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Recent Advances in Room-Temperature Direct C-H Arylation Methodologies

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Abstract:
In recent decades, direct C-H arylation has become a preferred tool for biaryl coupling over traditional cross-coupling methods owing to its operationally simple protocol, inherent atom and step economy, and reduced metallic waste. Several elegant methods have been developed that offer the facile transformation of usually inert Csp2-H bonds to Csp2-Csp2 bonds in a single synthetic operation. Despite many merits, a major drawback to this chemistry comes from aryl-C-H bonds' low reactivity, which often mandate harsh reaction conditions compromising sustainability. Hence, developing reaction protocols that require milder conditions has become an important goal in this area of research. This review article comprehensively highlights the synthesis and mechanistic aspects of direct C-H arylation reactions, which proceed at or below room temperature.

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Recent Advances in Room-Temperature Direct C-H Arylation Methodologies

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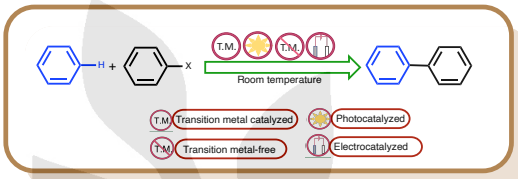

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Keywords: Direct C-H arylation, mild reaction conditions, room temperature, transition metal-catalyzed, Photocatalyzed, Electrocatalyzed

1. Introduction

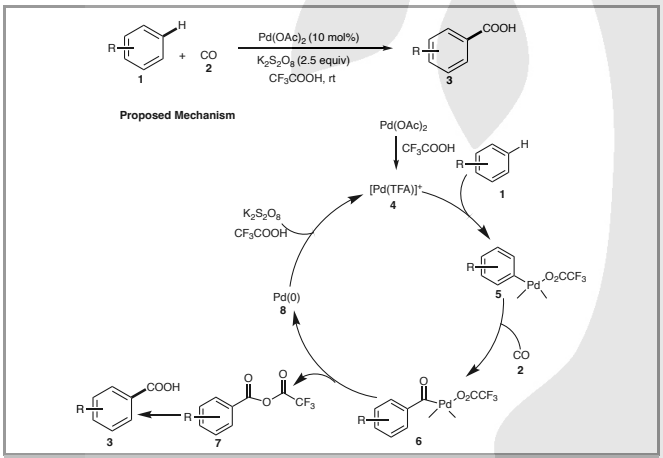
The advent of transition-metal-catalyzed cross-coupling reactions has transformed molecular synthesis, augmenting the repertoire of synthetic tools available to organic chemists.[1,2] Over the past decades, transition-metal-catalyzed cross-coupling reactions such as Suzuki-Miyaura,[3] Stille,[4] Negishi,[5] Sonogashira,[6] *etc.* have become imperative in synthesizing functional materials, natural products, and pharmaceutically active compounds.[7–9] While these reactions enable the construction of C-C bonds with high selectivity, the prerequisite functionalization of substrates with expensive organometallic reagents and often toxic metallic byproducts generated in stoichiometric quantities poses a serious challenge.[10] Therefore, the quest for synthetic methods improving the synthesis economics and fulfilling the environmental requirements has directed the attention of researchers toward discovering new cross-coupling methods.

In recent decades, direct C-H arylation, also known as direct (hetero)arylation, has emerged as an attractive strategy for synthesizing organic molecules.[11–13] Conceptually, the approach involves the direct activation of inert C-H bonds by transition metal catalysts requiring the functionalization of only one coupling partner. Importantly, as the method involves the C-C bond formation via coupling between an aryl halide and arene with hydrogen halide (HX) as the byproduct, it offers considerable environmental and economic benefits over traditional cross-coupling methods due to reduced metallic waste and intrinsic step economy. Because of these advantages and considering the ubiquitous presence of C-H bonds in organic molecules, the approach is recognized as a viable synthetic tool for preparing both small molecules and polymers. Indeed, significant advances in the field of direct C-H arylation during the past decades have enabled chemists to expeditiously construct complex molecular architectures enriching the chemistry of natural products, and functional materials and accelerating the drug discovery processes.[13–15]

Despite many merits, the widespread application of direct C-H arylation is hindered by harsh reaction conditions, poor regioselectivity, and limited substrate scope. For instance, due to high bond dissociation energies of C-H bonds (~110 Kcal for Aryl C-H bonds), typically high temperature (80-120 °C) is required,

preventing the use of substrates with heat-sensitive functional groups. Higher temperature also increases the probability of unwanted side reactions. Another challenge underlying this approach is controlling the regioselectivity of single C-H bonds due to their comparable dissociation energies. Furthermore, using a stoichiometric amount of oxidants for catalyst regeneration in some cases and high catalyst loading (20-30%) makes these processes not truly eco-friendly. Hence, as the field of direct C-H arylation directs its attention from fundamental studies to more practical applications, molecular synthesis using mild, greener, and resource economic approaches will be looked for.

The past 15 years have witnessed great attention from researchers to improve the sustainability of direct C-H arylation by developing mild protocols that proceed at or below room temperature and in the absence of acids or base and oxidants. In this regard, a pioneering work that strikingly reshaped the way activation of C-H bonds could be achieved was reported by Fujiwara and co-workers in 1995, demonstrating carboxylation of C-H bonds at room temperature (Scheme 1).[16] The key to success was a strongly electrophilic Pd-catalyst intermediate $[Pd(TFA)]^+$ (4) generated in-situ from $Pd(OAc)_2$ and trifluoroacetic acid (TFA). The cationic Pd catalyst lowered the energy barrier for C-H bond metalation, enabling the activation of the sp^2 C-H bond at room temperature. Thus the use of TFA as solvent supported the insertion of metal into the aryl C-H bond as well as the efficient regeneration of the Pd(II) catalyst. Five years later, the authors reported an unprecedented method for C-C coupling of arenes with alkenes and alkynes at room temperature using the same catalytic system.[17] Since then, various methods enabling C-H bond activation at room temperature have been realized, further reducing the environmental and economic footprint of direct C-H arylation reactions.

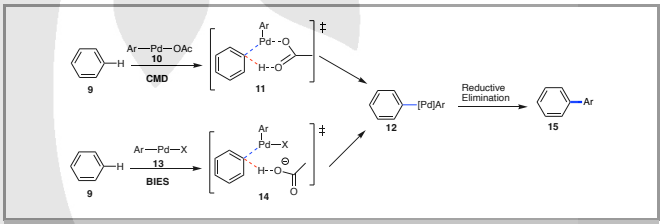


Scheme 1 Direct carboxylation of arenes at room temperature.

Several reviews and personal accounts provide a systematic analysis of direct C-H arylation reactions in general[15,18,19] as well as on specific topics such as directing group assisted arylation, direct arylation polymerization,[20,21] and sustainable approaches,[22,23] mild C-H activation[24]. Nonetheless, a detailed analysis of C-H bond activation at ambient temperature is lacking. Our approach, therefore, aims to highlight the strategies directed toward developing direct C-H arylation methodologies that proceed at or below room temperature. Since the appeal for such processes ultimately stems from the nature of the catalytic system and substrates, a comprehensive study would provide a better understanding of mechanistic features of such reactions and thus better control over the reaction conditions providing newer prospects.

2. Concepts and Examples

Given the ubiquitous presence of C-H bonds, the concept of their activation at room temperature has provided a perfect opportunity to drive the field of sustainable organic synthetic approaches. Several room temperature direct C-H arylation methodologies have been rapidly developed in past years. A part of this comes from the increased understanding of the mechanistic aspects of these reactions. Before reviewing these methodologies, a fundamental understanding of the key mechanistic steps and strategies that have been used to modulate these steps for achieving such transformations would be helpful. Though various mechanistic pathways, including electrophilic aromatic substitution, σ-bond metathesis, and Heck type coupling have been proposed, the concerted metalation-deprotonation (CMD) process stands out as the most likely mechanism through which activation of the C-H bond occurs.[18,25] In CMD-mediated direct arylation, the carboxylate anion assists in deprotonating the C-H bond undergoing functionalization by coordinating with the aryl-halo complex while simultaneously forming the C-M bond (Scheme 2).[26,27] Instead of intramolecular deprotonation, deprotonating the C-H bond through an externally non-coordinated carboxylate or a basic ligand known as base-assisted internal electrophilic substitution (BIES) is also a viable pathway.[28,29] As the refunctionalization of C-H to C-Pd is a crucial step during the arylation process, increasing the reactivity and promoting the C-H activation step would allow for lowering of the metalation energy barrier leading to reactions that proceed under mild conditions.



Scheme 2 CMD and BIES mechanism for direct C-H arylation.

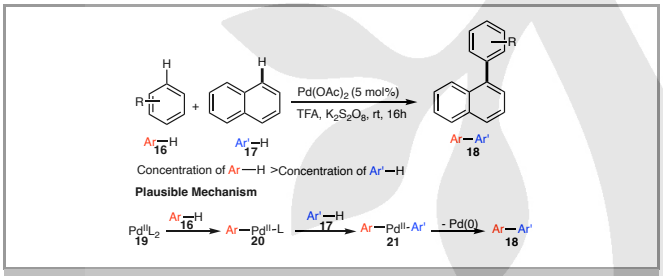
Typically, three approaches have emerged for enhancing the reactivity and promoting the C-H activation; the first approach involves tuning the catalytic system by employing strong acids like TFA or AcOH to increase the electrophilicity of catalyst[16] which subsequently increases the acidity of the C-H bond, facilitating its cleavage by a weak base for C-M bond formation and thus enabling sp^2 C-H bond activation under milder conditions. Several groups have successfully exploited this concept, but poor regioselectivity remains a significant challenge. The second alternative involves *ortho*-directing groups for promoting the C-H activation step by bringing metal catalyst and target C-H bond in proximity by forming a palladacycle intermediate.[30] Another alternative for promoting C-H activation relies on tuning the ligand around the metal center by employing a metal salt for anionic ligand abstraction from the metal-catalyst

intermediate.[31] Thus, with a suitable choice of catalytic systems and coupling partners, the reactivity of C-H bond activation can be enhanced, leading to reactions that proceed at or below the room temperature. For the sake of convenience and clarity, the examples discussed in this article are organized based on the reaction conditions.

2. 1 Transition-metal-catalyzed

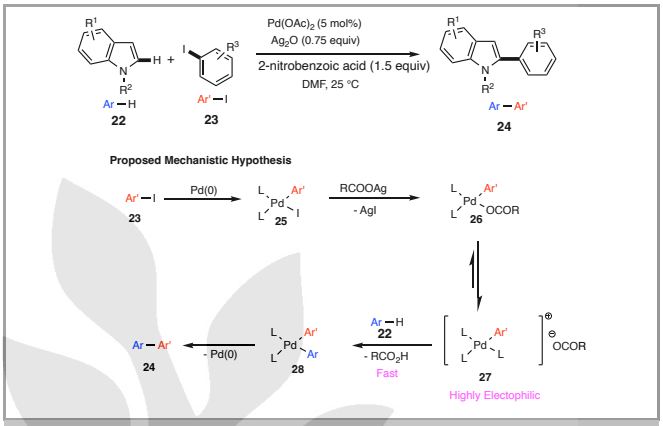
2.1.1 Pd catalysis

Pd catalysts have been extensively studied for C-H activation owing to their versatility and well-established chemistry.[32] Several Pd-based catalytic systems have been explored for the efficient arylation of arenes and heteroarenes. Following the pioneering work of the Fujiwara group,[16] Lu and co-workers accomplished the synthesis of unsymmetrical biaryls at room temperature using the same catalytic system ($Pd(OAc)_2$/TFA/$K_2S_2O_8$) (Scheme 3).[33] The author could control the regioselectivity by employing an excess of electron poorer arene (5-100 equiv). The reaction proceeds through $ArPd^{II}Ar$ intermediate (20) formed from in-situ generated cationic Pd^{II} species and electron poorer arene (ArH), followed by a preferential attack by electron-rich arene (Ar'H) affording the desired product. The highly electrophilic nature of $Pd(TFA)_2$ generated in situ from $Pd(OAc)_2$ and TFA facilitates the C-H bond cleavage enabling the C-H activation at room temperature. Though the method is appealing, a significant excess of arene and poor yield limits the practical utility.



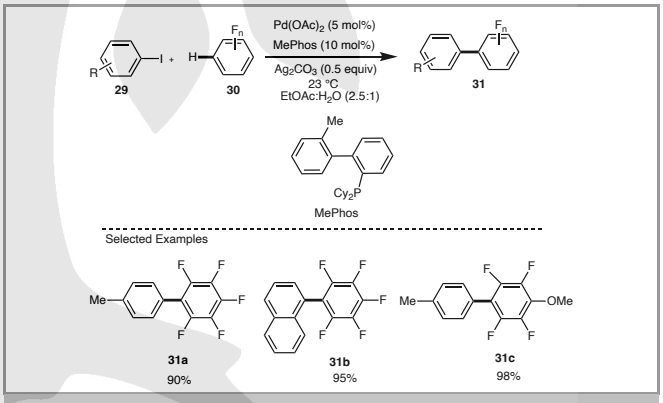
Scheme 3 Direct C-H arylation of arenes.

In 2008, an intriguing study describing phosphine-free Pd-catalyzed direct arylation between indoles and aryl iodide at room temperature was reported by Larrosa and co-workers (Scheme 4).[31] The use of Ag(I) salts and carboxylic acid circumvented the initial lack of reactivity as the C-H palladation step is believed to be the rate-limiting step in the arylation of indoles through the $Pd^{0/II}$ catalytic pathway.[34] The authors proposed that while Ag(I) salt assists the in-situ generation of a more electrophilic complex (**26**) by removal of iodide from Pd complex (**25**), the weakly coordinating carboxylate as the supporting ligand facilitates the rapid dissociation to highly electrophilic species (**27**) in catalytical amounts although our recent work described in Section 2.2 suggests a radical-mediated mechanism for this transformation. The method is highly efficient for N-methylindole and N-benzylindole and showed good tolerance to a wide array of functional groups in the aryl iodide and indole moiety. However, arylation of N-free indoles required a temperature of 50 °C. This route appeared more favorable than Fujiwara's,[16] which is plagued by poor yield and excess of one of the coupling partners. Furthermore, considering the ubiquity of indole derivatives in medicinally important natural and synthetic compounds, the method displays broad applications.



Scheme 4 α-arylation of indoles at room temperature.

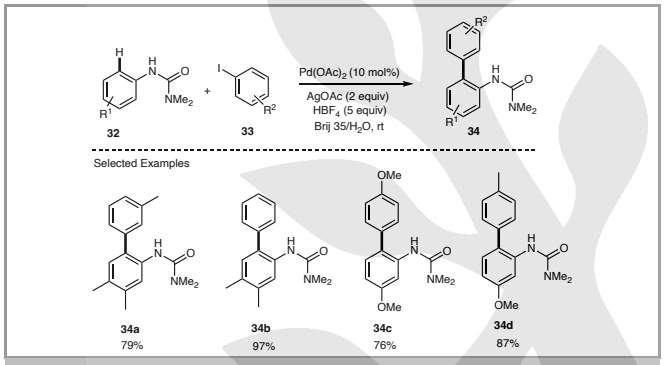
Electron deficient arenes can also be effectively arylated at room temperature. An example of such transformation demonstrating coupling between electron-deficient polyfluorinated arene and iodobenzene in a biphasic medium comprising water and the organic solvent was reported by Fagnou and co-workers (Scheme 5).[35] Importantly, no product formation was achieved in the absence of Ag_2CO_3. The method is particularly efficient in the case of organic solvents- i-ProAc, DMF, or EtOAc. Notably, a wide variety of functional groups on both the coupling partners could be tolerated affording the biaryl product in excellent yield. In contrast to the previously reported arylation protocol of 2-chlorothiophene, which required a temperature of 100 °C, this strategy gave the C-5 arylated product in good yield at 60 °C.



Scheme 5 Direct C-H arylation of polyfluorinated arenes under biphasic conditions.

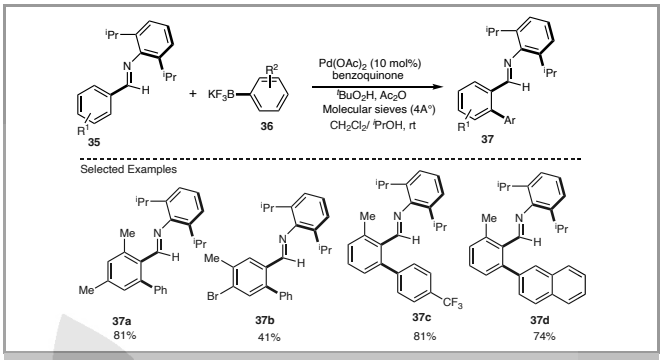
Though cationic Pd(II) catalysts proved to be effective for activating the sp^2 C-H bond at room temperature, the chelating behavior of groups such as oxime, acetanilide, amide, *etc.* along with cationic Pd catalysts was also identified as an effective approach for enhancing the reaction rate and selectivity control. Besides ligating nature and affecting the electrophilicity of the metal catalyst, the electronic behavior of a chelating group significantly influences the rate of C-H bond cleavage step, enabling C-H functionalization under mild conditions. In 2010, the Lipshutz group described the directing group-assisted room

temperature direct C-H arylation between anilide derivatives and aryl iodides in water/surfactant mixtures (Scheme 6).[36] This report illustrates the advantage of using a Lewis acid-HBF_4 instead of acetic acid (AcOH) or TFA to generate the cationic Pd-catalyst. At the same time, Ag(I) salts for halogen scavenging facilitated the formation of the cationic catalyst. Here, both directing group and cationic nature of Pd catalyst promoted the C-H activation step facilitating room temperature transformation. Though the method is compatible with a broad range of functional groups on both aryl urea and aryl iodides affording the desired mono-arylated product in 42-97% yield, reaction did not occur in the case of *ortho*-substituted aryl iodides due to steric hindrance. Notably, N-substituted urea showed lower reactivity than N-free counterparts due to coordination with Pd in the initial C-H activation step, while electron-rich aryl iodides showed increased reactivity compared to electron-deficient derivatives. Cationic Pd catalyst could also be generated from $Pd(OAc)_2$ and $AgBF_4$ without any external acid.



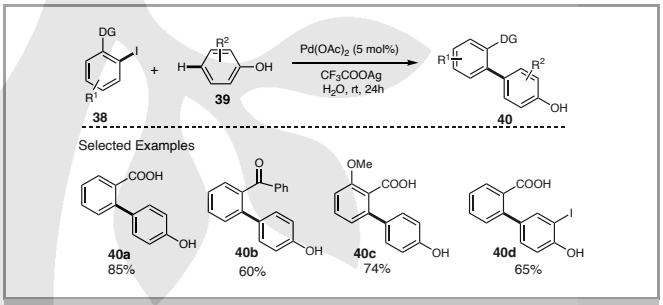
Scheme 6 Direct C-H arylation of anilide derivatives.

The mildness of the above-discussed method encouraged Gaunt and co-workers to focus on improving the catalytic system by tuning the electronic character of the directing groups (Scheme 7).[37] They envisaged a design strategy that employing imine as directing group (lesser electron withdrawing than other carbonyl groups), would enable the cyclopalladation at room temperature by lowering the electron deficiency of the parent aromatic nucleus. However, the poor stability of imines due to its hydrolysis to amine under mildly acidic conditions of Pd catalyzed C-H activation presents a significant challenge as the catalyst will become ineffective because of amine binding to the metal. To prevent imine hydrolysis, the authors increased the steric bulk around the amine component and successfully achieved the arylation of benzaldimines with aryltrifluoroborates at room temperature. The transformation is compatible with a wide variety of imine derivatives and aryltrifluoroborates affording the desired arylated product in good to moderate yields.



Scheme 7 Direct C-H arylation of benzaldimines.

The next contribution in this area came from the Zhou group describing the highly *para*-selective arylation between phenols and aryl iodides via a formal inverse direct arylation strategy (Scheme 8).[38] This work displays many advantages, including the use of water as the reaction medium and an unprotected and wide array of phenols as the precursors. Notably, no product formation was achieved with salicylic acid due to its chelating ability. Though a detailed mechanistic study was not carried out, the authors proposed that the presence of a coordinating group at the *ortho*-position of aryl iodide would lead to a thermodynamically stable intermediate by accelerating the oxidative addition to the transition metal, thereby enabling the phenol activation at room temperature in stark contrast to the well-established C-H arylations. Subsequent reductive elimination would provide the desired coupling product.

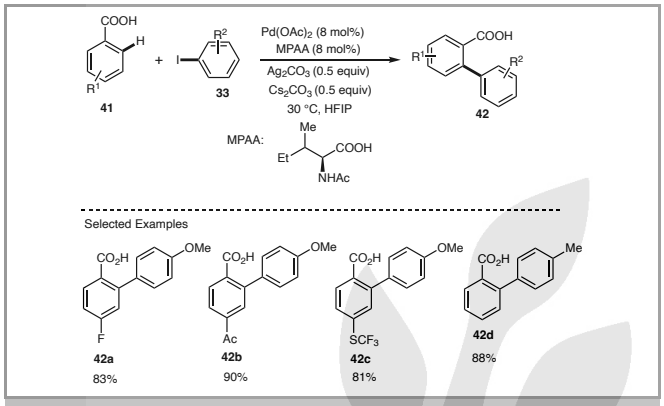


Scheme 8 Arylation of phenols via inverse direct C-H arylation strategy.

Following their initial study,[36] Lipshutz and co-workers developed another protocol utilizing commercially available $[Pd(MeCN)_4](BF_4)_2$ catalyst or a nitrile-free Pd(II) species generated in-situ from $Pd(OAC)_2$ and HBF_4.[39] It was found that an efficient *ortho*-arylation was achieved in the case of aryl ureas compared to acetanilides.

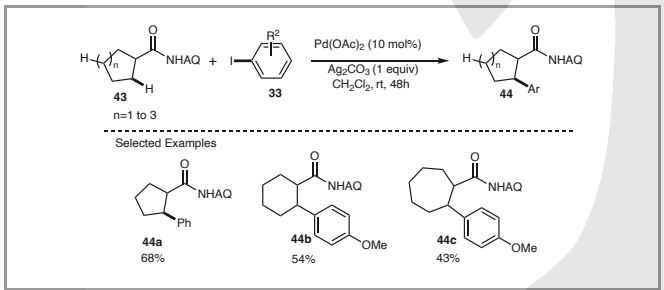
Another example of directing group promoted direct C-H arylation of arenes was reported by Zhu et al.[40] This study used mono-N-protected amino acids ligands (MPAA) to synthesize a library of arylated benzoic acids in moderate to excellent yields (Scheme 9). While solvents such as DMF, AcOH, and H_2O were ineffective, the reaction proceeded well with various substrates in the presence of hexafluoroisopropanol (HFIP) and Cs_2CO_3 in moderate to excellent yields. A series of MPAA were used, demonstrating an increase in the reaction yield, but the best performance was noted in the case of N-Ac-Ile-OH ligand. The mechanistic studies suggested that ligand accelerated the rate-determining step: the C-H activation process, besides improving the catalyst lifetime. Apart from bidentate coordination with Pd

metal, N-H moiety of ligand facilitates C-H bond cleavage by acting as intramolecular proton shuttle potentially enabling the room temperature C-H bond arylation.



Scheme 9 Ligand supported Pd-catalyzed *ortho* C-H arylation of benzoic acids.

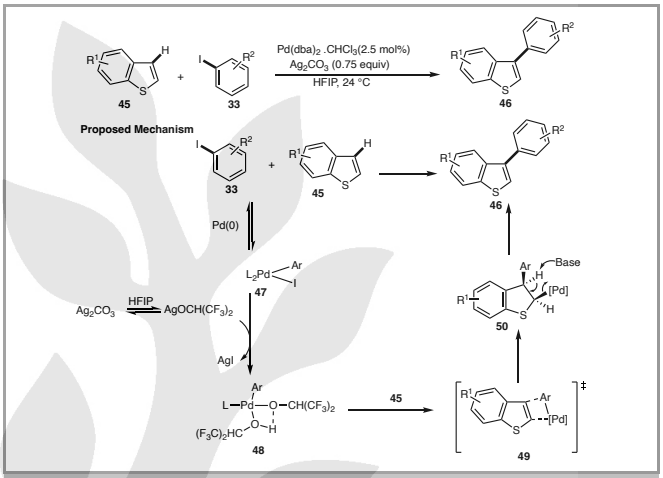
In 2016, Chen and co-workers reported the aminoquinoline-directed sp^3C-H arylation of carboxamide derivatives with aryl iodide (Scheme 10).[41] Compared to previous reports of diarylation at elevated temperatures,[42,43] the protocol enabled the formation of mono-arylated products in good to moderate yields with good mono- and diastereoselectivity at room temperature due to facile transmetalation. While a higher arylation yield was achieved in the case of electron-rich iodides, sterically hindered aryl iodides gave poor yield. Room temperature C-H arylation is favored by Pd^{II}/Pd^{IV} catalytic cycle. The catalytic cycle commences with the metal insertion of aminoquinoline moiety by Pd^{II} allowing activation of β-sp^3 C-H bond, which after intramolecular addition of aryl iodides and reductive elimination affords the final product. Besides bringing the metal center close to the substrate to facilitate the C-H bond insertion, the increased electron density around the metal center as a result of chelation allows for the facile oxidation of Pd^{II} to Pd^{IV} enabling C-H activation under milder conditions.



Scheme 10 Directing group assisted sp^3C-H arylation of carboxamide derivatives.

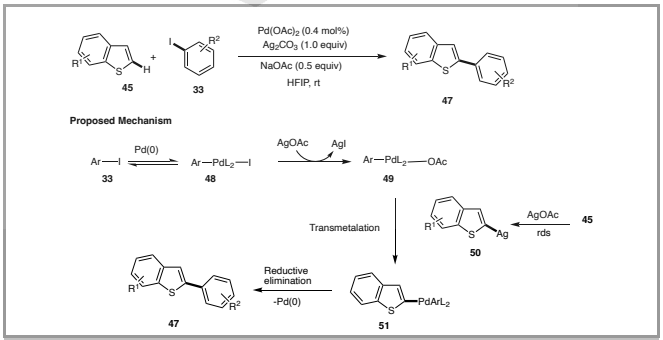
Sulfur-containing heterocycles, particularly thiophenes and benzo[b]thiophenes, are recognized as important structural units prevalent in biologically active compounds, drugs, and functional materials. In this regard, significant efforts have been directed toward the efficient synthesis of these useful molecules. Though most of these studies have targeted the most acidic α-positions, the β-arylation has proven to be challenging, requiring high temperature (80-150 °C) or directing groups. In 2016, the Larrosa group made a significant contribution toward the arylation of thiophenes and benzo[b]thiophenes (Scheme 11).[44]

The significantly challenging β- arylation of these molecules was accomplished by employing the catalyst $Pd(dba_2)_3{\cdot}CHCl_3$ in combination with HFIP and Ag_2CO_3. Not only does the method show broad functional group tolerance, but the reaction can be carried out in air without any phosphine ligands (except for highly electron-poor iodoarenes). Preliminary mechanistic studies are consistent with Heck-type direct arylation pathway (Scheme 11).[44]



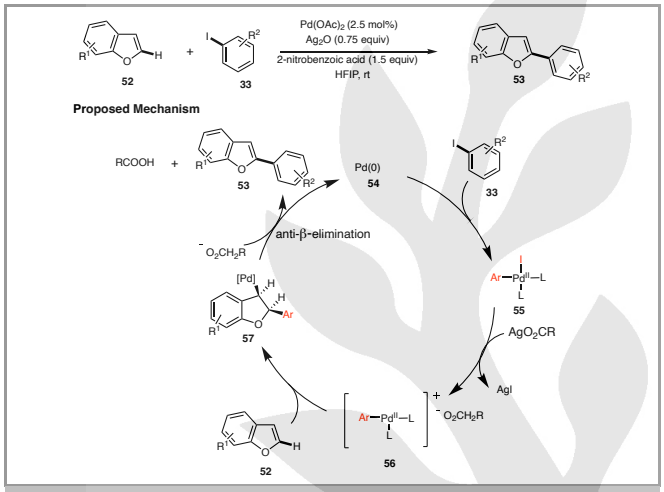
Scheme 11 Regioselective β-arylation of benzothiophenes at room temperature.

In another subsequent study, the Larrosa group demonstrated α-arylation of benzo[b]thiophenes at room temperature (Scheme 12) in 2018.[45] The reaction provides an unprecedented approach for thiophene's α-arylation based on α/β- regioselectivity switch noted in their previous study. This switch in the regioselectivity is resulting from an alternative co-catalyzed process (not Heck type arylation) supported by the fact that in a Pd/Ag-mediated C-H arylation, it is the Ag(I) carboxylate that catalyzes the C-H bond activation via CMD pathway instead of Pd(II) species as noted in their previous β-arylation study of thiophenes.[44] Mechanistic studies suggested that Ag(I) mediates the α-C-H activation-the rate-determining step(rds) selectively followed by the transmetalation to Pd and reductive elimination. Furthermore, this approach allowed the arylation of iodoarenes with alcohol, aldehyde, and ketone substituents efficiently that usually suffer from chemoselectivity issues under harsh conditions. Notably, the group of Sanford[46] and Hartwig[47] had previously described the role of Ag(I) salts in the arylation of perfluorobenzene in the year 2017 and selective allylation of aryl C-H bonds in 2016, respectively.



Scheme 12 Ag(I) C-H activation for α-arylation of benzothiophenes.

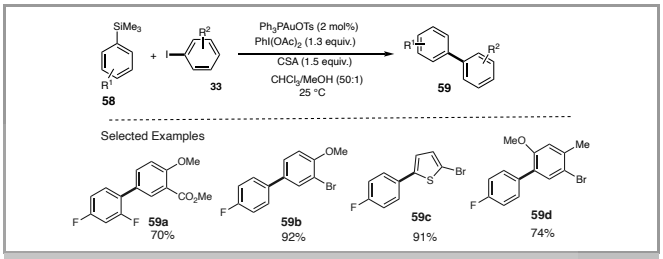
The Luscombe group recently succeeded in developing a robust methodology for α-arylation of benzofuran, another important heteroaryl scaffold (Scheme 13).[48] Though the reaction condition is very similar to the indole arylation method developed by the Larrosa group[31] except for the use of HFIP as the solvent instead of DMF, the reaction proceeds via a Heck-type arylation pathway (Scheme 13) instead of a radical mechanism as evidenced by the dark condition studies, deuterium scrambling, and KIE studies. Many functional groups such as -OH, NHAc, and -CHO, and halogens were well tolerated.



Scheme 13 α-arylation of benzofurans at room temperature via Heck-type pathway.

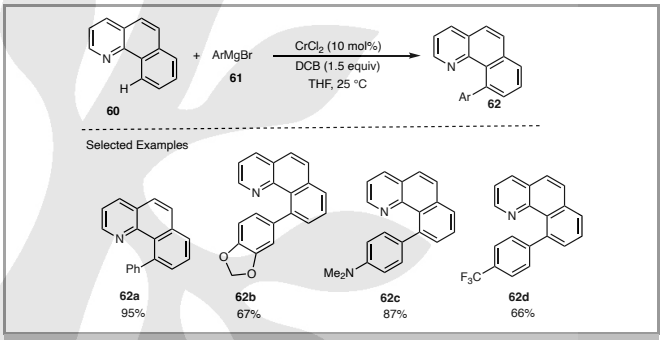
2.1.2 Other metals-based

While ample of the reported work in room temperature direct C-H arylation reactions employ Pd catalysts, reports focusing on other transition metals are limited. In 2012, Llyod-Jones, Russel and co-workers reported a seminal method for gold-catalyzed C-H bond activation for biaryl synthesis at room temperature.[49] The method uses precatalyst $(Ph_3P)AuOTs$, and an oxidant $PhI(OCSA)_2$ generated in-situ from iodobenzene diacetate $[PhI(OAc)_2]$ and camphorsulphonic acid (CSA) which helped in preventing the formation of fluorinated side products (Scheme 14). Furthermore, the reaction required a low concentration of methanol (2 vol%) for activating arylsilane and facilitating the C-Si transmetalation. The method takes advantage of C-Si bond activation mode due to high reactivity and chemoselectivity of aryl silanes as both the C-H and C-Si bond activation by Au(III) occurred through the electrophilic aromatic substitution pathway allowing arylation at room temperature. The transformation demonstrated broad substrate scope with respect to many electron-poor and some moderately electron-rich aryl silanes with various electron-rich arenes.



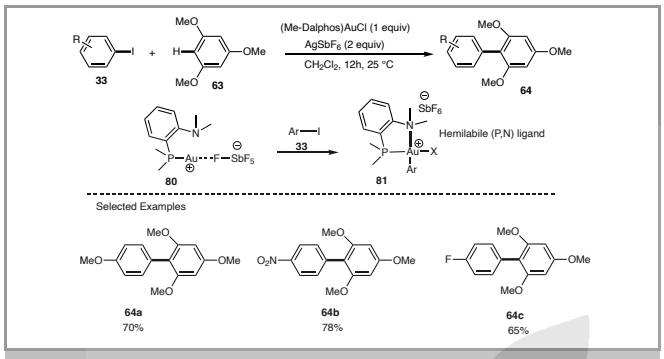
Scheme 14 Gold catalyzed direct arylation of aryl silanes with aryl iodides.

An interesting example describing the use of Cr(II) catalyst in combination with 3-dichlorobutane(DCB) as an oxidant for smooth arylation of N-heterocycles with Grignard reagent at room temperature was reported by Knochel and co-workers (Scheme 15).[50] The reaction proceeded rapidly at room temperature without the need for any additional ligand. The scope of this transformation is broad with good compatibility to a series of N-heterocycles including benzo[h]quinoline, 2-arylpyridine, aryloxazlines and aryl imines. The high reactivity of $CrCl_2$ is responsible for enabling the arylation at room temperature. Notably, the arylation of N-butylimines was achieved for the first time with this method.



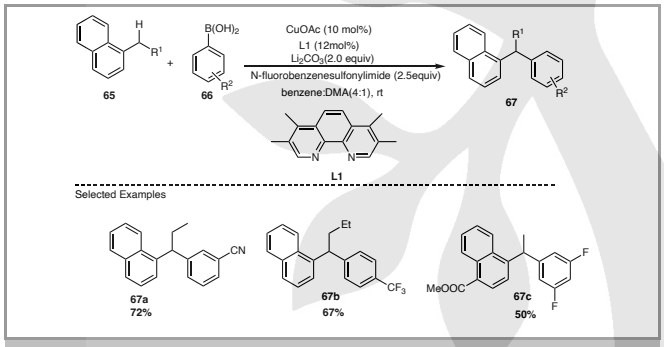
Scheme 15 Cr(II) catalyzed arylation of N-heterocycles.

In 2017, Amgoune and Bourissou's group developed an Au(I)/Au(III) catalytic cycle, which enabled the direct arylation of arenes with aryl halide at room temperature (Scheme 16).[51] Their design strategy was based on employing simple (P, N) bidentate ligand Me-DalPhos to control the stability and further reactivity of Au(III) species. The authors reasoned that while the reactive cationic gold complex is formed by coordination of the Phosphorus atom of the ligand with the soft Au(I) center, the pendant amine group modulates the reactivity of the Au(III) complex upon oxidative addition. This is important as it is easier to temper the reactivity of stable four coordinated Au(III) complexes compared with an unstable three co-ordinated Au(III). The method's scope is broad, with efficient coupling of arenes with a variety of aryl halides and bromides. Notably, counter anion also demonstrated a significant influence on the reaction rate. For instance, oxidative addition of aryl iodide occurred spontaneously with SbF_6^- compared with Ntf^{2-}. Considering the reluctance of Au(I) towards oxidative addition, his is an attractive approach allowing the gold-catalyzed arene coupling under milder conditions without the need for any oxidant for generating the key Au(III) catalytic species.



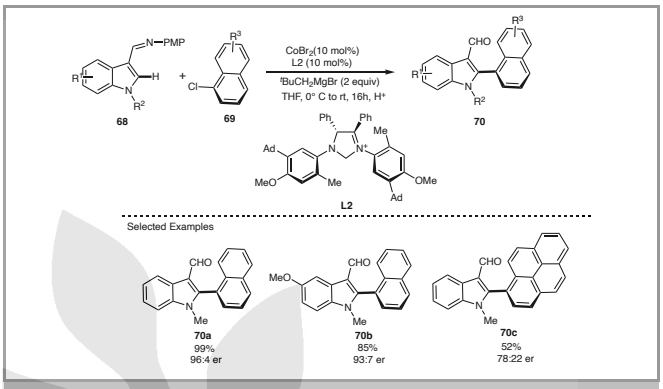
Scheme 16 Gold- catalyzed arylation of arenes.

In 2019, the Liu group developed a novel copper-catalyzed arylation method of alkylarenes at room temperature (Scheme 17).[52] Considering the difficulty associated with asymmetric Csp³-H functionalization, this approach offers an attractive route for the arylation of benzylic C-H bonds by using aryl alkanes as limiting reagents instead of using them in large excess as needed in previously reported methods. The method applies the use of radical relay process. Though detailed mechanistic studies was not carried out, the authors explained that benzylic radicals generated by sp³C-H bond oxidation by metal catalyst via hydrogen atom abstraction process of alkyl arenes could be captured by ArCu(II) species enabling the formation of new C-C bonds.



Scheme 17 Cu(I) catalyzed arylation of benzylic C-H bonds.

Very recently, Ackermann, Wencel-Delord and co-workers reported cobalt (II) catalyzed direct enantioselective C-H arylation at room temperature.[53] The reaction uses precatalyst $CoCl_2$, tertiary butylmethylmagnesium bromide as base for in-situ generation of catalytically active Co(I) species, and N-heterocyclic carbene precursors as chiral inductors. Considering the high reactivity of Co(I) species towards C-H metalation, reactions catalyzed by cobalt usually occur at lower providing a new perspective to atropfunctionalization. Notably, carbene ligands containing meta-dispersion groups were crucial for achieving the desired stereoselectivity in agreement with DFT studies. Kinetic and DFT studies indicated that it is the oxidative addition that determines the reaction rate along with stereocontrol. As proposed by the authors, catalytically active Co(I) species generated by base reacts with imine moiety which undergoes the C-H metalation (fast) in the next step forming metallacycle intermediate. The next step involves the oxidative addition of 1-chloronapthalene to metallacycle intermediate affording Co(III) intermediate, which undergoes reductive elimination and ligand exchange to afford the final enantiopure product.

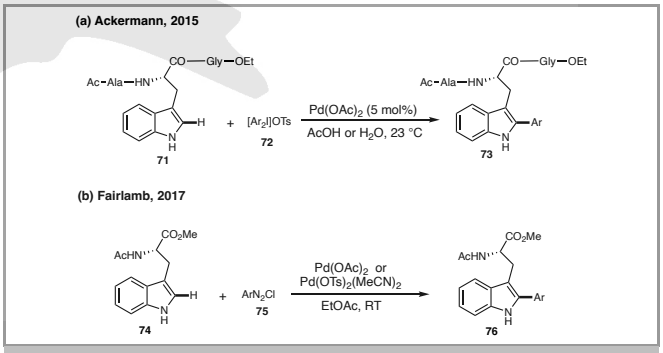


Scheme 18 Cobalt-catalyzed atropoenantioselective arylation of indoles.

2.1.3 Additive-free

Though the C-H activation protocols may be entirely redox neutral, a vast majority of them employ additives such as acid/base or metal salts like Ag(I) or Cu(II) in stoichiometric quantity for catalyst regeneration, thereby increasing toxic metallic waste generated during the process. Also, undesired side reactions have been noted in certain cases due to the ability of Ag(I) to act as oxidant and Lewis acid. These reasons have stimulated the research interest in additive-free direct arylation methodologies.

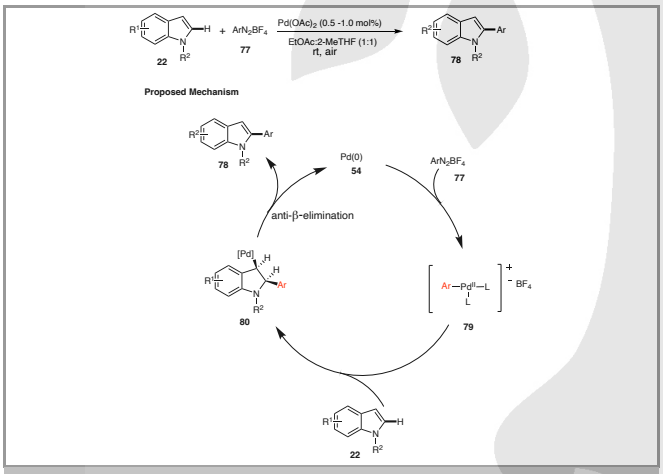
In the context of additive-free direct arylation, the majority of studies present in the literature have employed aryldiazonium and diaryliodonium salts as the arylating agent. In 2015, the Ackermann group demonstrated a method for the Pd-catalyzed arylation of tryptophan derivatives using diaryliodonium salts without any metal oxidant at ambient temperature (Scheme 19a).[54] The methodology was highly efficient, showing excellent chemo and site selectivity, and being amenable to electron-donating and electron-deficient diaryliodonium salts. While moderate yields were obtained using DMF and toluene, AcOH as solvent led to the quantitative formation of the desired product. Furthermore, the method could also tolerate water as the reaction medium (isolated yield: 70%) showcasing the great potential for peptide ligation and fluorescence labeling in physiological conditions.



Scheme 19 Additive-free direct C-H arylation of tryptophan derivatives at room temperature.

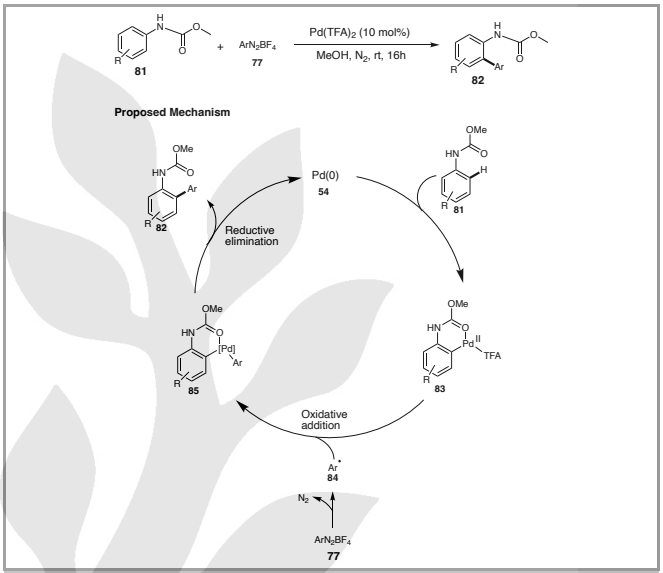
In the same year, a similar study describing the Pd catalyzed C-2 arylation of tryptophan derivatives with presynthesized diaryliodonium salts in ambient conditions was reported by the Fairlamb group.[55] Unfortunately, poor selectivity due to the formation of phenyl and mesityl substituted products limited the synthetic utility. Addressing this, the Fairlamb group further developed a novel and highly regioselective tryptophan arylation method using aryldiazonium salts instead of diaryliodonium salts, considering the structural similarity and reactivity (Scheme 19 b).[56] Since the aryldiazonium salt undergoes oxidative addition with Pd rapidly without any base, the protocol provides a clean and mild method for arylating tryptophan and tryptophan peptides. It is worth mentioning that the arylation rate was enhanced when the catalytic amount of either tosic acid (TsOH) or $Pd(OTS)_2(MeCN)_2$ were used instead of $Pd(OAc)_2$. Though the scope of the method is broad, it is not suitable for aryldiazonium salts substituted with strongly electron-withdrawing groups. Instead, diazo side products are obtained resulting from the nucleophilic attack of C-2 arylated indole on electron-poor aryldiazonium salts also noted by Correria and co-workers.[57]

Early in 2017, Noël and coworkers reported base-free arylation of heteroarenes using aryldiazonium salts at room temperature in aerobic conditions (Scheme 20).[58] The reaction proceeds under mild conditions in an open flask with broad substrate scope, green solvents (EtOAc/2-MeTHF or MeOH), and a short reaction time demonstrating good tolerance to the functional groups. In this method, the author used an equimolar amount or slight excess of diazonium salts as the arylating agent and low Pd loadings (0.5 to 2 mol% Pd). The protocol was shown to be highly selective with coupling at C-2 for indoles and benzofurans, while C-3 in the case of benzothiophenes. The transformation was proposed to follow the Heck-Matsuda type mechanism via Pd(0)/Pd(II) catalytic cycle.



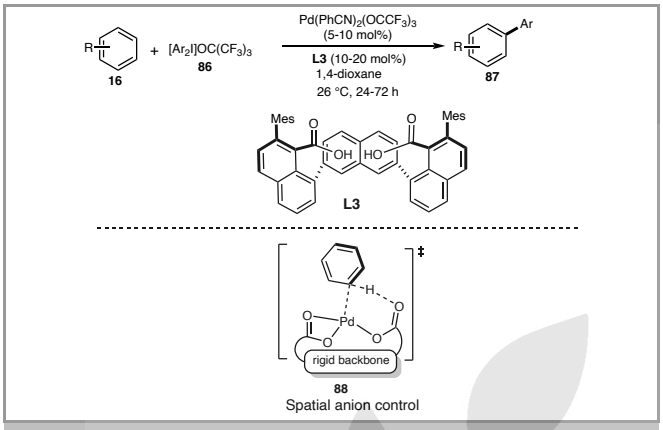
Scheme 20 Base free Direct C-H arylation of indole.

A year later, Jana and co-workers reported a protocol in which arylcarbamates can be *ortho*-arylated with aryldiazonium salts at room temperature without the need for an acid, base, or metal oxidant, or photoredox catalyst.[59] This study was built on the concept of directing group-assisted arylation (Scheme 21). The authors applied this method for synthesizing carbazole alkaloids such as clausine V, clauszoline-K, O-methoxymahanine, and O-methylmurrayamine-D. The reaction proceeds via directing group-assisted electrophilic metalation (96) at the *ortho*-position thereby generating palladacycle intermediate (97) which reacts with aryldiazonium salt through oxidative addition followed by reductive elimination to furnish the desired product (95). Given the easy removal of the carbamate group, the method is, therefore, suitable for industries and academia. However, the protocol faces major challenges from the limited substrate availability.

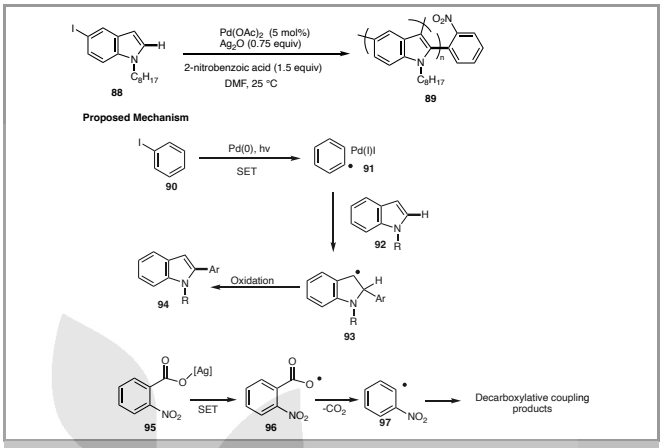


Scheme 21 Additive-free direct arylation of arylcarbamates

In 2020, the Coric group developed an interesting approach for achieving direct arylation of arenes at room temperature by utilizing the concept of rational design of catalyst sites (Scheme 22).[60] The authors considered specially designed bis(carboxylate) anions for controlling the geometrical parameters of the carboxylate coordination sites on Pd in the CMD state. By controlling the spatial arrangement of anions namely, O-P-O angles and Pd-O distances, the geometry of CMD state could be stabilized thus promoting facile C-H activation by lowering the energy barrier. DFT studies provided supportive evidence for the role of constrained anion on key CMD step, that the lower catalyst strain in the transition state than the geometrically relaxed state in case of bis(carboxylate) anion is accountable for reducing the overall electronic energy compared to mononuclear Pd(II) catalyst. The mild reaction conditions, wide substrate scope, and late-stage functionalization reflect the robustness of this method.



Scheme 22 Spatial anion control for directing group/ additive-free arylation of arenes.



Scheme 23 DArP of indole derivatives at room temperature.

2.2 Direct arylation polymerization

Direct arylation of small molecules motivated the polymerization studies, with several small-molecule arylation methodologies successfully adapted for the synthesis of conjugated polymers which constitutes active components of next-generation electronic devices including organic photovoltaics, organic field-effect transistors, sensors, and electrochromic devices *etc*.[61] Indeed, a vast library of conjugated polymers prepared by direct heteroarylation polymerization (DArP) can be found in the literature, with properties comparable to the conventional polymerization methods.[62]

Though small molecule arylation methodologies became the springboard for polymerization studies, only one example of DArP performed at room temperature is known in the literature. In 2021, the Luscombe group successfully demonstrated the polymerization of indole at room temperature[63] by adapting the protocol developed by the Larrosa group for small molecule synthesis[31] at room temperature. The authors observed that the resulting polymer is highly branched due to the incorporation of nitrobenzene unit along with the β-branching (Scheme 23). This observation ruled out the CMD pathway adapted by indole small molecule arylation reaction. A series of control experiments provided supportive evidence for a radical-mediated pathway. As shown in Scheme 14, the catalytic cycle commences with single electron transfer (SET) process between Pd catalyst and aryl iodide (**90**), generating aryl radical (**91**), which is then trapped by indole (**92**), affording the observed product (**94**). While the incorporation of nitrophenyl into the polymer chain could be explained by the transformation of metal benzoate(**95**) into aryl radical by single electron activation.[64] Though room temperature DArP is underdeveloped, milder reaction conditions hold great potential for industrial-scale synthesis of conjugated polymers.

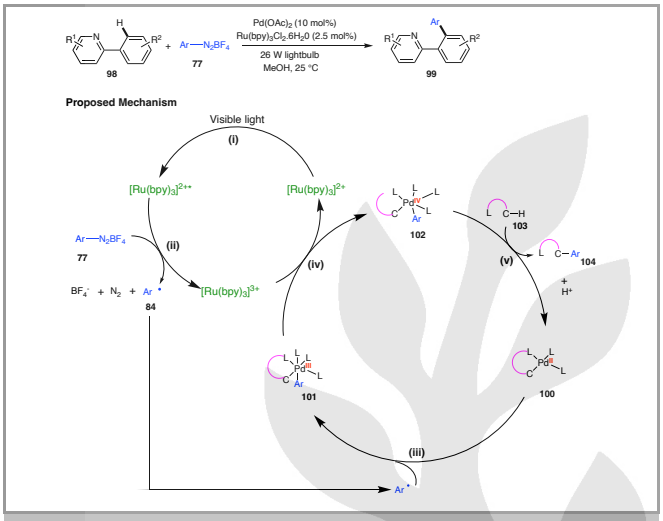
2.3 Photocatalyzed

Photocatalyzed reactions have been generally known to the synthetic community for many years for aryl-aryl coupling. The C-C bond formation through photoredox catalysis is classically achieved by the SET pathway involving aryl radicals or ionic intermediates providing a good alternative to classical cross-coupling reactions.[65] Such methods involve the use of photoredox chemistry to generate aryl radicals via SET process, that undergo either transmetalation[66,67] or single electron oxidative addition providing a good alternative to classical cross-coupling reactions.[67,68] The high reactivity of aryl radical promotes the C-H functionalization under mild conditions, typically at room temperature. The examples presented in this section have been classified on the basis of photocatalyzed organometallic C-H activation and radical addition-based C-H arylation.

2.3.1 Organometallic C-H activation based

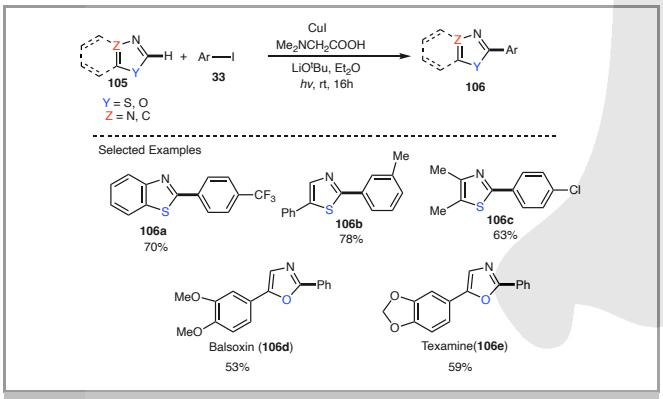
An exciting development in recent times is merging photocatalysis and traditional C-H bond activation to achieve coupling under milder reaction conditions with efficient selectivity control and broad functional group tolerance. These approaches are lucrative as C-C coupling can be achieved without any external additive and with a smaller amount of catalysts. Typically, the palladacycle formed by C-H bond activation could react with aryl radical generated through SET process via photoredox catalysis at room temperature. The concept was first introduced by Sanford group in 2011, where a dual Pd/Ru catalytic system was employed for the arylation of arenes with aryldiazonium salts at room temperature (Scheme 24).[69] The method uses $Pd(OAc)_2$, photocatalyst $Ru(bpy)_3Cl_2.6H_20$, and a visible photo source, demonstrating good compatibility with a wide variety of substrates having substituents such as halogens, mides, pyrimidines, oxime ethers, and pyrazoles. Among many advantages, using a non-acidic solvent MeOH alongside the generation of easily removable N_2 and HBF_4 as the side product, fulfills the objective of more sustainable chemistry. The proposed mechanistic path involves the reaction of aryl radical species (84) with palladacycle (**100**) generated from the reduction of aryldiazonium salts (**77**) by photoexcited $[Ru(bpy)_3]^{2+*}$, to Pd^{III} intermediate (**101**). Subsequent one-electron oxidation of the Pd^{III} intermediate (**101**) forming Pd^{IV} complex (**102**) by $[Ru(bpy)_3]^{3+}$ and reductive elimination furnishes the arylated

product (**103**). The authors further expanded the scope of their study to include diaryliodonium salts as the source for aryl radical species.[68] Arylation was performed using Pd/Ir dual catalytic system and a 26 W visible light source at room temperature. [70]



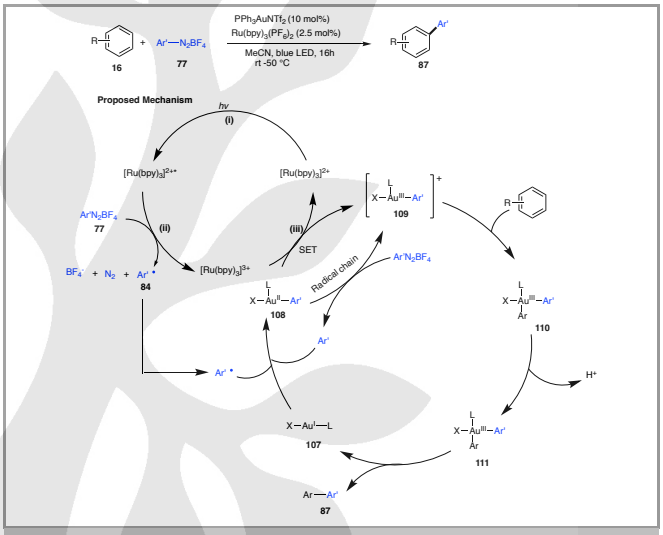
Scheme 24 Pd/Ru photocatalyzed direct C-H arylation of arenes.

In 2016, Ackermann and co-workers reported an unusual photoinduced arylation of heteroarenes at room temperature. This seminal work demonstrated that earth-abundant copper(I) catalysts could arylate both azoles and non-aromatic oxazolines without any photocatalysts and directing groups (Scheme 25).[71] A combination of CuI and Et_2O-solvent was effective in arylating; higher catalyst loading was needed for good yields. Notably, amino acids as the ligand showed rate acceleration with the best results obtained in the presence of N, N-dimethylglycine. Control experiments evidenced the photocatalytic nature of the process. With good functional group tolerance and broad substrate scope, including aromatic and nonaromatic heterocycles, the approach offers a convenient synthesis of naturally occurring alkaloids balsoxin and texamine at room temperature.



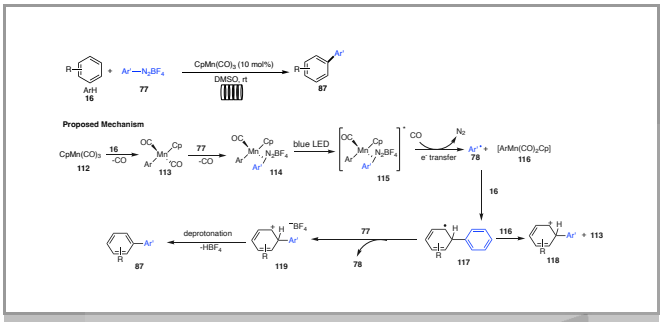
Scheme 25 Photoinduced Cu(I) catalyzed direct arylation of heteroarenes

In 2017, Lee and co-workers reported the first dual Au/Ru photocatalyzed arylation of arenes without additives.[72] By using $Ru(bpy)_3(PF_6)_2$ and $PPh_3(AuNTf)_2$ as the catalyst and acetonitrile (MeCN) as the solvent (Scheme 26), a series of mesitylene derivatives were regioselectively arylated with aryldiazonium salts under blue light at room temperature in good yields. Though eosin and fluorescein dyes were also employed, providing a greener alternative to the $Ru(bpy)_3(PF_6)_2$, the authors opted for a better performing Ru catalyst for further studies. Based on the mechanistic studies, the authors proposed SET process distinct from the conventional photocatalysis-only reaction since the regioselectivity is supported by Au catalyzed C-H activation instead of unselective product formation in the latter case. While intramolecular arylation showed great promise, intermolecular coupling suffers from limited substrate scope. This approach provides an attractive alternative to avoid the necessity of a catalytic oxidant in the Au(I)/Au(III) catalyzed direct arylation. Another additive-free dual Pd and photoredox catalyzed arylation of 6-arylpurine nucleosides was reported by Guo and co-workers in 2017.[73] In the same year, Balaraman and co-workers developed a protocol for dual Pd/Ru catalyzed arylation of anilides without any external additives in dimethyl carbonate- a green solvent.[74]



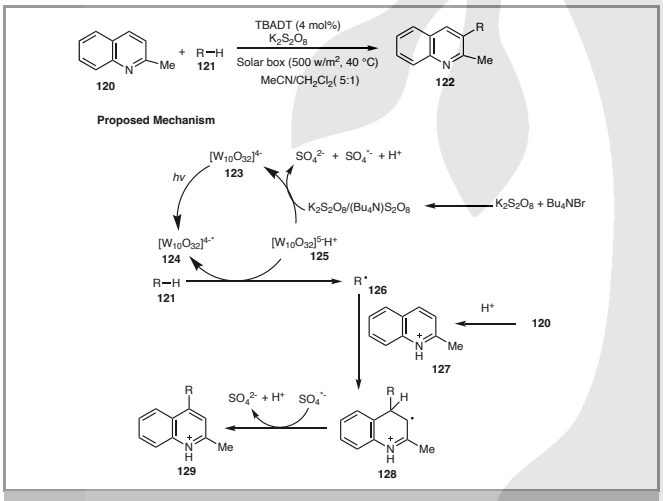
Scheme 26 Dual Au/Ru photocatalyzed arylation of arenes

In 2018, Ackermann group achieved a manganese catalyzed photoflow arylation strategy of heteroarenes (Scheme 27).[75] The reaction required $CpMn(CO)_3$ catalyst in combination with blue LED to achieve C-H activation at room temperature indicating the aryl radical formation from control experiment studies. Aprotic solvents were needed for optimal results with best yield obtained in DMSO. The reaction could tolerate a wide variety of functional groups including fluoro, chloro, ester and nitro substituents along with good regioselectivity in heteroarenes. In addition to this, the reaction can be scaled at the gram scale as demonstrated by higher yield(65%) obtained in flow process as compared to batch setup (25%) indicating its synthetic potential. The mechanistic studies proposed by the authors indicate the formation of Mn species (**113**) by ligand exchange between arene and $CpMn(CO)_3$, followed by the formation of complex **114**. In the next step, an aryl radical species (**78**) generated from photoexcitation and electron transfer of complex **114** reacts with arene(**16**) to form intermediate **117**. Subsequent oxidation and deporotonation afford the desired product **87**.



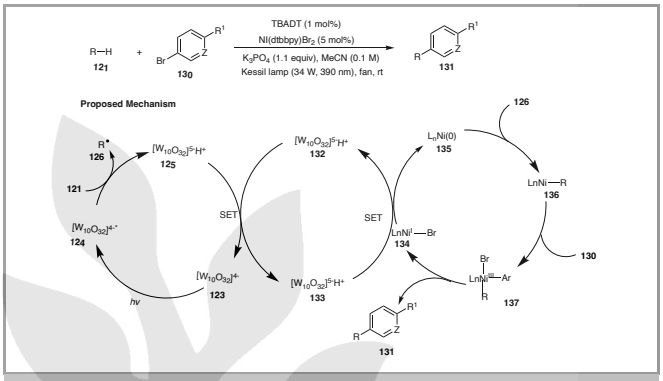
Scheme 27 Manganese-catalyzed continuous photoflow arylation of arenes.

In 2017, Ravelli and co-workers demonstrated an intriguing method for sp³C-H arylation (Scheme 28)[76]. The authors achieved sp³ C-H arylation at room temperature using an efficient and robust photocatalyst tetrabutylammonium decatungstate (TBADT) for arylation of heteroarenes. The use of TBADT promoted the radical formation via hydrogen abstraction from sp³C-H bonds via Minisci reaction, enabling aromatic homolytic substitution of heterocycles under mild conditions. A wide range of heterocycles were smoothly alkylated with a series of hydrogen donor substrates including ethers, amides, aldehydes, cycloalkanes, cycloalkanones. As depicted in Scheme 28, the reaction commences with homolytic cleavage of sp³C-H bond by excited TBADT from alkane to form the corresponding radical **126** which is trapped by protonated heterocycle **127** to produce radical intermediate **128.** Subsequent oxidation of the adduct radical **128** by strong oxidant $SO_4^{\cdot -}$ formed from persulfate by either thermal or photochemical cleavage produces the final alkylated product.



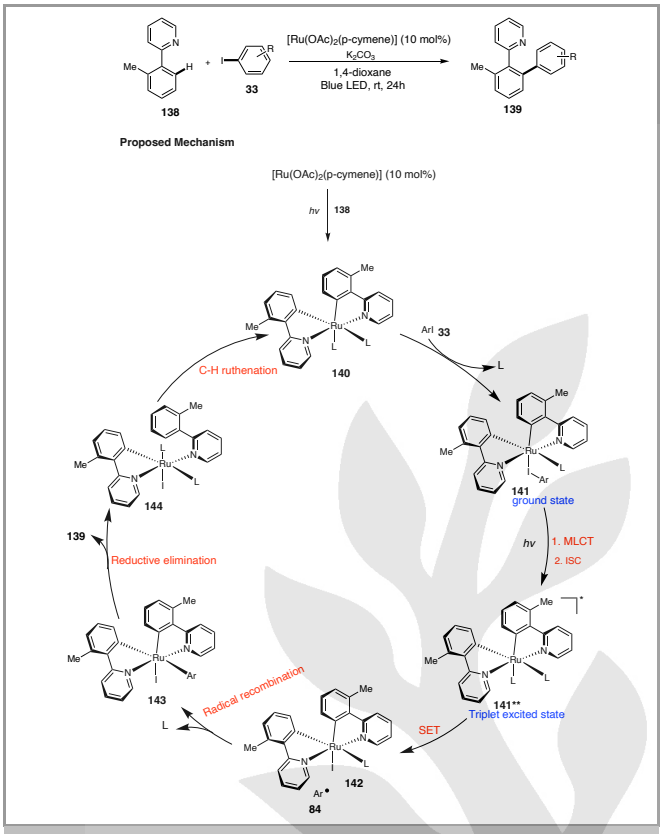
Scheme 28 TBADT catalyzed photoarylation of isoquinoline.

A year later, Macmillan and coworkers achieved sp³ C-H arylation at room temperature by merging photoredox mediated hydrogen atom transfer and transition metal catalysis.[77] The authors used TBADT as co-catalyst for generating carbon radicals from electron-rich, sterically accessible sp³ C-H bonds that acts as a nucleophile in nickel catalyzed cross-coupling with aryl bromides(Scheme 29). Among various high-energy polyoxometalates, they preferred decatungstate anion $[(W_{10}O_{32})]^{4-}$ as hydrogen atom transfer (HAT) photocatalyst for C-H abstraction because of its successful application in various oxygenations, dehydrogenations, conjugate additions, and fluorinations. By using commercially available HAT photocatalyst TBADT, Ni(dtbbpy)Br_2, and potassium phosphate, the authors were able to selectively alkylate a series of aryl bromides with cyclic and acyclic substrates in good to moderate yields.



Scheme 29 Dual HAT and Ni catalysis for sp³C-H activation.

In 2020, the Ackermann group demonstrated a mild Ru-photoinduced catalysis method for arylation of 2-arylazines at room temperature (Scheme 28).[78] The substrate scope is broad, including pyrazoles, triazoles, sensitive nucleotides, and nucleosides, demonstrating the synthetic utility of this approach. Based on experimental and DFT studies, the authors propose that the catalytic cycle commences by carboxylate-assisted C-H ruthenation followed by p-cymene's dissociation generating photoactive biscyclometalated complex (**140**). Complex **140** coordinates with the iodoarene, forming a ruthenacycle (**141**) complex that takes part in the inner sphere electron transfer process producing aryl radical and ruthenium (III) species (**142**) only to undergo recombination affording stable ruthenium (IV) species (**143**). Subsequent reductive elimination and ligand exchange produced the desired arylated product **139**. A very similar method was developed by the Greaney group prior to this report.[79]

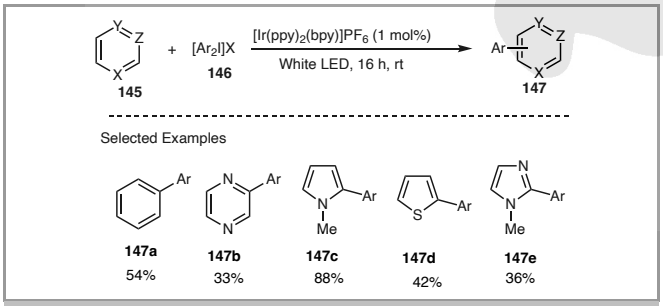


Scheme 30 Ru catalyzed direct arylation of 2-arylazines.

2.3.2 Radical addition-based

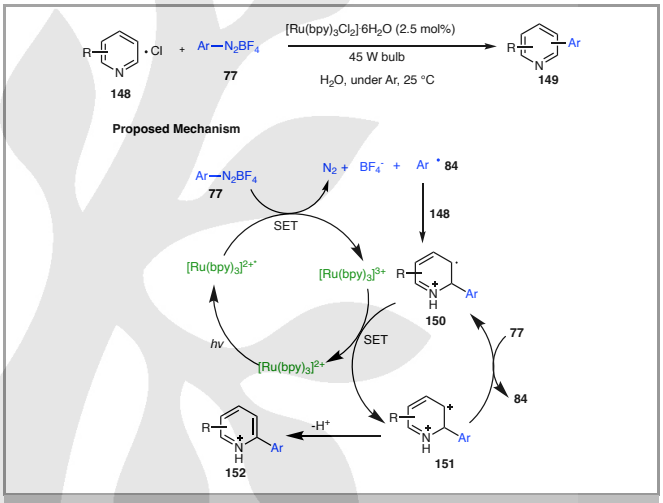
In radical addition-based photoredox catalysis, aryl radical formed via SET process gets trapped by arene. The resulting radical species undergo SET and deprotonation to afford the desired product. The aryl radical through photoinduced SET can be achieved by both organic photocatalysts and inorganic transition metal complexes.

Transition metal catalyzed: In 2013, Chatani and co-workers demonstrated white light promoted arylation of heteroarenes using diaryliodonium salts as the coupling partner (Scheme 31).[80] Interestingly, arylation of pyrrole proceeded without $[Ir(ppy)_2$ (bpy)]PF_6 while reaction with benzene and other heteroarenes required photocatalyst, indicating two different pathways even though aryl radical is generated by photoinduced SET in both cases. The authors reasoned the formation of the charge-transfer complex on photoirradiation promoting C-2 arylation in pyrrole.



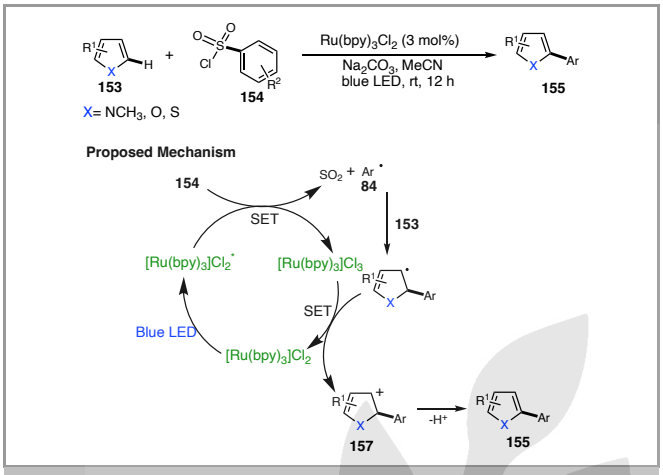
Scheme 31 Ir(III) catalyzed the arylation of arenes and heteroarenes with diaryliodonium salts.

A year later, Xue and co-workers demonstrated a photocatalyzed arylation of electron-deficient arenes in water at room temperature.[81] This protocol uses $[Ru(bpy)_3]Cl_2.6H_2O$ as a photosensitizer and a commercial household light bulb for photon source (Scheme 32). While C4-substituted pyridines afforded monosubstituted products(C2), a mixture of regioisomers was obtained in the case of C2 or C3 derivatives. The authors show that the method is also effective for xanthenes, thiazole, pyrazine, and pyradizine when aqueous formic acid is used as the solvent. As depicted in Scheme 32, photoreduction of aryldiazonium salt produces aryl radical, which gets trapped by pyridine hydrochloride to give another radical species. Subsequent formation of carbocation and deprotonation affords the desired product. There are two possible pathways for carbocation formation: the common oxidation pathway by $[Ru(bpy)_3]^{3+}$ or oxidation by aryldiazonium salt. Following this work, Lei group arylated isoquinolines by using TFA for protonating the heterocycle instead of using pyridinium salts as substrate. [82]



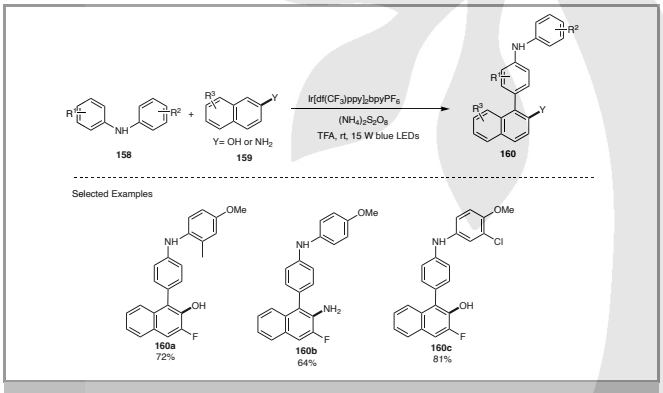
Scheme 32 Photoredox catalyzed arylation of pyridines in water.

Owing to the biocompatibility, stability, and commercial availability, arylsulfonium chlorides serve as attractive precursors to aryl radical over aryldiazonium and diaryliodonium salts. In 2016, Bhasin and co-workers developed a cheaper and environmentally advantageous protocol for employing arylsulfonium salts (Scheme 33).[83] Heteroarenes, including pyrrole, furan, and thiophene derivatives, were arylated with arylsulfonyl chloride in the presence of photocatalyst $Ru(bpy)_3Cl_2$ affording the desired products in moderate to good yields. Notably, mechanistic investigations revealed that the reaction proceeded via the SET mechanism. This method is of great synthetic importance owing to its mild and general conditions.



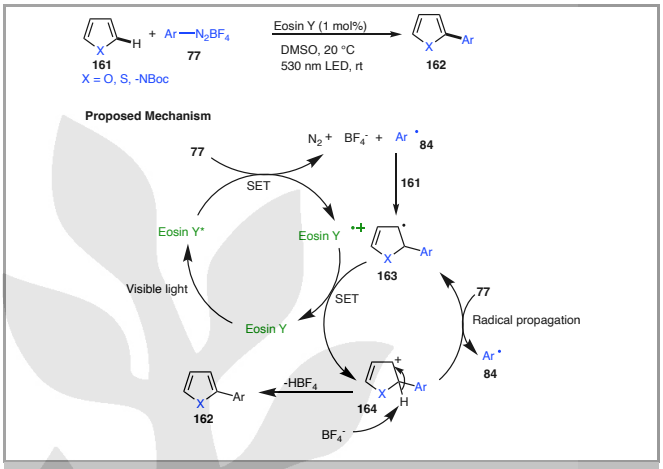
Scheme 33 Ru photocatalyzed direct C-H arylation of heteroarenes with aryl sulfonyl chlorides.

The direct transformations of C-H bonds to C-C bonds avoiding any prefunctionalization, known as cross dehydrogenative coupling (CDC) is highly desirable for constructing biaryls. In this regard, Xia and co-workers demonstrated the use of Ir(III)/visible light catalytic system for dehydrogenative coupling of anilines and or phenols (Scheme 34).[84] Though other photocatalytic systems including Ru and Eosin Y were also studied, [Ir{dF(CF$_3$)ppy}$_2$(bpy)]PF$_6$ gave the best results. While in the case of oxidants, $K_2S_2O_8$, Na_2S_2O8, selectfluor led to decrease in the product yield in comparison to $NH_2S_2O_8$. A good tolerance to a wide variety of aniline and phenol derivatives for coupling of asymmetric atropisomeric biaryls reflects the usefulness of this method.



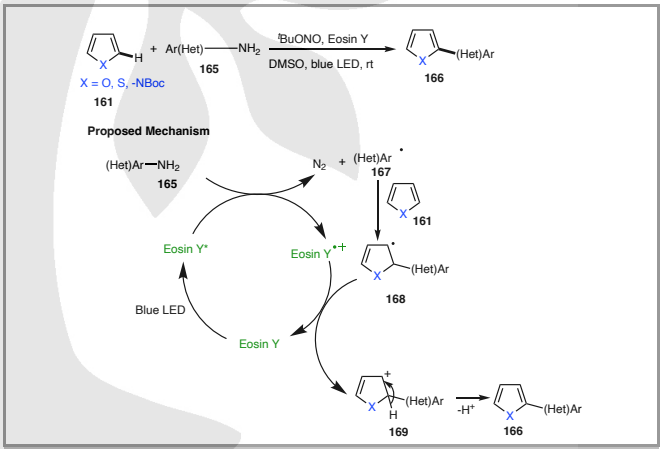
Scheme 34 Ir(III) catalyzed photoredox cross-dehydrogenative coupling of heteroarenes.

Organophotocatalysis: Apart from metal complexes, direct C-H arylation reactions catalyzed by organic dyes are an established tool for facilitating C-C coupling under mild conditions. Employing organic dyes as photosensitizers offers a cost-effective and greener approach compared to metallaphotoredox reactions. An early example of organic dye catalyzed direct C-H arylation was reported by König and co-workers in 2012.[85] Their work entailed arylating heteroarenes with diazonium salts using only eosin Y as a photocatalyst and green light (Scheme 35). The developed protocol effectively arylated a broad range of diazonium salts and heteroarenes with good tolerance to functional groups. The proposed mechanistic pathway commences with the aryl radical formation by SET from Eosin Y to aryl diazonium salt, followed by its addition to arene to form a radical intermediate. The subsequent step involves the transformation of the radical intermediate to a cationic intermediate, followed by deprotonation to afford the desired coupling product.



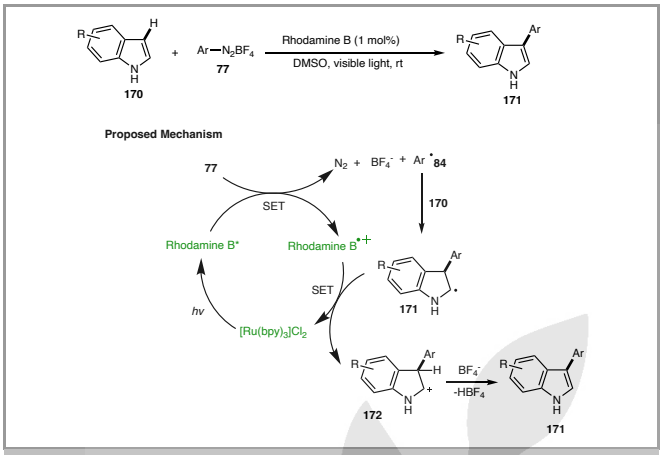
Scheme 35 Eosin Y catalyzed direct arylation of heteroarenes.

In 2015, Ranu, Kundu, and co-workers developed a metal-free, visible light-mediated arylation of heteroarenes with in-situ ^{t}BuONO diazotized heteroaryl amines (Scheme 36).[86] Eosin Y in combination with visible light, afforded the synthesis of functionalized biheteroaryls at room temperature without any metal nitrites, high temperature, and acidic medium. Unlike other previously reported methods, this approach enables the arylation of heteroarenes by heteroarylamines.



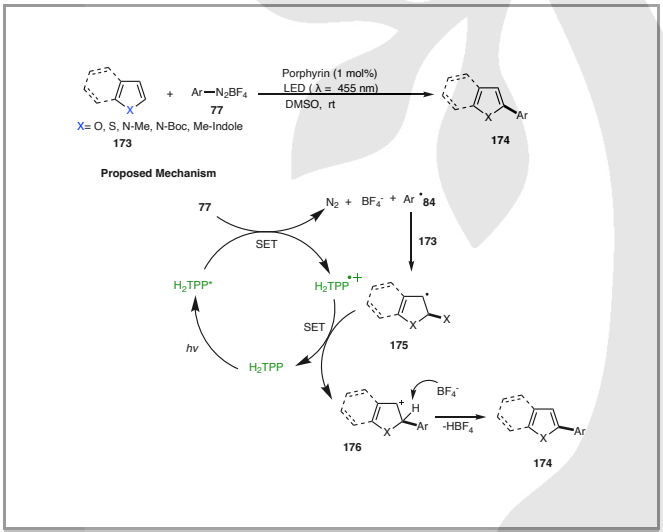
Scheme 36 Eosin Y catalyzed arylation of heteroarylamines.

A year later, Zhang and co-workers introduced rhodamine B as a photocatalyst for the arylation of indoles with aryldiazonium salts (Scheme 37).[87] The protocol is metal-free, efficient, and environmentally benign, operating under green light at room temperature. The reaction proceeds through a radical pathway via the SET of excited rhodamine B to aryldiazonium salts. While the method was successful with various indole derivatives and diazonium salts, substrates with electron-donating groups were more effectively arylated than electron-accepting ones.



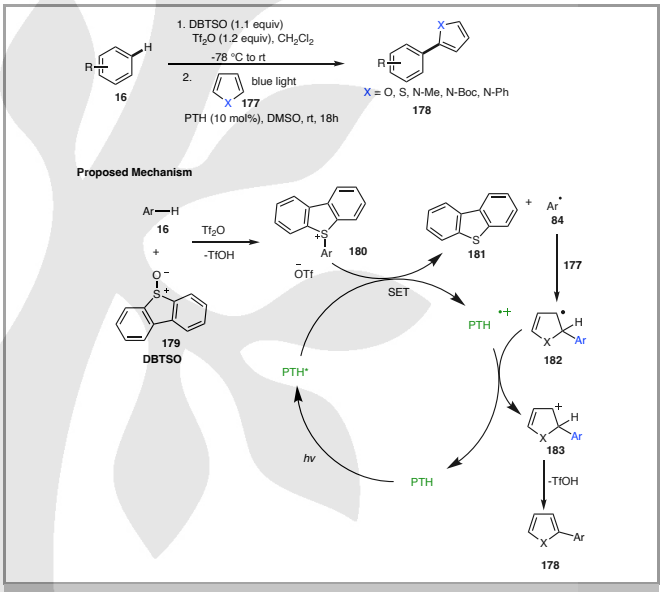
Scheme 37 Rhodamine B mediated arylation of indoles.

In 2017, Gryko and co-workers demonstrated that porphyrins are effective reductants in the excited state, catalyzing the light-induced direct C-H arylation of heteroarenes via oxidative quenching.[88] The photoredox activity of a series of porphyrin derivatives (H_2TPP) was investigated by tuning the substituents present at the periphery of the macrocycle, with the best results obtained with electron-poor tetra(pentafluorophenyl)porphyrin ($H_2T(F_5P)P$). As depicted in Scheme 23, the reaction follows a radical path. In the first step, photoexcited porphyrin (B) reduces aryldiazonium salt(1) to aryl radical(2) while forming a cation radical (C). The highly reactive aryl radical (2) subsequently reacts with heteroarene(3) to form another radical 4. Oxidation of intermediate 4 by porphyrin cation radical followed by proton elimination furnished the arylated product (6).



Scheme 38 Porphyrin catalyzed photoredox direct arylation of heteroarenes.

In the same year, Feng, Xu, and co-workers employed 9,10-dihydro-10-methylacridine($AcrH_2$) coenzyme model compound as a photocatalyst for the cross-coupling of heteroarenes.[89] This photocatalytic protocol was successfully applied to a wide range of heteroarenes and aryldiazonium salts. In 2020, an exciting study by Procter *et al.* demonstrated the use of interrupted Pummerer activation and organophotocatalysis for one-pot coupling of non-pre functionalized arenes. In order to achieve this, the authors used dibenzothiophene S-oxide (DBTSO) as a process mediator and 10-phenylphenothiazine (PTH) as a photocatalyst(Scheme 39).[90] Besides the high reactivity and selectivity ensured by DBTSO during sulfenylation and aryl radical formation, the easy recovery and regeneration of the dibezothiophene as byproduct render it an attractive mediator. The catalytic system exhibits good compatibility with a wide variety of substrates with complete chemo- and regiocontrol, a result of DBTSO. The authors noted problems with hydroxyl and amino-substituted substrates. As depicted in Scheme 24, mechanistically, the process begins with interrupted Pummerer activation of arene generating aryldibenzothiophenium salt (Ar-DBT^+), which is reduced by photoexcited PTH to aryl radical with the expulsion of dibenzothiophene.[90] This highly reactive radical species couples with heteroarene to form another radical intermediate. Single-electron oxidation of intermediate 181 by phenothiazine cation radical, followed by deprotonation, yields the arylated product. The success of this method with the arylation of complex biologically important products- boscalid, fenofibrate, clofibrate, salicin pentaacetate, and N-acetylmexiletine demonstrates its potential utility for natural product diversification.



Scheme 39 One-pot photoredox catalyzed arylation of arenes enabled by interrupted Pumerer activation.

2.4 Transition metal-free

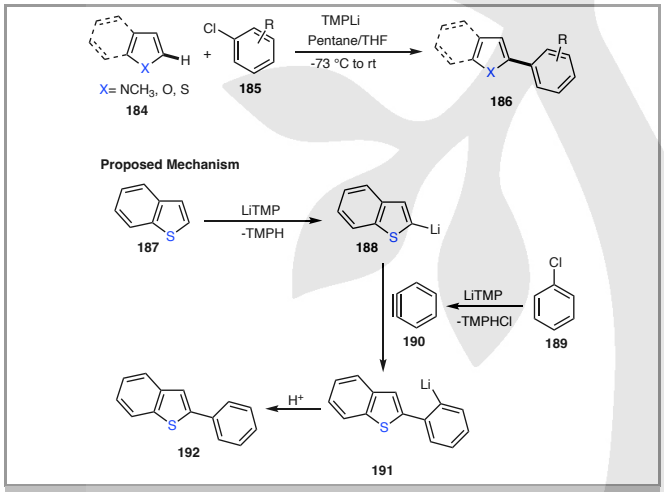
Despite the many benefits of direct arylation reactions, expensive transition metal catalysts and supporting ligands represent a significant limitation of this approach. Furthermore, considering their toxicity, removing the trace amount of metal residues from desired products is essential and challenging prior to their application, particularly in pharmaceuticals and industries. Hence, developing metal-free approaches is highly desirable. In this context, transition metal-free reactions have seen significant development in the past years[91] as they offer an inexpensive and environmentally benign yet efficient route for direct activation of C-H bonds for C-C coupling.

2.4.1 Base mediated

In a seminal study, Itami and coworkers reported potassium tert-butoxide (KO^tBu) catalyzed transition metal-free C-C coupling between N-heterocycles and aryl iodides at 50 °C under

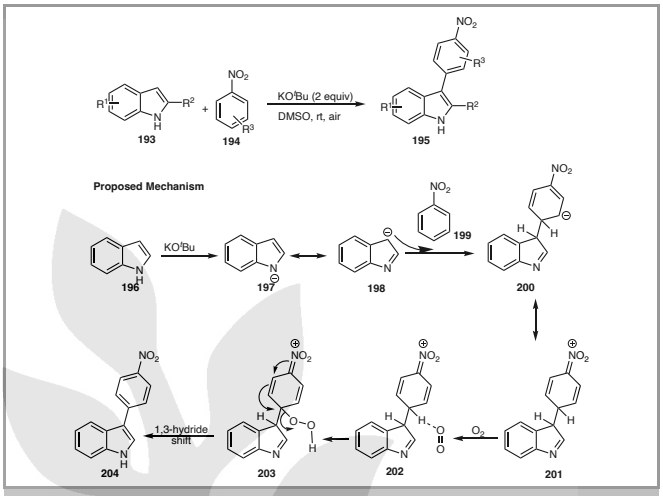
microwave irradiation in 2008.[92] Though this early report set the stage for the development of base promoted transition metal-free reactions, the need for a large excess of C-H coupling partners (1:40 equiv) hampered the synthetic utility of this approach.

Addressing the excess monomer issue, an interesting approach based on generating a highly reactive aryne intermediate was reported by Daugulis and co-workers in 2011 (Scheme 40).[93] The reaction of electron-rich and electron-poor arenes with aryl halides mediated by 2,2,6,6-tetramethylpiperidine (LITMP) in THF or THF-pentane mixture provided the desired arylated products in good to excellent yield at room temperature. In this case, functionalization was achieved at the most active C-H bond with less than ~2.5 equivalent of aryl coupling partner and one equivalent of arenes. Notably, using LDA as a base, sequential one-pot arylation of N-methylimidazole with chlorobenzene was also accomplished. A similar approach using lithium bases was also developed for direct C-H arylation of heteroarenes with aryl chlorides and aryl triflates as the coupling partner with modest yield. While the best results were obtained with LiTMP and LDA, the method could tolerate hydroxy and chlorine functional groups. Continuing their studies, the Daugulis group reported a general methodology that involved adding a mixture of heteroarene and aryl halide/triflate in THF or THF-Et_20 to LiTMP to obtain the required product.[94] The reaction mechanism outlined in Scheme 40 involves the coupling between benzyne and aryl anion to afford the desired product.



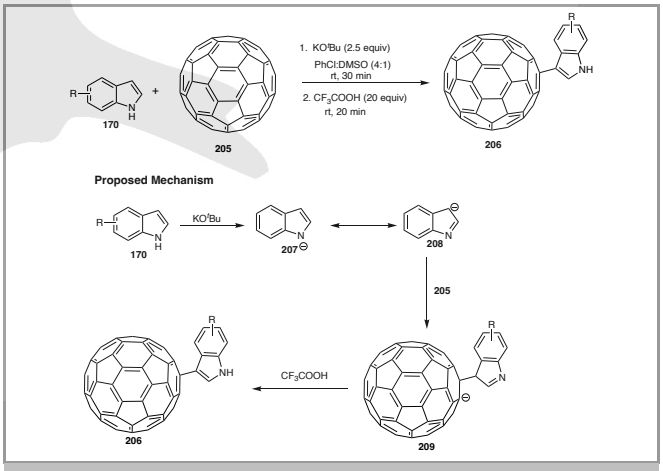
Scheme 40 LiTMP mediated direct C-H arylation of heteroarenes.[94]

In 2010, Kumar and co-workers demonstrated the KO^{t}Bu-mediated β-arylation of unprotected indoles at room temperature in the absence of transition metal catalysts (Scheme 41).[95] The reaction occurred via intermolecular oxidative coupling of indole with nitroarene under an atmosphere of air. The proposed mechanism outlined in Scheme 23 highlights the role of the free N-H group for the reaction. In presence of KO^{t}Bu, abstraction of free N-H could transform indole (I) into indole-1-ide(II) which undergoes resonance to form a more stable intermediate indole-3-ide(III). A subsequent nucleophilic attack of III on nitrobenzene generates intermediate (IV) which on resonance forms V. In the next step, atmospheric O_2 would interact with the hydrogen of VI which leads to the formation of hydroperoxide radical and intermediate VII, which tautomerizes to give the desired product (VIII). The scope of functionality is broad, including both electron-rich and poor groups.



Scheme 41 KO^{t}Bu mediated arylation of indoles.

In the same year, Tian and coworkers aimed at synthesizing 1,2-(3-indole)(hydro)[60] fullerene derivatives via one-pot arylation of indoles and fullerene catalyzed by KO^{t}Bu (Scheme 42).[96] The reaction proceeds efficiently in a highly selective manner at room temperature giving C-3 arylated product. While the reaction could tolerate electron-withdrawing groups such as chloro, nitro, and ester on the benzene ring of indole, electron-donating substituents such as OMe at 5- or 7-position showed lower reactivity affording the corresponding products in moderate yields. Despite raising the temperature to 80°C, no improvement was achieved in the case of OMe substituted indole derivative. Notably, the free N-H group in indole is crucial for reaction as the coupling failed with N-substituted indoles- N-methylindole and N-Boc indole. Mechanistically, abstraction of NH proton leads to the formation of indole-1-ide-A, which undergoes resonance to form indol-3-ide B. The next step involves nucleophilic attack of B to C60, forming C, which on quenching with CF_3COOH, gives the desired product. It is worth noting that poor reaction yields were obtained in the air due to oxidation of intermediate C, while moisture in the air could quench the base.

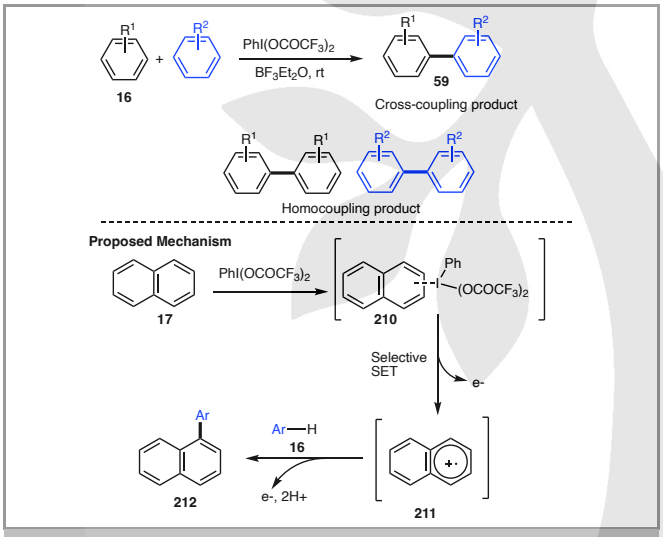


Scheme 42 KO^{t}Bu mediated coupling of indoles with [60]fullerene.

2.4.2 Iodonium and diazonium salts based

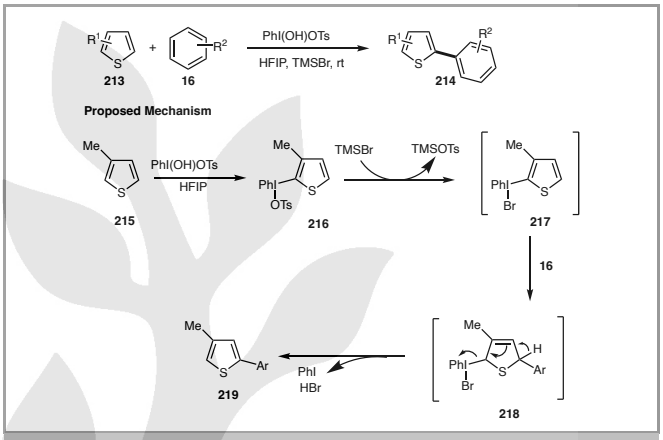
Another well-established solution to achieve transition metal-free direct C-H arylation involves using diaryliodonium and aryldiazonium salts as the coupling partner. Examples involving iodonium salts are described first in this section.

A seminal development in the field of iodonium salt-based direct arylation comes from the Kita group. In 2008, the authors reported the first example of hypervalent iodine (III) promoted metal-free cross-coupling for arenes with mesitylenes (Scheme 43).[97] The coupling is driven by SET oxidation of electron-rich arenes by iodine (III) salt to generate a radical that couples with other existing molecules. It is worth mentioning that the reaction of naphthalene with pentamethylbenzene in the presence of PIFA and BF_3Et_2O afforded the cross-coupling product in 82% yield without any homocoupling product, while other oxidants reduced the efficiency of the reaction. Oxidants such as DMP and DDQ gave only homoproduct, whereas no product formation was achieved with $Pd(OCOCF_3)_2$ and $Cu(OAc)_2$. These results indicated the importance of a hypervalent iodine oxidant for efficient reaction progress. Notably, the halogen functionality gave the best results as directing group with excellent control of regioselectivity, while the presence of the electron-poor group changed the regioselectivity leading to the formation of another regioisomer along with the desired one signifying the resonance effect of halogen for regioselective coupling.



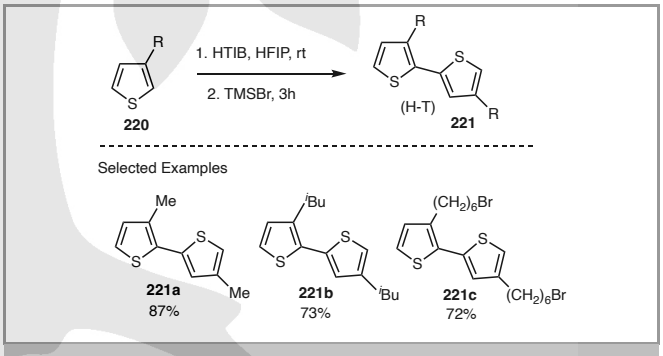
Scheme 43 Oxidative direct C-H arylation of arenes induced by iodine(III) salts.

In another subsequent study, Kita and co-workers demonstrated a new strategy for regioselective C-2 arylation of heteroarenes using α-thienyliodonium salts in the presence of bromotrimethylsilane at room temperature.[98] α-thienyliodonium salts were generated in situ from the reaction of thiophene derivatives, hydroxy(tosyloxy)iodo] benzene (Koser's reagent), and HFIP (Scheme 44). Notable features of this approach include broad substrate scope due to good functional group tolerance, no requirement of excess heteroarenes, mild reaction conditions, and no oligomer formation. A number of aromatic substrates, such as phenyl ethers, pyrroles, and thiophenes underwent C-2 arylation with electron-rich thiophenes. The proposed mechanism of the reaction is outlined in Scheme 44. The proposed mechanism involved the formation of stable iodonium (III) tosylate salts upon the selective reaction of electron-rich heteroaromatic at 2-position with Koser's reagent. The reaction proceeded rapidly in the presence of HFIP solvent. Being inert, the formed iodonium salt (**216**) was activated by adding TMSBr in HFIP to iodonium bromide salts (**217**), which underwent formal hydroarylation (**218**) with heteroarene followed by elimination of iodobenzene to provide the desired arylated product (**219**).



Scheme 44 Oxidative arylation of thiophenes.

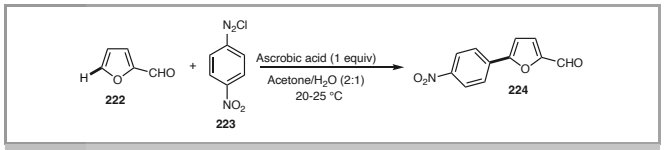
A year later, the Kita group made another contribution to this area, developing a unique and selective oxidative coupling method for the synthesis of head-to-tail linked (H-T) thiophenes based on iodonium mediated strategy (Scheme 45).[99] This strategy involved the reaction of 3-alkoxythiophenes with HITB in the presence of HFIP at room temperature, followed by the subsequent addition of TMSBr in HFIP to afford regioselective bithiophenes in good yield providing a new approach for the synthesis of H-T oligothiophenes without using any transition metal.



Scheme 45 Oxidative cross-coupling of 3-alkylthiophenes.

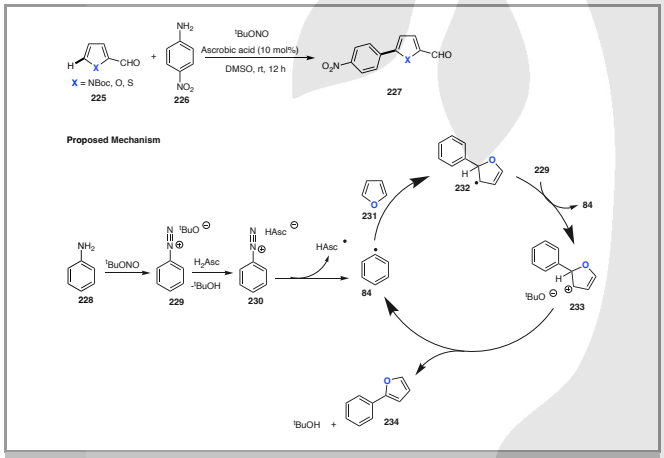
The use of aryldiazonium salts as the coupling partner for the development of transition metal-free direct C-H arylation has attracted significant attention since Obushak and co-workers demonstrated the first report in 2009.[100] In this case, ascorbic acid as a reducing agent generates aryl radical from 4-nitrobenzenediazonium chloride for coupling with furfurol in acetone: water mixture (2:1) at 20-25 °C (Scheme 46). This work drew inspiration from the Gomberg-Bachmann reaction in which aryl radicals generated from aryldiazonium salts undergo homolytic aromatic substitution. It is worth noting that no heating or irradiation was needed, thus providing a greener

approach to arylation. However, this study did not generate interest because of the low yield (15%) of the desired product 5-(4-nitrophenyl)furan-2-carbaldehyde.



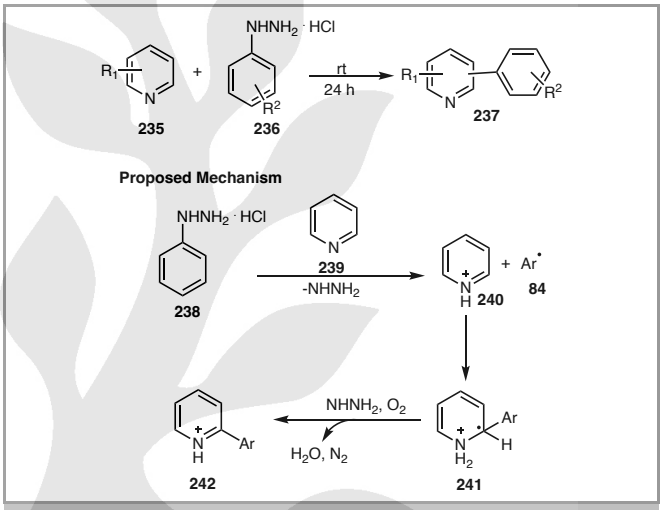
Scheme 46 Ascorbic acid-mediated transition-metal-free direct C-H arylation of furfural.

Five years later, Martin and Carrelio reported that by using in-situ generated aryldiazonium salts due to their stability issues, metal-free arylation with heteroarenes could be achieved in good yield in presence of ascorbic acid as the initiator.[101] Aryldiazonium salts were generated in-situ from aniline precursors on treatment with tert-butyl nitrite(^{t}BuONO) (Scheme 47). The reaction was compatible with a series of heteroarenes, including furan, thiophene, tert-butyl 1H-pyrrole-2-carboxylate, and pyridine-N-oxide. The mechanism proposed by the authors for the arylation of furan is highlighted in Scheme 33. In the first step, the in-situ generated diazonium salt is protonated by ascorbic acid-forming **230** which is then reduced by SET from ascorbate via the inner-sphere mechanism to form diazo ether. The diazoether (**230**) undergoes homolytic rupture to produce nitrogen, aryl radical (**84**), and ascorbyl radical. The aryl radical (**84**) adds onto the furan to yield radical intermediate (**232**), which propagates the reaction by losing an electron to form radical cation (**233**), and yields the desired product (**234**) after proton abstraction by counterion KO^{t}Bu. Meanwhile, the ascorbic acid generated from the dismutation of ascorbyl radical can reduce another diazonium ion.



Scheme 47 Direct C-H arylation of heteroarenes using in-situ generated arenediazonium salts.

In the same year, Kuang and co-workers reported the direct arylation of pyridines with aryl hydrazine hydrochloride without any catalyst or base (Scheme 48).[102] The result was interesting because commercially available hydrazines were used, and the reaction was carried out in the air. This approach went well with aryl pyridines obtained in moderate to good yields. Though monomethyl substituted pyridines showed to be suitable substrates with arylhydrazines having electron-withdrawing and electron-rich groups at the para position affording the desired arylated product in good yields minimal regioselectivity, the reaction of 4-methodxyphenylhydrazine hydrochloride with 3,5-dimethylpyridine selectively yielded the desired C-2 arylated product. The method also gave moderate to good yields in case of arylation of electron-poor heteroarenes such as pyrazine and quinoline with the corresponding hydrazine hydrochloride. The reaction follows a radical pathway in which an aryl radical generated from phenylhydrazine hydrochloride in the presence of pyridines, reacts with the protonated heteroarenes to form the radical cation(**241**). In the next step, the radical cation is reoxidized by O_2 to form the desired product(**242**). However, the synthetic utility of this approach is limited by substrate-governed regioselectivity and moderate yield.



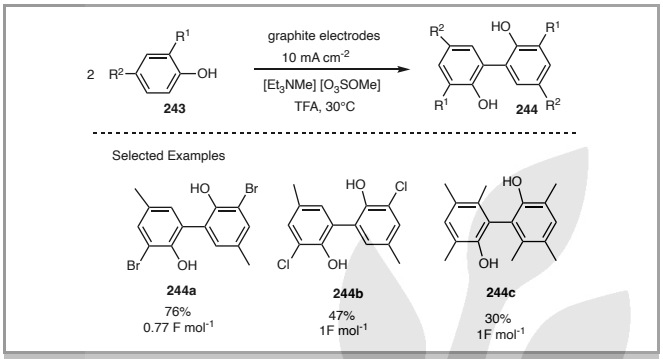
Scheme 48 Direct arylation of pyridines with arylhydrazine hydrochloride.

2.6 Electrocatalyzed

The amalgamation of direct C-H arylation and electrochemistry can also help in reducing the oxidant dependency besides eliminating prefunctionalization of substrates. Indeed, using electricity as the oxidant in place of toxic and expensive stochiometric metal oxidants and iodine (III) salts, many studies have appeared for effective C-H activation. In particular, the extensive research performed by Waldvogel's group during the 2000s and 2010s has been instrumental in advancing the electricity-enabled aryl-aryl coupling. As the electrocatalyzed arylation has been extensively reviewed,[103,104] we discuss only the select examples.

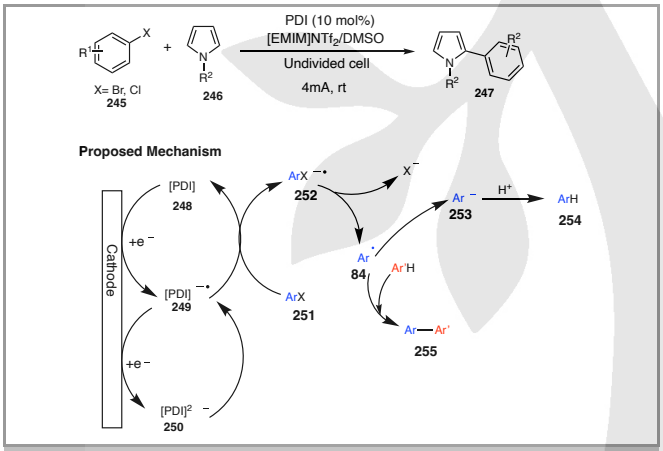
After several years of work, the Waldvogel group in 2009 developed a seminal protocol describing the electric current-enabled oxidative cross dehydrogenative coupling of phenols at room temperature.[105] In this case, the *ortho*-selective coupling of phenols was efficiently achieved (upto74% yield) with the boron-doped diamond anodic electrode and fluorinated alcohols as mediators at 50 °C. Aiming to develop a more general and efficient approach for the electrosynthesis of biphenols, the authors replaced the expensive boron-doped diamond electrode with a graphite electrode (Scheme 49).[106] The optimized condition indicated that maximum reaction yield was achieved with TFA and by applying an electric current of 0.77 F per mole of the substrate and a constant current of 10mAcm^{-2}. It is noteworthy that the formation of ketone derivative was

suppressed while biphenyl product was obtained 64% yield in the case of fluorinated carboxylic acids. In addition to good *ortho*-selectivity, reaction scope is broad with good tolerance to many electron-rich and halogenated phenols.



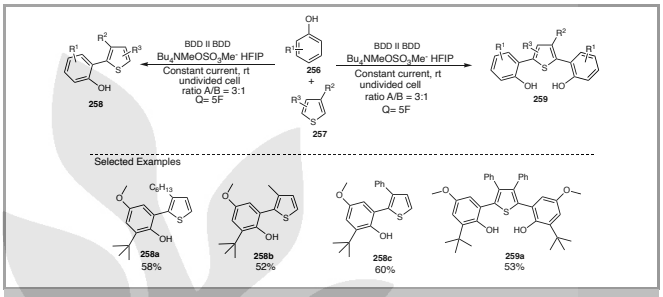
Scheme 49 Anodic C-C cross-coupling of phenols.

In 2016, Zhu and co-workers developed a novel methodology for one-pot arylation of pyrroles with aryl halide using perylene-3,4:9,10-tetracarboxylic acid diimide (PDI) derivatives as redox mediator in 1-ethyl-3-methylimidazolium bis((trifluoromethyl)sulfonyl)imide [EMIM]NTf_2:DMSO mixture.[107] Though electron-rich and electron-poor arene effectively coupled with pyrrole, reaction with other heteroanalogues such as furan, thiophene, and indole did not occur. The mechanism of the reaction is outlined in Scheme 50.



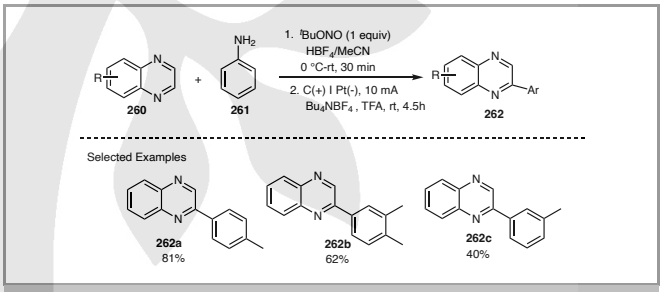
Scheme 50 Electroreductive coupling of phenols with arenes.

Extending their previous studies, the Waldvogel group described an impressive application of electricity for arenes coupling. In 2017, they demonstrated the C-C coupling between phenols and anilines at room temperature by electrochemical means.[108] A subsequent report further showed that this strategy could enable the regioselective C-2 or C-3 arylation of benzothiophenes with phenols (Scheme 51).[109] A notable aspect of this method is its high selectivity as the desired C-2 or C-3 arylated products can be obtained by simply blocking the other position besides the scalability and robustness. Employing the 0.5-fold excess of benzothiophenes and 2F of electricity with respect to phenols, the authors were able to synthesize a broad variety of 2- or 3- (hydroxyphenyl)benzo[b]thiophenes. Though no homocoupling was detected under the optimized conditions, partial polymerization of benzothiophenes could not be ruled out by the authors. The proposed mechanism involves the oxidation of phenol to phenoxyl radical followed by a nucleophilic attack by benzothiophenes and then subsequent oxidation results in a cross-coupling product. In the same year, Charusin and co-workers reported C-C bond formation between azaaromatics and nucleophilic arenes without any metal catalyst/ base or leaving groups at room temperature.[110]



Scheme 51 Electrocatalyzed C-C coupling of thiophenes with phenols.

In 2019, Lei and co-workers reported the coupling between electron-deficient arenes with aryldiazonium salts using cathode reduction (Scheme 52).[111] The electrolysis was carried out in an undivided cell with a graphite anode and Pt cathode electrode. The method showed good compatibility with a variety of aryldiazonium tetrafluoroborate and electron-deficient heteroarenes. In addition, one-pot arylation with in-situ diazonium salt generated from anilines could also be achieved in good yield, with better results noted in anilines having electron donating group than electron-deficient ones.



Scheme 41 Electrolysis of electron-deficient arenes.

3. Summary and outlook

Direct C-H arylation has become an important synthetic tool for molecular synthesis in the past two decades. Though the early research in this field focused on obtaining reasonable reactivity and selectivity, the focus has now shifted to developing reactions that can occur at room temperature, and in absence of any additives. Given the sustainable nature of C-H bond activation chemistry, such types of transformation will have an increasingly meaningful impact on pharmaceuticals development and materials science application. In this review, we highlight the use of conventional transition metal catalysis, photoredox catalysis, and electrochemistry to achieve Csp^2-H bond activation at or below room temperature for Csp^2-Csp^2 coupling. Mechanistic aspects of these reactions have also been discussed as a detailed understanding will guide towards efficient catalytic systems for sustainable development. Based on above discussions we summarize some future key research areas: We noticed that

though 3d transition metals are being widely explored in conventional direct arylation because of their abundance and non-toxic nature, however, their usage in achieving room temperature C-H bond activation arylation will become one of the key focuses in future. Secondly, transition metal-free coupling reactions offer more simple and milder conditions as compared to transition metal-catalyzed reactions, however, the poor chemo and regioselectivity due to intrinsic mechanistic limitations are problematic and need attention. Furthermore, the development of direct arylation polymerization under milder conditions presents exciting research questions in terms of regioselectivity control and yield. Finally, we hope that the examples discussed in this review will further contribute to developing energy-efficient reactions.

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Conflict of Interest

The authors declare no conflict of interest.

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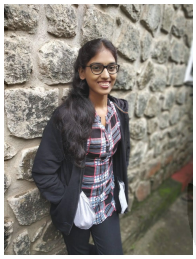
Biosketches

	Preeti Yadav obtained her MSc in chemistry from the University of Delhi in 2015. She completed her Ph.D. from CSIR-National Physical Laboratory under the supervision of Dr. Asit Patra in 2021. Since October 2021, she is working as a postdoc scholar focusing on conjugated polymer syntheses in the group of Prof. Christine K. Luscombe at Okinawa Institute of Science and Technology Graduate University, Okinawa, Japan.
	Nivedha Velmurugan is a graduate student in the field of Chemistry at Okinawa Institute of Science and Technology, Japan. She was born in Chennai, India and obtained her Masters's degree in Chemistry in 2019. Her broad field of research interest includes catalyst designing. At the moment, she is at the process of joining Prof. Christine Luscombe's lab for her PhD, working towards the synthesis of pi-conjugated polymers.
	Christine Luscombe has been a Professor at the Okinawa Institute of Science and Technology Graduate University in Japan since 2021. She obtained her PhD under the supervision of Profs. Andrew Holmes and Wilhelm Huck at the University of Cambridge and subsequently did her post-doctoral work with Prof. J. M. J. Fréchet at UC Berkeley. She was a faculty member at the University of Washington, Seattle for 15 years prior to moving to Japan.