Medicine and Materials*, ed. D. G. Hall, Wiley-VCH, Weinheim, 2nd edn, 2011.

4 Y. Saito, Y. Segawa and K. Itami, *para*-C–H Borylation of benzene derivatives by a bulky iridium catalyst, *J. Am. Chem. Soc.*, 2015, **137**, 5193.

5 For rhodium-catalyzed silylation of less sterically defined arenes, see: C. Cheng and J. F. Hartwig, Rhodium-catalyzed intermolecular C–H silylation of arenes with high steric regiocontrol, *Science*, 2014, **343**, 853.

6 (*a*) T. A. Boebel and J. F. Hartwig, Silyl-directed, iridium-catalyzed *ortho*-borylation of arenes. A one-pot *ortho*-borylation of phenols, arylamines, and alkylarenes, *J. Am. Chem. Soc.*, 2008, **130**, 7534; (*b*) B. Ghaffari, S. M. Preshlock, D. L. Plattner, R. J. Staples, P. E. Maligres, S. W. Krska, R. E. Maleczka and M. R. Smith, Silyl phosphorus and nitrogen donor chelates for homogeneous *ortho*-borylation catalysis, *J. Am. Chem. Soc.*, 2014, **136**, 14345; (*c*) S. M. Preshlock, D. L. Plattner, P. E. Maligres, S. W. Krska, R. E. Maleczka and M. R. Smith, A traceless directing Group for C–H borylation, *Angew. Chem., Int. Ed.*, 2013, **52**, 12915.

7 R. Bisht and B. Chattopadhyay, Formal Ir-catalyzed ligand-enabled *ortho*- and *meta*-borylation of aromatic aldehydes *via* in situ-generated imines, *J. Am. Chem. Soc.*, 2016, **138**, 84.

8 T. M. Boller, J. M. Murphy, M. Hapke, T. Ishiyama, N. Miyaura and J. F. Hartwig, Mechanism of the mild functionalization of arenes by diboron reagents catalyzed by iridium complexes. Intermediacy and chemistry of bipyridine-ligated iridium trisboryl complexes, *J. Am. Chem. Soc.*, 2005, **127**, 14263.

9 H. Tamura, H. Yamazaki, H. Sato and S. Sakaki, Iridium-catalyzed borylation of benzene with diboron. Theoretical elucidation of catalytic cycle including unusual iridium(V) intermediate, *J. Am. Chem. Soc.*, 2003, **125**, 16114.

10 C. Haldar, M. E. Hoque, R. Bisht and B. Chattopadhyay, Concept of Ir-catalyzed C–H bond activation/borylation by noncovalent interaction, *Tetrahedron Lett.*, 2018, **59**, 1269.

11 R. Bisht and B. Chattopadhyay, *ortho*- and *meta*-Selective C–H Activation and Borylation of Aromatic Aldehydes via in situ Generated Imines, *Synlett*, 2016, **27**, 2043.

12 (*a*) S. Das, C. D. Incarvito, R. H. Crabtree and G. W. Brudvig, Molecular recognition in the selective oxygenation of saturated C–H bonds by a dimanganese catalyst, *Science*, 2006, **312**, 1941; (*b*) R. F. Moreira, P. M. Wehn and D. Sames, Highly regioselective oxygenation of C–H bonds: Diamidomanganese constructs with attached substrates as catalyst models, *Angew. Chem., Int. Ed.*, 2000, **39**, 1618.

13 Y. Kuninobu, H. Ida, M. Nishi and M. Kanai, A *meta*-selective C–H borylation directed by a secondary interaction between ligand andsubstrate, *Nat. Chem.*, 2015, **7**, 712.

14 X. Lu, Y. Yoshigoe, H. Ida, M. Nishi, M. Kanai and Y. Kuninobu, Hydrogen bond-accelerated *meta*-selective C–H borylation of aromatic compounds and expression of functional group and substrate specificities, *ACS Catal.*, 2019, **9**, 1705.

15 H. J. Davis, M. T. Mihai and R. J. Phipps, Ion pair-directed regiocontrol in transition-metal catalysis: A *meta*-selective C–H borylation of aromatic quaternary ammonium salts, *J. Am. Chem. Soc.*, 2016, **138**, 12759.

16 M. T. Mihai, H. J. Davis, G. R. Genov and R. J. Phipps, Ion pair-directed C–H activation on flexible ammonium salts: *meta*-selective borylation of quaternized phenethylamines and phenylpropylamines, *ACS Catal.*, 2018, **8**, 3764.

17 B. Lee, M. T. Mihai, V. Stojalnikova and R. J. Phipps, Ion-pairdirected borylation of aromatic phosphonium salts, *J. Org. Chem.*, 2019, **84**, 13124.

18 H. J. Davis, G. R. Genov and R. J. Phipps, *Meta*-selective C−H borylation of benzylamine, phenethylamine, and phenylpropylamine-derived amides enabled by a single anionic ligand, *Angew. Chem., Int. Ed.*, 2017, **56**, 13351.

19 M. T. Mihai, B. D. Williams and R. J. Phipps, *para*-selective C−H borylation of common arene building blocks enabled by ion-pairing with a bulky counteraction, *J. Am. Chem. Soc.*, 2019, **141**, 15477.

20 J. R. M. Bastidas, T. J. Oleskey, S. L. Miller, M. R. Smith and R. E. Maleczka, *Para*-selective iridium-catalyzed C−H borylations of sulfated phenols, benzyl alcohols, and anilines directed by ion-pair electrostatic interactions, *J. Am. Chem. Soc.*, 2019, **141**, 15483.

21 E. Hoque, R. Bisht, C. Haldar and B. Chattopadhyay, Noncovalent interactions in Ir-catalyzed C−H activation: L-shaped ligand for *para*-selective borylation of aromatic esters, *J. Am. Chem. Soc.*, 2017, **139**, 7745.

22 R. Bisht, E. Hoque and B. Chattopadhyay, Amide effects in C−H activation: Noncovalent interactions with L-shaped ligand for *meta* borylation of aromatic amides, *Angew. Chem., Int. Ed.*, 2018, **57**, 15762.

23 L. Yang, K. Semba and Y. Nakao, *para*-selective C−H borylation of (hetero)arenes by cooperative iridium/aluminum catalysis, *Angew. Chem., Int. Ed.*, 2017, **56**, 4853.

24 L. Yang, N. Uemura and Y. Nakao, *meta*-selective C−H borylation of benzamides and pyridines by an iridium-Lewis acid bifunctional catalyst, *J. Am. Chem. Soc.*, 2019, **141**, 7972.

25 (*a*) A. J. Metrano and S. J. Miller, Peptide-based catalysts reach the outer sphere through remote desymmetrization and atroposelectivity, *Acc. Chem. Res.*, 2019, **52**, 199; (*b*) S. Y. Hsieh, Y. Tang, S. Crotti, E. A. Stone and S. J. Miller, Catalytic enantioselective pyridine N-oxidation, *J. Am. Chem. Soc.*, 2019, **141**, 18624.

26 G. R. Genov, J. L. Douthwaite, A. S. K. Lahdenperä, D. C. Gibson and R. J. Phipps, Enantioselective remote C−H activation directed by a chiral cation, *Science*, 2020, **367**, 1246.

27 (*a*) U. H. Dolling, P. Davis and E. J. J. Grabowski, Efficient catalytic asymmetric alkylations. 1. Enantioselective synthesis of (+)-indacrinone via chiral phase-transfer catalysis, *J. Am. Chem. Soc.*, 1984, **106**, 446; (*b*) S. Mukherjee and B. List, Chiral counteranions in asymmetric transition-metal catalysis: Highly enantioselective Pd/brønsted acid-catalyzed direct α-allylation of aldehydes, *J. Am. Chem. Soc.*, 2007, **129**, 11336; (*c*) R. J. Phipps, G. L. Hamilton and F. D. Toste, The progression of chiral anions from concepts to applications in asymmetric catalysis, *Nat. Chem.*, 2012, **4**, 603; (*d*) M. Mahlau and B. List, Asymmetric counteranion–directed catalysis: Concept, definition, and applications, *Angew. Chem., Int. Ed.*, 2013, **52**, 518.

28 (*a*) R. Beaud, R. J. Phipps and M. J. Gaunt, Enantioselective Cu-catalyzed arylation of secondary phosphine oxides with diaryliodonium salts toward the Synthesis of P-chiral phosphines, *J. Am. Chem. Soc.*, 2016, **138**, 13183; (*b*) Y. Sun and N. Cramer, Rhodium(III)–catalyzed enantiotopic C−H activation enables access to P–chiral cyclic phosphinamides, *Angew. Chem., Int. Ed.*, 2017, **56**, 364; (*c*) Y.-S. Jang, M. Dieckmann and N. Cramer, Cooperative effects between chiral Cpx–iridium(III) catalysts and chiral carboxylic acids in enantioselective C−H amidations of phosphine oxides, *Angew. Chem., Int. Ed.*, 2017, **56**, 15088.

29 (*a*) *Phosphorus ligands in asymmetric catalysis: Synthesis and applications*, ed. A. Borner, Wiley-VCH, Weinheim, 2008, vol. 1–3; (*b*) J. B. Rodriguez and C. Gallo-Rodriguez, The role of the phosphorus atom in drug design, *ChemMedChem*, 2019, **14**, 190.

30 R. L. Reyes, M. Sato, T. Iwai, K. Suzuki, S. Maeda and M. Sawamura, Asymmetric remote C−H borylation of aliphatic amides and esters with a modular iridium catalyst, *Science*, 2020, **369**, 970.

