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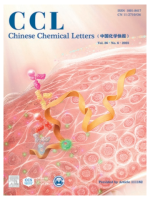

Recent advances in directing group assisted transition metal catalyzed *para*-selective C-H functionalization

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ARTICLE INFO

Article history:
Received 30 July 2024
Revised 23 September 2024
Accepted 9 October 2024
Available online 11 October 2024

Keywords:
C-H activation
Transition metal catalysis
Selectivity
Remote functionalization
Directing group

ABSTRACT

The transition metal-catalyzed C−H activation have been considered as increasingly useful approach for installing new functional groups onto organic small molecules due to their high step- and atom-economy, the abundance of hydrocarbon compounds, and the potential for late-stage functionalization of complex organic molecules. The *ortho*- and *meta*-C-H activation and functionalization of aromatic compounds have been widely explored in recent years, however the distal *para*-C-H activation and functionalization has remained a significant challenge because of the difficulty in forming energetically favorable metallacyclic transition states. The utilization of appropriate directing groups or templates as well as the meticulous design of catalysts and ligands has proven to be effective in transition-metal-catalyzed remote *para*-C-H bonds activation and functionalization of aromatic compounds. This review aims to summarize the strategies for controlling *para*-selective C−H functionalization using the directing group, template engineering, and catalyst/ligand design under transition metals catalysis in recent years.

1. Introduction

The C-H bond, as the fundamental structural unit in organic chemistry, is ubiquitously present in various organic molecules. Its significance in the realm of organic synthesis cannot be overstated. In contrast to conventional cross-coupling reactions, the direct functionalization of C-H bonds offers a promising synthetic strategy for constructing novel compounds by directly cleaving and functionalizing the C-H bond, avoiding the need for prefunctionalized coupling partners [1–3]. This approach enhances the atom- and step-economy of the organic synthesis [4–6].

Despite the many benefits associated with the direct functionalization of C-H bonds, two challenges have impeded development in C-H bond activation [7]. Firstly, the C-H bond possesses a high bond energy and low reactivity, rendering its mild and efficient conversion a formidable task. Secondly, selectivity poses a significant hurdle. In the context of further functionalizing C-H bonds in carboxylic acids, ketones, amines, alcohols, and other organic substrates, the presence of inherent functional groups in these substrates leads to distinct C−H bonds, necessitating the identification and differentiation of various C-H bonds [8–12]. Complex organic synthesis typically requires not only a specific transformation reaction but also a series of synthetic steps to achieve efficient synthesis.

Regioselective functionalization of C-H bonds is significant for aromatics as it allows for the alteration of the physicochemical properties of aromatic compounds. Distal C-H functionalization has expanded the synthetic pathways for the production of value-added chemicals. The key challenge in advancing the practicality of this chemistry lies in the development of environmentally friendly, cost-effective, scalable, and sustainable catalytic systems with exceptional conversion rates [8,13–16]. Expanding the catalytic toolbox in this manner enables the synthesis and modification of previously inaccessible sites in organic molecules, thereby enhancing the discovery and synthesis of pharmaceuticals, agrochemicals, and other desired materials. Notably, *para*-functionalization exhibits unique advantages compared to *meta*- and *ortho*-functionalization, it not only perturbs the dipole moment but also enhances π-conjugation when the π-system is directly connected in the *para*-site. These two factors play a crucial role in biological sys-

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https://doi.org/10.1016/j.cclet.2024.110543

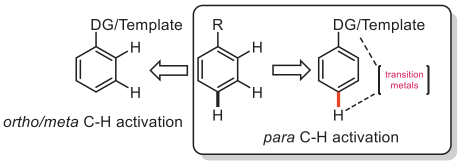


Fig. 1. Indirect and direct C-H functionalization logic.

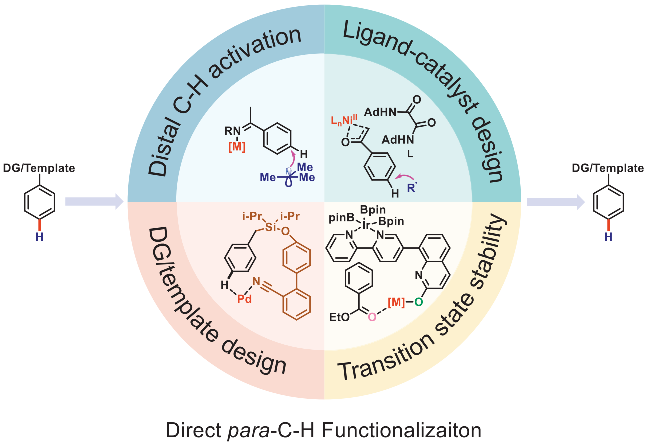
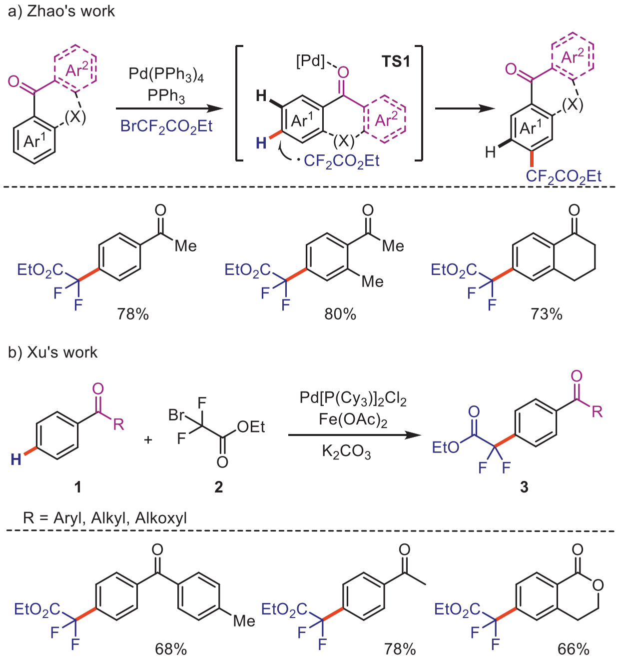


Fig. 2. Transition metal catalyzed remote C-H direct functionalization.

tems and enzyme activity, making *para*-selective C-H functionalization of great impact for drug discovery and diversification [10,17–21].

With the rapid development of transition metal chemistry, notable improvement has been made in the application of transition metal catalysis in C-H activation research over the past few decades. In most cases, the formation of directing groups (DG)-assisted metallacycle has proven to be an effective strategy to ensure valuable regioselectivity [1,22,23]. In this regard, various proximal *meta*- and *ortho*-C-H functionalizations [24] have been extensively studied. However, DG-assisted selective *para*-C-H functionalization in aromatics remains largely unexplored, primarily due to the formation of geometrically constrained cyclometallic intermediates [17]. Activating C-H bonds closer to the metal catalyst is typically easier due to their proximity. In addition, activating distal C-H bonds presents a challenging, entropically unfavorable process, especially when multiple similarly reactive C-H bonds are present on the remote aromatic ring. Despite these challenges, electron-donating functional groups or bulky substituents that provide electronic and steric effects can simplify site-selective functionalization to some extent. Therefore, the identification of suitable catalytic platforms or substrate designs to harness site-selective functionalization has garnered significant attention in the past few decades. The recent trend in research gradually focuses on the utilization of DG electronic and steric capabilities and non-covalent interactions to mitigate inherent spatial and electronic biases within molecules, enabling site-selective C-H functionalization (Fig. 1).

Herein, we provide an overview of the recent advances in transition metal catalyzed *para*-selective C-H functionalization particularly involving DG and those with similar functions (Fig. 2) based on the literature up to June 2024. The catalytic activities of various transition metal catalysts show considerable variation, with distinct preferences and selectivity for different directing groups. However, existing reports predominantly focus on reaction types, overlooking the importance of catalyst differentiation. This review categorizes catalysts primarily based on the types of transition metals, placing particular emphasis on the distinctions between different catalytic systems.



Scheme 1. Ligand-enabled Pd-catalyzed *para*-difluomethylation of aromatic ketone.

2. Pd catalyzed *para*-selective C-H functionalization

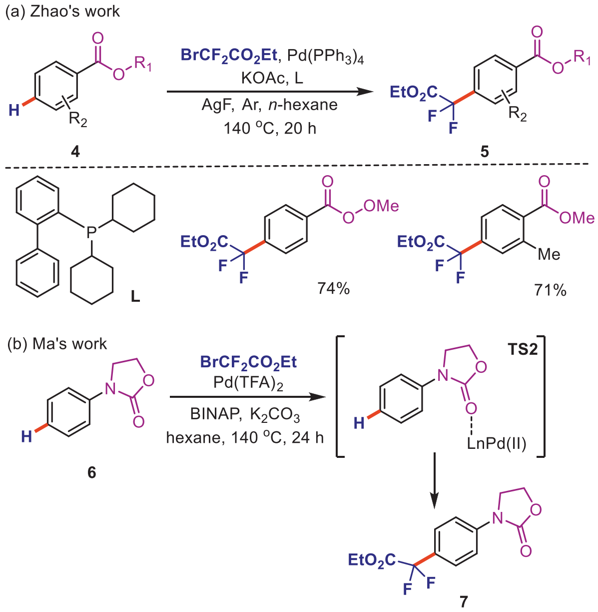
Palladium catalysts allow fine tuning of reaction conditions (temperature, solvents, ligands, bases and other additives), making them a powerful tool in organic synthesis. Pd catalysts are highly tolerant of a wide range of functional groups and often provide excellent steric and regiospecificity, avoiding the introduction of protecting groups. Considerable progress [25–29] has been made in the research of Pd-catalyzed direct C−H functionalization of aryl rings in *meta* and *ortho* positions, owing to the benefits associated with mentioned properties. On the contrary, the continued application of DG-assisted strategy for distal *para*-C-H functionalization remains a challenging task due to the requirement of generating energetically unfavorable metallacycle of significant size.

Despite the aforementioned challenges, it is exciting to note that over the past decade, research on palladium-catalyzed *para*-selective C-H functionalization has been steadily increasing, primarily focusing on alkylation, olefination, and arylation.

2.1. Alkylation

In general, carbonyl-directed C-H alkylation of aromatics typically occurs at the *ortho* or *meta* positions. Recently, the group of Zhao [30] has reported a strategy that achieves *para*-activation through PPh_3 ligand coordination with the carbonyl group. Under the conditions of $Pd(PPh_3)_4$ complex as the catalyst, potassium acetate as the base, and *n*-hexane as the solvent, aryl ketone derivatives react with ethyl bromodifluoroacetate to afford the corresponding *para*-difluoromethylated products (Scheme 1a) in moderate to good yields. Mechanistic studies have revealed that the palladium complex only coordinates with the carbonyl group of the aryl ketone, without forming a five-membered palladium complex. The steric hindrance of the triphenylphosphine ligand prevents *ortho*- and *meta*-difluoromethylation reactions on the aromatic ring, leading to high regioselectivity at the *para* position.

Xu *et al.* [31] also achieved *para*-selective difluoromethylation reactions of aromatic ketones and benzyl esters (**1**) using the same difluoromethylating reagent (**2**), obtaining the desired *para*-selective difluoromethylated products (**3**) (Scheme 1b). The group



Scheme 2. Pd-catalyzed *para*-selective difluoromethylation of aromatic esters.

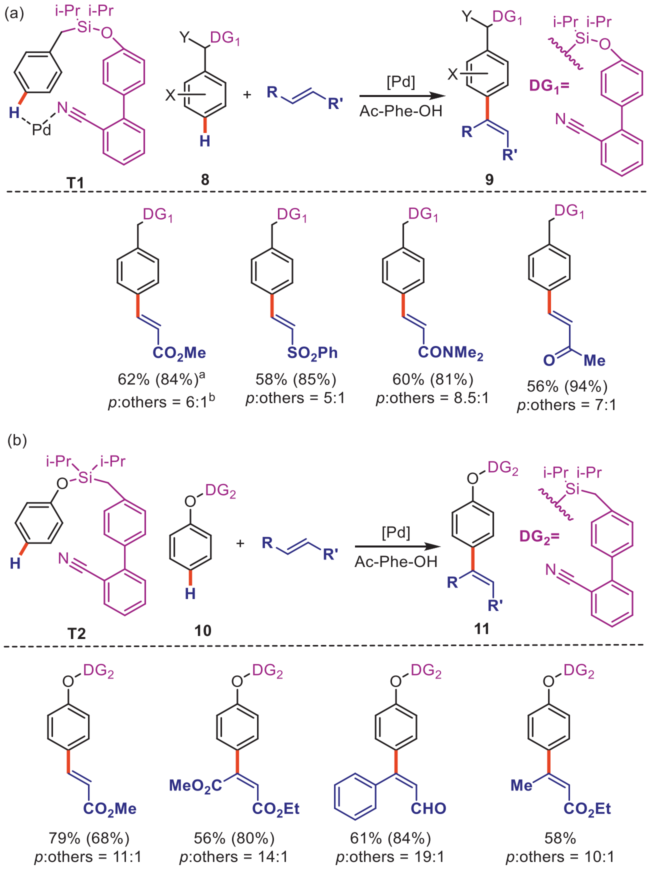
successfully identified an appropriate Pd catalyst, Pd[P(Cy)$_3$]$_2$Cl$_2$, through optimization of reaction conditions. Similarly, the Pd complex activates the *para* position of the aromatic ring by coordinating with the carbonyl group, thereby enabling *para*-selective difluoromethylation.

In 2020, the carbonyl- and ligand-directed *para*-selective difluoromethylation reaction was further advanced by group of Zhao [32]. Under optimized conditions, aromatic esters (**4**) and [1,1′-biphenyl]−2-di(cyclohexyl)phosphine were employed to achieve *para*-selective product (**5**) (Scheme 2a). Mechanistic investigations have revealed that, with the appropriate ligand, ester group can also serve as DG achieving *para*-selectivity. Further studies demonstrated the applicability of benzamides and benzenesulfonamides in this reaction strategy, exploring possibilities for the synthesis of biologically active molecules and pharmaceuticals. Subsequently, Ma and coworkers [33] investigated the feasibility of *para*-difluoromethylation using oxazolidinones (**6**) as substrates under Pd(TFA)$_2$ catalysis (Scheme 2b). The oxazolidinone can coordinate with the Pd catalyst, forming an intermediate, and the difluoroacetic acid moiety directly couples with the *para*-site of the phenyl ring in this intermediate, ultimately affording the *para*-difluoromethylated product (**7**).

2.2. Olefination

Maiti [34] proposed a novel silicon-containing biphenyl-based template (**T1**) that effectively functionalizes the remote *para*-C-H bond of toluene (**8**) through the formation of a D-shaped assembly. This DG allows the necessary flexibility to support the formation of a sufficiently large pre-transition state, overcoming electronic and steric biases to achieve *para*-olefination product (**9**) (Scheme 3a). The biphenyl moiety in the template contains easily coordinating heteroatoms, and the incorporation of biphenyl can modulate the chain length of the macrocyclic assembly. The morphology of the template and the coordination of heteroatoms with Pd have been demonstrated as key factors for achieving this reaction. Additionally, due to the rigidity of the biphenyl portion, the activation of *o*- and/or *m*-C-H bonds involves highly strained cyclophane assemblies, which impose significant kinetic barriers.

The same group [35] further developed a silicon-containing biphenyl-based template-assisted remote *para*-olefination of phenol derivatives (**10**). This strategy involved the use of a methyldiphenylsilyl biphenyl DG as the template (**T2**) for Pd-catalyzed *para*-olefination of phenols (**11**) (Scheme 3b) Similarly, the transition metal palladium and the donor heteroatom on the template establish non-covalent interactions, directing the olefination of the *para*-site for C-H functionalization. The olefination of both strategies are successfully achieved with a wide range of functional groups (Scheme 3b).



Scheme 3. Template-assisted *para*-C-H olefination of arene with alkenes. Yields in parentheses are based on the recovered starting material. Ratio of products with substituents at *para*-site and other sites, same after.

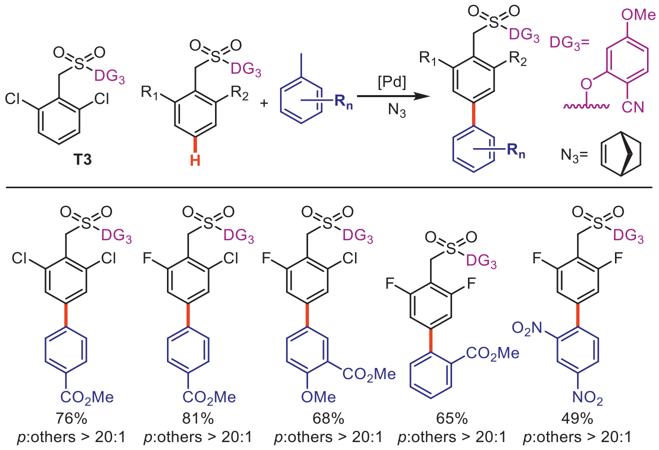
2.3. Arylation

In 2020, Maiti [36] designed a *meta*-directing group based on cyano-substituted phenol, enabling selective *para*-C-H arylation of sulfonic acids, phosphonic acids, and phenol substrates (Scheme 4). The optimized template and directing groups (**T3**, DG$_3$) exhibited precise *para*-selectivity. Palladium played a crucial role in this reaction, which relied on a single-bond relay palladation facilitated by the presence of a benzylic palladacycle as a transient intermediate, followed by *para*-C-H arylation of sulfonates, phosphonates, and phenols with a 2,6-disubstituted pattern.

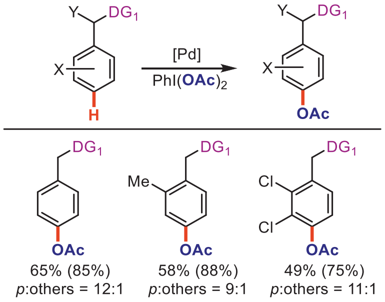
2.4. Others (C-Het bond)

2.4.1. Acetoxylation

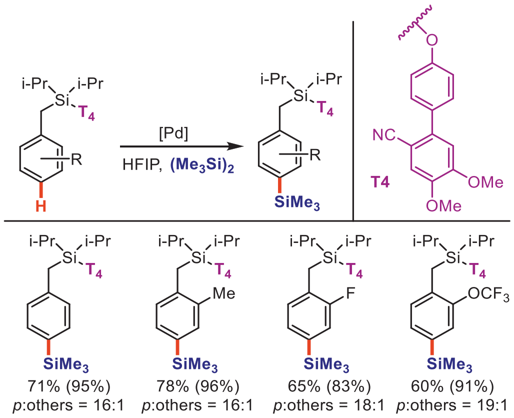
In aforementioned research of olefination, Maiti and coworkers [34] achieved acetoxylation alongside the alkenylation in a single study. By optimizing the reaction conditions, the team utilized the same directing group (DG$_1$) and employed PhI(OAc)$_2$ to achieve the acetoxylation of toluene derivatives (Scheme 5). This means that



Scheme 4. Templated-assisted *para*-C-H arylation of sulfonate scaffolds.



Scheme 5. *para*-Acetoxylation of substituted toluene derivatives.

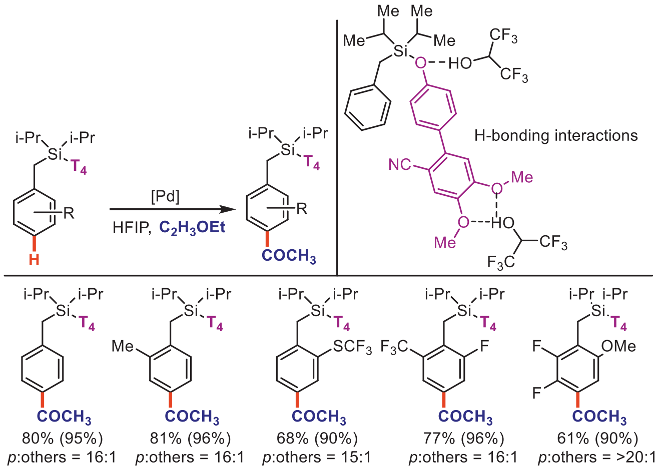


Scheme 6. Template-assisted directed *para*-silylation of toluene derivatives.

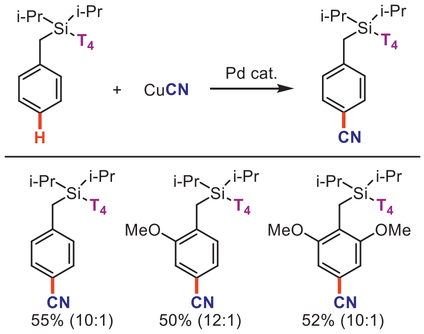
the C-C bond formation process explored in the previous C-H functionalization was extended to the formation of carbon-heteroatom bonds. This study provides new insights and strategies for introducing heteroatoms in C-H functionalization.

2.4.2. Silylation

Maiti and coworkers proposed a template-assisted regioselective *para*-silylation of toluene derivatives and analyzed the source of selectivity through experimental and computational investigations (Scheme 6) [37]. Notably, the guiding principle of the directing group in this reaction is a substrate-solvent hydrogen bonding interaction. A relatively strong H-bonding interaction is formed between the ether oxygen on the template (**T4**) and two molecules of HFIP (hexafluoroisopropanol). This explicit solvent coordination stabilizes the bent geometry of the template, facilitating the binding of the Pd metal and leading to enhanced selectivity.



Scheme 7. Template-assisted directed *para*-ketonisation of toluene derivatives.



Scheme 8. Template-assisted *para*-cyanation of toluene derivatives.

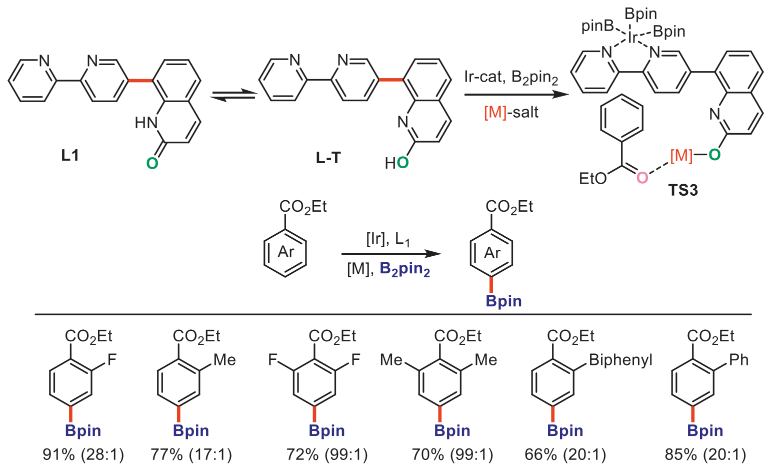
2.4.3. Ketonisation

Maiti [38] further developed a directed *para*-selective ketonization technique for aromatic hydrocarbons. In the presence of the polar protic solvent HFIP, toluene derivatives overcome electronic bias and structural congestion. The HFIP solvent molecules form H-bonding interactions with the methoxy group on the template (**T4**), favoring the bent geometry of the C-H metalation transition state (Scheme 7). This facilitates metal binding to form a Pd cycle and promotes *para*-selectivity. This protocol can be applied to a wide range of vinyl ethers and aromatic hydrocarbons. Additionally, multi-halogenated compounds, especially polyfluorinated compounds, can also be functionalized using this approach.

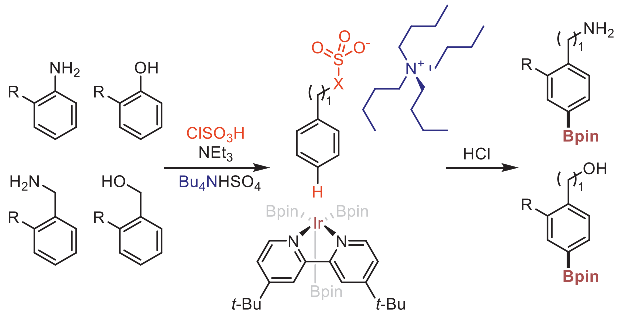
2.4.4. Cyanation

In 2020, Maiti *et al.* [39] designed a strategy utilizing an H-bond template for the selective cyanation of the toluene scaffold (Scheme 8). They employed T_4 (dimethoxy-substituted template) as the directing group in conjunction with the H-bond template. The presence of the dimethoxy group potentially enhanced the electron density, improving metal binding and yield. The H-bonding interaction with the solvent may provide increased structural rigidity, favoring specific conformations and enhancing site selectivity.

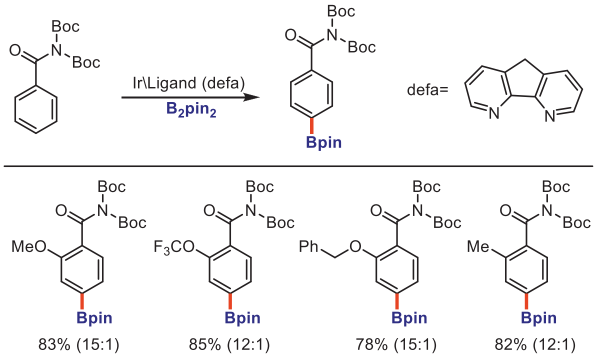
Furthermore, the reaction utilized a nitrile source with slow release of CuCN. The effectiveness of CuCN as a cyanide source is mainly attributed to the favorable interaction between copper and the palladacycle, which significantly stabilizes the transition state for CN ligand exchange. This choice of nitrile source aimed to minimize the formation of tetracyanopalladate(II) or palladium(II) cyanide complexes, which could lead to catalyst poisoning due to the potentially higher solubility of cyanide ions exceeding the initial concentration of the catalyst.



Scheme 9. Ligand-assisted directed *para*-borylaiton of aromatic ester *via* noncovalent interactions.



Scheme 10. Ion-assisted *para*-C-H borylation of aromatics.



Scheme 11. Ligand-assisted *para*-borylation of aromatic amides.

3. Ir catalyzed *para*-selective C-H functionalization

3.1. Borylation

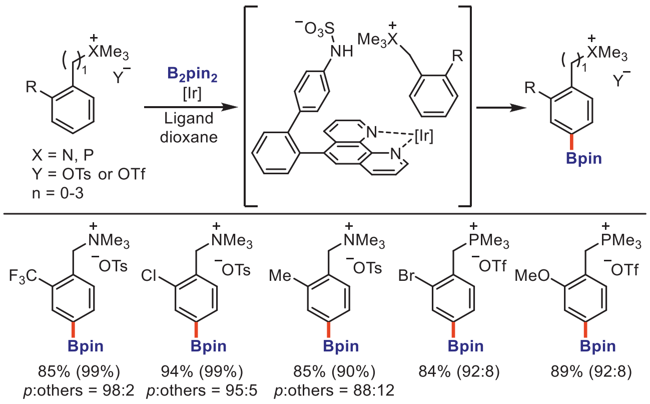
Chattopadhyay and coworkers [40] reported an iridium-catalyzed *para*-borylation of aromatic esters (Scheme 9). The team designed and synthesized an L-type ligand (**L1**) containing a pyridine and quinolone moiety through Miyaura borylation and Suzuki coupling. The B part of the ligand (**L1**) can undergo interconvertible isomerization, with the aromatic form (**L-T**) being more stable due to resonance. In the presence of [Ir(cod)(OMe)]$_2$ and B$_2$ pin$_2$, it forms a standard tris(boryl)iridium complex, which catalyzes the C-H borylation. The hydroxyl group on L-T or the *in situ*-generated O-[M] moiety from the ligand (**L1**) recognizes the carbonyl oxygen of the ester group directly attached to the benzene ring through non-covalent interactions, forming a stable transition state (**TS3**), leading borylation to the *para* position.

The aforementioned methodologies exhibit remarkable creativity; however, their widespread applicability is limited by two key factors. Firstly, they are constrained to a relatively narrow range of substrate classes. Secondly, they necessitate the utilization of custom-designed or non-commercial ligands and catalysts, which poses a challenge for individuals, particularly those in the pharmaceutical industry, who prefer readily available reagents.

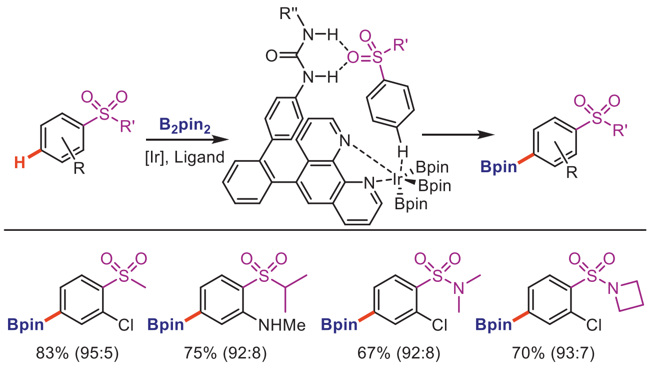
In order to address these limitations, Phipps and coworkers [41] devised a more versatile and practical approach in 2019 (Scheme 10). They harnessed the potential steric shielding effect imparted by the tetrabutylammonium cation, enabling its pairing with a diverse array of common aromatic moieties (such as anilines, benzylamines, phenols, and benzyl alcohols) to affect their transformation into the corresponding sulfates (X=O) or sulfamic acid salts (X=N). Employing an iridium catalyst, the bulkiness of the NBu^{4+} cation effectively obstructed the *meta* position, thereby facilitating selective *para*-borylation at the most distal *ortho* position with B_2pin_2, ultimately affording *para*-substituted products featuring the Bpin moiety. Distinct from prior methodologies reliant on steric effects conferred by catalysts or ligands, this study achieved the generalization and universality of iridium-catalyzed *ortho*-borylation through the exploitation of non-covalent ion-pairing interactions to dictate regioselectivity.

In 2022, the Chattopadhyay group [32] further expanded the scope of *para*-borylation reactions controlled by bulky ligands by introducing a novel defa ligand, 4,5-diazafluorene (Scheme 11). The defa ligand exhibits in-plane distortion due to the insertion of a methylene group. Leveraging the combination of geometric constraints imposed by the fully distorted structure of the double-Boc amide moiety on the aromatic ring, the spatial hindrance from the ligand, and electronic factors, selective *ortho*-borylation of aromatic compounds was achieved. Compared to previous studies, the presence of the double-Boc protecting groups offers the advantage of facile deprotection through conventional methods, thereby enhancing the efficiency of existing *para*-borylation protocols.

Liang and coworkers [42] developed an ion-pairing strategy for directing *para*-borylation reactions (Scheme 12). They designed a readily accessible anionic ligand called "dipyridylphenanthroline" and developed an iridium-catalyzed protocol for the selective C-H borylation of several different classes of aromatic quaternary ammonium and phosphonium salts. In contrast to previous approaches that relied on spatial repulsion between the bulky counterion of the iridium catalyst and the substrate, the directed effect of ion pairing between the cationic portion of the substrate and



Scheme 12. *para*-Borylation of aromatic ammonium/phosphonium salts.



Scheme 13. *para*-Borylation of aryl sulfonyl substrates.

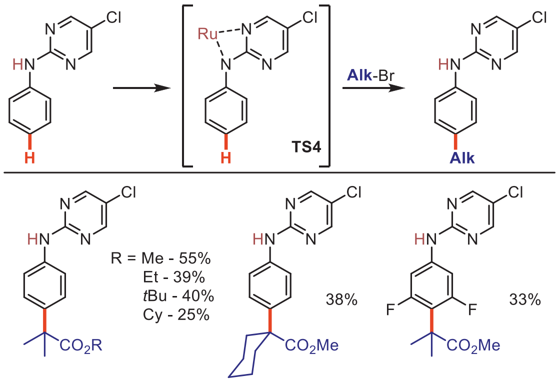
the anionic portion of the ligand **L2** had vital influence on achieving regioselectivity. This work provided a new avenue for achieving *para*-selectivity in the field of C–H activation, expanding the possibilities for controlling site-selective functionalization reactions.

Liang and coworkers [43] explored the directing potential of sulfonamide groups in *para*-borylation reactions (Scheme 13). Unlike Phipps group, they did not rely on steric hindrance effects of ion pairs to control selectivity. Instead, they controlled the reaction at the *para* position by using a ligand that interacts with both the sulfonamide group and the Ir catalyst. This approach enabled the introduction of boronic acid groups at positions that were previously challenging to access, such as in aryl sulfones and aryl sulfonamides. By employing this strategy, they successfully achieved *para*-selective borylation reactions, providing a new avenue for utilizing sulfonamide-directed *ortho*-functionalization reactions.

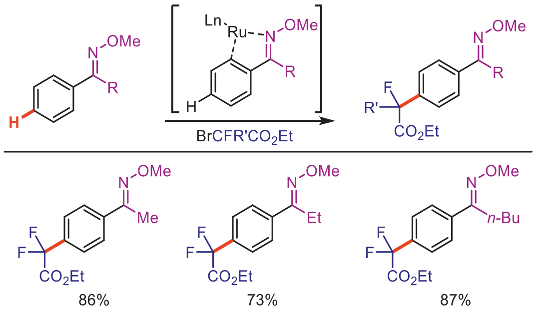
However, despite these advancements, the application of these non-covalent interactions in the field of *para*-C-H borylation reactions is still in its early stages. Further development and enrichment of principles, concepts, and new hypotheses are needed in the direction of C–H activation/borylation chemistry to ultimately achieve systematic applications. The successful progress made in recent years with the use of non-covalent interactions in iridium-catalyzed reactions undoubtedly provides the impetus to achieve these goals.

4. Ru catalyzed *para*-selective C-H functionalization

In addition to the *para*-selective C-H functionalization by costly iridium and palladium catalysts, recent research has focused on the development of ruthenium-based catalysts for achieving *para*-selective C-H functionalization at distant positions [44-47]. These endeavors have yielded numerous innovative strategies capable of remote C-H functionalization using ruthenium complexes. These methodologies have demonstrated remarkable efficacy across diverse substrate classes, enabling the construction of both C-C and C-Het (carbon-heteroatom) bonds with exceptional *para*-selectivity.



Scheme 14. *para*-C-H alkylation of aniline derivatives with α-bromo esters.



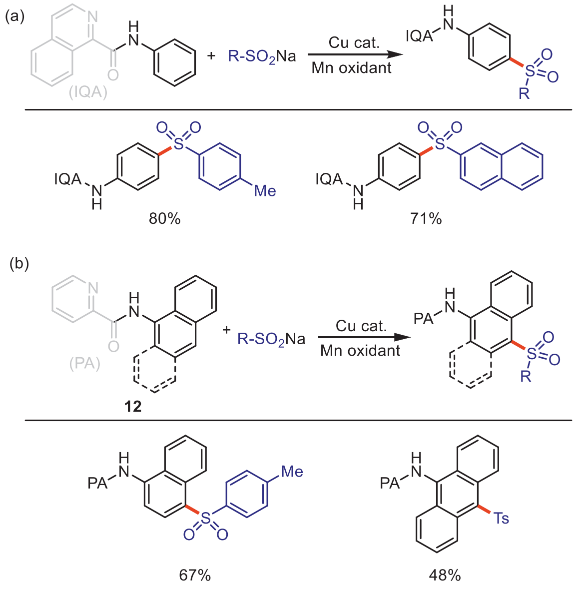
Scheme 15. *para*-Difluoromethylation of keroximes.

In the pursuit of remote *para*-selective C-H alkylation, independent research efforts by Frost's group [48] have disclosed the use of quinazolinone as a directing group for selective C-H alkylation of aniline derivatives with α-bromo esters (Scheme 14). In particular, the presence of a chlorine atom at the 5-position of the quinazolinone effectively suppresses functionalization at the *para* position. Subsequent computational and mechanistic studies conducted by the Frost group proposed that this addition occurs *via* a radical process at the N-H position of the cyclometalated ruthenium complex rather than at the C-H bond.

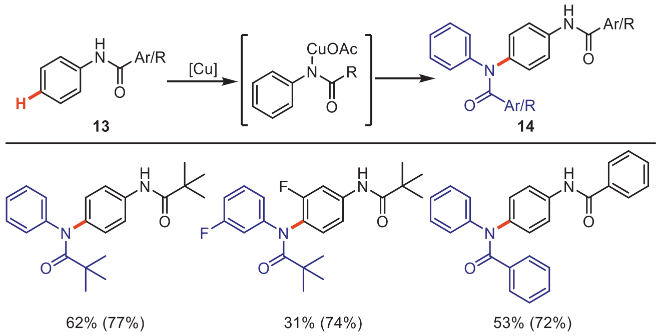
Zhao *et al.* [30] achieved highly *para*-selective difluoromethylation of ketoximes using ruthenium catalysis (Scheme 15). Mechanistic studies revealed that chelation-assisted cyclometalation is crucial for the *para*-selectivity. DFT calculations showed that the differential contributions of frontier molecular orbitals control the selectivity. Distortion/interaction analysis indicated that TS-*para* has smaller C atom distortion and lower activation energy, contributing to the *para*-selectivity. This work provides a valuable strategy for remote difluoromethylation and offers insights for further regioselectivity control.

5. Cu catalyzed *para*-selective C-H functionalization

Manolikakes *et al.* [49] reported a copper-catalyzed *para*-C-H sulfonation of aniline with sulfonyl hydrazine salts (Scheme 16a). The reaction employed a synergistic reaction system consisting of $Cu(OAc)_2$ as the catalyst, $Mn(OAc)_3$ as the oxidant, and 1-isoquinolinyl amide (IQA) as the directing group. It achieved selective single-electron oxidation of aniline molecules. Further studies demonstrated that benzoylated anilines, such as **12** underwent facile C-H sulfonation (Scheme 16b). The reaction proceeded at room temperature and required a minimal excess of oxidant and



Scheme 16. DG-assisted *para*-sulfonylation of anilines.



Scheme 17. *para*-Acylation of anilines by using APS.

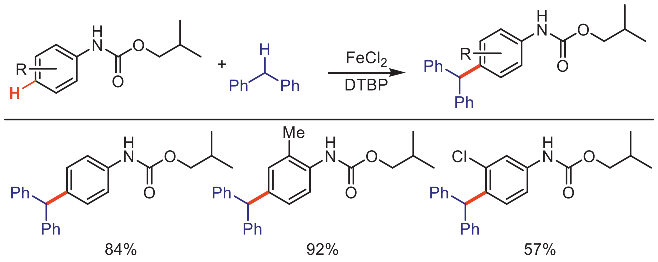
sulfonyl hydrazine salts. Additionally, it only required a simple pyridinyl amide (PA) directing group.

The group of Mhaske [50] revealed a copper-catalyzed *para*-selective acylation of anilines using ammonium persulfate (APS) as the oxidant (Scheme 17). The study indicated that the acylamide group on anilines first chelated with the copper catalyst to form an intermediate complex (**13**), which underwent aromatic C–H functionalization through a radical pathway upon the action of APS, resulting in the formation of product (**14**). The strategy exhibited remarkable regioselectivity, further establishing the directing role of the acylamide group in copper-catalyzed reactions.

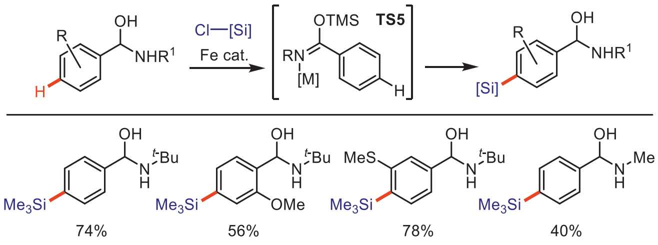
The aforementioned methods both demonstrate the *para*-selective reactivity of aniline under copper catalysis. Copper can coordinate with the nitrogen atom to form the intermediates, which subsequently undergo single-electron transfer reactions facilitated by radical formation.

6. Fe catalyzed *para*-selective C-H functionalization

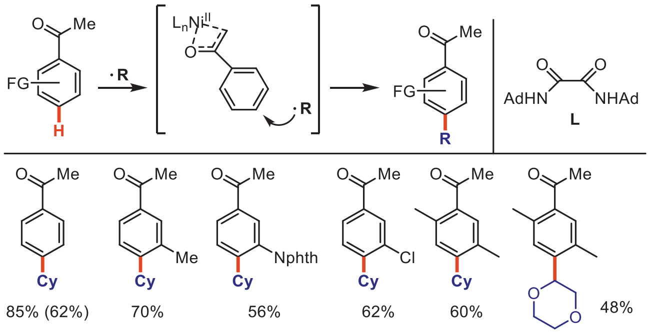
Compared to the noble metals, iron is also a widely used catalyst but has been less explored in the field of *para*-selective C-H functionalization [51–54]. In the past decade, there have been only a few reports on this topic [55]. However, iron is one of the most abundant transition metals in the Earth crust and possesses advantages such as low cost and environmental friendliness, making it an attractive candidate for research in this direction.



Scheme 18. *para*-Benzylation of aniline derivatives and diphenylmethane.



Scheme 19. Iron-catalyzed *para*-selective C-H silylation of benzamide derivatives with chlorosilanes.



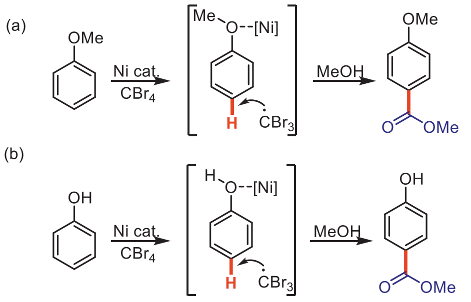
Scheme 20. Ni-catalyzed *para*-selective alkylation.

The Zhao's group [56] employed DTBP and $FeCl_2$ to abstract a hydrogen atom from diphenylmethane, generating a diphenylmethyl radical and Fe(III). Subsequently, Fe(III) interacted with aminoformate phenyl ester to form intermediate. The diphenylmethyl radical reacted with the intermediate, which underwent deprotonation and aromatic C-H functionalization to afford the *para*-benzylated product (Scheme 18). The high regioselectivity of the product was achieved under the protection of a bulky tert-butoxy group at the higher position.

Kong *et al.* [57] reported the *para*-selective silanization reaction of benzamides with chlorosilanes catalyzed by $FeCl_2$ (Scheme 19). Mechanistic studies revealed that benzamide was deprotonated by *i*-PrMgCl and TMSCl, followed by coordination with the metal catalyst to form intermediate (**TS5**). Through a radical reaction, an aryl radical was generated, which underwent single-electron transfer (SET)/proton transfer to ultimately yield the *para*-silanized benzamide product. This reaction offers a green and versatile approach for the synthesis of various *para*-silicon-functionalized benzamides, as it utilizes readily available starting materials, operates under mild conditions, and exhibits excellent selectivity.

7. Ni catalyzed *para*-selective C-H functionalization

Zhao and coworkers [58] utilized the Ni(acac-6F)$_2$ catalyst combined with formamide as a ligand (**L**) to develop a direct *para*-selective alkylation of aromatic ketones with alkanes (Scheme 20). The Ni(II) complex formed a stable intermediate by coordinating



Scheme 21. High *para*-C-H carboxylation of (a) phenyl methyl ethers and (b) phenol derivatives.

with the α-methyl group of the acetophenone, enabling the activation of a radical at the *para* position of the benzene ring and subsequent alkylation.

Subsequently, Zhao's group [59,60] designed a ligand, 2,9-dimethyl-4,7-diphenyl-1,10-phenanthroline, which coordinated with Ni(II) as a catalyst to achieve *para*-selective carboxylation of phenyl methyl ethers using bromoform as a radical source (Scheme 21a). The Ni(II) complex coordinated with the methoxy group of the aromatic ring, introducing steric hindrance at the *ortho*- and *meta*-positions. This weak interaction reduced the aromaticity of the aromatic ring, facilitating the activation of the *para* position and leading to highly regioselective carboxylation. Similarly, Zhao and coworkers also achieved *para*-selective carboxylation of phenol derivatives (Scheme 21b). The hydroxyl group of phenol provided steric hindrance, and through coordination with the Ni(II) catalyst, increased the reactivity at the *para* position of the benzene ring, enabling direct C-H carboxylation. Various substituted methoxybenzenes were effectively tolerated, producing the desired products with comparable yields.

8. Others

In addition to aforementioned categories, there are some other transition metals perform catalytic activation of *para*-C-H functionalization. Some of work is outlined despite of the limited research.

8.1. Chromium

Researches associated with *para*-C-H functionalization using chromium catalysts has been rarely reported. However, in 2018, Zeng *et al.* [61] proposed a method using Cr(III) salts as precatalysts in combination with trimethylsilyl bromide to achieve alkylations of benzamides with alkylmagnesium bromides at room temperature, thereby achieving selective *para* alkylation of aryl-substituted quaternary carbon centers (Scheme 22). This reaction proceeds with high selectivity, selectively alkylating only the *para* carbon of the benzamide without generating bulky alkyl isomers. The key step in the reaction involves the nucleophilic substitution of the radical intermediate benzyl iminates (**TS6**) (Scheme 22).

8.2. Rhodium

Both Pd and Ru, neighboring Rh on the periodic table, have shown catalytic potential in *para*-C-H functionalization. However, research on the site-selective C-H functionalization catalytic ability of Rh has been limited to *ortho* positions only. Recently, Maiti *et al.* [62] designed a directing group, DG_4 (62%, *p*:others 15:1), which contains a combination of bulky methylsilyl linker, nitrile group, and alkoxyl group (Scheme 23). This innovative design has enabled the first successful implementation of Rh-catalyzed *para*-C-H functionalization. The research group connected the DG_4 to toluene *via* a Si linker, and the strong coordination between the nitrile group and Rh stabilized the C-H activation transition state, allowing for highly selective *para*-alkenylation reactions in the presence of an alkene.

In 2022, Wang *et al.* [63] proposed a multicomponent reaction catalyzed by dirhodium(II)/Xantphos for the synthesis of various phenol derivatives bearing an allyl moiety and a quaternary carbon center (Scheme 24). Mechanistic studies revealed that the reaction proceeds through base-promoted *para*-selective C(sp^2)−H functionalization of phenols to form Rh(II) carbenoids, which are then subjected to allylic alkylation. Importantly, the resulting allyl aryl ether products can undergo facile and selective *O*-deallylation under mild conditions, providing the corresponding free phenol derivatives with a quaternary carbon center.

8.3. Molybdenum

The Zhao and coworkers [64] proposed a highly *para*-selective C-H perfluoroalkylation of aniline substrates using a hexacarbonyl molybdenum catalyst (Scheme 25). The Mo catalyst coordinates with the amide in aniline, activating the aromatic ring connected to the amide group, which is crucial for achieving *para*-selectivity. The generation of free perfluoroalkyl radicals (Rf) occurs through single-electron transfer (SET) oxidation and selectively undergoes C-H functionalization at the *para* position.

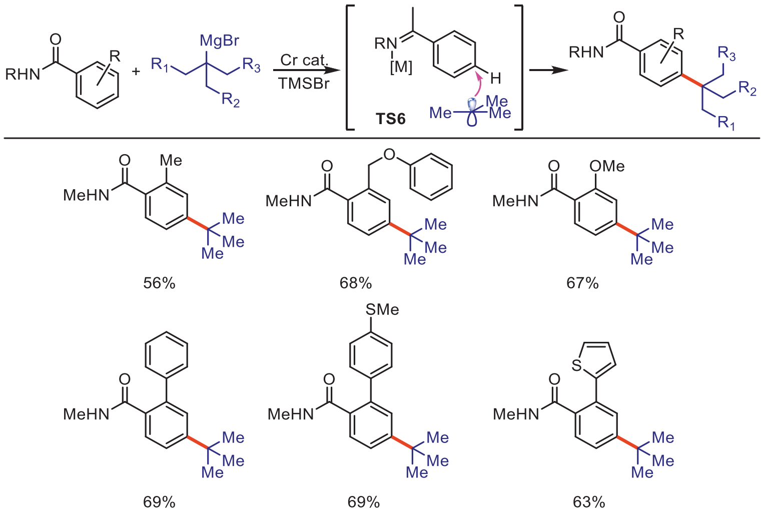
8.4. Cobalt

As early as 2010, Ryohei *et al.* [65] reported the reaction of cyclic secondary amines with chloronitrobenzene or dichloronitrobenzene under cobalt(II) chloride catalysis. Although no *meta*-products were formed, both *ortho* and *para* products were obtained, indicating the need for further optimization of the reaction selectivity. Significant progress in this direction was achieved in 2022. Su *et al.* [66] proposed a highly site-selective amination of diazonium benzene catalyzed by cobalt (Scheme 26). Hammett analysis revealed that this method essentially involves a metal-coordinated Co-promoted SNArH (nucleophilic aromatic substitution with hydrogen) process: the nitrogen of the diazonium benzene coordinates with the cobalt center, increasing the electrophilicity of the diazonium benzene ring. This induces nucleophilic addition of the amine at the *para* position of the diazonium benzene, followed by rapid oxidation and deprotonation through intramolecular electron transfer to the Co center, and ultimately leads to the formation of the *para*-aminated product *via* ligand exchange.

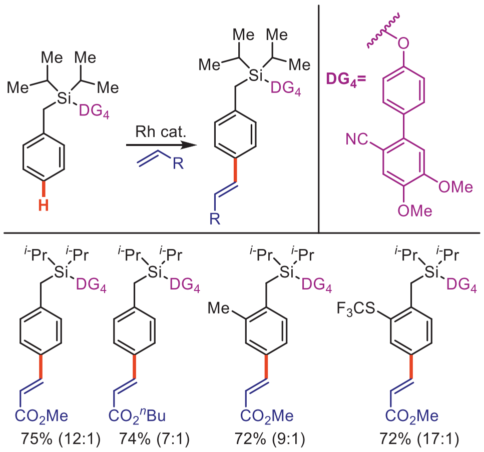
Furthermore, there are reactions involving synergistic catalytic systems composed of more than one metal. For example, the Ni/Al bimetallic catalysis [67–70] and Ir/Al cooperative catalysis [71] are beyond the scope of this article and will not be discussed here.

9. Conclusion and prospect

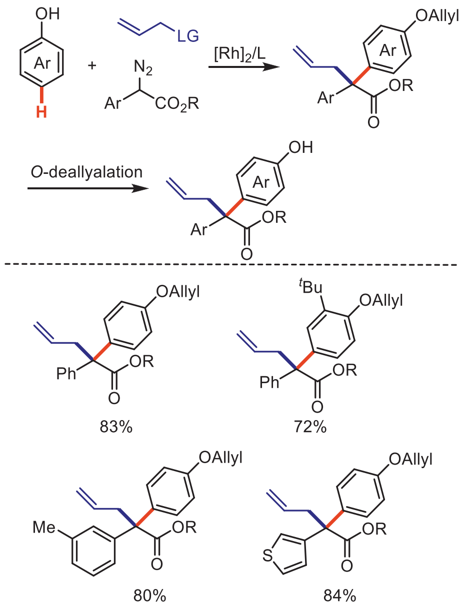
In conclusion, we have summarized recent advances on transition metal catalyzed direct *para*-selective C-H functionalization. Selective C-H direct functionalization of arenes is one of the most important branches of organic synthesis research. The use of a directing group can increase the regioselectivity. Nevertheless, this approach requires meticulous design of direction group or template which attached covalently with the unfunctionalized substrates. The DG or template was then weakly coordinated with donor atoms as an intermediate to transport the transition metal to expected C-H activation site. The bulky ligands or pre-installed direction groups have been utilized to create steric hindrance and electronic control for precise *para*-selectivity. The key to C-H bond activation is the formation of a bulky metallacycle intermediate,



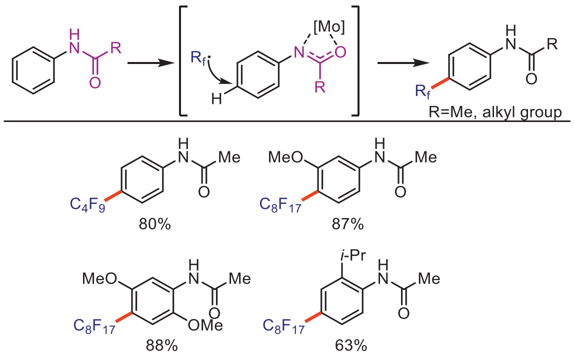
Scheme 22. *para*-Alkylations of benzamides with alkylmagnesium bromides.



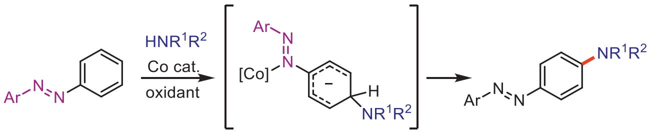
Scheme 23. First example of Rh catalyzed *para*-C-H olefination.



Scheme 24. *para*-Selective C-H functionalization of free phenols: Rh(II)/Xantphos catalyzed geminal difunctionalization of diazo compounds.



Scheme 25. Mo-enabled *para*-C-H perfluoroalkylation.



Scheme 26. Co-catalyzed *para*-selective amination of diazonium benzene.

which however is unfavorable thermodynamically. Consequently, template engineering overcame such dependence of substrate or catalysts. Promotion effect of transition metal, coordinated atoms, bulk of template and interaction of the atoms was tuned properly, and highly regio-selectivity of desired functionalization was achieved in a synergetic approach. In this regard, non-covalent interaction was prevalent for *para*-C-H functionalization. In addition, the ease of removal and reusability of directing groups in *para*-functionalization provide an economic advantage and offer a straightforward route for the synthesis of various pharmaceutical molecules and natural products. In addition to Pd and Rh catalysts, the more cost-effective Ru or Ni have also been found to effectively facilitate *para*-C–H activation with the aid of certain directing groups. Over the past decade, strategies based on transition metal catalyzed directing groups have successfully produced numerous reports on C–H functionalization, demonstrating satisfactory yields and selectivity. Moreover, the co-catalysis of transition metal catalysts with Lewis acids has also been successfully applied to the *para*-C–H functionalization of aromatics. In this review, these reports are also mentioned to outline the latest advancements in this strategy for *para*-C–H functionalization.

Despite these advancements in the field, there are many unresolved issues and challenges. The limitations of template-assisted functionalization include the need for pre-installation of directing groups (DGs) and their removal after functionalization, which requires additional synthetic steps. Functionalization controlled by electronic and steric factors is limited to a few aromatics with strong electron-donating functional groups. Furthermore, bulky ligands or substituents are crucial determinants for obtaining *para*-selective products. Consequently, such strategies are highly restricted to specific classes of compounds. Therefore, developing robust protocols that broaden the functionalization scope across various substrates without spatial or electronic bias is highly desirable. The mechanisms of many current catalytic strategies remain elusive, and the interactions between transition metal catalysts and the C-H bonds in the transition states are poorly understood. Therefore, the surge of new discoveries in the field of selective *para*-C-H functionalization is expected to continue over the coming decades.

Declaration of competing interest

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

CRediT authorship contribution statement

Wei-Bin Li: Writing – original draft, Investigation. **Xiao-Chao Huang:** Methodology. **Pei Liu:** Writing – review & editing, Project administration, Methodology. **Jie Kong:** Writing – review & editing, Methodology. **Guo-Ping Yang:** Writing – review & editing, Project administration, Methodology.

Acknowledgments

We acknowledge financial support from the National Natural Science Foundation of China (No. 21901206), Postdoctoral Science Foundation of China (No. 2022M712589), General Key R & D Projects in Shaanxi Province (No. 2023-YBGY-321), Natural Science Foundation of Chongqing (No. CSTB2022NSCQ-MSX0826), National & Local Joint Engineering Research Center for mineral Salt Deep Utilization, Huaiyin Institute of Technology (No. SF202407) for financial support.

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