Prayogik Rasayan

Native Functional Group Directed *para*-C−H Bond Functionalization

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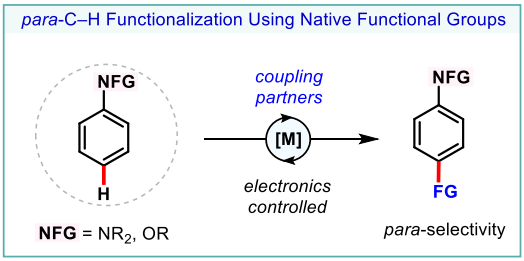
Abstract

Arenes or heteroarenes bearing amine (NR_2) or alkoxy (OR) functional groups are ubiquitous in numerous natural products and pharmaceuticals. Site-selective C−H bond functionalization of these scaffolds could ideally open up new avenues for building complex molecular architectures. With the aid of the above-mentioned native functional groups (NR_2 and OR), *para*-C−H bond functionalization of these arenes can be achieved in an atom-and-step economic fashion. In this review article, we have summarized a variety of *para*-C−H bond activation and functionalization of arenes and heteroarenes guided by electronics. We have critically assessed the reaction design and the key challenges and mechanistic rationale are underlined for better understanding. We hope this review article will give a guiding platform for further development in this area of research.



Keywords: Native Functional Groups, Electronics-Controlled Approach, C−H Functionalization, para-Selectivity, TM Catalysis

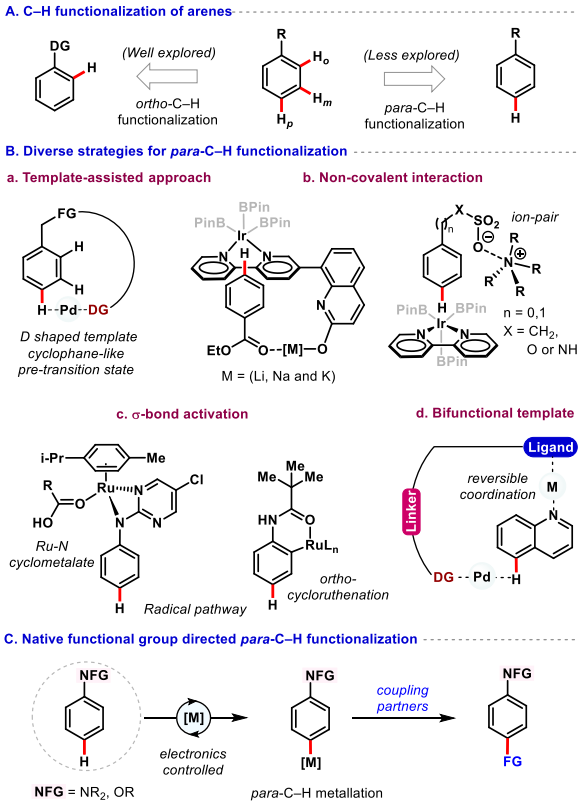
1. Introduction

The catalytic functionalization of inert C−H bonds represents one of the most powerful blueprints for building molecular complexity. Therein, the direct transformation of arene C−H bonds to carbon−carbon or carbon−heteroatom bonds is particularly attractive due to its high efficiency and sustainability features compared to traditional cross-coupling reactions.[1, 2] Despite the potential of this method, achieving C−H functionalization in a regioselective manner by distinguishing the subtle reactivity difference between multiple C−H bonds is highly challenging. Over the last three decades, tremendous advancement has been made in achieving *ortho*-C−H functionalization of arenes utilizing various directing groups, which entails the formation of stable metallacyclic intermediates with five-, six-, or even seven-members (Scheme 1A).[3-5] In contrast, reaching the distal C−H bonds remains a hurdle due to the inaccessibility of these sites by a transition metal catalyst. In this regard, realizing suitable catalytic platforms or substrate designs to harness distal C−H functionalization has drawn significant attention over the decades.[6, 7]

Selective functionalization of the *para*-C–H bond is highly intriguing as it can alter the physicochemical properties of arenes. For example, the incorporation of a π-system at the *para*-position can enhance the π-conjugation as well as it can perturb the dipole moment significantly. Therefore, *para*-C–H functionalization of arene is of substantial interest to drug discovery and diversification programs.[8, 9] Additionally, the *para*-substituted arenes are widely found in biological systems,[10] pharmaceutical reagents,[11, 12] and synthetic intermediates in material science.[13] These characteristics prompted chemists to design sustainable and practical strategies for adaptable *para*-C−H functionalizations. One representative approach is template-assisted *para*-C–H functionalization, in which the reaction proceeds via forming a large-membered macrocyclic transition state (Scheme 1Ba).[7, 14, 15] Other strategies include non-covalent interaction-enabled *para*-C–H borylation,[16-18] σ-bond activation assisted *para*-C–H functionalization using a ruthenium-catalyst,[19] and the use of a bifunctional template for achieving remote C–H functionalization (Scheme 1Bb-d).[20] All these approaches either require a suitable template or ligand design, which involves several synthetic steps for their preparation.

Another approach in which the *para*-C–H functionalization is governed by the electronics of the system is gaining more attention. Native functional groups such as NR_2 (amine) and OR (alkoxy) can activate the *para*-position of arene for selective metalation (Scheme 1C). This approach is operationally simple, and a variety of transformations can be achieved in both aromatic and heteroaromatic systems. In this review, we provide an overview of the transition metal-catalyzed *para*-C–H functionalization of arenes using native functional groups. We have critically assessed the reaction development to understand the role of native functional groups and reagents for particular transformations. We

expect this review will educate and excite readers and encourage young minds for further advancements in this field.

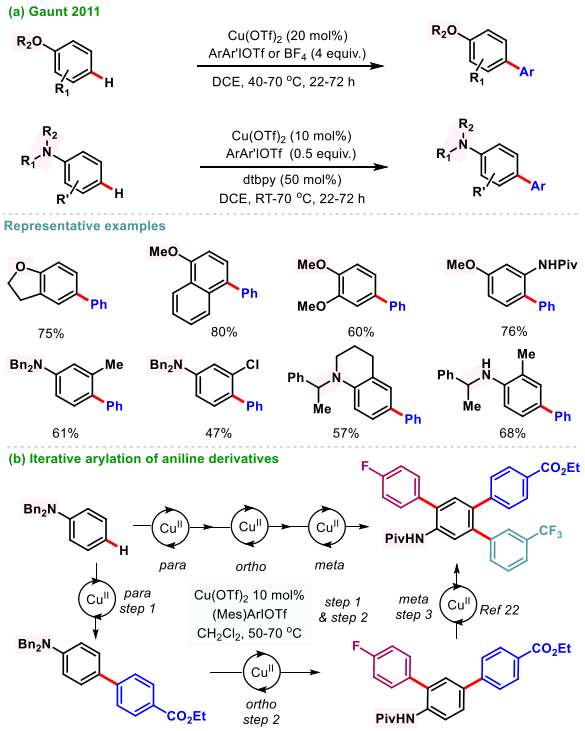


Scheme 1: Diverse strategies for *para*-C–H functionalization of arenes.

2.1 *para*-C−H functionalization of anilines and alkoxy arenes

In 2011, Gaunt and co-workers reported one of the pioneering works on the native NR_2 or OR group-directed *para*-C(sp^2)−H functionalization of phenol and aniline derivatives (Scheme 2a).[21] The reaction is controlled by electronics, and the authors hypothesized that electron-rich arenes might undergo direct arylation through a classical S_EAr-type mechanism. $Cu(OTf)_2$ was used as a catalyst, and diaryliodonium salt was employed as an arylating reagent. Diverse symmetrical and mesityl- and tri(isopropylphenyl)-bearing unsymmetrical iodonium salts could be successfully utilized for the *para*-selective arylation of phenol derivatives. Anilines needed 2,6-di-*tert*-butylpyridine (dtbpy) as a base to capture the generated TfOH. The authors also showcased an iterative arylation process to afford tri arylation at *ortho*, *meta*, and *para* positions of aniline under their developed Cu(II)-catalyzed conditions (Scheme 2b).[22] Although the exact mechanism of this copper-catalyzed reaction remained unclear, authors considered a "Friedel-Crafts arylation" based on the obtained selectivity.

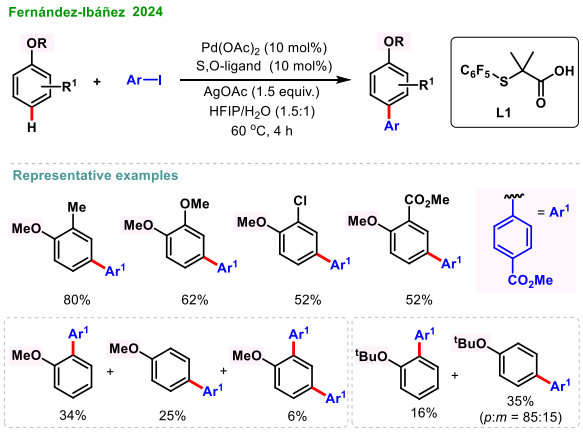
Very recently, Fernández-Ibáñez demonstrated an elegant approach for *para*-C(sp^2)−H arylation using readily available aryl iodides (Scheme 3).[23] The combination of Pd-catalyst with one-step synthesized S,O-ligand **L1** was the key to success for high catalytic activity. A high yield with excellent selectivity (*para*/*meta* = 95:5) for the *para*-arylation of 2-methylanisole could be obtained using 10 mol% $Pd(OAc)_2$/S,O-ligand **L1** in a mixture of HFIP:H_2O solvent at 60 °C. Using water as a co-solvent positively increased the yield and regioselectivity while reducing the formation of undesired homocoupled products from aryl iodides. For *ortho*-substituted anisoles, products were obtained with good to excellent yield and excellent *para*-selectivity. However, unsubstituted anisole and *tert*-butoxy benzene were challenging substrates and rendered a mixture of products. Reaction order determination and kinetic isotope effect (KIE = k_H/k_D = 7) studies indicated that the C−H activation step is the rate-limiting step of the process. The authors also proposed a Pd(II)/Pd(0) catalytic cycle based on the control experiments.



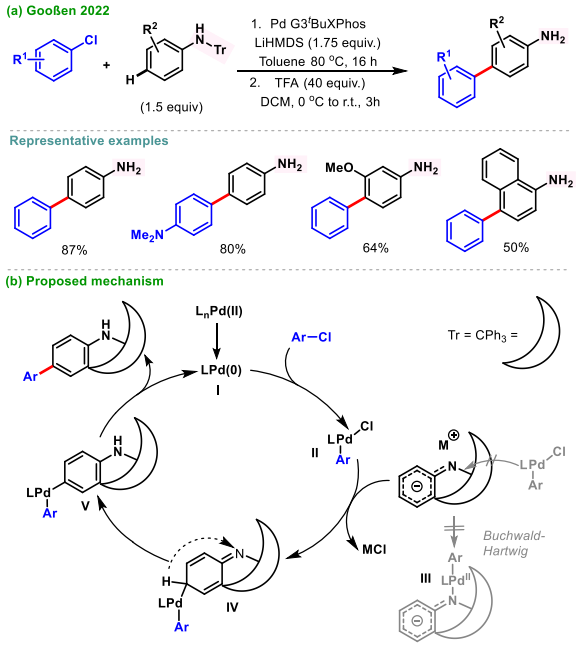
Scheme 2: Cu-catalyzed *para*-C–H arylation of anilines and alkoxy arenes.

In 2022, Gooßen et al. reported a straightforward protocol for *para*-selective arylation of secondary anilines with aryl halides (Scheme 4a).[24] The reaction was carried out in the presence of a bulky palladium/phosphine catalytic system with a non-nucleophilic base LiHMDS to deprotonate the N-H of aniline.[25] To prevent the undesired *N*-arylation and *ortho*-arylation, the nitrogen center of aniline was protected with a bulky trityl group that can be cleaved after the reaction's completion under acidic conditions. The obtained inverse KIE of k_H/k_D = 0.88 suggested that the concerted metalation deprotonation (CMD) pathway is not operative for the C−H cleavage step. Instead, it followed the electrophilic substitution mechanism, for which KIEs <1 have been

reported. The mechanistic blueprint for this transformation is based on the enamine/imine tautomerism concept illustrated in Scheme 4b. At first, the oxidative addition of aryl chloride to Pd(0) species produced an electrophilic Pd(II) complex **II** that binds at the *para* position of the aniline substrate and forms pallada-cyclohexadiene-imine tautomer **IV**. The latter undergoes rapid tautomerization to form an enamine intermediate **V** via a sterically insensitive suprafacial [1,5]-H shift. Subsequently, reductive elimination eliminated the desired arylated product and closed the catalytic cycle.

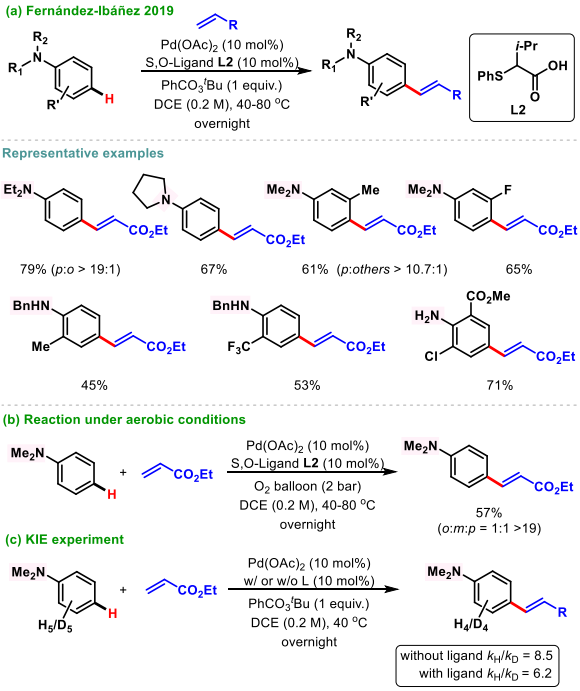


Scheme 3: Pd-catalyzed *para*-C–H arylation of anisoles.



Scheme 4: Pd-catalyzed *para*-C–H arylation of anilines.

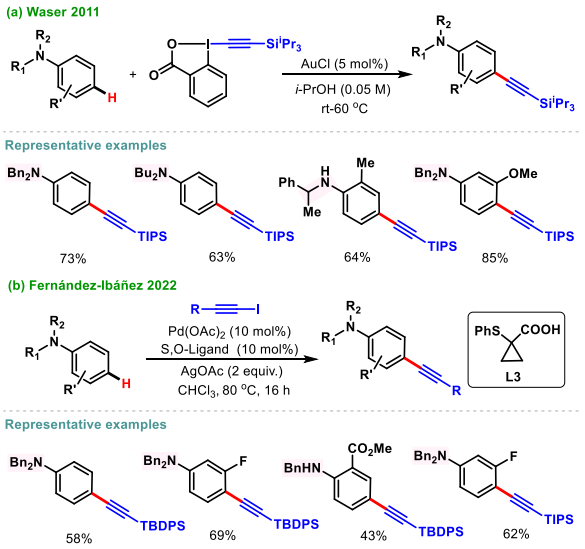
In 2019, the Fernández-Ibáñez group reported a highly *para*-selective C(sp^2)−H olefination of anilines using a Pd/S,O-ligand-based catalytic system (Scheme 5a).[26] The reaction of *N,N*-dimethylaniline with ethyl acrylate in the presence of Pd/**L2** combination, and 1.0 equiv of $PhCO_3{}^tBu$ as an oxidant in dichloroethane (DCE) at 40 °C provided the *para*-alkenylated product in 81% NMR yield with excellent *para*-selectivity (*p:o* > 19:1). In contrast, the reaction without the S,O-ligand resulted in poor yield (18% NMR yield) with a mixture of three isomers (*o:m:p* = 1:1:18). The protocol could be utilized for *para*-C(sp^2)−H olefination of a wide variety of substrates such as *N,N*-dialkylanilines, *N*-benzylanilines and primary anilines. The authors also showed that $PhCO_3{}^tBu$ could be replaced with an oxygen balloon (2 bar) to provide the desired product in good yield and *para*-selectivity (Scheme 5b). The KIE experiments were conducted with and without the ligand. The KIE values of 8.5 and 6.2, respectively, suggested that the C−H bond activation step is the turnover-limiting step in both scenarios (Scheme 5c).



Scheme 5: Pd-catalyzed *para*-C–H olefination of anilines.

In 2011, Waser et al. developed a *para*-selective alkynylation of aniline derivatives utilizing triisopropylsilylethynyl-1,2-benziodoxol-3(1H)-one (TIPS-EBX) as an electrophilic alkynylation reagent and AuCl as the catalyst (Scheme 6a).[27] The reaction outcome was found to be highly dependent on the solvent, and *i*-PrOH (0.05M) provided a superior result. The authors proposed a S_EAr-type mechanism for this *para*-alkynylation process based on the observed selectivity. Further, the method was applied for alkynylation of trimethoxybenzenes. Recently, Fernández-Ibáñez *et al.* demonstrated a *para*-selective C−H alkynylation of various aniline derivatives using 1-iodo-2-(triisopropylsilyl)acetylene as the alkynylating reagent (Scheme 6b).[28] The reaction was performed using a combination of $Pd(OAc)_2$/S,O-ligand **L3** as the catalyst in the presence of AgOAc (2 equiv) in $CHCl_3$ at 80 °C. Notably, the reaction was highly *para*-selective as

other isomers were undetected in the crude mixture. The S,O-ligand **L3** highly improved the reactivity of the catalyst as without the ligand, yields of the products were <5%. Many *ortho* and *meta*-substituted anilines bearing different substituents were compatible with the catalytic system. Furthermore, regio and stereoselective allylation of anilines was recently developed by the Baidya group using a combination of $Mg(OTf)_2$/HFIP.[29]

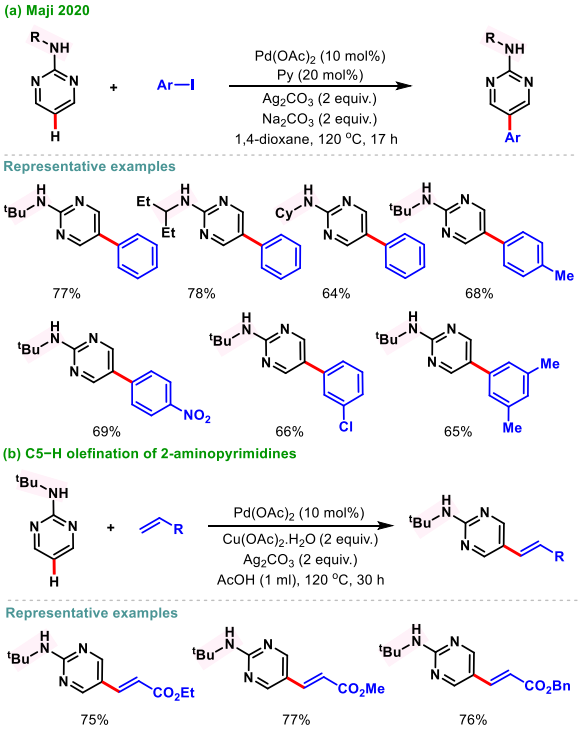


Scheme 6: *para*-C–H alkynylation of anilines.

2.2 Remote C−H functionalization of 2-amino/alkoxy azines

The C−H functionalization of azine rings, such as pyridines or pyrimidines, remains challenging.[30, 31] These azine rings are inherently electron-deficient, unlike anilines and alkoxy arenes. Additionally, the strong σ-coordination of the nitrogen center with the transition metal catalyst results in catalyst poisoning, making the C−H functionalization process highly challenging.[32, 33] An amine or alkoxy substituent at the C2 position of these azines might enhance the rate of dissociation of the N-coordination due to steric repulsion. Also, this would increase the local concentration of the electron-rich C5 position of the substrate around the catalyst.

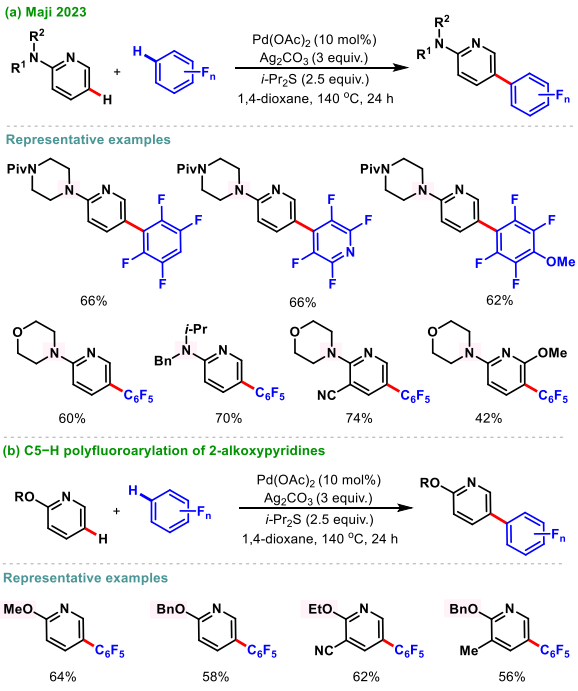
In 2020, Maji et al. reported the C5−H arylation and olefination of 2-aminopyrimidines by taking advantage of the amine functionality (Scheme 7a).[34] The C5−H arylation was achieved using $Pd(OAc)_2$/pyridine as the catalyst, with Na_2CO_3 and Ag_2CO_3 as the optimum base and silver salt, respectively. The base might facilitate the deprotonation of the N-H proton and increase the electron density at the C5 position, as suggested by the control experiments. Various aryl iodides bearing different functionalities were compatible under the reaction conditions. Notably, aryl bromides and aryl chloride could also be accommodated, albeit a higher temperature was necessary to obtain good yields for the products. A strategy for C5−H olefination was demonstrated in the same report (Scheme 7b). Combining Ag/Cu salts in AcOH as solvent was crucial to promoting the C5−H olefination of the 2-aminopyrimidine substrate. Diverse patterns of arylates could be used as coupling partners to afford the desired olefinated products with good to excellent yields.



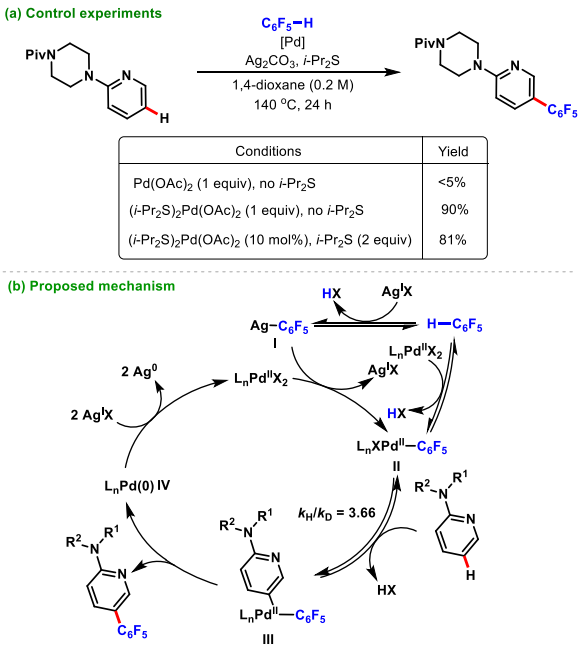
Scheme 7: Pd-catalyzed C5–H arylation and olefination of 2-aminopyrimidines.

After the success, the same group in 2023 reported the C(3)5−H polyfluoroarylation of 2-amino/alkoxy pyridines via the C−H/C−H coupling strategy (Scheme 8a).[35] The authors hypothesized that a highly electrophilic palladium catalyst might assist in promoting the C5−H palladation. This was further proved by the control experiment with bromopentafluorobenzene. Notably, the synergistic combination of $Pd(OAc)_2$, Ag_2CO_3, and *i*-Pr_2S was necessary to obtain the C5-polyfluoroarylated product. The product formation did not occur in the absence of any one of them. A wide range of polyfluoroarenes was coupled with 2-amnopyridines, providing the C5−polyfluoroarylated products in good to excellent yields with excellent selectivity. 2-Amniopyridines containing structurally complex subunits could be successfully employed in this reaction. Furthermore, 2-alkoxypyridines were also effectively polyfluoroarylated under the same reaction conditions (Scheme 8b). To probe the role of *i*-Pr_2S, a palladium complex (*i*-$Pr_2S)_2Pd(OAc)_2$ was synthesized, and several control experiments were conducted (Scheme 9a). These results proved that (*i*-$Pr_2S)_2Pd(OAc)_2$ is a catalytically active species, and *i*-Pr_2S acts as a ligand that might stabilize the palladium catalyst in different reaction stages. A Pd(II)/Pd(0) catalytic cycle was proposed in which polyfluoroaryl-Pd(II) species is generated via transmetallation with polyfluoroaryl-Ag(I) complex or via

direct C−H activation in the presence of Pd-catalyst (Scheme 9b). Next, the species **II** undergoes electrophilic palladation at the C5-position of 2-aminopyridine to afford a Pd(II)-hetero-biaryl complex **III**, which experiences reductive elimination to provide the polyfluorarylated product and Pd(0) species. Finally, the oxidation of Pd(0) **IV** to Pd(II) with the aid of Ag(I) salt closed the catalytic cycle.



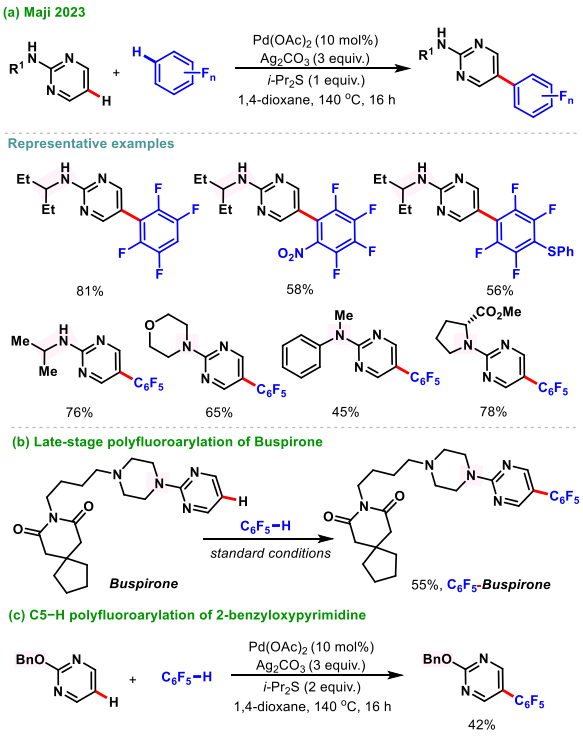
Scheme 8: Pd-catalyzed C5–H polyfluoroarylation of 2-amino/alkoxy pyridines.



Conditions	Yield
$Pd(OAc)_2$ (1 equiv), no i-Pr_2S	<5%
$(i\text{-}Pr_2S)_2Pd(OAc)_2$ (1 equiv), no i-Pr_2S	90%
$(i\text{-}Pr_2S)_2Pd(OAc)_2$ (10 mol%), i-Pr_2S (2 equiv)	81%

Scheme 9: Control experiments and proposed mechanism.

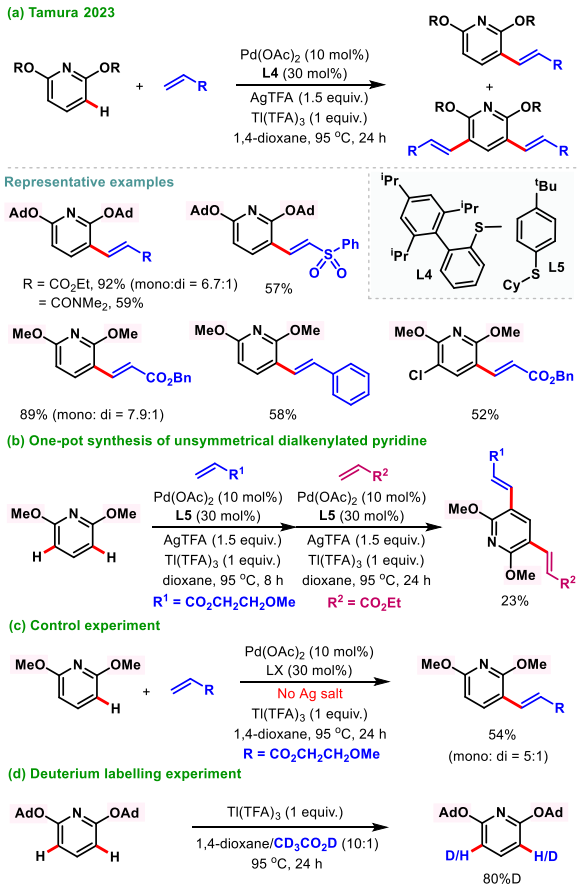
Controlling the selectivity of secondary or 2-aminoazines in the presence of an electrophilic catalyst is challenging as there are possibilities of both C5- and *N*-arylation. Recently, the Maji group demonstrated an interesting substrate-controlled divergent reactivity of secondary 2-aminopyrimidines with polyfluoroarenes (Scheme 10a).[36] The reaction between secondary N-alkylpyrimidine-2-amines and polyfluoroarenes results in C5−H polyfluoroarylation through C−H/C−H coupling. While, an *N*-H polyfluoroarylation was observed for secondary *N*-aryl substituents. Like their previous work, a similar mechanistic blueprint was proposed for the C5−H polyfluoroarylation of 2-aminopyrimidines based on Pd(II)/Pd(0) catalytic cycle. A range of secondary *N*-alkylpyrimidine-2-amines and tertiary 2-aminopyrimidines were polyfluoroarylated with excellent yields and selectively at the C5-position. To demonstrate the method's applicability, late-stage C−H polyfluoroarylation of an anxiolytic drug, Buspirone, was performed (Scheme 10b). Notably, C5−H polyfluoroarylation of 2-(benzyloxy)pyrimidine was also accomplished under similar reaction conditions (Scheme 10c).



Scheme 10: Pd-catalyzed C5−H polyfluoroarylation of 2-aminopyrimidines.

Utilizing a similar Pd/thioether catalytic system, the Tamura group reported an electrophilic C3−H alkenylation of 2,6-dialkoxypyridines (Scheme 11a).[37] An equivalent amount of $Tl(TFA)_3$ helped improve yield and mono-selectivity. The

control experiment and deuterium labeling experiment proved the dual role of $Tl(TFA)_3$: (1) the thallium reagent promoted the oxidation of in-situ generated Pd(0) to Pd(II),[38] (2) the C3-alkenylation involves electrophilic thallation first followed by Pd-catalyzed Heck-type reaction (Scheme 11c-d). Various alkene partners could be utilized as coupling partners for the C3−H alkenylation of 2,6-dialkoxypyridines. Further, they demonstrated the synthesis of unsymmetrical dialkenylated pyridine in a one-pot procedure via the sequential addition of two alkenes and other reagents (Scheme 11b).



Scheme 11: C3−H alkenylation of 2,6-dialkoxypyridines.

3. Conclusions

In this article, we have summarized the *para*-C−H bond functionalization reactions of electron-rich arenes and electron-deficient heteroaromatic systems with the aid of native functional groups. Various research groups have contributed to the establishment of this area of research by developing a range of reactions such as arylation, olefination, alkynylation, and polyfluoroarylation. Although the approach is operationally simple and atom economic, obtaining the exclusively *para*-selective product remains challenging. In addition, as this approach is controlled by electronics, there is always a possibility of *ortho*-C−H functionalization resulting in a mixture of products. Further efforts should be dedicated to improving the regioselectivity and mono-selectivity. The key to addressing these challenges would probably be careful catalyst/ligand design, substrate modification, and proper understanding of the system.

4. Acknowledgements

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5. Notes and References

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