CHEMISTRY

# Transition metal–catalyzed remote C—H borylation: An emerging synthetic tool

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**Transition metal–catalyzed C—H bond activation and borylation is a powerful synthetic method that offers versatile synthetic transformation from organoboron compounds to virtually all other functional groups. Compared to the ortho-borylation, remote borylation remains more challenging owing to the inaccessibility of these C—H bonds. Enforcing the metal catalyst toward the remote C—H bonds needs well-judged catalyst design through proper ligand development. This review article aims to summarize the recent discoveries for the remote C—H borylation by the employment of new catalyst/ligand design with the help of steric of the ligand, noncovalent interactions. It has been found that C—H borylation now takes part in the total synthesis of natural products in a shorter route. Whereas, Ir-catalyzed C—H borylation is predominant, cobalt catalyst has also started to affect this field for sustainable and cost-effective development.**

## INTRODUCTION

Arenes diversification through C—H functionalization (*1*–*4*) is an emerging practice among the synthetic organic chemists for the production of complex natural products and chemical entities toward lead optimization (*5*, *6*). Transition metal catalysts play an important role in C—H functionalization chemistry for the sustainable cost-effective production of important molecules (*7*–*11*). In principle, selective activation and functionalization of different C—H bonds provide the most direct as well as expedient strategy for the rapid growth of structural diversity and molecular complexity due to its atom-economical as well as eco-friendly approach avoiding the need of prefunctionalization of starting materials as well as mutistep processes. However, site-selective C—H functionalization always remains challenging due to ubiquity of C—H bonds within a molecule and its corresponding high energy as well as similar reactivities (*12*). For exemplification, Friedel-Crafts reaction (*13*, *14*) is one of the oldest reactions for the electrophilic aromatic substitution and has been used extensively to introduce different functional groups at aromatic compounds since its inception. In general, according to this pioneering reaction, electron donating group (EDG) directs the incoming electrophile toward ortho and para position, whereas electron withdrawing group (EWG) leads to meta-selective substitution. Nonetheless, for simplistic molecular scaffolds, predicting the outcome based on this fundamental concept is easy but becomes difficult with relatively complex molecular scaffolds, particularly when a functional group is needed to be introduced at a specific position of an aromatic system which cannot be predicted by these traditional rules. To obviate this issue, chemists often need multiple synthetic manipulations, which begets a chemically encumbered and non-atom economic route. Moreover, many aromatic compounds are the essential chemical connections within many biologically active molecules, diverse chemical probes, or natural products, thus an important question would be what will happen if the aromatic compounds with the substitution patterns that do not obey these basic rules of the electrophilic aromatic substitution? For example, what if chemists intend to put a substituent at the meta or para position in the presence of an EDG or EWG, respectively? Normally, these kinds of unconventional transformations are difficult. As alluded, involvement of multistep syntheses and functional group installations or manipulations engenders a synthetically undesirable route. To overcome these barriers of limitations, it is extremely anticipated to have direct C—H bond activation and functionalization, which is practically very difficult but can provide a better alternative toward sustainable synthesis (*3*).

Apart from this, the directed ortho metalation (DoM) process (*15*) is another tool for the C—H functionalization, where a preinstalled functional group directs the ortho position in the presence of alkali metal under cryogenic conditions. Although several developments have been accomplished with this approach, requirement of harsh cryogenic conditions and a preferable directing group restrict its scope toward the sustainable chemical synthesis (*16*). The regioselective C—H functionalization of arenes without having any directing group is also a great challenge. While directing group-assisted proximal C—H functionalization has been developed extensively by several pioneering research groups, nondirected regioselective C—H functionalization is now in the developing stage (*17*, *18*). Transition metal catalysts give a platform to regioselective functionalization (*11*, *19*–*21*) of arenes irrespective of directing group present in the arene systems. In this context, among various C—H functionalizations, the C—H borylation (*22*–*27*) has recognized as one of the most important mainstream reactions because of the unique properties of boron functionality that can act as a linchpin for the versatile functional group transformations (*28*, *29*). Before the development of this direct C—H borylation reaction from unfunctionalized arenes and heteroarenes, these were prepared either by the Miyaura cross-coupling (*30*) using organohalide compounds or by the lithiation with alkali metals followed by the functionalization of aromatic halides (*23*). While these methods are important, which have been used continuously in various synthetic transformations, nonetheless, it would be highly warranted if a more advanced methodology be developed, due to the aforementioned limitations of requiring a preinstalled halide group in the molecules and cryogenic reaction conditions for the lithiation

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chemistry. Thus, one such practical and useful complementary method is the direct C—H borylation that has the enormous power to overcome all these problems. Notably, the first footstep of arene C—H borylation was noticed by the group of Marder in 1993 where they observed the toluene solvent borylation detected by gas chromatography–mass spectrometry and isolated the iridium tris-(catechol boryl) complex (**1**) (Fig. 1A) (*31*). However, they did not study further the catalytic activity of the iridium tris-

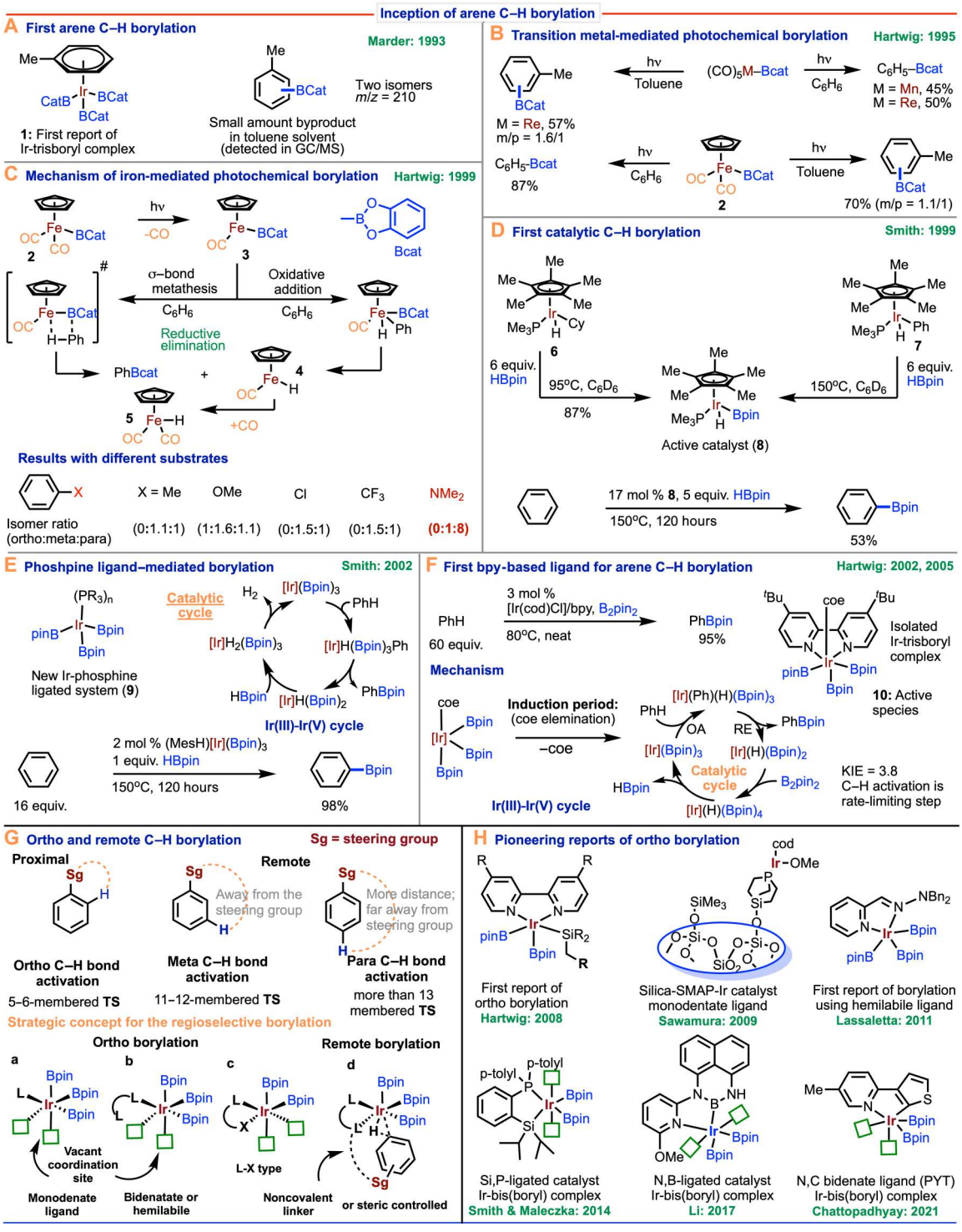


**Fig. 1. Inception of CH borylation and journey toward Ir-catalyzed CH borylation.** (**A**) First arene C—H borylation (*31*). (**B**) Transition metal mediated photochemical borylation (*32*). (**C**) Mechanism of iron mediated photochemical borylation (*33*). (**D**) First catalytic C—H borylation (*34*). (**E**) Phosphine ligand-mediated borylation (*35*). (**F**) First bpy based ligand for arene C—H borylation (*36–38*). (**G**) Ortho and remote C—H borylation (*11*, *37*, *39–41*). (**H**) Pioneering reports of ortho-borylation (*25*, *40*, *42–45*). m/z, mass/charge ratio.

(catechol boryl) complex (**1**) or the cause of the formation of the borylated toluene in the reaction mixture. In 1995, Hartwig group (*32*) first reported the C—H borylation of benzene and toluene systems using a stoichiometric amount of $(CO)_5Mn(Bcat)$, $(CO)_5Re(Bcat)$, and $Fe(CO)_2(Bcat)$ (**2**) complex under the photochemical conditions (Fig. 1B). In this study, they revealed that while Mn and Re complex afforded 45 and 50% borylated benzene, respectively, Fe-complex (**2**) resulted in 87% borylated benzene under the photochemical conditions. It was also found that whereas with Re complex, toluene resulted in 61% meta-selective borylation (meta/para = 1.6/1) with 57% conversion, in contrast, the Fe-complex (**2**) provided nonselective borylation of toluene with 70% conversion (Fig. 1B). A detailed mechanistic study of the Fe-complex (**2**) catalyzed C—H borylation indicated that in the presence of light, the complex (**2**) releases a CO ligand with the formation of an Fe-monoboryl complex (**3**), which undergoes either an oxidative addition or a σ—bond metathesis with benzene followed by the reductive elimination that resulted in borylated benzene with the generation of an Fe-H complex (**4**) (Fig. 1C) (*33*). Further studies disclosed that the activity of the Fe-complex (**2**) toward the C—H borylation of other arene systems, such as anisole, chlorobenzene, trifluoromethyl benzene and *N*,*N*-dimethylaniline, had profound effect in the borylation reactions. Moreover, *N*,*N*-dimethylaniline resulted in 89% para-selective borylation (ortho/meta/para = 0/1/8) under the developed reaction conditions that was the first report of a regioselective para–C—H borylation of *N*,*N*-dimethylaniline (Fig. 1C). At the same time, when Hartwig group reported (*33*) transition metal–mediated stoichiometric C—H borylation, Smith group reported the first catalytic C—H borylation by iridium complexes (**6** and **7**) having Cp* and phosphine ligand in the presence of HBpin as the boron source (*34*). The iridium complexes (**6** and **7**) in the presence of HBpin in benzene-$d_6$ generated a complex (**8**), which was proved to be an active catalyst by conducting a reaction using 17 mol % catalyst loading for the borylation of benzene (Fig. 1D). These were the reports of C—H borylation with the transition metal complexes containing cyclopentadienyl ligand where only iridium catalyst showed catalytic behavior reported by the Smith group. Later on, Smith and coworkers (*35*) reported another phosphine ligated Ir catalyst (**9**) for the C—H borylation of arenes where they developed regioselective meta borylation of 1,3-disubstituted arenes and benzene (Fig. 1E). The authors proposed a reaction mechanism where an iridium(III) to iridium(V) catalytic cycle was generated via the formation of an iridium-trisboryl complex. Notably, this was the first iridium-trisboryl complex–mediated arene C—H borylation after the first report of Ir-tris(catechol boryl) complex (**1**) reported by Marder *et al.* (*31*). On the other hand, the breakthrough discovery of the C—H borylation of arenes was reported by the Hartwig group (*36*) with bidentate bipyridine ligand along with iridium catalyst (Fig. 1F). The reaction occurred at room temperature, and the turnover number was about 8000, which indicated the efficacy of the catalytic system in the C—H borylation reaction. It was observed from a stoichiometric reaction of bipyridine ligand system that Ir-pre catalyst ($[Ir(cod)Cl]_2$) and $B_2pin_2$ generated a dinitrogen-ligated iridium tris(boryl) complex (**10**), which was proven to be the active potential species for the catalytic borylation of the arenes. Subsequently, in 2005, the detailed mechanistic investigations were carried out to understand the catalytic behavior (*37*) that concluded a primary kinetic isotope effect (KIE) of 3.8 for the C—H borylation of benzene. The primary KIE value of 3.8 indicated that the C—H activation step is the turnover limiting step. Moreover, several other important kinetic experiments further indicated that the cyclooctene ligand was eliminated from the complex (**10**) during the induction period, and on the basis of these collective experimental findings, the authors proposed an Ir(III) to Ir(V) catalytic cycle (Fig. 1F). The ITHM protocol (*36*, *38*), named after the pioneering scientists Ishiyama, Takagi, Hartwig, and Miyaura, was developed for the arene C—H borylation using bidentate bipyridine based ligand scaffold. Notably, since this report, the method has continuously been used for the C—H borylation reactions either by modifying the catalytic systems or by the design of suitable substrates. Normally, the directed C—H bond functionalization of arenes undergoes the proximal ortho C—H activation mechanism (via either a five- or six-membered cyclic transition state), remote meta C—H activation mechanism (which follows a cyclic transition state via either an eleven- or a twelve-membered ring), or remote para C—H activation mechanism (which needs a cyclic transition state more than thirteen-membered ring) (Fig. 1G) (*11*, *39*). In the context of the C—H borylations, the directed ortho-borylations have studied extensively. For ortho-borylation, usually, two different approaches (*40*, *41*) (depending on the nature of the used ligand frameworks) are possible that followed the standard Ir(III)-Ir(V) catalytic cycle (*37*). For example, while in the case of monodentate, bidentate, and hemilabile ligand systems, the borylation occurs via the generation of a tris(boryl)Ir complex (Fig. 1G, a and b), but when a L-X type of ligand is used, the borylation undergoes via the formation of a bis(boryl)Ir complex (Fig. 1G, c) (*41*). On the basis of the different strategies of ortho borylations, several iridium-catalyzed pioneering concepts have been reported by many leaders in the field, such as Hartwig and Boebel (hydrosilyl directed ortho borylation of phenol) (*42*), Sawamura *et al.* (silica-supported phosphine-bearing Ir catalyst for ortho-borylation) (*25*), Fernandez *et al.* (hemilabile ligand system for iridium-catalyzed ortho-borylation) (*43*), Smith *et al.* (P/N-Si bidentate monoanionic ligand system for ortho borylation) (*40*), Li *et al.* (pyridineboryl ligand) (*44*), and Chattopadhyay *et al.* (*N*,*C*-bidentate monoanionic ligand, known as PYT ligand) (Fig. 1H) (*45*). Notably, while all the reported C—H borylation reactions undergo via the generation of the tris(boryl)Ir complex, the catalytic cycle introduced by Smith and Maleczka (*40*), Li (*44*), and Chattopadhyay (*45*) proceeds via the formation of a bis(boryl)Ir complex, which is distinct from the traditional catalytic cycle, although the overall cycle follows the Ir(III)-Ir(V) pathway. In this context, while substantial efforts have been devoted toward the development of ortho C—H borylation of arenes as well as heteroarenes, which added a great dimension to the C—H borylation reactions, albeit remote C—H borylation of those substrates are still scarce. It can be understood considering the highest distance between the functional/directing groups of the substrates and the remote C—H bonds. However, despite the above-mentioned critical challenges for the remote C—H bond activation and borylation reactions, many pioneering studies revealed that suitable catalyst design, ligand design, use of various noncovalent interactions, and tuning other important factors can afford a straightforward solution for these remote C—H borylation reactions (Fig. 1G, d) (*22*). In this review article, we have sought to highlight the recent developments for the remote C—H borylations and its evolution that has now been considered as an emerging synthetic tool.

## STERICALLY CONTROLLED REMOTE C—H BORYLATION

### Sterically controlled meta-selective C—H borylation

Control of regioselectivity in C—H borylation is always a challenging task for the organic chemists, and it was started developing in the realm of discovery of C—H borylation reactions. In 2000, the Smith group (*46*) reported Ir- and Rh-catalyzed arene C—H borylation, where they described a comparative study between Ir catalyst and Rh catalyst. It was observed that while iridium-catalyzed (**8**) C—H borylation of benzene took 120 hours to afford 53% yield, Rh catalyst (**11**) completed this reaction within 2.5 hours with an improved yield of 92% (Fig. 2A). Moreover, it was seen that Rh catalyst (**11**) played a notable role over the iridium catalyst (**8**) for the regioselective borylation of 1,3 disubstituted arenes with respect to the improved outcome of the borylation. For example, while rhodium catalyst (**11**) resulted in ortho-selective borylation of amide functionality with isomer ratio (ortho/meta/para = 4.17/1.98/1), iridium catalyst (**8**) failed to do the borylation. The ortho borylation of amide can be attributed due to the coordinating effect of the amide carbonyl to the metal center. The mechanism of the Rh-catalyzed C—H borylation of arenes can be understood from the Rh-catalyzed C—H borylation of alkane disclosed by the Hartwig group (*47*), where Rh-mono boryl complex was the active catalytic intermediate (Fig. 2A, a). Smith *et al.* (*35*) also reported the regioselective meta-borylation of a 1,3-disubstituted arenes with a new type of iridium catalyst (**12**) using a phosphine ligand They found that the reaction can further be improved compared to previous iridium catalyst (**8**) along with the selective borylation of the 1,2-disubstituted arenes. While 1,2- and 1,3-disubstituted arenes were proved to be the viable substrates that produced site-selective C—H borylation, the mono-substituted iodobenzene resulted in a mixture of isomers with 79% meta-selectivity (Fig. 2B).

The breakthrough discovery of bidentate bipyridine ligand enabled C—H borylation (*36*) made the regioselective borylation of 1,3-disubstituted arenes more practicable at a comparatively lower temperature than the phosphine ligated catalysts (**8**, **9**, and **11**) (*34*, *35*, *46*). With the developed BPy-based ligand system, Hartwig and coworkers (*36*) discovered a regioselective meta-borylation of 1,3-disubstituted arenes with high isolated yields (Fig. 2C). Later, this strategy was applied to the meta functionalization of different arenes having 1,3-disubstitution via meta-C—H borylation (*23*). Smith group (*48*) reported a unified one pot borylation and oxidation strategy for the synthesis of phenols, which overcomes the requirement of multistep synthesis to prepare the 5-hydroxy-1,3 disubstituted arenes. The origin of the meta selectivity is controlled by steric factor between the boryl group attached to the iridium metal in iridium tris(boryl) complex and substituent present in the arene ring (Fig. 2D) (*23*). Notably, this strategy was taken up by the Merck process chemistry laboratory for the kilogram scale synthesis of Doravirine (**13**), a non-nucleoside reverse transcriptase inhibitor (Fig. 2D) (*49*).

This unified sterically controlled C—H borylation process was successfully applied to some other developments like C6 borylation of silyl group protected indole derivatives using 1,10-phen as the bidentate ligand by the Baran group (*50*). With this developed synthetic protocol, they performed C6-selective borylation of tryptophan derivative (**14**) with 89% selectivity, and the borylated tryptophan (**15**) was applied for the total synthesis of bioactive alkaloids fumitremorgin A (**16**) and verruculogen (**17**) in 2015 (Fig. 2E). A high catalyst loading and excess boron reagent is required for the borylation of various 3-substituted indole derivatives. The origin of high selectivity is fully governed by the steric crowding between the catalyst and the substituents present in the substrates. Moreover, the method had also been used for the total synthesis of teleocidins B-1 to B-4 via the C6 borylation of silyl group protected indole derivatives on a gram scale (*51*).

Thus, it is evident from the abovementioned pioneering examples (Fig. 2, A to E) that while simple bipyridines are the best choice of ligand frameworks to achieve the meta-selective borylations that are solely controlled by the steric, the same ligand frameworks are found to be incompatible for mono-substituted substrates that normally provide a mixture of isomers. Monosubstituted arenes do not provide enough steric congestion with bipyridine-Ir catalyst systems for the regioselective meta-C—H borylation reactions (*23*, *24*, *52*). As a result, introduction of a boron group selectively to the mono-substituted arenes is extremely challenging and thus demanding as well. In this scenario, very recently, the group of Ilies (*53*) discovered an elegant strategy for the meta-selective borylation of a range of mono-substituted arenes using a spiro bidentate bipyridine ligand (**L5**) framework (Fig. 2F). The initial studies were performed using a number of ligands with the tert-butyl benzene as a model substrate, which gave appreciable amount of meta-borylation (meta/para = 4/1) in the presence of dtbpy ligand. Employment of a modified defa ligand (**L1**) resulted in poor selectivity (meta/para = 3.1/1) compared to the standard dtbpy ligand. Upon slight modification of the ligand (spirobidenate ligand) with phenyl substitution (**L3**) proved to be better ligand framework that gave improved meta selectivity (meta/para = 7.5/1). Slight improvement (meta/para = 8.3/1) occurred upon introducing a silyl group at the phenyl ring (**L4**). But the highest meta-selectivity (meta/para = 23/1) was achieved when a Bpin group is installed in the ligand system (**L5**). In this context, it is important to note that since substantial amount of the meta,meta diborylation occurred, thus the meta-selectivity was calculated by combining meta and meta,meta diborylated isomers. This developed ligand framework (**L5**) was found to be excellent for a range of arenes bearing several functional groups. The meta selectivity is found to be less for the 1,2-disubstituted arenes compared to the monosubstituted arenes. The authors speculated that the origin of the remote meta-selectivity is solely controlled by the steric effects of the ligand environment that was further supported by the density functional theory (DFT) calculation. They envisioned that the ligand (**L5**) creates a roof top by the ligand substitution, which creates a steric shield with the substituent of the substrate. On the other hand, for the meta-selective approach, this steric shield of the ligand roof top with the substrate's substitution does not hamper and favors the high meta-selective borylation reactions (Fig. 2F).

### Sterically controlled para-selective C—H borylation

While the last few years have realized excellent developments in the remote meta-selective C—H borylation reactions, the developments of remote para-C—H borylation (*54*) reactions are significantly less compared to the meta-C—H functionalization. Thus, realizing remote para-selectivity in arene C—H bond borylation is a great challenge but is extremely important and desirable. The reason for this challenge may be understood considering the highest distance of the para-C—H bond of arenes with the interacting metal

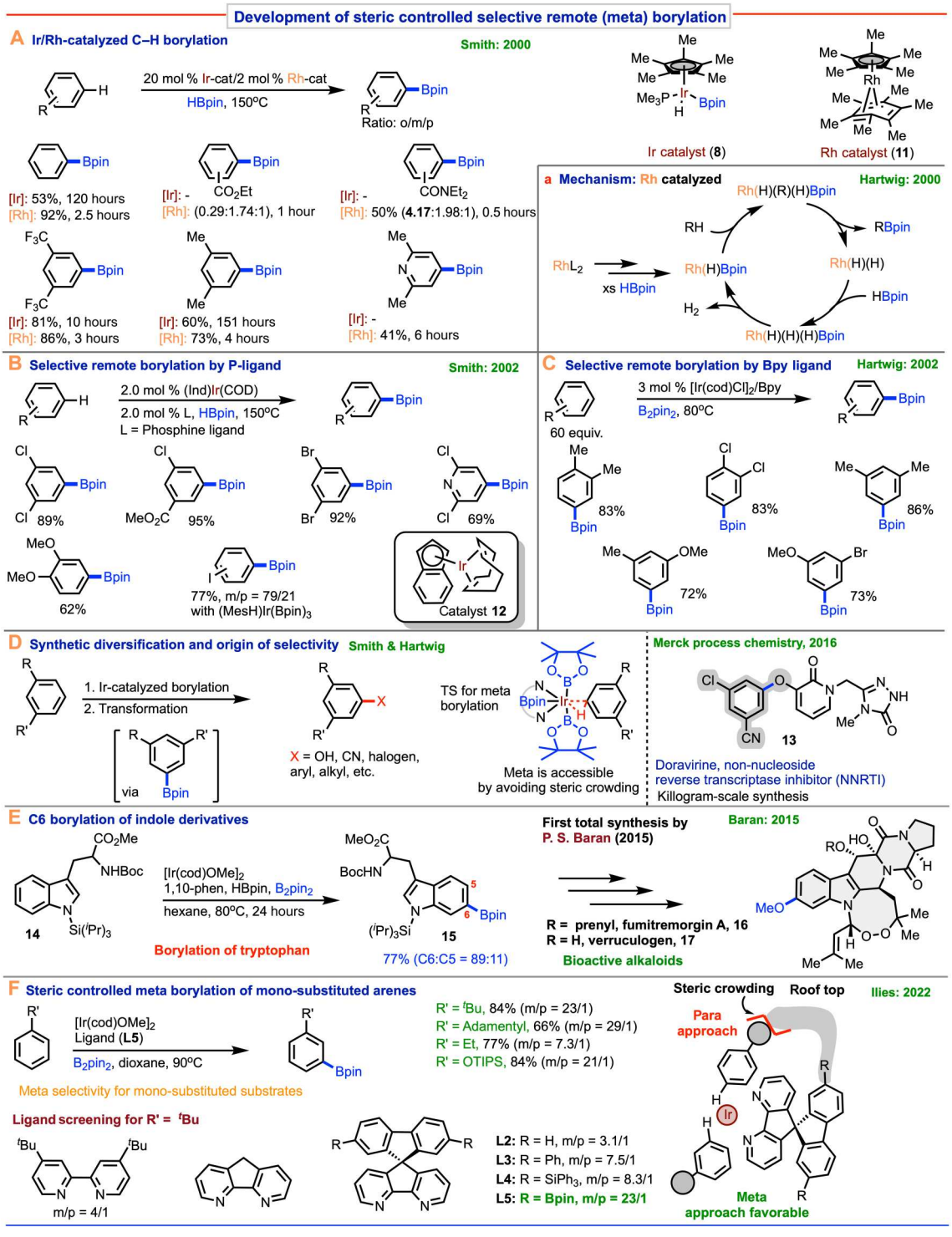


**Fig. 2. Development of steric controlled remote meta-selective borylation.** (**A**) Ir/Rh catalyzed C—H borylation (*46*, *47*). (**B**) Selective remote borylation by P-ligand (*35*). (**C**) Selective remote borylation by Bpy-ligand (*36*). (**D**) Synthetic diversification and origin of selectivity (*23*, *48*, *49*). (**E**) C6-borylation of indole derivatives (*50*, *51*). (**F**) Steric controlled meta-borylation of mono substituted arenes (*53*).

center. In 2005, Smith group (*55*) noticed that a Bpin group attached with an arene had some para-directing effect at room temperature that can provide up to 64% para selectivity, which was then revalidated by Tajuddin *et al.* (*52*) that bis-(2,4,6-trimethylphenyl) boryl group can enhance the para selectivity up to 68%. Subsequently, Hata *et al.* disclosed para borylation of porphyrin ring with 86% selectivity, and the origin of para selectivity was due to the bulkiness of the porphyrin group (*56*). Thus, although a common para-C─H borylation reaction could considerably accelerate the development of this field of research, unfortunately, examples of para-borylations are extremely restricted.

In 2015, Itami *et al.* (*57*) reported an elegant approach for the iridium-catalyzed para-selective borylation of arenes containing large substituents with the bulky bidentate phosphine ligand (**L6**). The origin of the para-selectivity is fully governed by the steric crowding between the large substituents of the substrate and bulky phosphine ligand. The screening results showed the importance of the developed ligand (**L6**). While trimethyl silyl benzene in the presence of the standard dtbpy ligand afforded 74% meta selectivity, ligand (**L6**) switched the selectivity from meta to 88% para isomer. The developed method was found to be well applicable for a range of ortho-disubstituted arenes, although the 1,3-disubstituted arenes resulted in meta-borylation. It was also found that no borylation occurred with the arene bearing a bulky tert-butyl group at the meta positions, which clearly indicated that the bulky groups in the ligand create sufficient amount of steric shield that hampered the reaction (Fig. 3A, a). It was also observed that with decreasing the bulkiness of the substituents, the para-selectivity getting diminished. The developed method was then showcased for the late-stage para-C─H borylation of caramiphen drug with 83% para selectivity (Fig. 3A, b). The mechanistic details were disclosed by Haines *et al.* for the para-selective borylation of arene containing bulky substituents with bulky Meo-Xyl-BIPHEP ligand (**L6**) by computational analysis (*58*). In this study, the authors concluded that a reaction pocket was created by the combination of the Ir-catalyst, ligand (**L6**), and $B_2pin_2$, and the substrates that enter into this

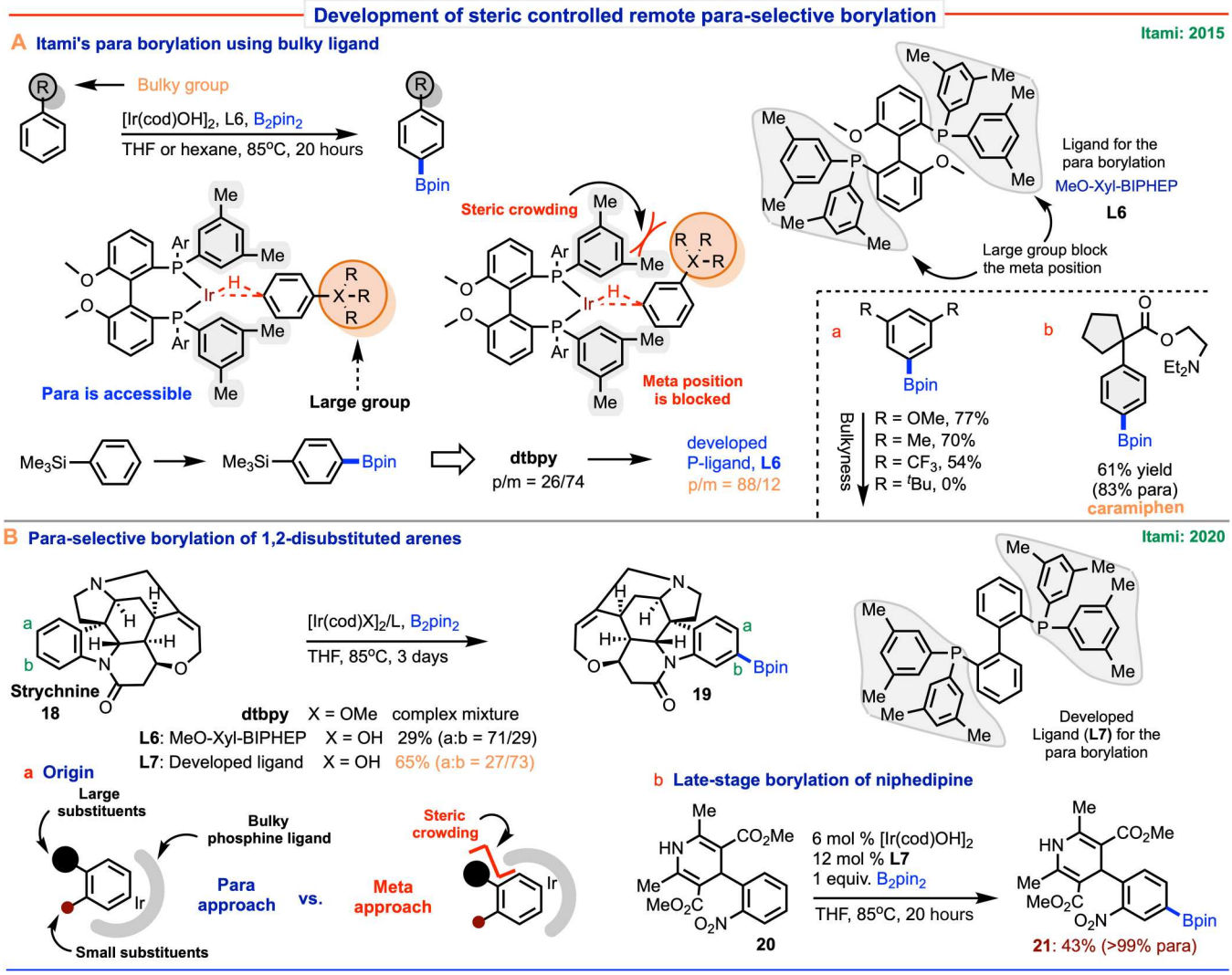


**Fig. 3. Sterically controlled para-CH borylation.** (**A**) Itami's para-borylation using bulky phosphine ligand (*57*). (**B**) Para-selective borylation of 1,2-disubstituted arenes (*60*).

supramolecular pocket for the para-C—H borylation as meta-approach were hindered by the steric crowding. In 2017, Zhu *et al.* demonstrated (*59*) another alternative mechanism of this para-borylation reaction by DFT calculation. They disclosed that in the presence of bulky phosphine ligand (**L6**), Ir(I) to Ir(III) catalytic cycle occurred instead of the Ir(III) to Ir(V) catalytic cycle. The computed analysis supports the experimental observation of the major para isomer, and it disproves the possible formation of meta isomer predominantly due to the high energy barrier.

In 2020, the same group revisited their para-borylation method and redesigned a new ligand framework (**L7**) (*60*) for the 1,2-disubstituted arenes. This developed method using the redesigned ligand (**L7**) was successfully applied for the borylation of strychnine (**18**). The importance of the method was demonstrated by the para-selective borylation of a range of 1,2-disubstituted arenes having one bulky substituent over previously developed ligand (**L6**) as it resulted in 71% meta-selective borylation with respect to the bulky substituents. The origin of the para-selectivity is explained by the steric shielding between the bulky substituents and the bulky phosphine ligand, and para-borylation occurred with respect to the large substituents of the 1,2-disubstituted arenes (Fig. 3B, a). Moreover, the developed method was further showcased for the late-stage borylation of niphedipine drug that resulted in exclusive para-borylation with 43% isolated yield (Fig. 3B, b).

In 2022, when Ilies *et al.* (*53*) reported a meta-selective borylation of mono-substituted arenes using a defa ligand system, at the same time, our group reported a para-C—H borylation of twisted aromatic amides containing bis-Boc group (**20**) with a new type of bidentate defa ligand framework (**L1**), which we call as the first generation defa ligand (Fig. 4A) (*61*). The steering group optimization with the dtbpy ligand indicated that increasing the twisted nature of the amide functionality and electron-withdrawing properties, para-selectivity gradually increases to 64% (para/others = 1.8/1) from 40% (para/others = 1/1.5). After careful investigation, it was found that while the defa ligand (**L1**) afforded 95% para-borylation (para/others = 20/1), simple bipyridine ligand gave 71% para-selectivity (para/others = 2.5/1). The developed method was used for a number of substrates containing different substituents in the aromatic ring, which afforded excellent para selectivity; however, the method was found to be limited for the para-borylation for those

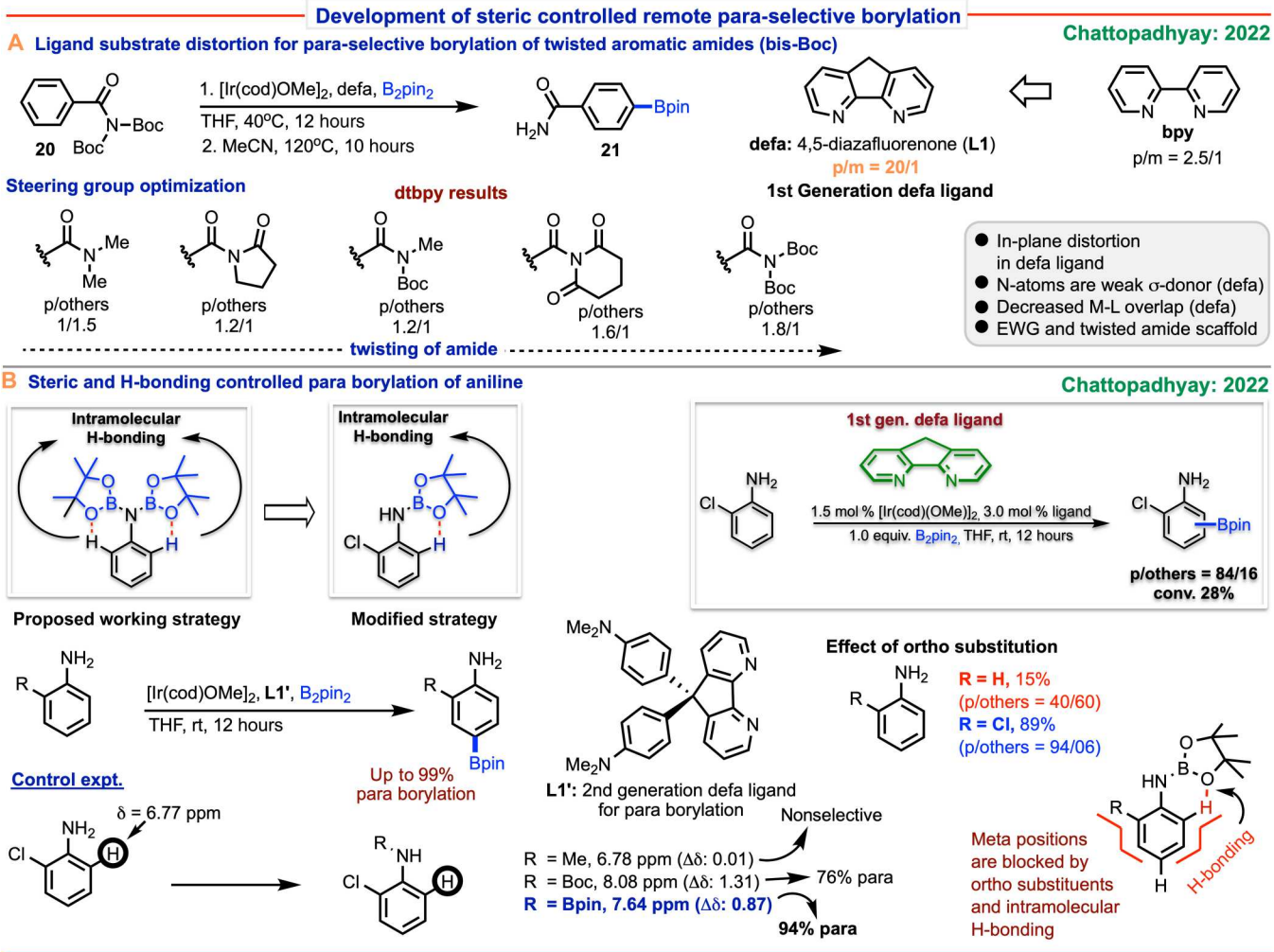


**Fig. 4. Sterically controlled para-CH borylation.** (**A**) Ligand-substrate distortion for para-selective borylation of twisted aromatic amides (bis-Boc) (*61*). (**B**) Steric and H-bonding controlled para-borylation of aniline (*63*).

substrates having a substituent at the 3-position except in few cases. The utility of this developed method was showcased by the removal of bis-Boc group from the para-borylated product by heating in acetonitrile solvent at 120°C (*62*). From several experimental findings and DFT calculations, it was concluded that the high degree of the para-selectivity can be understood considering the substantial amount of the distortion between the defa ligand and twisted aromatic amide substrate.

For further employment of our first generation defa ligand (**L1**) in remote borylation, we then targeted unprotected anilines. We hypothesized that if a bis-borylated aniline (Fig. 4B) can be formed in situ, then both the ortho hydrogens will be blocked by the intramolecular H-bonding with the oxygen atoms of the N—Bpin group, and if so, this will automatically create a steric shield at the meta positions and thus the only available position for the borylation will be para position (Fig. 4B). Unfortunately, even after several attempts, we failed to make the bis-borylated aniline due to the huge steric crowding between the two Bpin units around the N atom. Thus, we had to modify our original design principle. The modified design plan was putting a substituent at the ortho position that will a create shield next to its C—H bond (i.e., one of the meta positions of the aniline) and in situ generation of mono-borylated aniline. As a result, the ortho hydrogen atom will be blocked by an intramolecular H—bonding, and the other meta-C—H bond will be inaccessible due to its steric shield. Following this hypothesis, borylation of 2-chloroaniline was performed using our first generation defa ligand that gave a good amount of para-selectivity (para/others = 84/16), although conversion was not great (28%), which indicated the necessity of the next generation defa ligand.

Accordingly, when the same reaction was performed using our second generation defa ligand framework (**L1′**), it resulted in high level of para-selectivity (*63*). The para-selective borylation underwent with the formation of the in situ N-Bpin aniline intermediate. The electronics of the developed ligand (**L1′**) promotes the para-borylation at room temperature without the need of any pre-protection steps. Performing several control experiments, it was realized that to achieve high para-selectivity, it is necessary to have an ortho substitution at the substrate; otherwise, nonselective borylation may occur. For example, the unsubstituted aniline resulted in only 40% para-selective borylation. Moreover, the method also failed to afford high para-selectivity for the 3-substituted substrates. Several nuclear magnetic resonance (NMR) experiments indicated that with protection of electron-withdrawing group having heteroatom resulted in intramolecular hydrogen-bonding with the ortho C—H proton (C—H…O hydrogen bond). It was found that Boc protection gave 76% para-selective borylation, and Bpin protected aniline gave 94% para-borylation. These sets of control experiments concluded that both ortho substitution and intramolecular hydrogen bond block the meta position and resulted in para-selective C—H borylation.

## WEAK INTERACTIONS FOR REMOTE C—H BORYLATION

### Attractive weak interactions for meta-selective C—H borylations

While sterically controlled remote C—H bond activation and borylation is one of the most attractive strategies, it has many limitations. For example, design and synthesis of bulky ligand frameworks, narrow substrate scope, selectivity issues, and so on enormously limit the scope of this strategy. To address these issues, alternative methods are highly warranted, and one such important concept is the attractive weak noncovalent interaction guided remote C—H bond activation and borylation. As discussed earlier, catalytic C—H bond borylation (*22*, *26*) is one of the most powerful synthetic strategies that offers immense synthetic benefits in terms of atom, step, and redox economy, provided that it is equally reactive and selective. However, simultaneously realizing both high reactivity and selectivity might be extremely difficult. It is often assumed that a strong catalyst-substrate interaction (*64*) is the key to obtain the best selectivity. However, a strong catalyst-substrate interaction occasionally may be a death penalization for the reactivity. Thus, to get both the high reactivity and selectivity, it is essential to have an excellent balance between these two important factors. In this context, various types of attractive weak noncovalent interactions may be the alternative options to tackle this challenging issue. Usually, these types of weak attractive noncovalent interactions may be routinely observed in biological systems (Fig. 5A) (*65*) and in organo-catalysis (*66*).

For instance, these interactions are recognized in hydrophobic-hydrophobic interactions between the cyclodextrins and steroids in the C—H hydroxylation reactions, host–guest size–differentiated C—H functionalization processes, hydrogen bond–directed C—H bond functionalization strategies, enantioselective synthesis, and so on. Contrastingly, even few years back, it was extremely difficult to think about these weak interactions to use in the transition metal catalyzed C—H bond activation and borylation reactions. As a result, if one can integrate these two parameters, i.e., attractive weak noncovalent interaction and transition metal catalyst, then it would certainly be an extremely powerful approach to develop new concept and hypothesis in the C—H bond activation and borylation chemistry, which would eventually enable to invent smart technologies in organic synthesis. A proper strategy may be something like that where a functional group of the substrate will recognize the noncovalent interacting site of the designed ligand via weak interactions. As a result, the C—H bond of the substrate will be oriented in such a way that the metal will be interacting one particular C—H bond among several similar types of C—H bonds and will be functionalized accordingly, leading to the high degree of site selectivity (Fig. 5B).

In 2015, Kuninobu *et al.* (*67*) introduced a new type of ligand framework (**L8**) containing a hydrogen bond donor urea moiety that is far from the core bipyridine ligand unit for the meta-selective borylation of arenes bearing a number of functional groups (Fig. 5C). In this report, they disclosed that the meta-selective borylation can be realized under iridium-catalyzed conditions using this designed ligand framework (**L8**). While various 2-substituted amides resulted in good to excellent meta-selectivity, the same reaction underwent nonselective for the 4-substituted amides that may be attributed considering the steric crowding between the substituent at the 4-position and C—H activation site. They postulated that the oxygen atom of the carbonyl group may be engaged through an intramolecular H—bonding interaction with the ligand that would guide the pattern of the remote selectivity. As a proof of concept, the authors performed several control experiments including some crucial NMR titrations between the ligand (**L8**) and substrates and found that the NH proton of the urea moiety gets deshielded due to the hydrogen-bonding interaction with the amide carbonyl oxygen atom. To prove it further, the

ligand (**L11**) was used in the NMR titration and observed no change in the chemical shift value. Moreover, it was found that the ligand (**L11**) resulted in a nonselective borylation reaction (Fig. 5C). In continuation of the hydrogen-bonding–guided meta-C—H borylation of amide, in 2019, the same group reported that the catalytic activity of the catalyst can even be accelerated with the ligand (**L9**) by modifying the ligand (**L8**) via methyl incorporation. It was observed that incorporation of a tert butyl group at the bipyridine core of the ligand (**L9**), the ligand (**L10**) accelerates the reaction rate by three times than the ligand (**L9**) (*68*). Later on, Sunoj

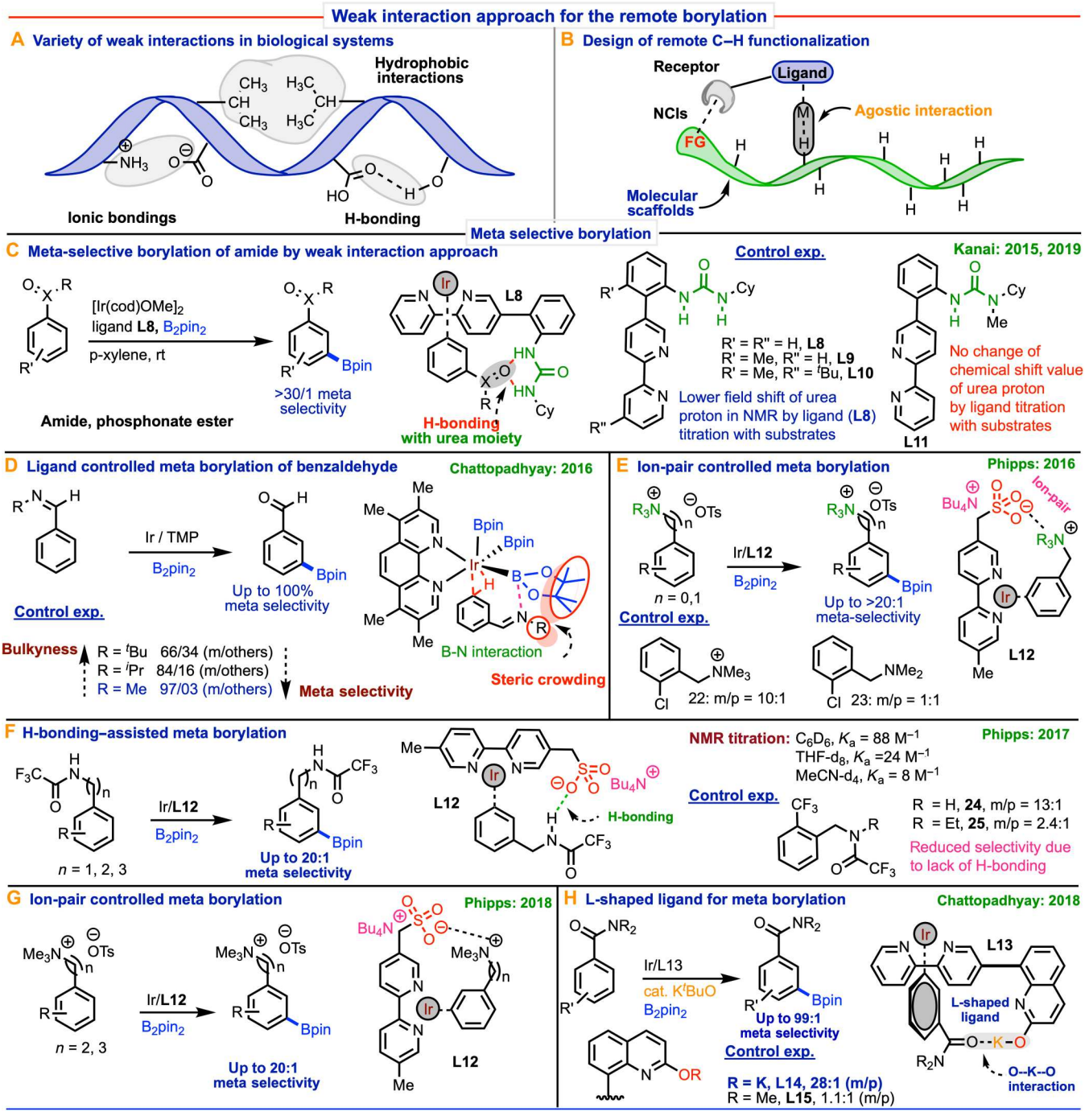


**Fig. 5. Weak interaction approach for the remote meta-selective CH borylation.** (**A**) Variety of weak interactions in biological systems (*65*). (**B**) Design of remote C—H functionalization. (**C**) Meta-selective borylation of amide by weak interaction approach (*67*, *68*). (**D**) Ligand controlled meta-borylation of benzaldehyde (*70*, *71*). (**E**) Ion-pair controlled meta-borylation (*72*). (**F**) H-bonding assisted meta-borylation (*73*). (**G**) Ion-pair controlled meta-borylation (*74*). (**H**) L-shaped bifunctional ligand for meta-borylation (*76*).

and Unnikrishnan (*69*) performed detailed DFT calculations, which concluded that hydrogen-bonding interaction is the major contributing factor to the remote meta-C—H borylation of amides.

At the same time, in 2015, our group introduced a concept for the remote meta-selective C—H borylation of aromatic aldehydes via the in situ generation of imines using a commercially available tetramethyl phenanthroline ligand (Fig. 5D) (*70*, *71*). In this report, it was proposed that an electrostatic interaction and a boron-nitrogen interaction may control the meta-selectivity. It was observed that a number of substrates can efficiently be borylated using the developed reaction conditions. However, the choice of amine as the traceless protecting and directing group plays a significant role. For example, while use of tert-butylamine as the directing group, it was observed that there is a trade-off between the weak interaction and steric factor for the 2- and 4-substituted aromatic aldehydes. However, when using primary amine, no such type of issues was found. Notably, the main drawback of this developed method is the requirement of the excess amount of the amine for the imine generation.

In 2016, Phipps *et al.* (*72*) designed an anionic ligand (**L12**) for the iridium-catalyzed meta-selective borylation of quaternary ammonium salts of aniline and benzylamine (Fig. 5E). The developed method showed high selectivity for a range of substrates containing different substitution in the arene ring, but unsubstituted arenes resulted in meta,meta diborylated products instead of the mono-borylated product. The purification of meta-borylated product was also difficult due to the presence of cationic and anionic counter parts in the substrates. The origin of the meta-selectivity is governed by an attractive ion-pair interaction between the cationic ammonium part of the substrate and the anionic sulfonate group of the ligand (**L12**). To prove the ion-pair interaction, the authors performed several control experiments, where 2-Cl tri-methyl benzyl ammonium salt (**22**) was compared with the 2-Cl dimethyl benzylamine (**23**) with the ligand (**L12**). They found that due to lack of cationic counterpart, the substrate (**23**) resulted in a nonselective borylation as there was no scope for the ion-pair interaction. For further utilization of the same ligand system (**L12**), the same group applied the meta-selective borylation of N-protected benzylamine substrates that smoothly underwent the borylation reaction via the hydrogen-bonding interaction between the ligand and N—H proton of the substrate (Fig. 5F) (*73*). The method exhibited excellent reactivity and selectivity for a range of substituted benzylamines including those benzylamine substrates having extended chain length. Moreover, unsubstituted benzylamines also proved to be excellent substrates for the meta-selective borylation, although they afforded exclusively meta,meta diborylated products instead of the mono-borylated products. Apart from the benzylamines, unsubstituted acetanilide gave 92% meta-selectivity, but due to steric reason, 2-substituted acetanilide provided nonselective borylation. To prove the hydrogen-bonding interaction between the ligand and substrate, an NMR titration experiment was carried out using deuterated solvents. From the titration results, a strong association was observed even in highly polar acetonitrile solvent. A background titration with a 5,5′-dimethyl bipyridine ligand lacking an anionic sulfonate group resulted in no association between the substrate and the ligand. For better understanding of the H-bonding interaction, they performed another control experiment using the substrate (**25**) having N-protected ethyl group that resulted in nonselective borylation compared with meta-selective borylation of the substrate (**24**) as the substrate (**25**) is devoid of N—H proton for the hydrogen-bonding interaction (Fig. 5F). In 2018, Phipps and coworkers demonstrated (*74*) that the designed ligand (**L12**) is also efficient for the meta-selective borylation of substrates bearing extended chain length of the nitrogen substitution (Fig. 5G).

In 2017, after developing the para-selective borylation of aromatic ester designing a bifunctional L-shaped ligand (**L13**) (*75*), we were curious whether the same bifunctional ligand (**L13**) would be suitable for the remote C—H borylation of aromatic amides. The reason for this curiosity was because of the contrasting structural properties between the aromatic esters and amides (*62*). Thus, we hypothesized that the borylation would undergo via either a distorted O····K noncovalent interaction leading to the meta-selective borylation, or if not, then it would follow a normal O····K noncovalent interaction leading to the para-selective borylation. So, following this hypothesis, we performed the borylation and found that the reaction goes via a distorted O····K noncovalent interaction leading to the meta-borylation. Since this borylation follows an O····K distorted noncovalent interaction, thus chain length of the alkyl groups played a significant role that can be understood with the switchable meta-selectivity of the substrates bearing various *N*,*N*-disubstituted alkyl groups of amides (Fig. 5H) (*76*). The developed method with a catalytic amount of KO$^t$Bu showed a broad spectrum of substrate scope for the meta-selective borylation of amides. It has been found that relatively less meta selectivity was observed for the amides containing *N*,*N*-dimethyl groups. To know the actual governing factors for the origin of the meta selectivity, several control experiments were performed using the other designed ligands such as (**L14**) and (**L15**). It was observed that while the ligand (**L14**) afforded high degree of meta-selectivity (meta/para = 28/1), the ligand (**L15**) resulted in nonselective borylation that clearly indicates the role of the catalytic amount of the KO$^t$Bu, which generates the O····K unit that might eventually interact with the carbonyl oxygen atom of the amide functionality and control the regioselectivity.

Meanwhile, Nakao and coworkers (*77*) reported two bifunctional ligands (**L16** and **L17**) for the meta borylation of aromatic amides and pyridines under iridium-catalyzed conditions (Fig. 6A). The designed ligand (**L16**) having an aluminum binding site participated in Lewis acid-base interaction with the amide carbonyl group for the meta-selective borylation. The control experiment using the ligand (**L18**) having a protected biphenolic unit with the MOM group resulted in nonselective borylation, which indicated that Al acted as key controlling factor for the Lewis acid-base interaction. Notably, the method was found to be effective to produce meta-selective borylation reactions only for 2- and 3-substituted aromatic amides. On the other hand, the designed ligand (**L17**) bearing a boron functionality at the ligand part takes part in Lewis′s acid-base interaction with the pyridine nitrogen atom for the C3-selective borylation of pyridine substrates. The control experiment with the ligand (**L19**) in the absence of a boron functionality resulted in nonselective borylation. The developed method demonstrated its utility for the meta- and C3-selective borylation of a number of aromatic amides and pyridines, respectively, with the designed ligands.

In the context of the remote meta-borylation by the catalyst/ligand design concept, while several powerful approaches appeared in last few years, in sharp contrast, no methods were reported for the enantioselective meta-borylation until recently by the Phipps group

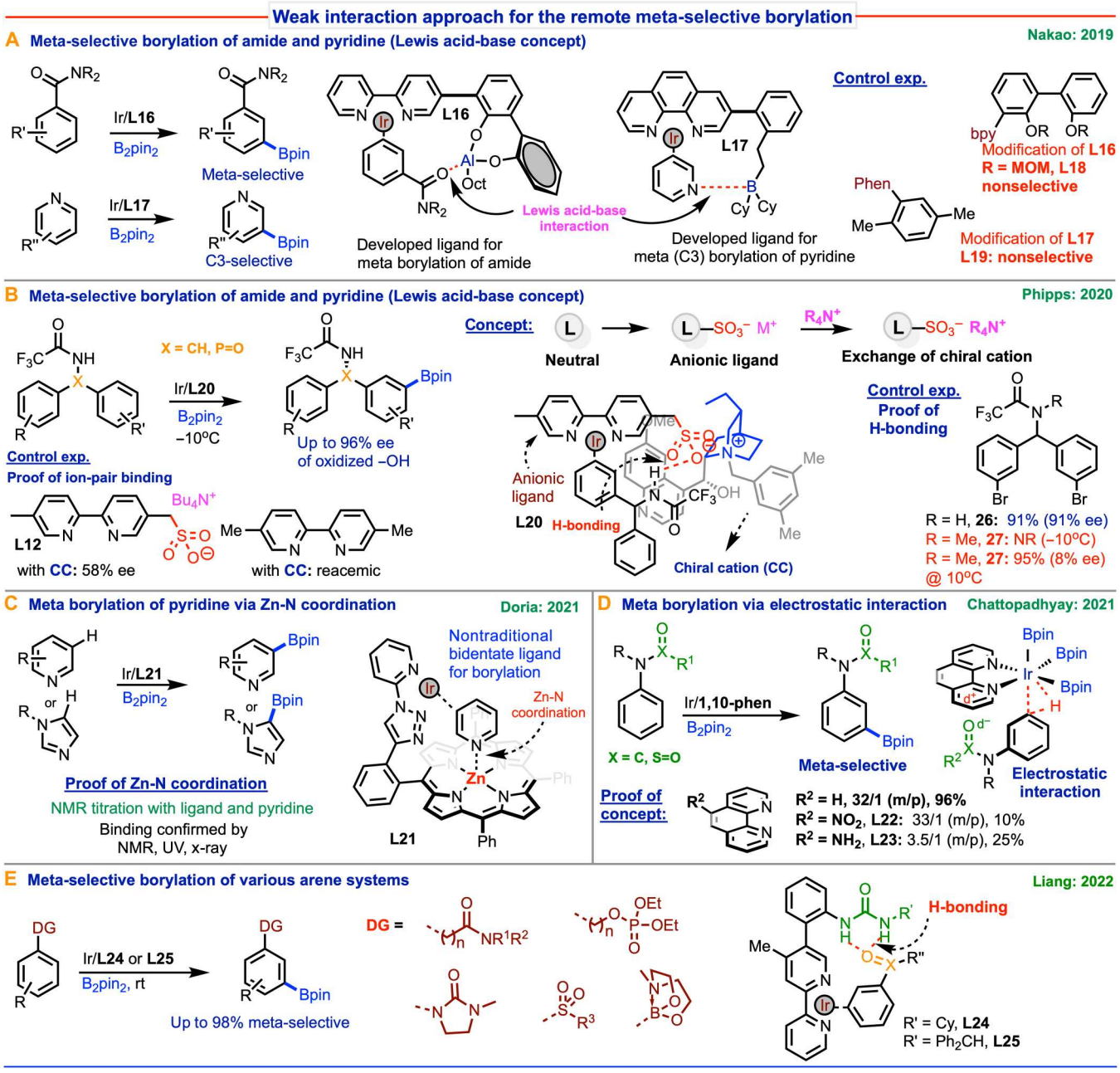


**Fig. 6. Weak interaction approach for the remote meta-selective borylation.** (**A**) Meta-selective borylation of amide and pyridine (Lewis acid-base concept) (*77*). (**B**) Meta-selective borylation of amide and pyridine (Lewis acid-base concept) (*78*). (**C**) Meta-borylation of pyridine via Zn-N coordination (*79*). (**D**) Meta-borylation via electrostatic interaction (*80, 81*). (**E**) Meta-selective borylation of various arene systems (*82, 83*).

(Fig. 6B) (*78*). In 2017, Phipps group (*72*) developed an anionic ligand (**L12**) having a counter tetrabutyl ammonium cation for the meta-C—H borylation. At this point, they hypothesized that if the achiral counter cation can be replaced with the chiral cinchona-based cation, then asymmetric chiral center may be generated in the molecule. Following this hypothesis, they synthesized ligand (**L20**) for the borylation that resulted in highly regioselective meta-C—H borylation with excellent enantioselectivity at −10°C temperature. The developed reaction conditions were found to be well applicable to the phosphoramide substrates as well. The main prevailing factor for the enantioselective meta-C—H borylation is the hydrogen-bonding with the anionic sulfonate group and ion-pair interaction between the ligand anionic part and the counter chiral cation (**CC**). To prove this hypothesis, they had performed various control experiments. For example, the substrate (**27**) that lacks free N—H group was used in the reaction conditions, which resulted in nonselective borylation as compared to the substrates (**26**) having a free N—H group that afforded 91% enantioselectivity. Increasing the reaction

temperature to 10°C, although the substrate (**27**) gave 95% conversion, the enantioselectivity dropped to only 8%. This result indicated that the hydrogen-bonding interaction is one of the major contributing factors that controls the meta selectivity. Moreover, to see the effect of the ion-pair interaction, the ligand (**L12**) was used along with the **CC** in the reaction which afforded the enhanced enantioselectivity (58%). Furthermore, it was observed that 5,5′-dimethyl bipyridine ligand along with the **CC** gave a racemic mixture of the meta-borylated products (Fig. 6B). These two experiments proved that both the ion-pair and hydrogen-bonding interactions played as a major contributing factor for the enantioselective meta-C—H borylation reaction.

In 2021, Doria and coworkers (*79*) reported a method for the Ir-catalyzed C3-selective borylation of pyridines and some other heteroarenes using a new type of porphyrin-derived ligand (**L21**). The ligand is slightly different from the conventionally used bidentate nitrogen ligands (Fig. 6C). The designed ligand framework entails of a Zn-incorporated porphyrin unit and a pyridyl triazole unit. The origin of the selective borylation of pyridines was realized by a weak secondary interaction between the pyridine nitrogen atom and Zn atom attached with the porphyrin unit of the catalyst system. The authors stated that the developed catalyst system behaves as an enzyme-like supramolecular framework. To gain some understanding of the enzyme-like behavior of this catalyst system, the authors conducted NMR and ultraviolet experiments for the measurement of the binding constant between the Zn-coordinated ligand and pyridine, which indicated the postulated interaction between the Zn atom and pyridine′s nitrogen atom. Moreover, cocrystallization of the ligand and pyridine further supported that the Zn indeed binds with the pyridine′s nitrogen atom. The postulated cationic iridium complex that was formed by the reaction between the ligand and iridium precatalyst was confirmed by NMR and high-resolution mass spectrometry (HRMS) studies. Furthermore, the ligand titration experiment between the cationic complex and pyridine confirmed that the externally added pyridine was coordinated with the Zn atom. Notably, it has been found that solvent plays a significant role for the successful borylation of these heterocycles. The authors reported that 4-substituted pyridines and pyrimidines failed to provide borylated products due to steric crowding under their developed reaction conditions.

In 2021, our group reported a meta-selective borylation strategy of arenes bearing a range of functional groups using an electrostatic interaction (Fig. 6D) (*80*, *81*). It deserves mentioning that for meta-selective borylation, the commonly used substrates are those arenes bearing a substituent either at the 2-position, 3-position, or substituents at the 2,3-positions. However, meta-borylation in the presence of a substituent at the 4-position is extremely challenging because of the steric effects. Moreover, borylation of mono-substituted arenes bearing electronically distinct functional groups is also challenging. Thus, considering all these challenges, we envisioned that it would be highly desirable to develop a method that would overcome all these shortcomings. Upon careful screening of various ligand frameworks, we observed that the commercially available 1,10-phenanthroline ligand that is not normally used in the C—H borylation reaction can efficiently be used to direct the boron functional group at the meta position of a range of arenes bearing several functional groups. The main concept of this strategy was the creation of an electrostatic interaction between the partial positively charged ligand framework and the partial negatively charged functional group of the substrates. To prove the proposed hypothesis, a series of ligands were screened where ligand (**L22**) containing electron-withdrawing nitro group resulted in almost the same selectivity as 1,10-phen ligand of 32/1 (meta/para) meta-selectivity, whereas ligand (**L23**) containing an electron-donating amine group resulted in poor meta-selective borylation (meta/para = 3.5/1) under the developed iridium-catalyzed reactions conditions. This experiment indicated that with increasing electron density, the partial positive charge in the ligand system of Ir(trisboryl) complex decreased and failed to participate in the electrostatic interaction with the partially negatively charged triflate group. The developed reaction conditions were so powerful that a wide range of 4-substituted substrates that were considered an extraordinary challenge for the borylation provided meta-selective borylation regardless of the steric bulk of the substituents. However, lack of 2-substituted substrates to provide meta-selectivity somewhat limits the scope for wide application.

Liang group (*82*, *83*) recently reported a meta-selective borylation of various arenes containing different functional groups using a urea-based bipyridine ligand (**L24** or **L25**) similar to the ligand developed by the Kanai group for meta-selective borylation of amide (Fig. 6E). In this method, the authors described that the ligand was designed on the basis of the computational analysis that has demonstrated excellent efficiency toward controlling the remote meta selectivity. Using this developed method, they have shown that meta-selective borylation of different substrates containing amides, sulfonate, phosphonate ester, and mida boronate can be performed with high selectivity, although it is limited to only 2-substituted derivatives. The key controlling element for the selectivity is an intramolecular H-bonding between the ligand and substrate.

### Attractive weak interactions for para-selective C—H borylations

In 2017, Nakao group (*84*) introduced an elegant concept for the para-selective borylation of aromatic amides and pyridines. The key element of this para borylation was the catalyst-controlled remote para-borylation via a cooperative Ir/Al catalysis (Fig. 7A). For this cooperative catalysis, the authors designed a template with the help of aluminum metal. The key design principle of this para borylation was as follows: (i) use of bidentate nitrogen ligands (dtbpy or **L26**) that may form a standard catalytic system with the iridium precatalyst and (ii) a Lewis acid-base weak interaction between the Lewis base of the substrate with the template′s Lewis acidic aluminum metal, which block the ortho and meta positions. Using this cooperative Ir/Al catalysis, a wide range of *N*-substituted benzamides and pyridines were selectively borylated at the para position. The control experiment through proton NMR study confirmed that a Lewis acid-base interaction has been involved, which guides the para-selectivity. Notably, the method failed to provide meta-borylation for some of the substrates (arylketones, benzoates, arylsulfonamides, and homologous amide) having Lewis basic character.

Concurrently, in 2017, our group reported a para-selective borylation strategy for a number of aromatic and heteroaromatic esters. For that, we designed an L-shaped bifunctional tautomeric ligand (**L13**) that has two parts, such as part A and part B (Fig. 7B) (*75*). We hypothesized that this L-shaped bifunctional ligand will be suitable for the remote para-selective borylation because of the following important considerations, for example, (i) part B of the ligand

may undergo tautomerization due to the aromatic resonance stabilization leading to the more stable form; (ii) in the presence of iridium metal and boron source, the ligand will form the standard tris(boryl)Ir complex; (iii) either OH group of the tautomeric ligand or the in situ–generated O····M unit (by the use of alkali metal salts such as Li, Na, or K) will recognize the carbonyl functionality through the noncovalent interaction that will facilitate the remote para C—H activation and borylation. Following these hypotheses, borylation was performed that exhibited excellent level of para-selectivity by the use of a catalytic amount of KO$^t$Bu, which was in line with our proposed hypothesis. This reveals a very rare case of a noncovalent interaction that is being designed to realize high para-selectivity. To support the proof of concept for the proposed O····K noncovalent interaction, numerous control experiments were designed. For example, when the borylations were performed using the ligand (**L14** and **L15**), it was observed that whereas the ligand

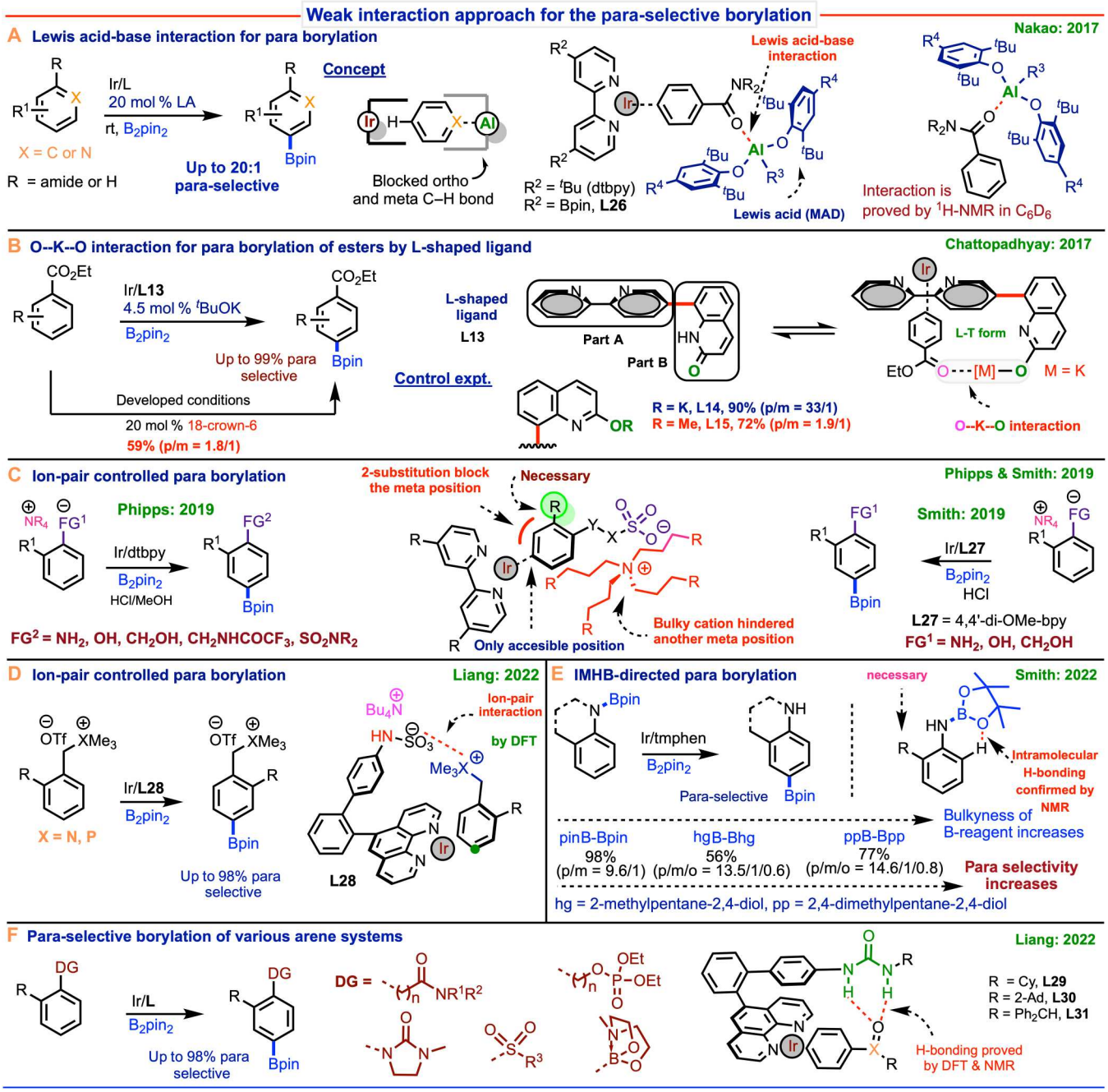


**Fig. 7. Weak interaction approach for the para-selective borylation.** (**A**) Lewis acid-base interaction for para-borylation (*84*). (**B**) O--K--O interaction for para borylation of esters by L-shaped bifunctional ligand (*75*). (**C**) Ion-pair controlled para-borylation (*85*, *86*). (**D**) Ion-pair controlled para-borylation (*87*). (**E**) IMHB directed para-borylation (*89*). (**F**) Para-selective borylation of various arene systems (*82*, *83*).

(**L14**) gave 33/1 para/meta selectivity, the ligand (**L15**) resulted in only 1.9/1 para/meta selectivity, which demonstrates the proof of concept for the O····K noncovalent interaction. To gain further experimental evidences, we performed control experiments in the presence of 18-crown-6 and found that the para-selectivity went down from 33/1 to 1.8, because of the strong binding affinity of the 18-crown-6 with the $K^+$ ion since it forms a deactivated complex which decreased the para-selectivity and supported the concept of the proposed O····K noncovalent interaction. It was observed that our developed ligand system failed to undergo borylation for simple indole which might be due to the preferential chelation between the NH group of the substrate and the catalyst. Moreover, the method does not work for some other classes of substrates, such as benzamides, arylketones, aromatic carboxylic acids, and aromatic aldehydes.

In 2019, Maleczka (*85*) and Phipps (*86*) groups independently reported a powerful concept for the para-selective C—H borylation of 2-substituted phenols, anilines, benzyl alcohols, and benzylamines via a sterically directed ion-pair interaction approach using bipyridine ligands (dtbpy or **L27**) (Fig. 7C). The proposed design principle was formulated on the basis of the following two important considerations, for example, (i) an ion-pair interaction will enforce to block one of the meta and ortho positions because of the steric bulk of the counter ion and (ii) requirement of a blocking substituent at the ortho position will also create a steric shield at the other meta position and the available position will be the para position. This is one of the most important examples that can be used to put the boron functionality at the remote para position for a number of important substrates. However, the scope of the reaction is limited to only for the 2-substituted substrates, and unsubstituted substrate and 3-substituted substrates are not compatible in this method.

In 2022, Liang group (*87*) designed an elegant ligand (**L28**) framework based on the computational analysis that was implemented successfully for the para-C—H borylation of ammonium or phosphonium salts under the iridium-catalyzed conditions through the ion-pair interaction between a substrates cationic part and a ligand anionic part (Fig. 7D). In this method of para-C—H borylation reaction, the authors modified the 1,10-phen ligand framework by attaching a noncovalent pendant sulfonate anionic part that is similar to Phipps′s anionic ligand (**L12**). With this developed method, they examined the scope of the reaction exploration and found that mostly ortho-substituted substrates are compatible in the reaction conditions. Concurrently, this group also reported an elegant method for the para-borylation of other types of substrates containing different functional groups with computationally designed ligands (**L29**, **L30**, or **L31**) having a urea pendant (Fig. 7F) (*82*, *83*). The designed strategy showed para-C—H borylation of amide, sulfonate, phosphonate ester, and midaborate substrates. The main governing factors for the para-borylation are the hydrogen-bonding interaction between the substrates′ functional group and the ligand′s urea part. To prove the concept, DFT calculation and NMR titration experiments were carried out. It was observed that mostly ortho-substituted substrates are compatible in the reaction conditions, whereas unsubstituted arenes are not compatible.

The most recent example for the para-selective borylation was reported by Maleczka and Smith in 2022. Earlier, Smith *et al.* reported (*88*) that an ortho-selective borylation can be achieved for 2-substituted anilines using a modified boron reagent using an intramolecular H-bonding concept. The groups of Smith and Maleczka (*89*) subsequently introduced a powerful concept for the remote para-selective borylation of 2-substituted anilines and some other related substrates using the commonly used boron reagent (Fig. 7E). The developed method was restricted to only ortho-substituted aniline systems, and unsubstituted aniline failed to provide para-borylation reaction since lack of ortho substitution does not block the meta position to deliver the para-borylation. The developed concept was based on the in situ generation of N—Bpin intermediate that will form an intramolecular H—bonding with one ortho hydrogen atom, which will also create a steric shield at the meta position. To prove the proposed concept, the authors performed several NMR experiments that demonstrated that indeed an intramolecular H bonding is the controlling factor for the origin of the remote para-selectivity.

### Remote C—H borylations by cobalt catalysis

Among several transition metal catalysts, iridium is one of the leading contributors for the direct C—H borylations (*22*). By the time going, a huge development of C—H borylation reactions was studied including detailed mechanistic insight. It may be stated that the C—H borylation reaction could be the ultimate solution in C—H functionalization field for the synthesis of complex molecules or arene diversification if sustainable and cost-effective development is achieved. Although the iridium catalyst is the prime catalyst for the C—H borylation reactions, an inexpensive metal catalyst is required for the cost-effective organic synthesis as iridium catalyst is very expensive. In this journey of sustainable catalytic C—H borylation reactions, an inexpensive cobalt catalyst has started to affect (*90*). The initiation and pioneering developments were made by Chirik and his team.

In 2014, they found that (PNP) pincer cobalt complex (**28**) can participate in C—H activation reaction with the arene system after treatment of $NaBEt_3H$ and MeLi, which produced Co(I)-methyl (PNP) pincer complex (**30**) and this Co(I)-methyl complex (**30**) was taking part in the activation of benzene-$d_6$ (Fig. 8A) (*91*). From this initial finding, they reported a breakthrough discovery of C—H borylation reaction using Co-pincer catalyst (*92*). Several pincer catalysts were tested for the borylation of 2-methyl furan, and the results are embedded in Fig. 8B. Among those, cobalt catalyst (**36**) gave very good outcomes with 98% conversion, and the reaction was completed within 5 hours at 60°C. With the developed reaction conditions, several other arenes were tested for the borylation reaction, and it was found that benzene afforded 98% borylated product. Moreover, it was also found that pyridine derivatives provided selective C—H borylation. While monosubstituted toluene and anisole resulted in regioisomeric mixture, 1,2 dimethyl benzene gave selective borylation. Fluorobenzene gave 89% ortho-selective borylation under the developed reaction conditions.

The mechanistic investigation with the cobalt catalyst (**36**) indicated that the catalyst is activated with boron reagent by the elimination of $CH_2SiMe_3Bpin$ to produce an active Co(I) ($H_2$)-Bpin complex (**38**), which participated in the catalysis (*92*–*94*). A Co(I)-Bpin complex (**39**) was generated from the complex (**38**) by the elimination of $H_2$. Subsequently, in the presence of arene or heteroarene oxidative addition occurred to generate the intermediate (**40**), which then, by virtue of the reductive elimination, afforded the borylated product producing the Co(I)-hydride (**41**) complex,

which, in the presence of boron reagent, closed the catalytic cycle. During the detailed mechanistic investigations, it was observed that the complex (**38**) acted as a resting state (*94*). In addition, a different behavior was observed for the turnover limiting step of the borylation of arene and heteroarene. For the arene borylation, the turnover limiting step is the oxidative addition, whereas turnover limiting step for the heteroarene borylation is the elimination of hydrogen from the complex (**38**). Catalyst inhibition of the complex (**36**) was observed during the C—H borylation reaction through the borylation at the C4 position of pyridine moiety of the PNP pincer catalyst.

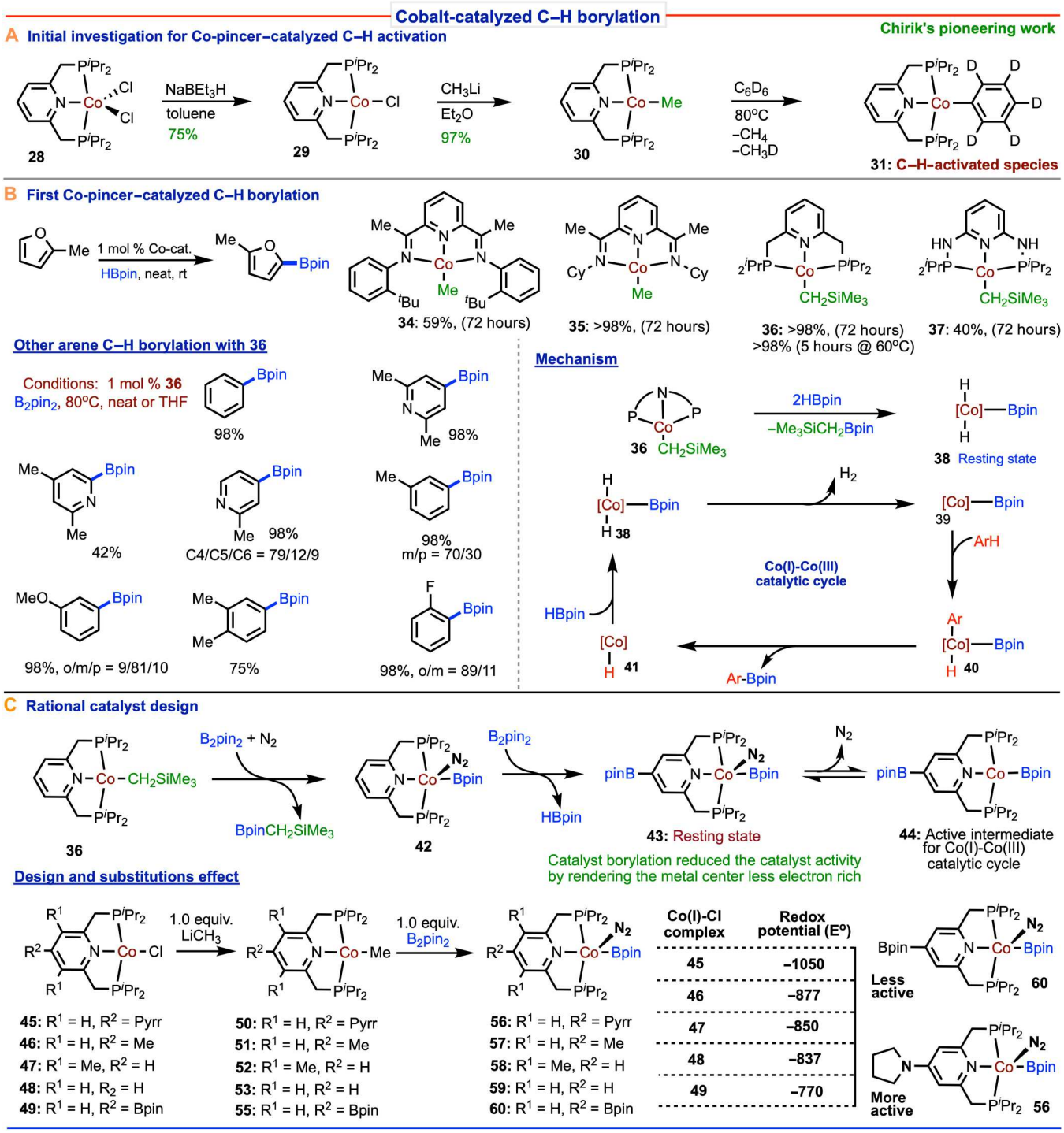


**Fig. 8. Development of Cobalt-catalyzed CH borylation.** (**A**) Initial Investigations for Co-pincer catalyzed C—H activation (*91*). (**B**) First Co-pincer catalyzed C—H borylation (*92–94*). (**C**) Rational catalyst design (*93*).

Thus, for better design of the catalyst systems, the authors prepared various cobalt catalysts (**45** to **49**) with varied substitutions at the pyridine moiety and measured their corresponding reduction potential to get some insights of the electronic properties of the cobalt center (*93*). It was found that the redox potential becomes more negative from Bpin (**49**) to pyrrolidine (**45**) substituents, which indicated that pyrrolidone at the 4-position makes the cobalt center more electron rich than the Bpin substitution. On the other hand, on Bpin substitution, cobalt center getting electron deficient and substitution at the 4-position by electron donating group is pushing the electron toward the cobalt center more compared to other 3,5-substitution. With these experimental results, they synthesized active cobalt catalysts (**56** to **60**) and tested for the borylation reaction, and among them, 4-pyrr containing cobalt catalyst resulted in faster reaction than the other catalysts (**57** to **60**) as more electron-rich cobalt catalyst (**56**) helped to improve the C—H oxidative addition (*93*). So, blocking the 4-position by an electron donating group not only inhibits the catalyst borylation but also helps to improve the reaction conditions.

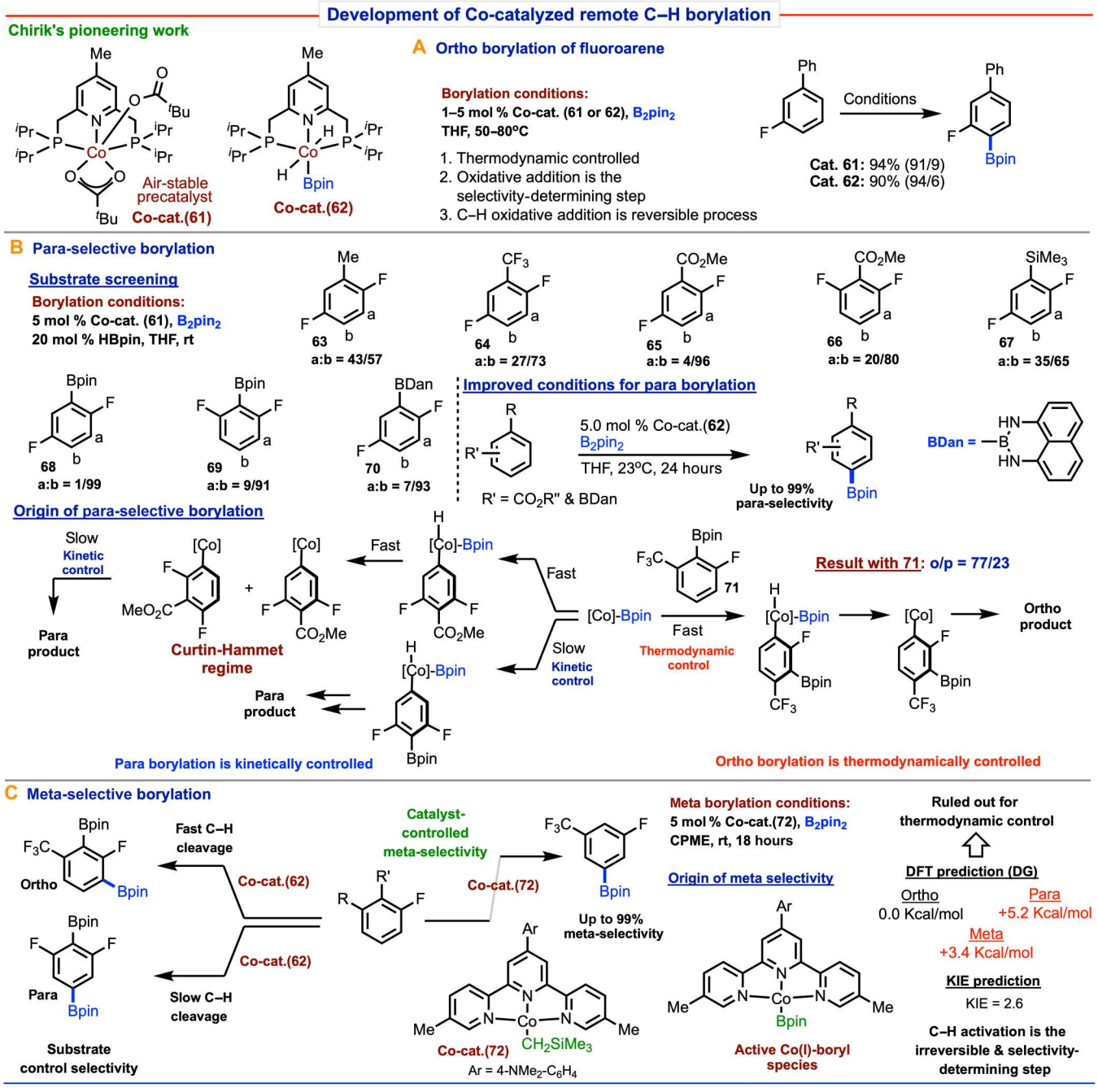


**Fig. 9. Cobalt-catalyzed remote CH borylation.** (**A**) Ortho-borylation of fluoroarenes (*95*). (**B**) Para-selective borylation (*96*). (**C**) Meta-selective borylation (*97*).

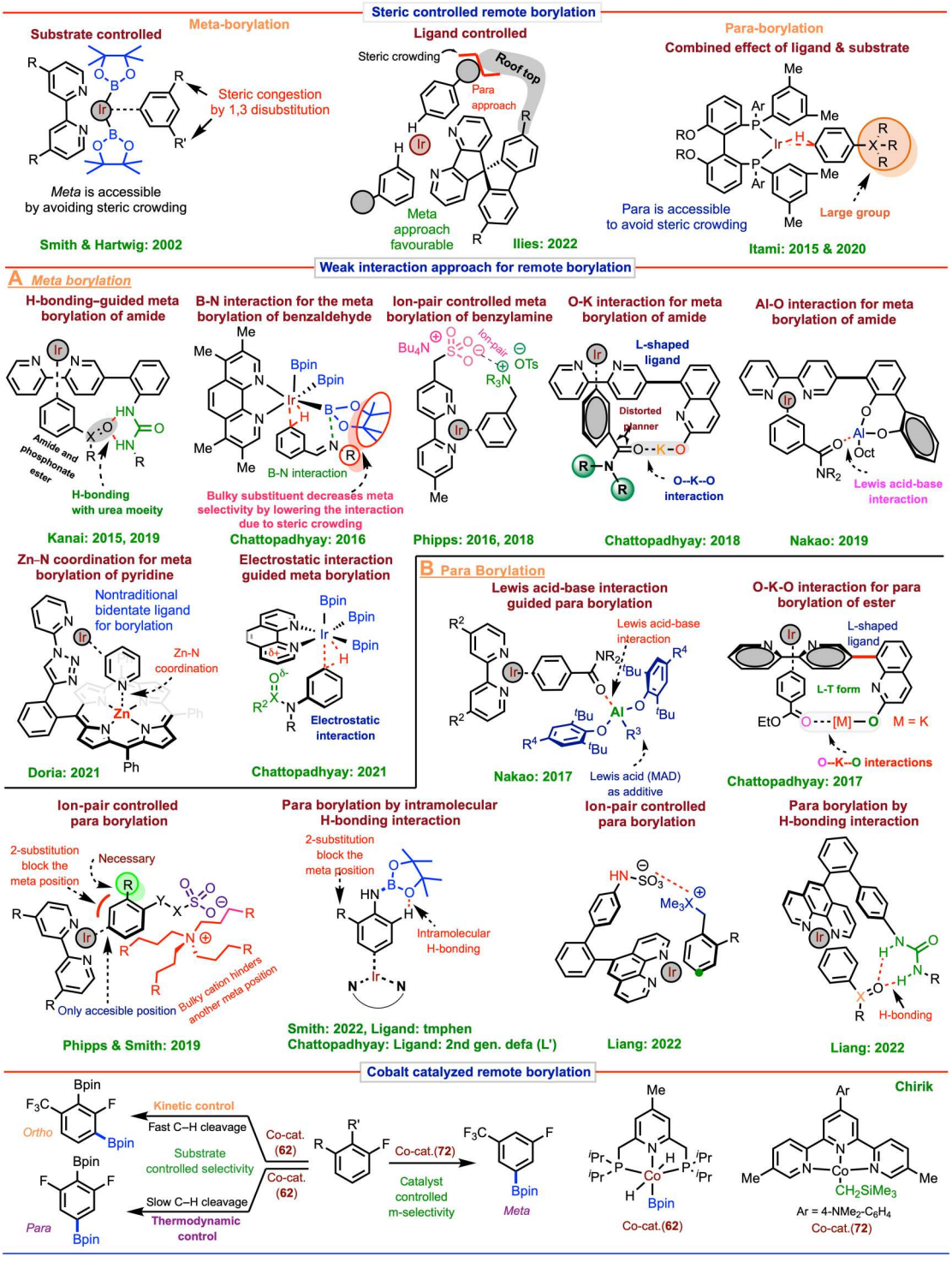


**Fig. 10. Summary of pioneering concepts for the remote CH borylation.** Steric controlled remote borylation (*35*, *36*, *53*, *57*, *60*). Weak interaction approach for remote borylation: (**A**) Concepts of meta borylation using various weak interactions (*67*, *68*, *70–72*, *74*, *76*, *77*, *79–81*), (**B**) Concepts of para borylation using various weak interactions (*63*, *75*, *82–87*, *89*). Cobalt catalyzed remote borylation of arenes (*95–97*).

Next, the same group revisited their previous chemistry of ortho-borylation of fluorobenzene (see Fig. 8B) (*92*) and reported an improved catalytic system for the ortho-borylation of various other fluoroarenes (*95*). The catalysts (**61**) (air stable) and (**62**) both are highly active for the ortho-borylation of fluoroarenes with high regioselectivity at 50° to 80°C. The detailed mechanistic investigations concluded that the reaction is thermodynamically controlled, and the reversible C—H activation step is the selectivity-determining step (Fig. 9A). Inspired by these important outcomes for this ortho-borylation, a thorough investigations were performed, which disclosed that some substrates such as esters and borylated arenes resulted in para-selective borylation (*96*) with the catalyst (**61**). An improved result was observed with the catalyst (**62**), and substrate scope exploration was performed successfully with the ester- and arene-containing BDan group (Fig. 9B). The detailed mechanistic investigations indicated that the para-selective borylation was the result of a kinetically controlled pathway, whereas ortho-borylation was the result of the thermodynamically controlled pathway (Fig. 9B).

These are the reports of ortho and para-borylation of fluorinated arenes where the substrates′ electronics control the regioselectivity. Very recently, an elegant approach was reported where designed sterically crowded cobalt (NNN) pincer catalyst (**72**) provided meta-selective borylation of fluorinated arenes (Fig. 9C) (*97*). With this catalyst, the meta-selective borylation of different fluorinated arenes was achieved with high level of regioselectivity. The origin of the meta-selectivity is kinetic controlled as DFT calculation did not allow to form the meta-selective product as Gibbs free energy is relatively high than the ortho C—H activation. Moreover, it was found that the KIE value was 2.6. This KIE and other controlled experiments indicated that the C—H activation is irreversible and selectivity-determining step.

## CONCLUSIONS AND OUTLOOK

The field of remote C—H borylation is an ongoing interest for the chemical sciences as it offers a platform for the diversification of the important molecular scaffolds. In this review article, we have dedicated our endeavors to uphold the inception and conceptual analysis of different aspects for the remote C—H borylation. The area of remote C—H bond activation and borylation has realized marked developments in terms of designing new catalysts for understanding the reactivity and selectivity by designing new types of ligand frameworks. We have showcased how detailed understanding of mechanistic rationale, modifications of substrates, reaction partners, and ligand-controlled catalysts can greatly affect the reactivity of the imposed catalytic cycle thereby changing the overall reaction course. It is evident that while the developments of remote meta-selective borylation have occupied a reasonable space in the field, reports of para-selective borylations are very few in comparison as it is always challenging to cleave the more distanced para-C—H bonds (Fig. 10). One of the key challenges associated with this area of remote C—H borylation is that iridium metal still considered as the main catalyst element that might not be beneficial for the long-term goal with respect to the practical deployments.

Thus, it is highly desirable to focus the catalyst design based on the earth abundant metal catalysts that can impart cost-effective, scalable, and sustainable catalytic systems with very high turnover number. The key concept would be the ligand design that can change the scenario enormously. In this vein, emergence of earth-abundant, cost-effective, and less toxic three-dimensional metal systems, such as Co, Mn, Fe, Ni etc., as competent and complementary catalysts to achieve the same goal will not only be attractive but also begets powerful paradigm toward synthetic amelioration. In this review, we have highlighted Co-based pincer ligated catalysts by Chirik and coworkers that have gained remarkable attention nowadays. In this purview, engineering new rational catalyst, with improved catalyst kinetics and dynamics, proper utilization of biomass-derived solvents, and reusability of heterogeneous catalysts may lead to a new sustainable horizon for the development of remote C—H activation. Besides, the discovery and development of more diverse and synthetically useful strategies for enantioselective remote C—H activation hold immense potential to greatly enhance the value of current C—H functionalization methodologies in the context of late-stage diversification and synthesis of compounds of interest to medicinal chemists. Furthermore, while many methods have enabled highly efficient and site-selective C—H bond activation of aromatic substrates using a variety of reaction conditions incorporating different ligand frameworks; the employment of a single catalyst system for activating all the three distinguished C—H bonds of a given substrate remains unknown, but if realized, this would give an access to activate and functionalize all the desired C—H bonds in a sustainable and atom economical way, which would be beneficial for both industry and academy. Optimistically, the cumulation of these aforementioned strategies for C—H activation chemistry will provide an added impetus for the development of novel transformations for remote C—H activation. Given the impressive development rate of this field, we envisage that in the future, evolution of new conceptually designed ligand scaffolds having interesting noncovalent procreators (as discussed in this review) and progressive advances in sustainability will implement the industrial potential of remote C—H activation, and certainly, it will harvest motivation to explore and design new concepts of remote C—H activation and borylation to different synthetic practitioners.

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