Site-Selective C–H Functionalization of Arenes Enabled by Noncovalent Interactions

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ABSTRACT: The direct metal-catalyzed C–H functionalization of arenes has emerged as a powerful tool for streamlining the synthesis of complex molecular scaffolds. However, despite the different chemical environments, the energy values of all C–H bonds are within a fairly narrow range; hence, the regioselective C–H bond functionalization poses a great challenge. The use of covalently bound directing groups is to date the most exploited approach to achieve regioselective C–H functionalization of arenes. However, the required installation and removal of those groups is a serious drawback. Recently, new strategies for regioselective metal-catalyzed distal C–H functionalization of arenes based on noncovalent forces (hydrogen bonds, Lewis acid–base interactions, ionic or electrostatic forces, etc.) have been developed to tackle these issues. Nowadays, these approaches have already showcased impressive advances. Therefore, the aim of this mini-review is to cover chronologically how these groundbreaking strategies evolved over the past decade.

1. INTRODUCTION

The transition metal (TM) catalyzed C–H functionalization has been recognized as an efficient synthetic approach to access molecular diversity. Other TM-catalyzed chemical transformations usually exploit coupling partners that create new C–C bonds without regioselectivity issues, e.g. cross-coupling reactions. On the contrary, the regioselective C–H bond transformations are challenging due to the energy values of the C–H bonds, which fall within a narrow range. Taking a historical perspective, one can safely conclude that the major breakthroughs in the area of TM-catalyzed C–H functionalization have been triggered by regio- and site-selective issues. The very early achievements in TM-catalyzed C–H functionalization date back to the end of the 19th century. The modern efforts in this area began in the 1970s with the implementation of reversibly covalently bonded directing groups (DGs) and, later, of the transient directing groups (TDGs), which rely on the reversible covalent binding of an organocatalyst to a particular functional group of the substrate. These approaches have already showcased impressive advances in several transformations. Even though the DG-technology is unique in its ability to regioselectively functionalize C–H bonds, these methods are limited by the difficulty to install and then remove such groups after functionalization. Furthermore, the DG approaches have been especially successful for ortho-selective functionalization of arenes. Up to this stage, chemists had achieved satisfactory success in distal regioselective C–H functionalization by using a stoichiometric transient mediator or covalently bound templates. However, although allowing in many cases highly regioselective C–H functionalizations, the substrates have often been specifically designed for that purpose. Furthermore, the covalently bound templates suffer from the common drawback of laborious preinstallation and postremoval of covalently bounded DGs.

During the past decade, the use of noncovalent interactions emerged as a new tool to tackle regioselectivity or site-selectivity issues in TM-catalyzed C–H functionalization of arenes. This somehow biocatalytically inspired approach does not rely on the covalent installation of DGs thus lack their drawbacks. Instead, a noncovalent interaction is used to anchor the substrate to an exogenous template, which is used for positioning the reaction site in a favorable orientation relative to the catalytic center.

The potential of these methodologies to control regio- and site-selectivity in the field of distal C–H functionalization of arenes has been intensively studied over the past decade. The efforts of a number of research groups led to impressive advances in this area and the toolset of noncovalent interactions is constantly growing (Figure 1). Given the above, there is a high demand of reviews that cover the topic.

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and here in we aim to summarize and discuss the reported noncovalent concepts and strategies for regioselective C−H functionalization of arenes published over the past decade.

2. IR-CATALYZED C−H ACTIVATION

2.1. ortho-Selective Borylation Reactions. The utilization of the hydrogen bond (HB) as a noncovalent directing interaction for TM-catalyzed C−H activation was first demonstrated by Roosen et al.\(^\text{10}\) The authors achieved ortho-selective borylation of different N-Boc protected anilines by the use of bis(1,5-cyclooctadiene)di-μ-methoxydiiridium(I) as a catalyst and 4,4′-di-tert-butyl-2,2′-dipyridyl (dtbpy) as a ligand (Scheme 1). Computational studies revealed that an HB interaction between the NHBoc proton and the oxygen atom from the boron pinacolate group coordinated to the Ir-catalyst guides the latter to the ortho-position of the substrates relative to the N-Boc substituent (TS1).

In a consequent study, the authors reported the use of in situ borylation of the aniline nitrogen atom, with the additional advantage of performing the N−B bond formation, C−H activation, and hydrolysis of the N−B bond in a one-pot protocol (Scheme 2, top).\(^\text{11}\) The regioselectivity of the reaction was supposedly governed by the steric bulk provided by the Bpin group, thus leading to selective borylation at the less hindered ortho-position relative to the N-Bpin substituent.

Figure 1. Timeline of the advances in the use of noncovalent forces in TM-catalyzed arene C−H bond activation reactions.

### Scheme 1. Ir-Catalyzed ortho-Borylation of N-(Boc)-Anilines\(^\text{10}\)

![Scheme 1](image1.png)

Selected examples:

| Product | R¹ | R² | Yield, %\(^\text{20}\) |
|---------|----|----|----------------------|
| 2a      | Cl | H  | 50 (α/m = 67:33)     |
| 2b      | H  | Cl | 79                   |
| 2c      | H  | Br | 89                   |
| 2d      | F  | Cl | 68 (α/α' = 76:24)    |
| 2f      | Cl | OMe| 95                   |

Yield of ortho-borylated product.

In some instances this method led to improved yields and decreased catalyst loadings as compared to the borylation of N-Boc protected anilines. The substrate scope was extended to different N-heterocycles such as (aza)indole, pyrrole, and pyrazole. For substrates with less acidic N−H bonds (indole, pyrrole) the addition of a tertiary amine was necessary to facilitate the in situ N−B bond formation. Subsequently, the authors demonstrated that this could be used to tune the selectivity by simply performing the reaction in the presence (C-3 selectivity) or absence (C-2 selectivity) of a base (Scheme 2, bottom).

In 2016 Bisht and Chattopadhyay reported the ortho-selective borylation of benzaldehydes based on the formation of a transient imine, acting as a directing group for the Ir-catalyst to activate the corresponding C−H bond (Scheme 3).\(^\text{12}\) Various mono- and bis-substituted benzaldehydes have been successfully borylated at the ortho-position in very good...
yields and excellent selectivities. The regiochemical outcome of the reaction was governed by two factors: steric bulk of the N-alkyl substituent and electron density of the ligand. In the case of ortho-selectivity, the increased steric bulk of tert-butyl amine was beneficial compared to less hindered amines (methyl- and isopropyl amine).

Li et al. designed bipyridine ligand 13 for the ortho-selective functionalization of aryl sulphonilides (Scheme 4). The Lewis acidic boryl group in the ligand is capable of forming a Lewis acid–base interaction between the boryl ligand of the iridium catalyst and the substrate sulfur atom (TS3). The authors confirmed the important role of the Lewis acid–base interaction for the high ortho-selectivity by several experiments, which revealed that the following factors exhibit a detrimental effect on the selectivity: (1) polarity of the solvent; (2) high temperature; (3) bulky substituents on the sulfur atom; (4) less Lewis acidic boryl groups; and (5) bipyridine ligands without or with a boryl group at the para-position.

Selective ortho-C–H borylation of methylthiomethyl-protected phenol and aniline derivatives has been achieved by using bipyridine-type ligands bearing an electron-withdrawing substituent (Scheme 5). The authors suggested two possible reaction mechanisms—one based on a noncovalent Lewis acid–base interaction between the boryl ligand of the iridium catalyst and the substrate sulfur atom (TS4) and the other proceeding via coordination of the iridium center to the sulfur atom, which acts as a directing group (TS5). Almost at the same time, Chattopadhyay et al. reported the ortho-selective borylation of phenol derivatives via traceless protection of the OH group as O-Bglycolate (Scheme 6). Initial experiments with para-substituted phenols and Bpin as a protecting group led to the formation of ortho-substituted products with high degree of regioselectivity for substrates possessing sufficiently large substituents at the para-position (larger than CN or F). Computational and experimental studies revealed the factors that affect the catalytic activity: (a) the electrostatic interaction between the partially positive bipyridine ligand and partially negative Bpin-protected OH group and (b) the steric hindrance imposed by the Bpin methyl groups. Based on these results, the authors managed to increase the ortho-selectivity (conditions A vs B, Scheme 6) by using the less sterically hindered diborane reagent B2eg2 (B2eg2 = 2,2′-bi(1,3,2-dioxaborolane)).

Reek and co-workers reported the supramolecular iridium catalyst 23 for ortho-selective C–H borylation of secondary aromatic amides (Scheme 7). Based on DFT calculations, the authors concluded that the catalyst operates by substrate preorganization as a result of H-bonding between the indole
 amide motif and the substrate oxygen atom (TS7). This strategy allowed the successful ortho-borylation of a variety of secondary aromatic amides having functional groups at different positions, including on a gram scale (22aa, 22ba).

2.2. meta-Selective Borylation Reactions. The first efforts toward meta-selective borylation were made by Kuninobu, Kanai, and co-workers, who designed a catalytic system comprising of a bipyridine unit for metal coordination and urea moiety as a substrate binding site (Scheme 8).17 A hydrogen bond interaction between the urea moiety in ligand 26 and a Lewis basic atom in the substrate allows the Ir-catalyst to activate selectively the C−H bond in meta-position (TS8). This system was found to be applicable for a broad range of substrates, including different (hetero)aromatic amides, esters, and phosphorous compounds (phosphonates, phosphonic diamide, phosphine oxides).

Bish and Chattopadhyay achieved meta-borylation of a series of benzaldehydes using a strategy described in the previous subsection (Scheme 3).12 In contrast to the ortho-selective borylation, which was promoted by the steric bulk of the amine, an enhancement of the meta-selectivity was observed with less bulky substituents: Me > i-Pr > t-Bu. In addition, the application of electron-rich ligand such as 3,4,7,8-tetramethyl-1,10-phenanthroline (TMP) was crucial for the improvement of both yield and meta-selectivity. Based on this experimental findings, the authors proposed that the origin of meta-selectivity is due to the formation of transition structure TS9, which features a favorable electrostatic interaction between the Ir-complex and the substrate, together with a Lewis pair formation between the boryl boron atom and the imine nitrogen (Scheme 9).

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methodology was successfully extended to aromatic systems bearing phosphonium group as a cation component (Scheme 10C). The bipyridine/sulfonate ligand was also utilized as a potent H-bond acceptor for the selective meta-borylation of arenes bearing trifluorocetylated amine groups. This “hydrogen-bond accepting mode” provided effective regiocontrol over substrates bearing different carbon chains (up to three carbons) between the nitrogen atom and the aromatic ring (Scheme 11). The borylation of derivatives with alkyl chains longer than three carbons was inefficient resulting in poor regioselectivity. These results were attributed to the high entropic cost associated with an organized transition structure for substrates with increased flexibility.

A meta-selective borylation governed by cation−π non-covalent interaction between aromatic amides and L-shaped bipyrindine/quinolone ligand was developed by Bisht et al. A range of different N-substituted (hetero)-aromatic amides has been successfully borylated at the meta-position with high degree of regioselectivity.

2.3. para-Selective Borylation Reactions. A bimetallic approach for para-selective functionalization of (hetero)-arenes was developed by Yang et al. In order to achieve the desired selectivity, the authors designed a system based on cooperative iridium/aluminum catalysis (Scheme 15). An aluminum Lewis acid catalyst was employed to fulfill two essential tasks: (1) to form a Lewis acid−base pair with the substrate for increased reactivity; (2) to provide steric hindrance around the ortho- and meta-positions for effective regiocontrol. By using the commercially available Lewis acid and the bipyridine ligand, a series of benzamide derivatives was successfully borylated at the para-position with good to excellent selectivities (Scheme 15). The regioselectivity was influenced by the size of the substituents on the amide.
nitrogen and the nature of the substituents on the arene ring. The method was furthermore employed for the C−H borylation of several pyridine derivatives. However, the same catalytic system was effective only in a limited number of cases, thus an additional optimization of the Lewis acid and Ir-ligand was undertaken. The introduction of the bulky iso-butyl substituent, instead of methyl group, on the Al-center proved useful, providing an improved C₄-selectivity (Scheme 16).

Hoque et al. 26 achieved para-selective borylation of (hetero)aromatic esters by exploiting a strategy based on the cooperation of two metals. An L-shape ligand 47 was designed to recognize the ester functionality through a noncovalent O−π interaction (Scheme 12). 22

Scheme 12. Site-Selective C−H Borylation of (Hetero)Aromatic Amides Directed by Cation−π Noncovalent Interaction 22

Selected examples:

| Product | R¹ | Yield, %[a,b] |
|---------|----|---------------|
| 46a     | o-OMe | 94 (18/1) |
| 46b     | o-Cl  | 51 (17/1) |
| 46c     | o-Ph  | 79 (15/1) |
| 46d     | o-CO₂Me | 86 (20/1) |
| 46f     | m-CN  | 81 (24/1) |
| 46g     | p-CN  | 83 (24/1) |

[a] Yield of isolated borylated product. [b] in brackets: ratio of mono-borylated product to other regioisomers.

Scheme 13. meta-Selective C−H Borylation of (Hetero)Aromatic Amides Directed by an Ir/Al Bifunctional Catalyst 23

Selected examples:

| Product | R¹ | T, °C | Yield, %[a,b] |
|---------|----|------|---------------|
| 58a     | o-Ph  | 60   | 77 (98/2) |
| 58b     | o-OMe | 30   | 98 (94/6) |
| 58c     | o-Br  | 80   | 99 (99/1) |
| 58d     | o-CF₃ | 30   | 97 (99/1) |
| 58e     | o-OCF₃ | 50   | 65 (90/10) |
| 58f     | o-CO₂Me | 30   | 98 (95/5) |
| 58g     | m-F   | 30   | 88 (99/1) |

[a] Yield of meta-borylated product determined by ¹H NMR. [b] in brackets: ratio of meta-borylated product to other regioisomers. [c] Solvent: THF/Hexane = 0.5/2.5.

Scheme 14. Site-Selective C−H Borylation of Pyridines Directed by an Ir/B Bifunctional Catalyst 23

Selected examples:

| Product | R¹ | Yield, %[a,b] |
|---------|----|---------------|
| 66a     | OMe  | 99 (78:24) |
| 66b     | OTBS | 99 (94:6) |
| 66c     | NEt₂ | 99 (94:6) |
| 66d     | CO₂El | 92 (95:5) |
| 66e     | OPiv | 99 (94:6) |
| 66f     | Ph   | 99 (92/8) |
| 66g     | SiEt₃ | 99 (73:27) |

[a] Yield of C6(3-C)-monoborylated product determined by ¹H NMR. [b] in brackets: ratio of C6(5-C)-monoborylated product to other regioisomers.

Scheme 15. para-Selective Borylation of (Hetero)Aromatic Amides Directed by Cooperative Ir/Al Catalysis 25

Selected examples:

| Product | R¹ | Yield, %[a,b] |
|---------|----|---------------|
| 68b     | o-OMe | 90 (>20/1) |
| 68c     | o-Br  | 94 (>20/1) |
| 68d     | o-CF₃ | 89 (91/9) |
| 68e     | o-OCF₃ | 78 (>20/1) |
| 68f     | o-CO₂Me | 89 (91/9) |
| 68g     | m-F   | 93 (13/86) |
| 68h     | m-CN  | 57 (3.1:1) |

[a] Yield of isolated para-monoborylated product. [b] in brackets: p/o ratio determined by ¹H NMR analysis of the crude product. [c] Yield of isolated mixture of p- and m-monoborylated products. [d] p/o-Ratio determined by GC analysis of the crude product.
M–O interaction and simultaneously to deliver the Ir-catalyst next to the para-position with high degree of selectivity (Scheme 17). A K⁺ ion was found to provide the best interaction with the carbonyl oxygen, which was identified as the main factor for efficient regiocontrol.

Scheme 17. Site-Selective C–H Borylation of (Hetero)Aromatic Esters Directed by Noncovalent (C=O···K–O) Interaction

3. PD-CATALYZED C–H ACTIVATION

The impressive regioselectivities outlined in the studies discussed so far were only possible because of the high reactivity of the iridium catalysts in borylation reactions, which allows this transformation to be efficiently catalyzed under mild reaction conditions and provides the right environment for the weak noncovalent interactions to sustain. By contrast, the direct formation of C–C bonds via Pd catalyzed C–H activation requires harsher reaction conditions, thus limiting the number of noncovalent interactions that can be employed.

Zhang, Tanaka, and Yu have addressed this problem by making use of a reversible metal coordination chemistry to directly selectively the metal near the desired aromatic position.²⁹ For this purpose, a dual-action bis(pyridine-3-sulfonamide) template was designed as to coordinate two metal centers simultaneously (Scheme 19B). The bis-sulfonamide moiety serves to chelate the first metal center, which in turn anchors the substrate to the template, while the C₃ pyridyl group in ₉₆ plays the role of a noncovalently bound DG that coordinates the active catalyst (Scheme 19C). The concept was found to be efficient for the remote, site-selective olefination of various substituted 3-phenylpyridines. Notably, high selectivities were achieved using catalytic amounts of the template (20 mol %) even at high temperatures (Scheme 19A).

The authors tested the feasibility of this approach for site-selective C–H activation of other classes of heterocyclic compounds.²⁹ However, the bis(pyridine-3-sulfonamide) ₉₆ was found to be inefficient for quinoline substrates. Nevertheless, the bimetallic approach still provided an effective solution by the application of nitrile-based templates. In these

Mihai et al. and Bastidas et al. employed essentially the same approach to achieve para-selective Ir-catalyzed C–H borylation of a variety of ortho-substituted arenes. A bulky tetraalkyl ammonium cation, was utilized as a “steric shield”, creating highly sterically congested environment around the substrate anion, thus avoiding undesired C–H activations at ortho- and meta-positions (Scheme 18). In this manner, a wide range of ortho-substituted sulfates, sulfamates, and sulfonates were borylated at para-positions with good to excellent regioselectivities.²⁷,²⁸
assemblies, a tridentate ligand 99 was used to anchor the first metal center and to provide steric hindrance, while the active catalyst is relayed selectively to the remote C5−H bond by a directing CN-group in the side arm (Scheme 20). The utility of this approach has been additionally demonstrated for the functionalization of other heterocycles such as quinoxaline, benzoxazole, and benzothiazole.

Maiti and co-workers undertook an intensive screening of bifunctional templates, which can promote Pd-catalyzed site-selective olefination of heterocycles in a similar manner. Their studies identified the bifunctional template 103 as an effective promoter of meta-selective C−H activation of 3-phenylpyridine derivatives, while template 104 was effective for quinoline substrates (Figure 2).

In a further study, Maiti and co-workers reported a structure optimization of the 2,6-disubstituted pyridine bis-amide ligands that allowed the distal alkylation of fused nitrogen heterocycles with allylic alcohols (Scheme 21). The newly designed template 107 proved effective for the Pd-catalyzed site-selective alkylation of various heterocycles such as quinolines, benzoxazoles, and (benzo)thiazoles.

Recently, Jin, Xu, and co-workers developed a Pd-catalyzed meta-selective C−H olefination of aromatic carbonyl compounds directed by intermolecular hydrogen-bonding. The authors achieved the desired regioselectivity by the combination of an N,N′-disubstituted urea scaffold as an H-bond donor for substrate binding and a salicylitrile-bearing tether as a DG (Scheme 22). The template was found to induce high levels of selectivity with broad range of substrates, such as aromatic ketones, aldehydes, benzoate esters, and benzamides.

4. CONCLUSIONS

In conclusion, although in its infancy, the noncovalent control in C−H functionalization has already showed impressive advances. However, we would like to outline several future directions. Despite the few examples of Pd-catalyzed regioselective C−H activations highlighted above, most of these new synthetic paths fall in the realm of Ir-catalyzed borylation due to its mild reaction conditions. Hence, there is an obvious need for organic chemists to move out from this comfort zone and to focus more efforts on the direct distal formation of C−C bonds. So far other metals that could possibly provide further breakthroughs in this area (e.g., Ru, Co, etc.) have received less research focus and, hence, require additional diligence. Over the last years, we have seen many new noncovalent strategies for distal C−H functionalization of arenes with potential applications in organic synthesis. However, despite few examples, the applications of these methodologies for C−H functionalization of substrates that possess high conformational freedom is still underdeveloped.
Scheme 21. Pd-Catalyzed Distal Alkylation of Different Heterocycles 31

Selected examples:

| Product | R1 | R2 | Yield, %a,b |
|---------|----|----|-------------|
| 106aa   | Et | H  | 81 (71%)    |
| 106ab   | H  | H  | 79 (61%)    |
| 106ac   | C2H4 | H | 76 (61%)    |
| 106ad   | Et | H  | 81 (61%)    |
| 106ae   | Me | H  | 77 (61%)    |
| 106af   | H  | C2H4 | 69 (51%)   |
| 106ag   | H  | p-Me | 57 (61%)   |
| 106ah   | Me | Me | 65 (61%)    |

108a: X = S, R3 = Me (87%); 12:1[c] 108b: X = S, R3 = C2H4 (87%; 15:1)[c] 109a: X = O, R3 = Me (79%; 8:1)[a] 109b: X = O, R3 = C2H4 (77%; 15:1)[a] 109c: X = O, R3 = C2H4 (76%; 15:1)[a]

Scheme 22. Pd-Catalyzed meta-Olefination of Aromatic Aldehydes, Ketones, Benzoate Esters, and Benzamides 32

Selected examples:

| Product | R1 | R2 | Yield, %a,b,c,d |
|---------|----|----|----------------|
| 112aa   | H  | H  | 60 (2.1:1.3)   |
| 112ab   | H  | o-OMe | 68 (>20:1)   |
| 112ac   | H  | p-OMe | 67 (>20:1)   |
| 112ad   | H  | p-F  | 56 (>20:1)   |
| 112ba   | Me | H  | 69 (2:1)      |
| 112bb   | Me | o-OMe | 70 (>20:1)   |
| 112bc   | Me | p-OMe | 74 (>20:1)   |
| 112bd   | Me | p-F  | 65 (20:1)     |
| 112ca   | OMe| H   | 63 (3.5:1)    |
| 112cb   | OMe| o-OMe | 71 (>20:1)   |
| 112cc   | OMe| p-OMe | 70 (>20:1)   |
| 112cd   | OMe| p-F  | 66 (>20:1)    |
| 112da   | NPr2 | H  | 63 (1.2:1)    |
| 112db   | NPr2 | o-OMe | 71 (20:1)    |

[a] Yield of isolated meta-olefination product. [b] Ratio of meta-olefination product to other regioisomers.
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