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

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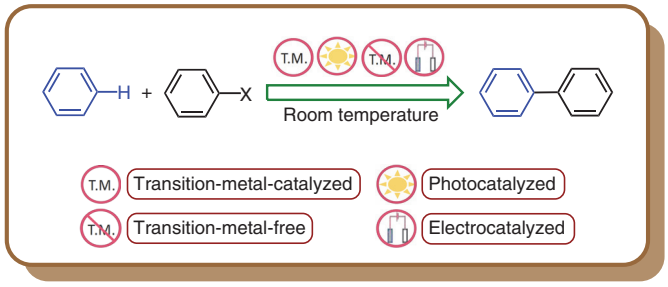

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Abstract In recent decades, direct C–H arylation has become a preferred tool for biaryl coupling over traditional cross-coupling methods owing to its operationally simple protocol, inherent atom and step economy, and reduced metallic waste. Several elegant methods have been developed that offer the facile transformation of usually inert Csp^2–H bonds into Csp^2–Csp^2 bonds in a single synthetic operation. Despite many merits, a major drawback to this chemistry comes from the low reactivity of aryl C–H bonds, 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.

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 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 C–C bond formation via coupling between an aryl halide and an 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, this 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

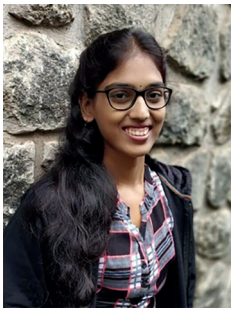
complex molecular architectures, enriching the chemistry of natural products, and functional materials and accelerating the drug discovery processes.[13–15]

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 the high bond dissociation energies of C–H bonds (~110 kcal for aryl C–H bonds), high temperatures (80–120 °C) are typically required, preventing the use of substrates with heat-sensitive functional groups. Higher temperatures also increase 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 an oxidant for catalyst regeneration in some cases and a 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 arylations by developing mild protocols that proceed at or below room temperature and in the absence of acids or base and oxidants. In this regard, 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 activation of the sp^2 C–H bond at room temperature. Thus the use of TFA as the solvent supported insertion of the metal into the aryl C–H bond as well as the efficient regeneration of the Pd(II) catalyst. Five years later, Fujiwara 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 environ-

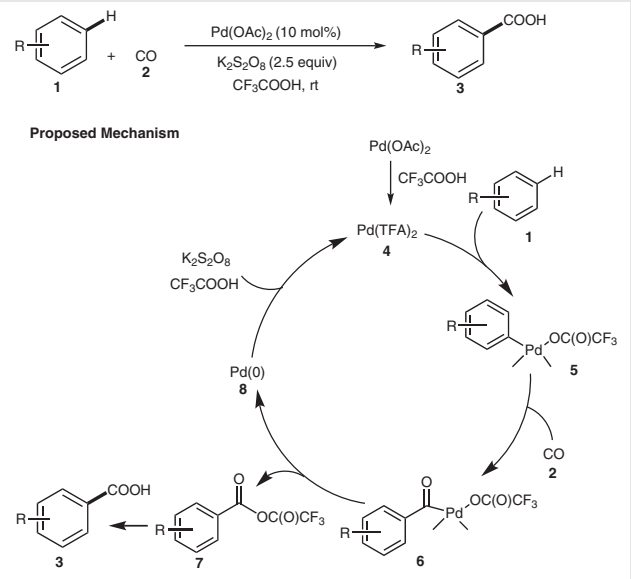
Biographical Sketches

Preeti Yadav obtained her M.Sc. in chemistry from the University of Delhi in 2015. She completed her Ph.D. at the CSIR-National Physical Laboratory under the supervision of Dr. Asit Patra in 2021. Since October 2021, she has been working as a postdoctoral scholar focusing on conjugated polymer syntheses in the group of Prof. Christine K. Luscombe at the Okinawa Institute of Science and Technology Graduate University, Okinawa, Japan.



Nivedha Velmurugan is a graduate student in the field of chemistry at the Okinawa Institute of Science and Technology Graduate University, Japan. She was born in Chennai, India and obtained her Master's degree in chemistry in 2019. Her broad field of research interest includes catalyst design. At the moment, she is in the process of joining Prof. Christine Luscombe's lab for her Ph.D., working toward 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 Ph.D. under the supervision of Prof. Andrew Holmes and Prof. Wilhelm Huck at the University of Cambridge, and subsequently undertook her post-doctoral studies 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.



Scheme 1 Direct carboxylation of arenes at room temperature

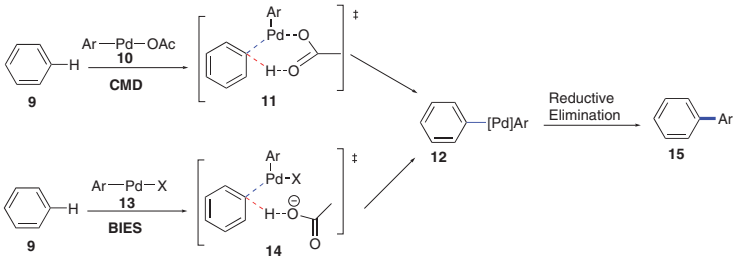
mental and economic footprint of direct C–H arylation reactions.

Several reviews and personal accounts provide a systematic analysis of direct C–H arylation reactions in general[12,15,18] as well as on specific topics such as directing-group-assisted arylation, direct arylation polymerization,[19,20] sustainable approaches,[21,22] and mild C–H activation.[23] 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 the mechanistic features of such reactions and thus better control over the reaction conditions, thereby 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 over the 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.[18,24] 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).[25,26] Instead of intramolecular deprotonation, deprotonating the C–H bond through an externally non-coordinated carboxylate or a basic ligand, a process known as base-assisted internal electrophilic substitution (BIES), is also a viable pathway.[27,28] 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.

Typically, three approaches have emerged for enhancing the reactivity and promoting C–H activation; the first approach involves tuning the catalytic system by employing strong acids like TFA or AcOH to increase the electrophilicity of the 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 acti-



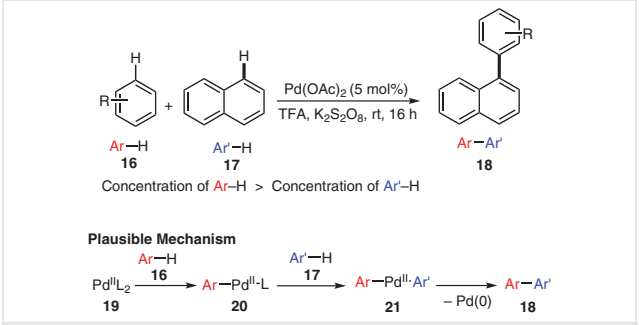
Scheme 2 CMD and BIES mechanisms for direct C–H arylation

vation step by bringing the metal catalyst and target C–H bond in proximity by forming a palladacycle intermediate.[29] 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.[30] 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 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 Procedures

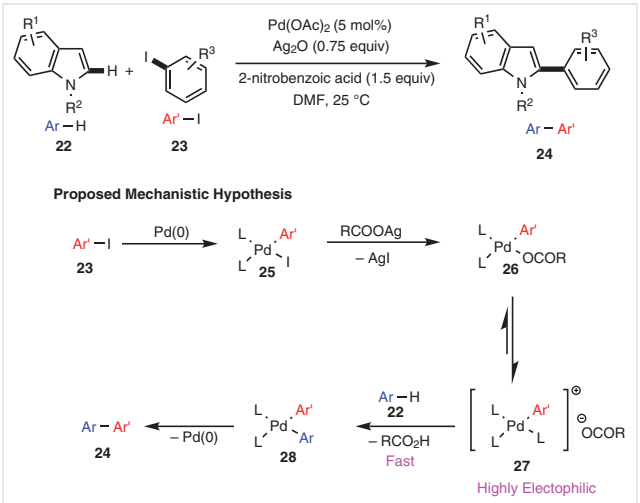
2.1.1 Pd Catalysis

Pd catalysts have been extensively studied for C–H activation owing to their versatility and well-established chemistry.[11] 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 by using the same catalytic system ($Pd(OAc)_2$/TFA/$K_2S_2O_8$) (Scheme 3).[31] The authors could control the regioselectivity by employing an excess of the electron-poorer arene (5–100 equiv). The reaction proceeds through the $ArPd^{II}L$ intermediate **20**, formed from an in situ generated cationic Pd^{II} species and the electron-poorer arene (ArH), followed by preferential attack by the electron-rich arene (Ar'H) to afford 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 and enables the C–H activation at room temperature. Though the method is appealing, the requirement of a significant excess of the arene and poor yields limits the practical utility.



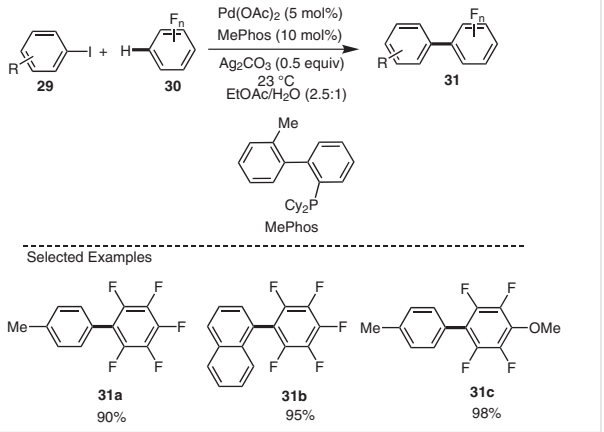
Scheme 3 Direct C–H arylation of arenes

In 2008, an intriguing study describing phosphine-free Pd-catalyzed direct arylation between indoles and aryl iodides at room temperature was reported by Larrosa and Lebrasseur (Scheme 4).[30] The use of a Ag(I) salt and a 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.[32] The authors proposed that while the Ag(I) salt assists the in situ generation of the more electrophilic complex **26** by removal of iodide from Pd complex **25**, the weakly coordinating carboxylate as the supporting ligand facilitates rapid dissociation to the 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 on the aryl iodide and indole moieties. However, the arylation of NH-indoles required a temperature of 50 °C. This route appeared more favorable than Fujiwara's,[16] which is plagued by poor yields and the necessity for an excess of one of the coupling partners. Furthermore, considering the ubiquity of indole derivatives in medicinally important natural and synthetic compounds, this method displays broad applications.

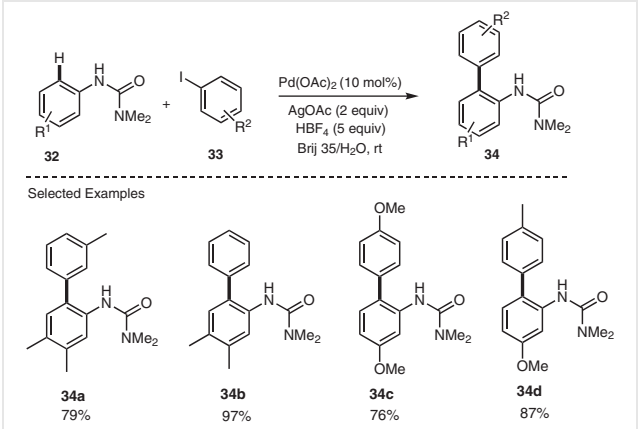


Scheme 4 α-Arylation of indoles at room temperature

Electron-deficient arenes can also be effectively arylated at room temperature. An example of such a transformation demonstrating coupling between electron-deficient polyfluorinated arenes and iodobenzenes in a biphasic medium comprising water and an organic solvent was reported by Fagnou and René (Scheme 5).[33] 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 products in excellent yields. 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.



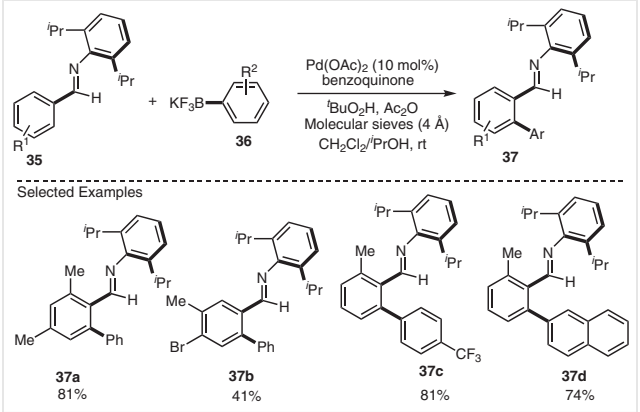
Scheme 5 Direct C–H arylation of polyfluorinated arenes under biphasic conditions



Scheme 6 Direct C–H arylation of anilide derivatives

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 its ligating nature and affecting the electrophilicity of the metal catalyst, the electronic behavior of a chelating group significantly influences the rate of the 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).[30] This report illustrates the advantage of using a Lewis acid, i.e., 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 the directing group and cationic nature of the Pd catalyst promoted the C–H activation step, facilitating the room temperature transformation. Though the method is compatible with a broad range of functional groups on both the aryl ureas and the aryl iodides, affording the desired mono-arylated products in 42–97% yield, the reaction did not occur in the case of *ortho*-substituted aryl iodides due to steric hindrance. Notably, N-substituted ureas 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. A cationic Pd catalyst could also be generated from $Pd(OAc)_2$ and $AgBF_4$ without any external acid.

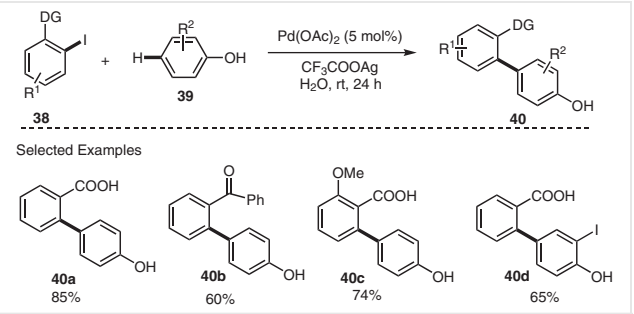
The mildness of the above-discussed method encouraged Gaunt and co-workers to focus on improving the catalytic system by tuning the electronic character of the directing groups (Scheme 7).[34] They envisaged a design strategy in which employing an imine as a directing group (less electron-withdrawing 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 their hydrolysis to amines under the 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 products 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).[35] 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 the aryl iodide would lead to a thermodynamically stable intermediate by accelerating the oxidative addition to the transition metal, thereby enabling phenol activation at room temperature in stark contrast to the well-established C–H arylations. Subsequent reductive elimination would provide the desired coupling product.

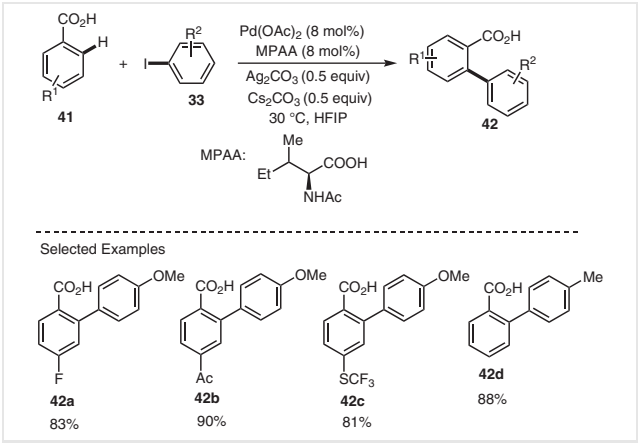


Scheme 8 Arylation of phenols via an inverse direct C–H arylation strategy

Following their initial study,[30] Lipshutz and co-workers developed another protocol utilizing commercially available $[Pd(MeCN)_4](BF_4)_2$ as a catalyst or a nitrile-free Pd(II) species generated in situ from $Pd(OAc)_2$ and HBF_4.[36] It was found that an efficient *ortho*-arylation was achieved in the case of aryl ureas compared to acetanilides.

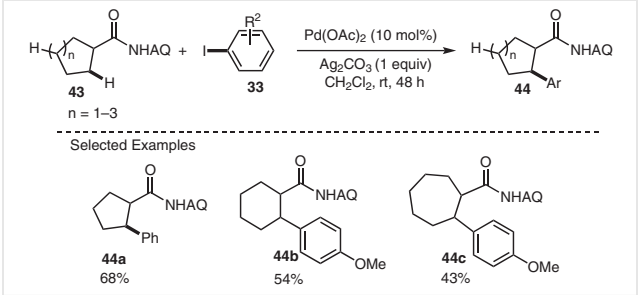
Another example of the directing-group-promoted direct C–H arylation of arenes was reported by Zhu et al.[37] This study used mono-N-protected amino acid ligands (MPAAs) to synthesize a library of arylated benzoic acids in moderate to excellent yields (Scheme 9). While solvents such as DMF, AcOH, and H_2O were ineffective, the reaction proceeded well with various substrates in the presence of hexafluoroisopropanol (HFIP) and Cs_2CO_3, affording moderate to excellent yields. A series of MPAAs was used, demonstrating an increase in the reaction yield, but the best performance was noted in the case of the N-Ac-Ile-OH ligand. Mechanistic studies suggested that the ligand accelerated the rate-determining step: the C–H activation process, besides improving the catalyst lifetime. Apart from bidentate coordination with Pd metal, the N–H moiety of the ligand facilitates C–H bond cleavage by acting as an intramolecular proton shuttle, potentially enabling the room temperature C–H bond arylation.

In 2016, Chen and co-workers reported the aminoquinoline-directed sp^3 C–H arylation of carboxamide derivatives with aryl iodides (Scheme 10).[38] Compared to previous reports of diarylation at elevated temperatures,[39,40] this 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



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

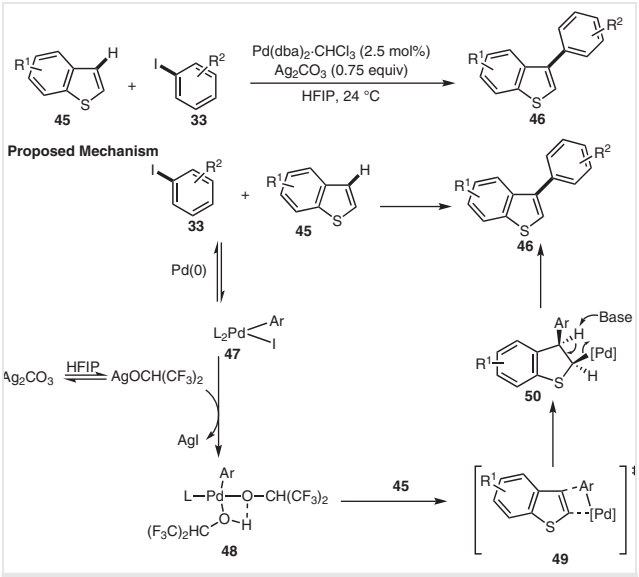
electron-rich iodides, sterically hindered aryl iodides gave poor yields. Room temperature C–H arylation is favored by a Pd^{II}/Pd^{IV} catalytic cycle. The catalytic cycle commences with metal insertion of the aminoquinoline moiety by Pd^{II} allowing activation of the β-sp^3 C–H bond, which after intramolecular addition of the aryl iodide 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^3 C–H arylation of carboxamide derivatives

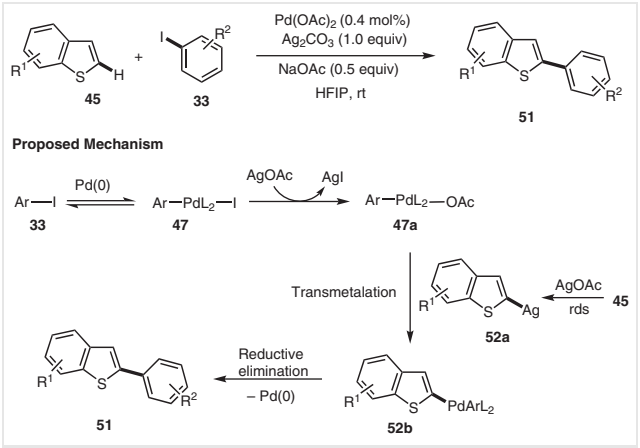
Sulfur-containing heterocycles, particularly thiophenes and benzo[*b*]thiophenes, are recognized as important structural units prevalent in biologically active compounds, drugs, and functional materials. In this regard, significant efforts have been directed toward the efficient synthesis of these useful molecules. Though the majority of these studies have targeted the most acidic α-positions, 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).[41] 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 a Heck-type direct arylation pathway (Scheme 11).[41]



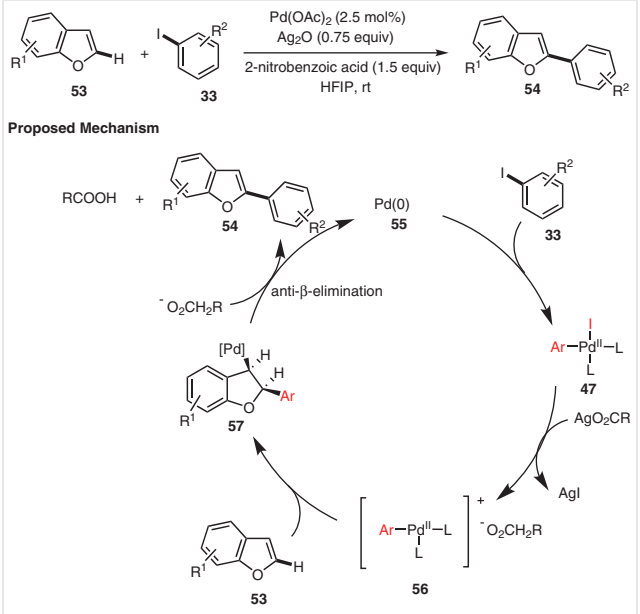
Scheme 11 Regioselective β-arylation of benzo[*b*]thiophenes at room temperature

In a subsequent study in 2018, the Larrosa group demonstrated the α-arylation of benzo[*b*]thiophenes at room temperature (Scheme 12).[42] The reaction provides an unprecedented approach for the α-arylation of thiophenes based on the α/β-regioselectivity switch noted in their previous study. This switch in the regioselectivity results 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 a CMD pathway instead of the Pd(II) species as noted in their previous β-arylation study of thiophenes.[41] 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, which usually suffer from chemoselectivity issues under harsh conditions. Notably, the groups of Sanford[43] and Hartwig[44] had previously described the role of Ag(I) salts in the arylation of perfluorobenzene in 2017 and the selective allylation of aryl C–H bonds in 2016, respectively.



Scheme 12 Ag(I)-mediated C–H activation for the α-arylation of benzothiophenes

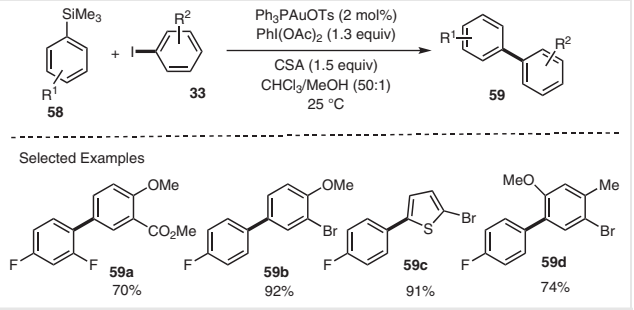
The Luscombe group recently succeeded in developing a robust methodology for the α-arylation of benzofurans, another important heteroaryl scaffold (Scheme 13).[45] Though the reaction conditions were very similar to the indole arylation method developed by the Larrosa group,[30] except for the use of 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 investigations under dark conditions, deuterium scrambling, and KIE studies. Many functional groups such as OH, NHAc, CHO, and halogens were well tolerated.



Scheme 13 α-Arylation of benzofurans at room temperature via a Heck-type pathway

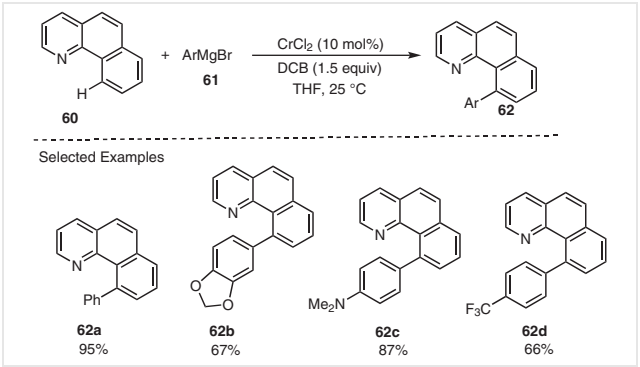
2.1.2 Other Metal-Based Procedures

While much 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, Lloyd-Jones, Russell and Ball reported a seminal method for gold-catalyzed C–H bond activation for biaryl synthesis at room temperature.[46] The method uses $(Ph_3P)AuOTs$ as a precatalyst, and $PhI(OCSA)_2$ as an oxidant, generated in situ from iodobenzene diacetate $[PhI(OAc)_2]$ and camphorsulfonic 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 the aryl silane and facilitating the C–Si transmetalation. The method takes advantage of the C–Si bond activation mode due to the high reactivity and chemoselectivity of aryl silanes as both the C–H and C–Si bond activation by Au(III) occurred through an 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.



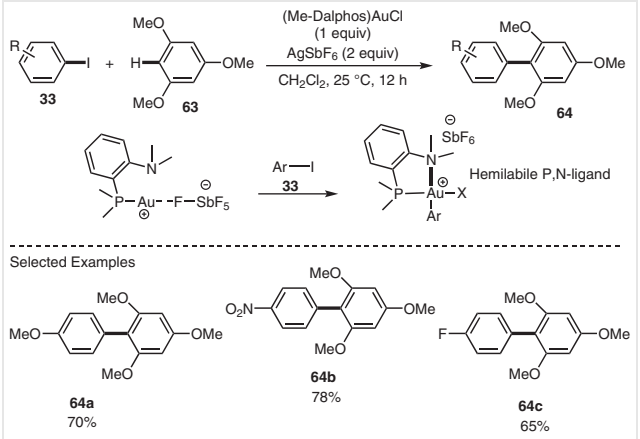
Scheme 14 Gold-catalyzed direct arylation of aryl silanes with aryl iodides

An interesting example describing the use of a Cr(II) catalyst in combination with 3-dichlorobutane(DCB) as an oxidant for the smooth arylation of N-heterocycles with a Grignard reagent at room temperature was reported by Knochel and Kuzmina (Scheme 15).[47] The reaction proceeded rapidly at room temperature without the need for any additional ligand. The scope of this transformation is broad with good compatibility toward a series of N-heterocycles including benzo[*h*]quinoline, 2-arylpyridine, aryl oxazolines 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.



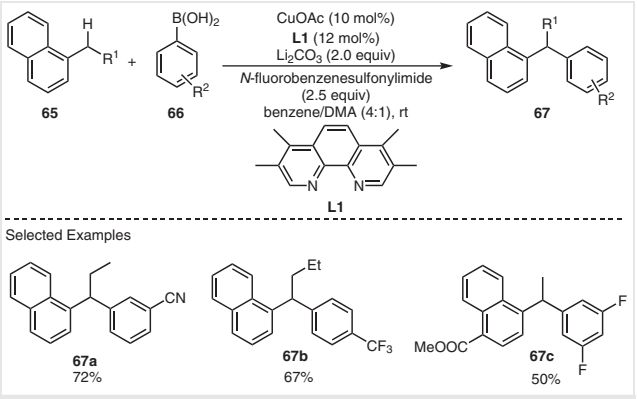
Scheme 15 Cr(II)-catalyzed arylation of N-heterocycles

In 2017, Amgoune and Bourissou's group developed an Au(I)/Au(III) catalytic cycle, which enabled the direct arylation of arenes with aryl halides at room temperature (Scheme 16).[48] Their design strategy was based on employing the simple *P,N*-bidentate ligand Me-DalPhos to control the stability and further reactivity of the 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-coordinated Au(III). The scope of the method is broad, with efficient coupling of arenes with a variety of aryl halides and bromides. Notably, the counter anion also demonstrated a significant influence on the reaction rate. For instance, oxidative addition of the aryl iodide occurred spontaneously with SbF_6^- compared with NTf^{2-}. Considering the reluctance of Au(I) toward oxidative addition, this 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.



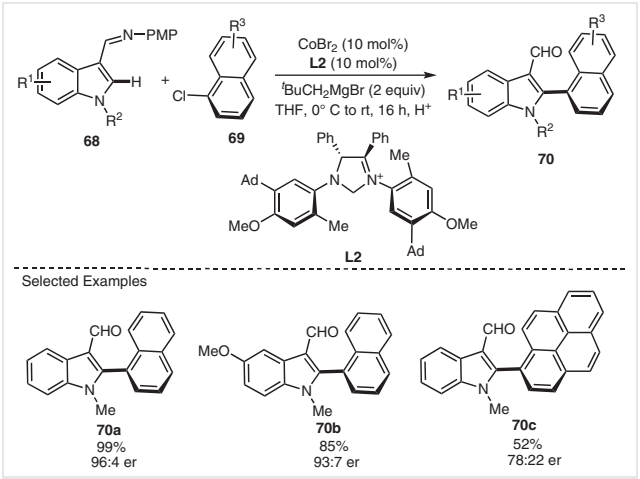
Scheme 16 Gold-catalyzed arylation of arenes

In 2017, the Liu group developed a novel copper-catalyzed method for the arylation of alkyl arenes at room temperature (Scheme 17).[49] Considering the difficulty associated with asymmetric sp^3 C–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 a radical relay process. Though detailed mechanistic studies were not carried out, the authors explained that benzylic radicals, generated by sp^3 C–H bond oxidation by the metal catalyst via a hydrogen atom abstraction process involving the alkyl arenes, could be captured by an 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 a cobalt(II)-catalyzed direct enantioselective C–H arylation at room temperature (Scheme 18).[50] The reaction uses $CoCl_2$ as the precatalyst, tertiary butylmethylmagnesium bromide as the base for in situ generation of a catalytically active Co(I) species, and N-heterocyclic carbene precursors as chiral inductors. Considering the high reactivity of the Co(I) species toward C–H metalation, reactions catalyzed by cobalt usually occur at lower temperature providing a new perspective to asymmetric atroposelective direct C-H functionalization. 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, the catalytically active Co(I) species generated by the base reacts with the imine moiety, which undergoes the C–H metalation (fast) in the next step forming a metallacycle intermediate. The next step involves the oxidative addition of the 1-chloronaphthalene to the metallacycle to afford a Co(III) intermediate, which undergoes reductive elimination and ligand exchange to afford the final enantiopure product.



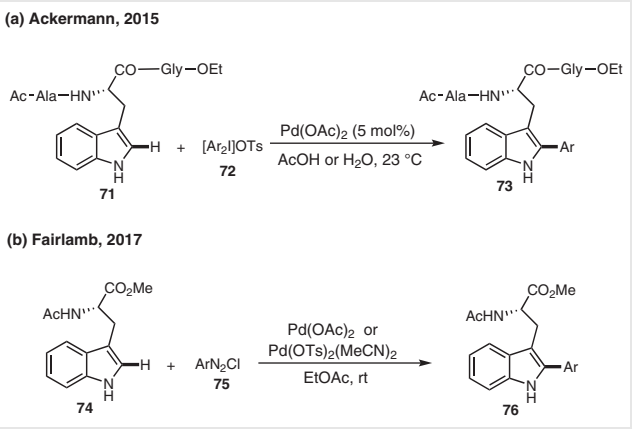
Scheme 18 Cobalt-catalyzed atropoenantioselective arylation of indoles

2.1.3 Additive-Free Procedures

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 an oxidant and a 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).[51] 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 the 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.

In the same year, a similar study describing the Pd-catalyzed C-2 arylation of tryptophan derivatives with presynthesized diaryliodonium salts under ambient conditions was reported by the Fairlamb group.[52] 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

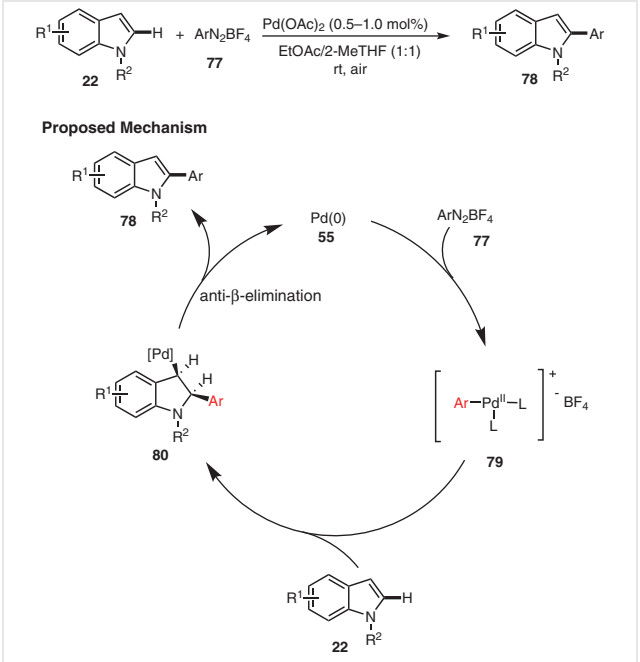


Scheme 19 Additive-free direct C–H arylations of tryptophan derivatives at room temperature

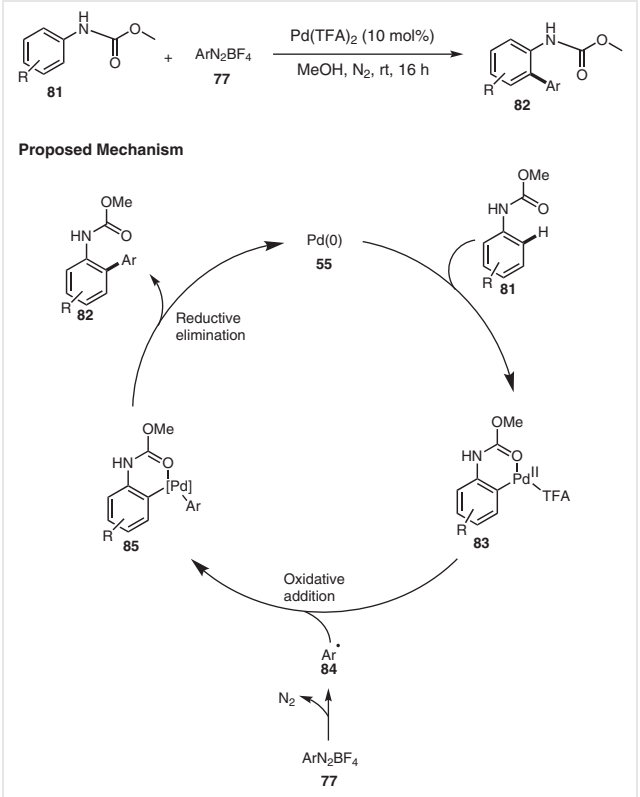
aryldiazonium salts instead of diaryliodonium salts, considering the structural similarity and reactivity (Scheme 19b).[53] Since the aryldiazonium salt undergoes oxidative addition with Pd rapidly without any base, the protocol provides a clean and mild method for arylating tryptophan and tryptophan peptides. It is worth mentioning that the arylation rate was enhanced when a catalytic amount of either tosic acid (TsOH) or $Pd(OTs)_2(MeCN)_2$ was 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 were obtained resulting from nucleophilic attack of the C-2 arylated indole on the electron-poor aryldiazonium salts, as also noted by Correia and co-workers.[54]

Early in 2017, Noël and co-workers reported the base-free arylation of heteroarenes using aryldiazonium salts at room temperature under aerobic conditions (Scheme 20).[55] The reaction proceeds under mild conditions in an open flask with broad substrate scope, green solvents (EtOAc/2-MeTHF or MeOH), and in a short reaction time, whilst demonstrating good tolerance to the functional groups. In this method, the author used an equimolar amount or a slight excess of the diazonium salt as the arylating agent and low Pd loadings (0.5 to 2 mol%). The protocol was shown to be highly selective with coupling at C-2 for indoles and benzofurans, while at C-3 in the case of benzothiophenes. The transformation was proposed to follow the Heck–Matsuda-type mechanism via a Pd(0)/Pd(II) catalytic cycle.

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.[56] 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-



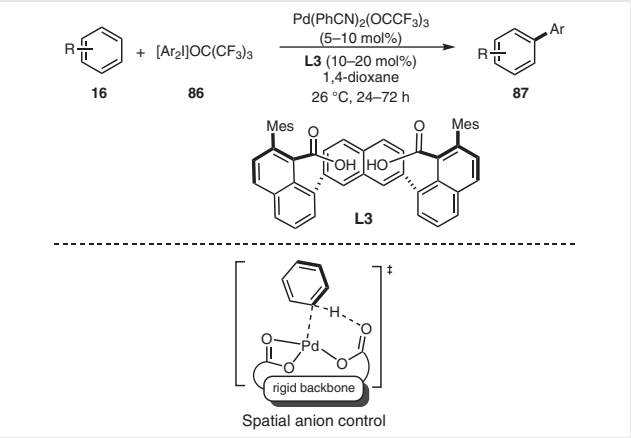
Scheme 20 Base-free direct C–H arylation of indoles



Scheme 21 Additive-free direct arylation of arylcarbamates

D. The reaction proceeds via directing-group-assisted electrophilic metalation at the *ortho*-position thereby generating palladacycle intermediate **83**, which reacts with the aryldiazonium salt through oxidative addition followed by reductive elimination to furnish the desired product **82**. 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.

In 2020, the Čorić 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).[57] 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 the O–P–O angles and Pd–O distances, the geometry of the 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 a constrained anion on the key CMD step, the lower catalyst strain in the transition state than in the geometrically relaxed state in the case of a bis(carboxylate) anion is accountable for reducing the overall electronic energy compared to a mononuclear Pd(II) catalyst. The mild reaction conditions, wide substrate scope, and late-stage functionalization reflect the robustness of this method.

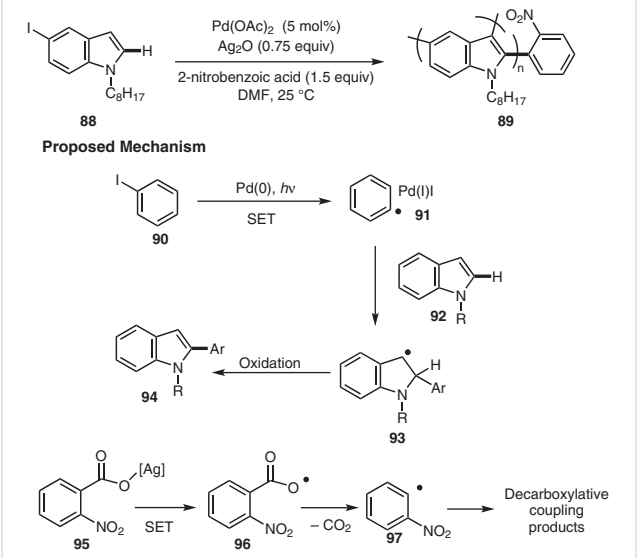


Scheme 22 Spatial anion control for directing-group/additive-free arylation of arenes

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 constitute active components of next-generation electronic devices including organic photovoltaics, organic field-effect transistors, sensors, and electrochromic devices, etc.[58] Indeed, a vast library of conjugated polymers prepared by direct heteroarylation polymerization (DArP) can be found in the literature, with properties comparable to those of conventional polymerization methods.[59]

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 2020, the Luscombe group successfully demonstrated the polymerization of indole at room temperature[60] by adapting the protocol developed by the Larrosa group for small-molecule synthesis[30] at room temperature. The authors observed that the resulting polymer is highly branched due to the incorporation of a nitrobenzene unit along with the β-branching (Scheme 23). This observation ruled out the CMD pathway adopted by indole small molecule arylation reaction. A series of control experiments provided supportive evidence for a radical-mediated pathway. As shown in Scheme 23, the catalytic cycle commences with a single-electron transfer (SET) process between the Pd catalyst and aryl iodide **90**, generating aryl radical **91**, which is then trapped by indole **92** to afford the observed product **94**. While the incorporation of nitrophenyl into the polymer chain could be explained by the transformation of metal benzoate **95** into an aryl radical by single-electron activation.[61] Though room temperature DArP is underdeveloped, milder reaction conditions hold great potential for industrial-scale syntheses of conjugated polymers.



Scheme 23 DArP of indole derivatives at room temperature

2.3 Photocatalyzed Procedures

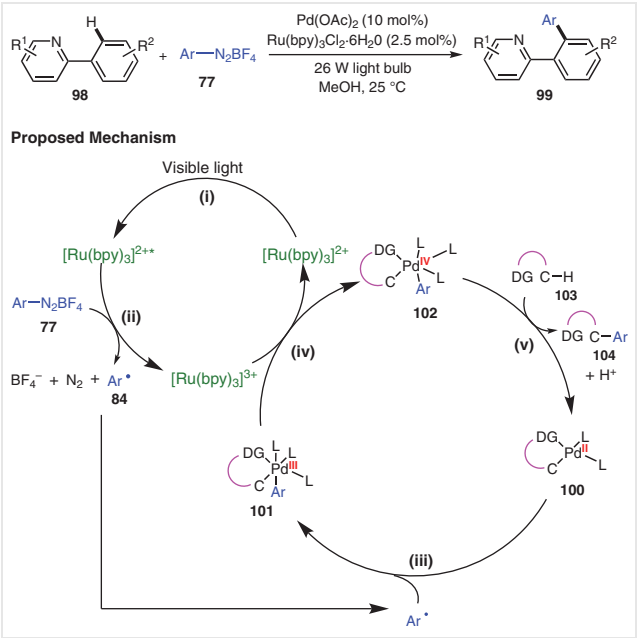
Photocatalyzed reactions have been generally known to the synthetic community for many years for aryl–aryl coupling. The C–C bond formation through photoredox catalysis is classically achieved by the SET pathway involving aryl radicals or ionic intermediates providing a good alternative

to classical cross-coupling reactions.[62] Such methods involve the use of photoredox chemistry to generate aryl radicals via a SET process, that undergo either transmetalation[63,64] or single-electron oxidative addition, representing a different process to typical cross-coupling reactions.[64,65] The high reactivity of aryl radicals 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 Procedures

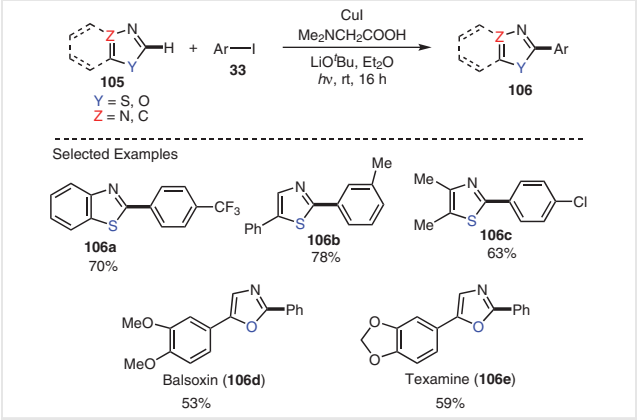
An exciting development in recent times involved merging photocatalysis and traditional C–H bond activation to achieve coupling under milder reaction conditions with efficient selectivity control and broad functional group tolerance. These approaches are lucrative as C–C coupling can be achieved without any external additive and with a smaller quantity of catalyst. Typically, the palladacycle formed by C–H bond activation could react with an aryl radical generated through a SET process via photoredox catalysis at room temperature. The concept was first introduced by Sanford's 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).[66] The method uses $Pd(OAc)_2$, $Ru(bpy)_3Cl_2{\cdot}6H_2O$ as a photocatalyst, and a visible photo source, demonstrating good compatibility with a wide variety of substrates having substituents such as halogens, amides, 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 side products, fulfills the objective of more sustainable chemistry. The proposed mechanistic path involves the reaction of aryl radical species **84**, generated from the reduction of aryldiazonium salts **77** by photoexcited $[Ru(bpy)_3]^{2+*}$, with palladacycle **100** to give Pd^{III} intermediate **101**. Subsequent one-electron oxidation of the Pd^{III} intermediate **101** by $[Ru(bpy)_3]^{3+}$ forms Pd^{IV} complex **102** and reductive elimination then furnishes the arylated product **104**. The authors further expanded the scope of their study to include diaryliodonium salts as the source of the aryl radical species.[65] Arylation was performed using a Pd/Ir dual catalytic system and a 26 W visible light source at room temperature.[67]

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 photocatalyst or directing groups (Scheme 25).[68] A combination of CuI and Et_2O as the solvent was effective in this arylation process, albeit a higher catalyst loading was needed for good yields. Notably, amino acids as the ligand showed rate acceleration,



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

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 non-aromatic heterocycles, this approach offers a convenient synthesis of the naturally occurring alkaloids balsoxin and texamine at room temperature.



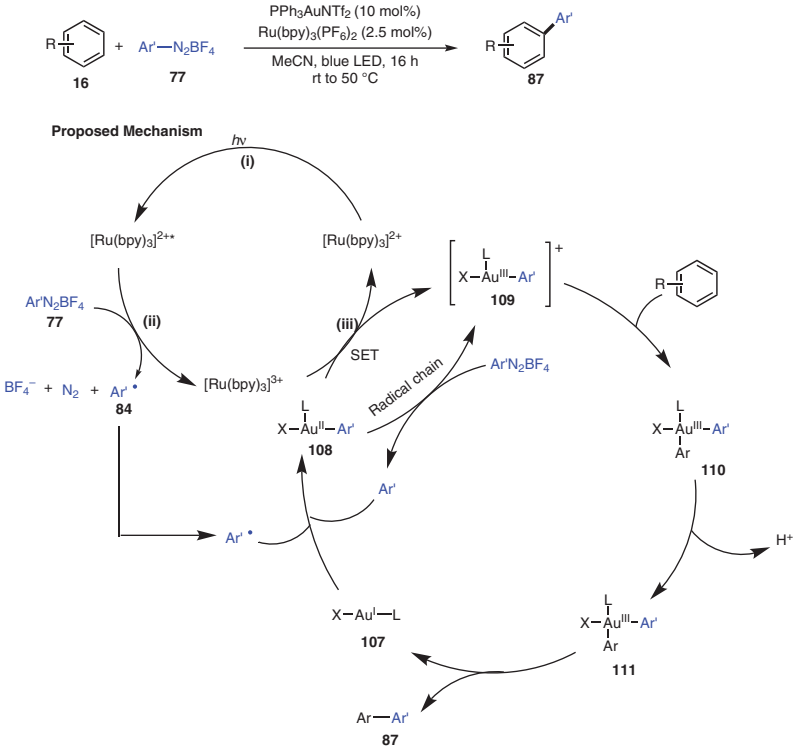
Scheme 25 Photoinduced Cu(I)-catalyzed direct arylation of heteroarenes

In 2017, Lee and co-workers reported the first dual Au/Ru-photocatalyzed arylation of arenes without additives.[69] 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 was regioselectively arylated with aryldiazonium salts under blue light at room tem-

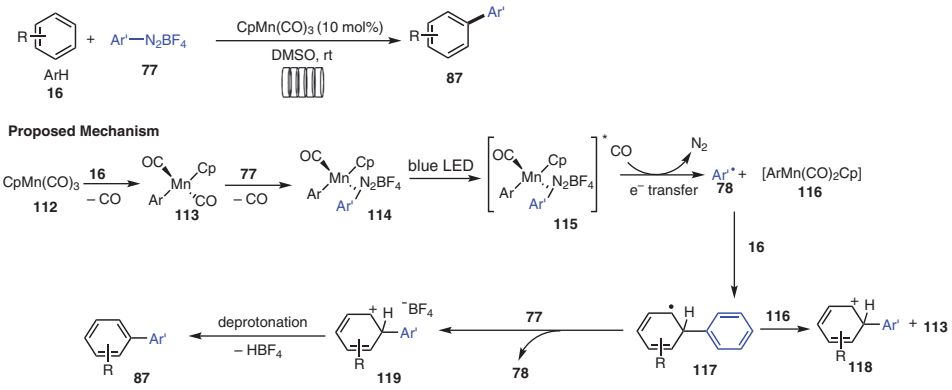
perature in good yields. Though Eosin and fluorescein dyes were also employed, providing a greener alternative to $Ru(bpy)_3(PF_6)_2$, the authors opted for the better performing Ru catalyst for further studies. Based on mechanistic studies, the authors proposed a SET process distinct from the conventional 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 suffered 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/photoredox-catalyzed arylation of 6-arylpurine nucleosides was reported by Guo and co-workers in 2017.[70] In the same year, Balaraman and co-workers developed a protocol for the dual Pd/Ru-catalyzed arylation of anilides without any external additive in dimethyl carbonate as a green solvent.[71]

In 2018, Ackermann's group reported a manganese-catalyzed photoflow arylation strategy utilizing heteroarenes (Scheme 27).[72] The reaction required $CpMn(CO)_3$ as the catalyst in combination with blue LEDs to achieve C–H activation at room temperature, with aryl radical formation being indicated from control experiment studies. Aprotic solvents were needed for optimal results with the best yield being obtained in DMSO. The reaction tolerated a wide variety of functional groups including fluoro, chloro, ester and nitro, and demonstrated good regioselectivity with respect to the heteroarenes. In addition, the reaction could be run on gram scale, as demonstrated by the higher yield (65%) obtained in the flow process as compared to the batch setup (25%), thereby indicating its synthetic potential. The mechanistic studies proposed by the authors indicate the formation of Mn species **113** by ligand exchange between the arene and $CpMn(CO)_3$, followed by the formation of complex **114**. In the next step, the aryl radical species **78**, generated from photoexcitation and electron transfer of complex **114**, reacts with arene **16** to form intermediate **117**. Subsequent oxidation and deprotonation affords the desired product **87**.

In 2017, Ravelli and co-workers demonstrated an intriguing method for sp^3 C–H arylation (Scheme 28).[73] The authors achieved sp^3 C–H arylation of heteroarenes at room temperature using tetrabutylammonium decatungstate (TBADT) as an efficient and robust photocatalyst. The use of TBADT promoted radical formation by hydrogen abstraction from sp^3 C–H bonds via the Minisci reaction, enabling aromatic homolytic substitution of heterocycles under mild conditions. A wide range of heterocycles was smoothly alkylated with a series of hydrogen donor substrates, including ethers, amides, aldehydes, cycloalkanes, and cycloalkanones. As depicted in Scheme 28, the reaction commences with homolytic cleavage of an sp^3 C–H bond of the alkane

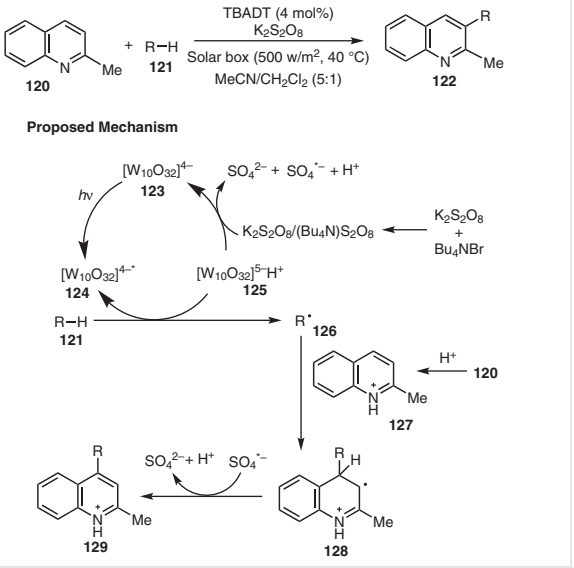


Scheme 26 Dual Au/Ru-photocatalyzed arylation of arenes



Scheme 27 Manganese-catalyzed continuous photoflow arylation of arenes

by excited TBADT 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 the strong oxidant $SO_4^{\bullet-}$, formed from persulfate by either thermal or photochemical cleavage, produces the final alkylated product.



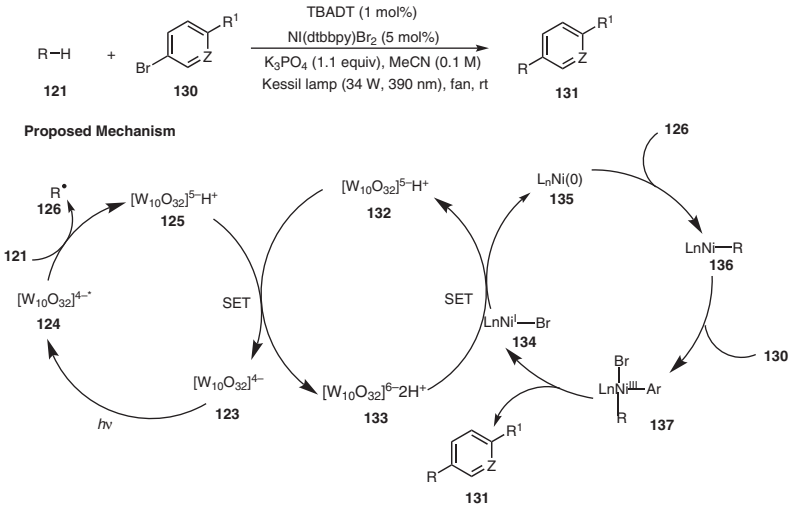
Scheme 28 TBADT-catalyzed photoarylation of an isoquinoline

A year later, Macmillan and co-workers achieved sp^3 C–H arylation at room temperature by merging photoredox-mediated hydrogen atom transfer and transition-metal catalysis.[74] The authors used TBADT as the co-catalyst for generating carbon radicals from electron-rich, sterically accessible sp^3 C–H bonds, which act as the nucleophile in nickel-catalyzed cross-coupling with aryl bromides (Scheme 29). Among various high-energy polyoxometalates, they preferred the decatungstate anion $[(W_{10}O_{32})]^{4-}$ as the hydrogen atom transfer (HAT) photocatalyst for C–H abstraction because of its successful application in various oxygenations, dehydrogenations, conjugate additions, and fluorinations. By using the 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.

In 2020, the Ackermann group demonstrated a mild Ru-photoinduced catalysis method for the arylation of 2-arylazines at room temperature (Scheme 30).[75] The substrate scope was broad, including pyrazoles, triazoles, sensitive nucleotides, and nucleosides, demonstrating the synthetic utility of this approach. Based on experimental and DFT studies, the authors proposed that the catalytic cycle commenced by carboxylate-assisted C–H ruthenation followed by dissociation of *p*-cymene to generate the photoactive biscyclometalated complex **140**. Complex **140** coordinates with the iodoarene to form the ruthenacycle complex **141** that takes part in the inner-sphere electron-transfer process producing an 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.[76]

2.3.2 Radical Addition-Based Procedures

In radical-addition-based photoredox catalysis, aryl radicals formed via a SET process can be trapped by an arene. The resulting radical species undergo SET and deprotonation to afford the desired product. Both organic photocatalysts and inorganic transition-metal complexes can be utilized in the photoinduced SET process to produce the aryl radical.



Scheme 29 Dual HAT and Ni catalysis for sp^3 C–H activation

2.3.2.1 Transition-Metal Catalysis

In 2013, Chatani and co-workers demonstrated white-light-promoted arylation of heteroarenes using diaryliodonium salts as the coupling partners (Scheme 31).[77] Interestingly, the arylation of pyrrole proceeded without $[Ir(ppy)_2(bpy)]PF_6$ while the reaction with benzene and other heteroarenes required a photocatalyst, indicating two different pathways even though the aryl radical is generated by photoinduced SET in both cases. The authors reasoned the formation of a charge-transfer complex on photoirradiation promoting C-2 arylation of pyrrole.

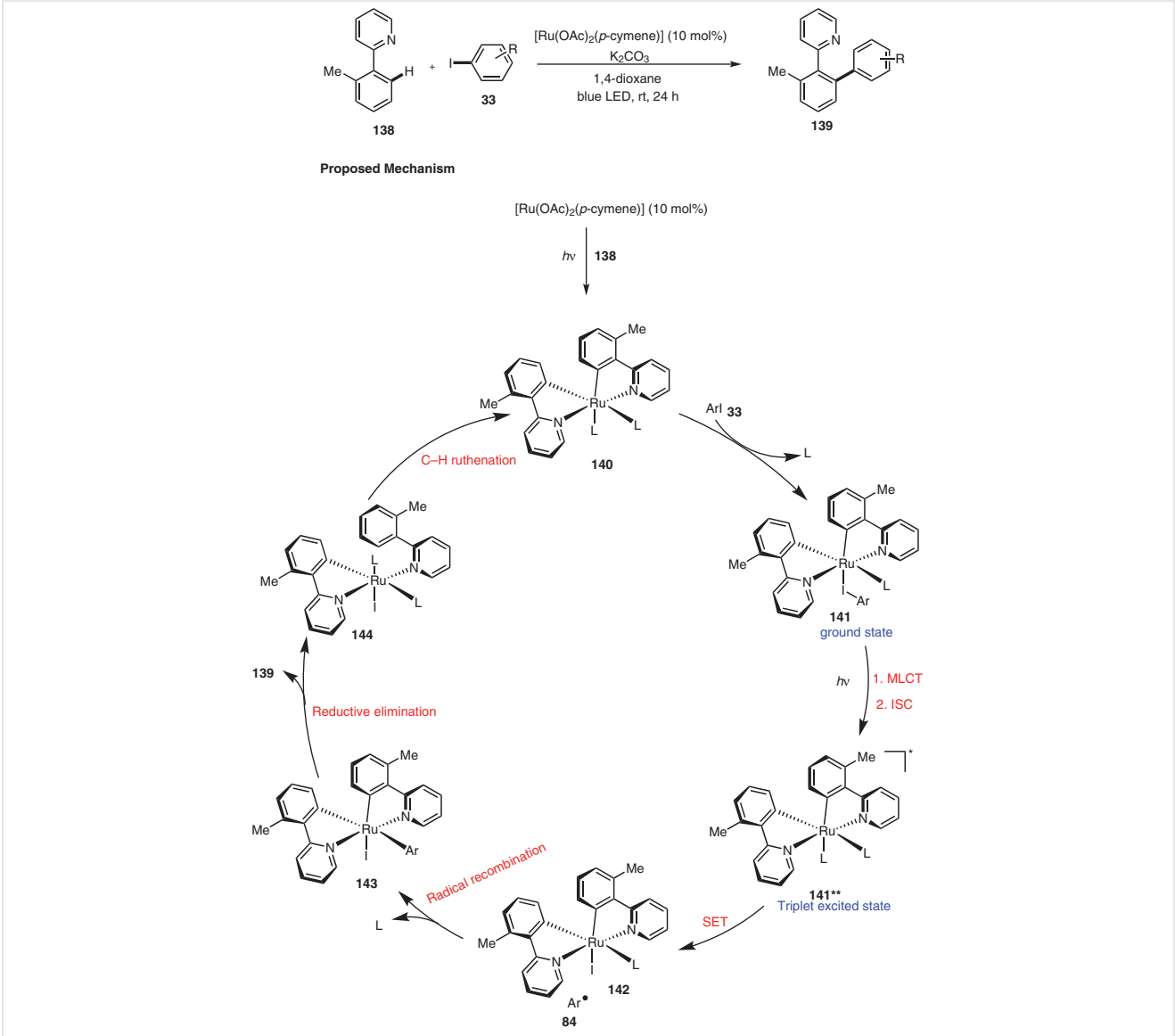
A year later, Xue and co-workers demonstrated a photocatalyzed arylation of electron-deficient arenes in water at room temperature.[78] This protocol uses $[Ru(bpy)_3]Cl_2{\cdot}6H_2O$ as a photosensitizer and a commercial household light bulb as the photon source (Scheme 32). While C4-substituted pyridines afforded monosubstituted products (C2), a mixture of regioisomers was obtained in the case of C2 or C3 derivatives. The authors showed that the method was also effective for xanthenes, thiazole, pyrazine, and pyridazine when aqueous formic acid was used as the solvent. As depicted in Scheme 32, photoreduction of the aryldiazonium salt produces an aryl radical, which is trapped by pyridine hydrochloride to give another radical species. Subsequent formation of a 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 the aryldiazonium salt. Following this work, Lei's group arylated isoquinolines by using TFA for protonating the heterocycle instead of using pyridinium salts as substrates.[79]

Owing to their biocompatibility, stability, and commercial availability, arylsulfonium chlorides serve as attractive precursors to aryl radicals over aryldiazonium and diaryliodonium salts. In 2016, Bhasin and co-workers developed a cheaper and environmentally advantageous protocol for employing arylsulfonium salts (Scheme 33).[80] Heteroarenes, including pyrrole, furan, and thiophene derivatives, were arylated with arylsulfonyl chlorides in the presence of the photocatalyst $Ru(bpy)_3Cl_2$ to afford 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.

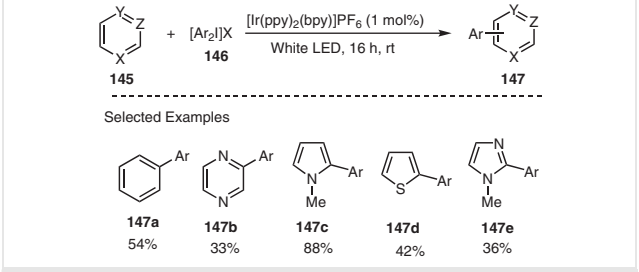
The direct transformations of C–H bonds to C–C bonds avoiding any prefunctionalization, known as cross-dehydrogenative coupling (CDC), is highly desirable for constructing biaryls. In this regard, Xia and co-workers demonstrated the use of an Ir(III)/visible light catalytic system for dehydrogenative coupling of anilines and or phenols (Scheme 34).[81] 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, $K_2S_2O_8$, $Na_2S_2O_8$, and Selectfluor led to decreased product yields in comparison to $(NH_4)_2S_2O_8$. A good tolerance to a wide variety of aniline and phenol derivatives for coupling of asymmetric atropisomeric biaryls reflects the usefulness of this method.

2.3.2.2 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.[82] Their work entailed arylating heteroarenes with diazonium

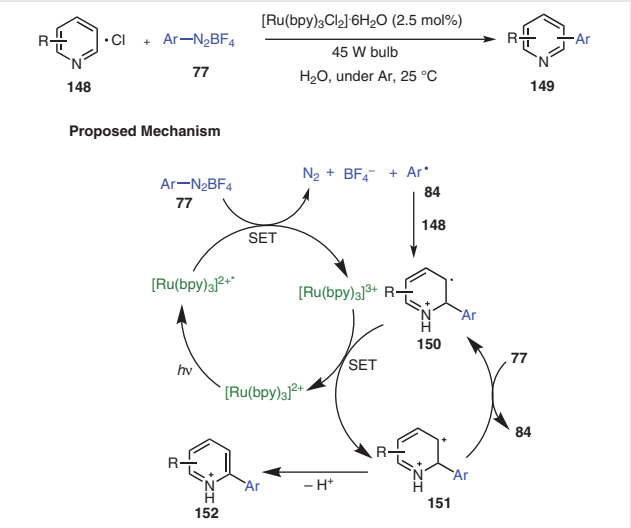


Scheme 30 Ru-catalyzed direct arylation of 2-arylazines

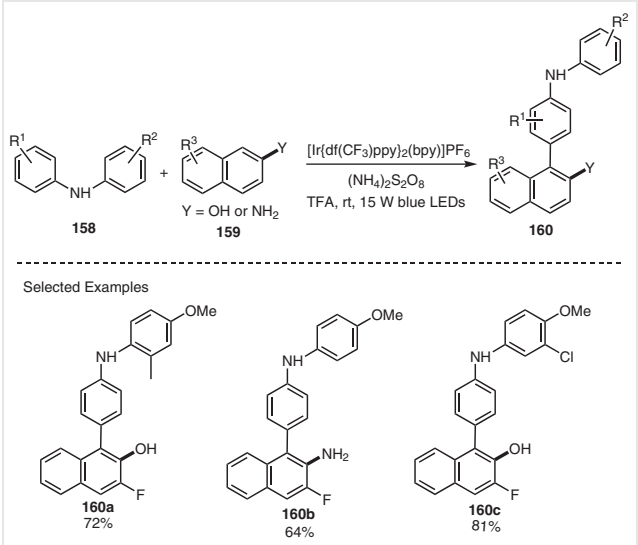


Scheme 31 Ir(III)-catalyzed arylation of arenes and heteroarenes with diaryliodonium salts

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 aryl radical formation by SET from Eosin Y to the aryl diazonium salt, followed by its addition to the 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.



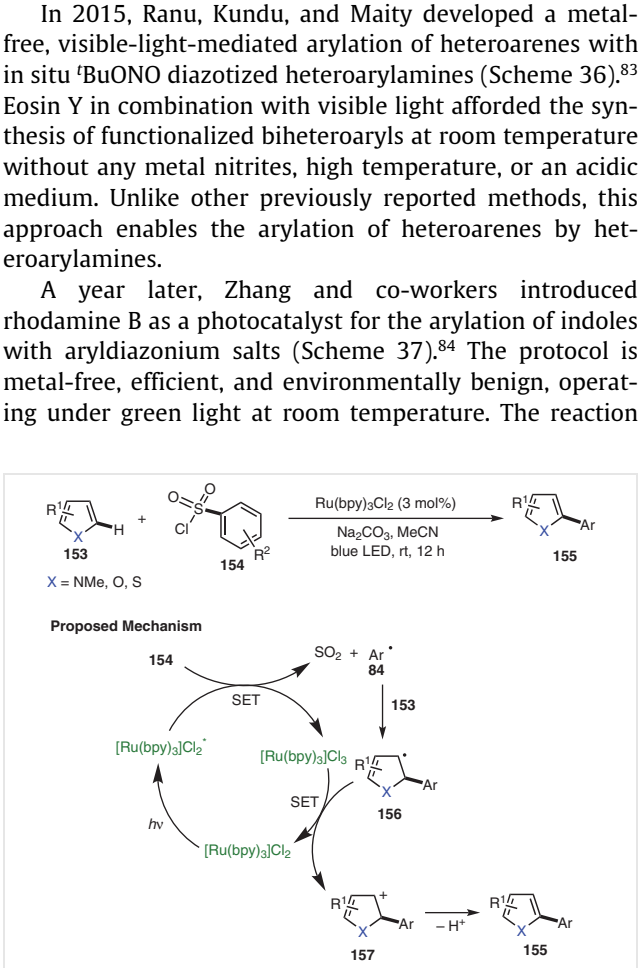
Scheme 32 Photoredox-catalyzed arylation of pyridines in water



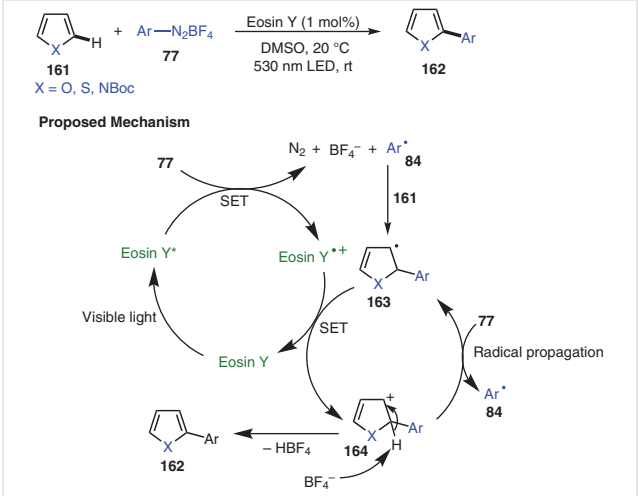
Scheme 34 Ir(III)-catalyzed photoredox cross-dehydrogenative coupling of heteroarenes

In 2015, Ranu, Kundu, and Maity developed a metal-free, visible-light-mediated arylation of heteroarenes with in situ ^{t}BuONO diazotized heteroarylamines (Scheme 36).[83] Eosin Y in combination with visible light afforded the synthesis of functionalized biheteroaryls at room temperature without any metal nitrites, high temperature, or an acidic medium. Unlike other previously reported methods, this approach enables the arylation of heteroarenes by heteroarylamines.

A year later, Zhang and co-workers introduced rhodamine B as a photocatalyst for the arylation of indoles with aryldiazonium salts (Scheme 37).[84] The protocol is metal-free, efficient, and environmentally benign, operating under green light at room temperature. The reaction



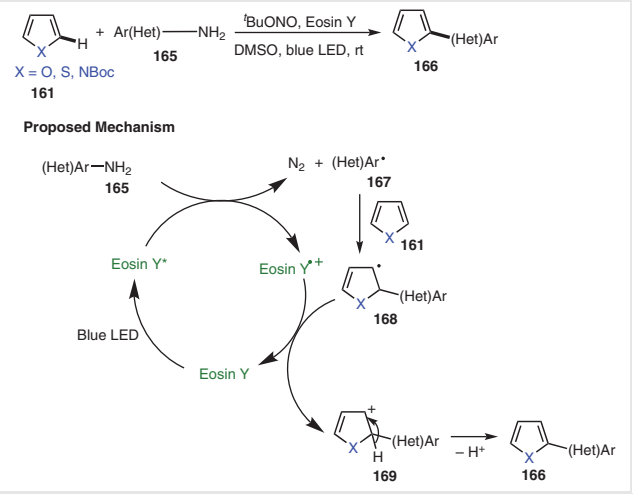
Scheme 33 Ru-photocatalyzed direct C–H arylation of heteroarenes with arylsulfonyl chlorides



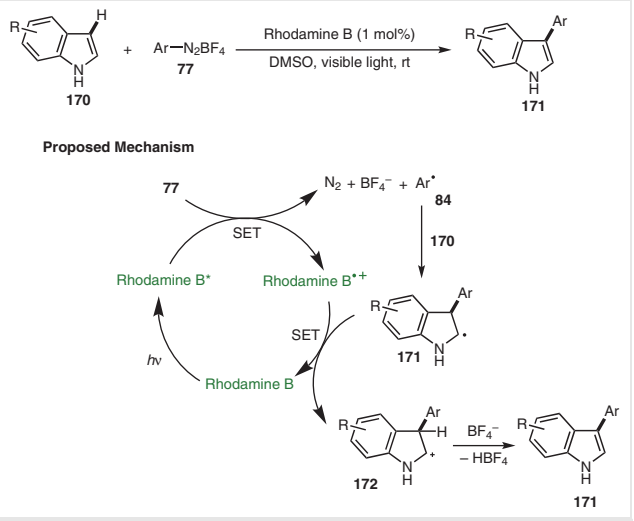
Scheme 35 Direct arylation of heteroarenes catalyzed by Eosin Y

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 those with electron-accepting groups.

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.[85] 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



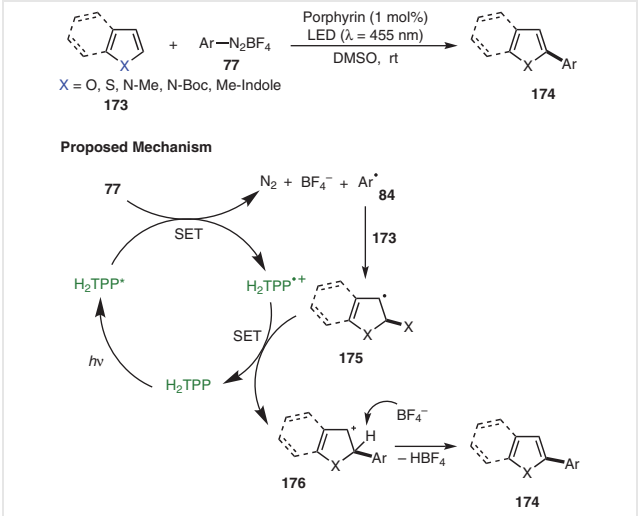
Scheme 36 Arylation of heteroarylamines catalyzed by Eosin Y



Scheme 37 Arylation of indoles mediated by rhodamine B

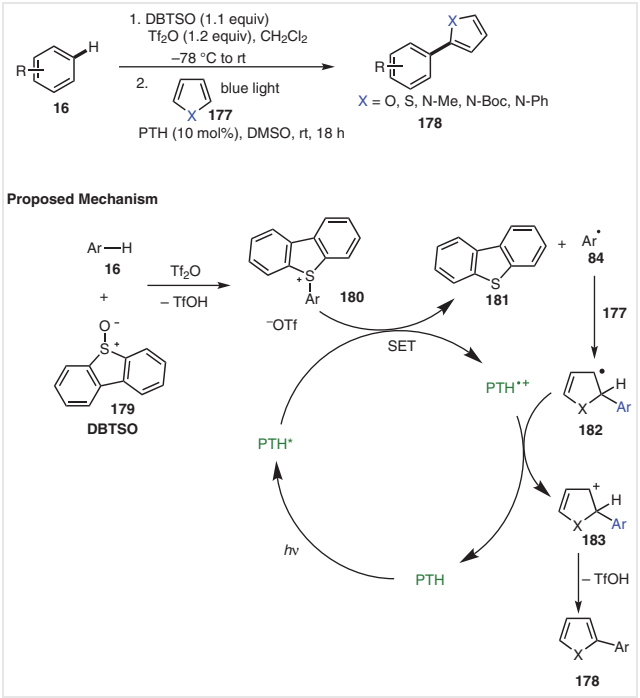
($H_2T(F_5P)P$). As depicted in Scheme 38, the reaction follows a radical path. In the first step, the photoexcited porphyrin reduces the aryldiazonium salt to an aryl radical while forming a cation radical. The highly reactive aryl radical subsequently reacts with the heteroarene to form another radical. Oxidation of this radical intermediate by the porphyrin cation radical followed by proton elimination furnishes the desired arylated product.

In the same year, Feng, Xu, and co-workers employed a 9,10-dihydro-10-methylacridine ($AcrH_2$) coenzyme model compound as a photocatalyst for the cross-coupling of heteroarenes.[86] 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 the one-pot coupling of non-pre-



Scheme 38 Porphyrin-catalyzed photoredox direct arylation of heteroarenes

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).[87] Besides the high reactivity and selectivity ensured by DBTSO during sulfenylation and aryl radical formation, the easy recovery and regeneration of the dibenzothiophene as a byproduct render it an attractive media-



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

tor. This 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 hydroxy- and amino-substituted substrates. As depicted in Scheme 39, mechanistically, the process begins with interrupted Pummerer activation of the arene to generate an aryldibenzothiophenium salt (Ar-DBT$^+$), which is reduced by photoexcited PTH to give an aryl radical along with the expulsion of dibenzothiophene.[87] This highly reactive radical species couples with the heteroarene to form another radical intermediate. Single-electron oxidation of intermediate **181** by the phenothiazine cation radical, followed by deprotonation, yields the arylated product. The success of this method with the arylation of complex biologically important products, including boscalid, fenofibrate, clofibrate, salicin pentaacetate, and *N*-acetylmexiletine, demonstrates its potential utility for natural product diversification.

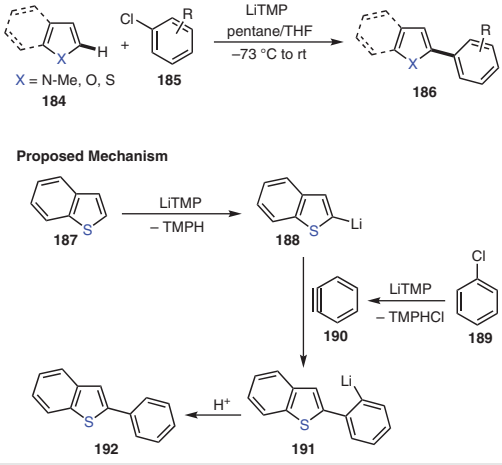
2.4 Transition-Metal-Free Procedures

Despite the many benefits of direct arylation reactions, expensive transition-metal catalysts and supporting ligands represent significant limitations of this approach. Furthermore, considering their toxicity, removing the trace amount of metal residues from the 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 over the years[88] 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 Procedures

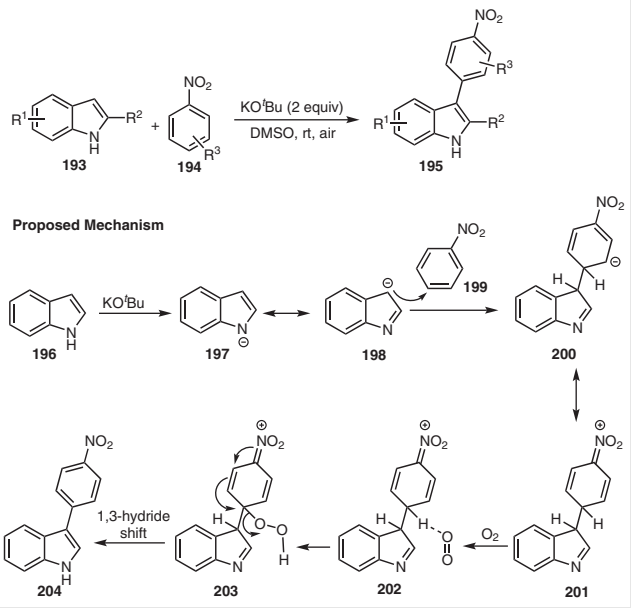
In a seminal study from 2008, Itami and co-workers reported the potassium *tert*-butoxide (KO^{t}Bu) catalyzed transition-metal-free C–C coupling between N-heterocycles and aryl iodides at 50 °C under microwave irradiation.[89] Though this early report set the stage for the development of base-promoted transition-metal-free reactions, the need for a large excess of the C–H coupling partner (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 Truong in 2011 (Scheme 40).[90] The reaction of electron-rich and electron-poor arenes with aryl halides mediated by lithium 2,2,6,6-tetramethylpiperidine (LiTMP) in THF or THF/pentane mixture provided the desired arylated products in good to excellent yields at room temperature. In this case, functionalization was achieved at the most active C–H bond with less than ~2.5 equivalents of the aryl coupling partner and one equivalent of the arene. 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 the direct C–H arylation of heteroarenes with aryl chlorides and aryl triflates as the coupling partners, with modest yields being obtained. 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_2O to LiTMP to obtain the required product.[91] The reaction mechanism outlined in Scheme 40 involves the coupling between benzyne and an aryl anion to afford the desired product.



Scheme 40 LiTMP-mediated direct C–H arylation of heteroarenes[91]

In 2015, 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).[92] The reaction occurred via intermolecular oxidative coupling of indoles with nitroarenes under an atmosphere of air. The proposed mechanism outlined in Scheme 41 highlights the role of the free N–H group in the reaction. In the presence of KO^{t}Bu, abstraction of the free N–H transforms indole **196** into indole-1-ide **197**, which undergoes resonance to form the more stable intermediate indole-3-ide **198**. A subsequent nucleophilic attack of **198** on nitrobenzene generates intermediate **200** that on resonance forms **201**. In the next step, atmospheric O_2 interacts with the hydrogen of **201** leading to the formation of a hydroperoxide radical and intermediate **203**, which tautomerizes to give the desired product **204**. The scope of functionality is broad, including both electron-rich and electron-poor groups.



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

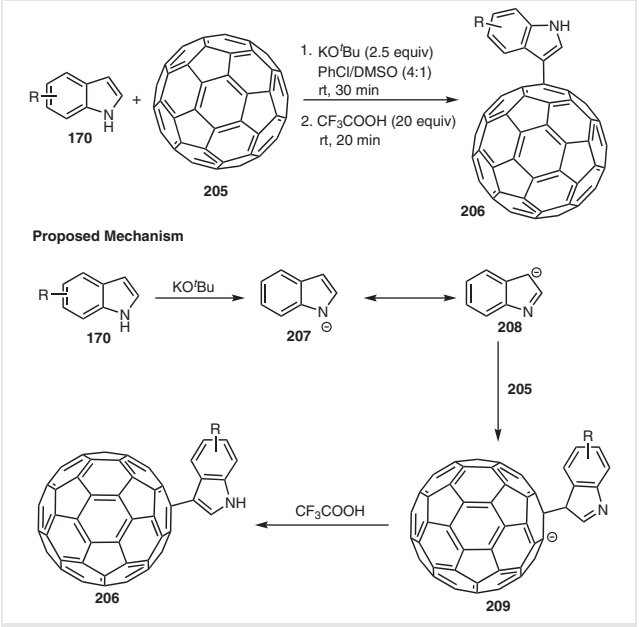
In the same year, Tian and co-workers aimed at synthesizing 1,2-(3-indole)(hydro)[60]fullerene derivatives via one-pot arylation of indoles and fullerene catalyzed by KO^{t}Bu (Scheme 42).[93] The reaction proceeds efficiently in a highly selective manner at room temperature giving C-3 arylated products. While the reaction could tolerate electron-withdrawing groups such as chloro, nitro, and ester on the benzene ring of the indole, electron-donating substituents such as OMe at the 5- or 7-positions 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 a methoxy-substituted indole derivative. Notably, the free N–H group in indole is crucial for a successful reaction as the coupling failed with N-substituted indoles, e.g., *N*-methylindole and *N*-Boc indole. Mechanistically, abstraction of the NH proton leads to the formation of indole-1-ide **207**, which undergoes resonance to form indol-3-ide **208**. The next step involves nucleophilic attack of **208** on C60 to form **209**, which on quenching with CF_3COOH gives the desired product. It is worth noting that poor reaction yields were obtained in air due to oxidation of intermediate **209**, while moisture in the air could quench the base.

2.4.2 Iodonium- and Diazonium-Salt-Based Procedures

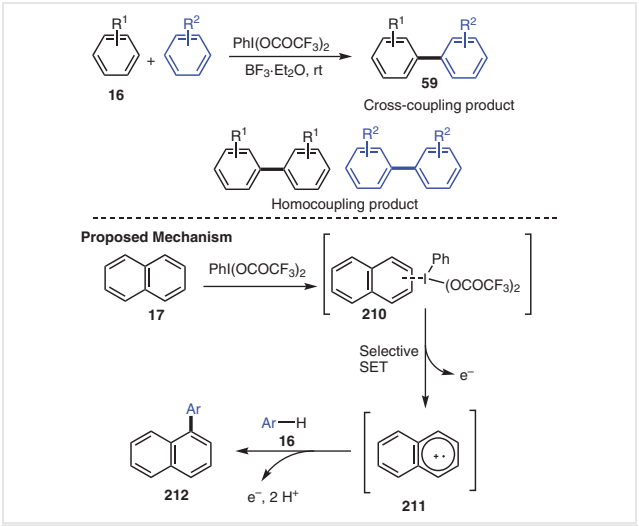
Another well-established solution to achieve transition-metal-free direct C–H arylation involves using diaryliodonium and aryldiazonium salts as the coupling partner. Examples involving iodonium salts are described first in this section.

A seminal development in the field of iodonium-salt-based direct arylation comes from the Kita's group. In 2008, Kita reported the first example of the hypervalent iodine(III) promoted metal-free cross-coupling of arenes with mesitylenes (Scheme 43).[94] The coupling is driven by SET oxidation of electron-rich arenes by the 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 $BF_3{\cdot}Et_2O$ 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 the homocoupling product, 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, a halogen functionality gave the best results as a directing group with excellent control of regioselectivity, while the presence of an electron-poor group changed the regioselectivity leading to the formation of another regioisomer along with the desired regioisomer signifying the resonance effect of the halogen in regioselective coupling.

In a 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.[95] α-Thienyliodonium salts were generated in situ from the reaction of thiophene derivatives, [hydroxy(tosyloxy)iodo]benzene (Koser's reagent), and HFIP (Scheme 44). Nota-

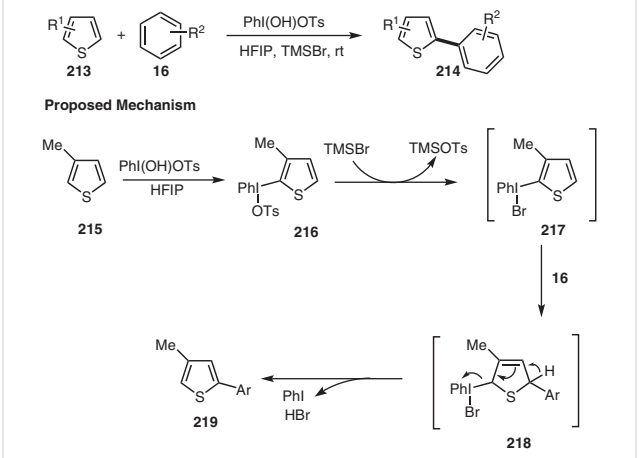


Scheme 42 KO^{t}Bu-mediated coupling of indoles with [60]fullerene



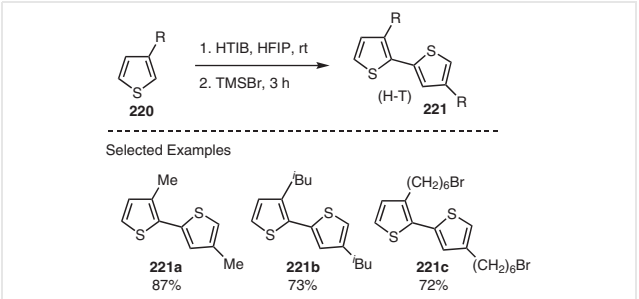
Scheme 43 Oxidative direct C–H arylation of arenes induced by iodine(III) salts

ble 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 and involves the initial formation of stable iodonium(III) tosylate salts upon selective reaction of the electron-rich heteroaromatic at the 2-position with Koser's reagent. The reaction proceeded rapidly in the presence of HFIP as the solvent. Being inert, the formed iodonium salt **216** was activated by adding TMSBr in HFIP to give iodonium bromide salts **217**, which underwent formal hydroarylation with the heteroarene to afford **218** followed by elimination of iodobenzene to provide the desired arylated product **219**.



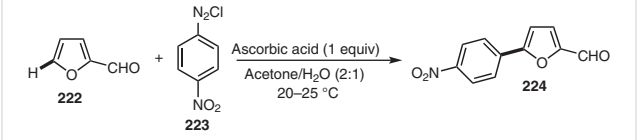
Scheme 44 Oxidative arylation of thiophenes

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 (H-T) linked thiophenes based on an iodonium-mediated strategy (Scheme 45).[96] 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 yields. This method provides a new approach for the synthesis of H-T oligothiophenes without using any transition metal.



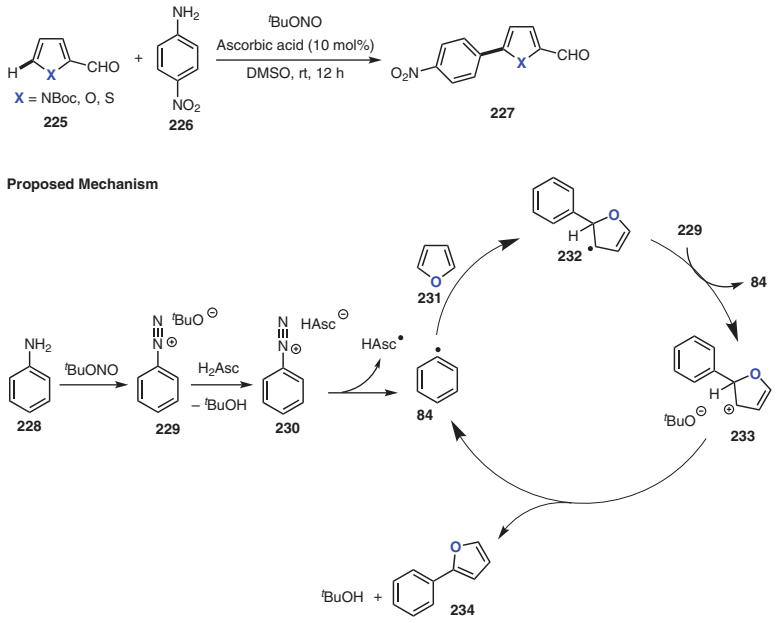
Scheme 45 Oxidative cross-coupling of 3-alkylthiophenes

The use of aryldiazonium salts as the coupling partner for the development of transition-metal-free direct C–H arylation was reported by Obushak and co-workers demonstrated in 2009.[97] In this case, ascorbic acid as a reducing agent generates an 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 (**224**).



Scheme 46 The transition-metal-free direct C–H arylation of furfural mediated by ascorbic acid

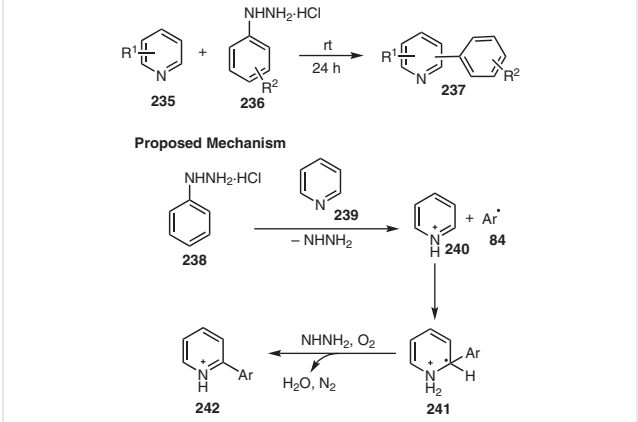
Five years later, Martin and Carrillo reported that by using in situ generated aryldiazonium salts due to their stability issues, metal-free arylation with heteroarenes could be achieved in good yield in the presence of ascorbic acid as the initiator.[98] Aryldiazonium salts were generated in situ from 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*-bu-



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

tyl 1*H*-pyrrole-2-carboxylate, and pyridine *N*-oxide. The mechanism proposed by the authors for the arylation of furan is highlighted in Scheme 47. In the first step, the in situ generated diazonium salt **229** is protonated by ascorbic acid and then reduced by SET from ascorbate via the inner-sphere mechanism to form diazo ether **230**. Diazo ether **230** undergoes homolytic rupture to produce nitrogen, aryl radical **84**, and an ascorbyl radical. The aryl radical **84** adds to the furan to yield radical intermediate **232**, which propagates the reaction by losing an electron to form radical cation **233**, and finally yields the desired product **234** after proton abstraction by the ^{t}BuO counterion. Meanwhile, the ascorbic acid generated from the dismutation of the ascorbyl radical can reduce another diazonium ion.

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).[99] The result was interesting because commercially available hydrazines were used, and the reaction was carried out in air. This approach worked well and arylpyridines were obtained in moderate to good yields. Though monomethyl-substituted pyridines were shown to be suitable substrates with arylhydrazines having electron-withdrawing and electron-rich groups at the *para* position, affording the desired arylated products in good yields and minimal regioselectivity, the reaction of 4-methoxyphenylhydrazine hydrochloride with 3,5-dimethylpyridine selectively yielded the desired C-2 arylated product. The method also gave moderate to good yields for the 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 the pyridine reacts with the protonated heteroarene 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 yields.



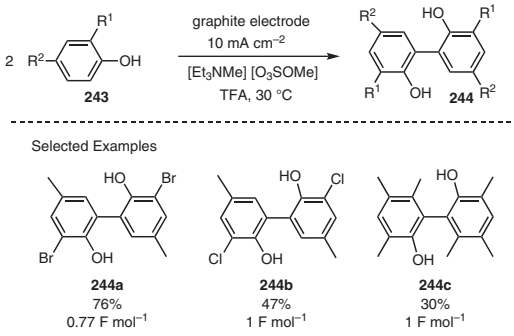
Scheme 48 Direct arylation of pyridines with arylhydrazine hydrochloride

2.6 Electrocatalyzed Procedures

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

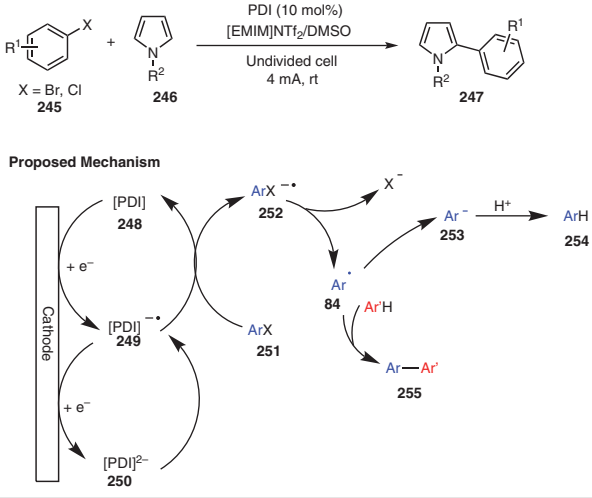
expensive stochiometric metal oxidants and iodine(III) salts, many studies have appeared for effective C–H activation. In particular, the extensive research performed by Waldvogel's group during the 2000s and 2010s has been instrumental in advancing the electricity-enabled aryl–aryl coupling. As the electrocatalyzed arylation has been extensively reviewed,[100,101] we discuss only selected examples herein.

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.[102] In this case, the *ortho*-selective coupling of phenols was efficiently achieved (up to 74% yield) with a 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).[103] The optimized conditions indicated that the 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 10 mA cm^{-2}. It is noteworthy that the formation of a ketone derivative was suppressed while the biphenyl product was obtained in 64% yield in the case of fluorinated carboxylic acids. In addition to good *ortho*-selectivity, the reaction scope is broad with good tolerance of many electron-rich and halogenated phenols.



Scheme 49 Anodic C–C cross-coupling of phenols

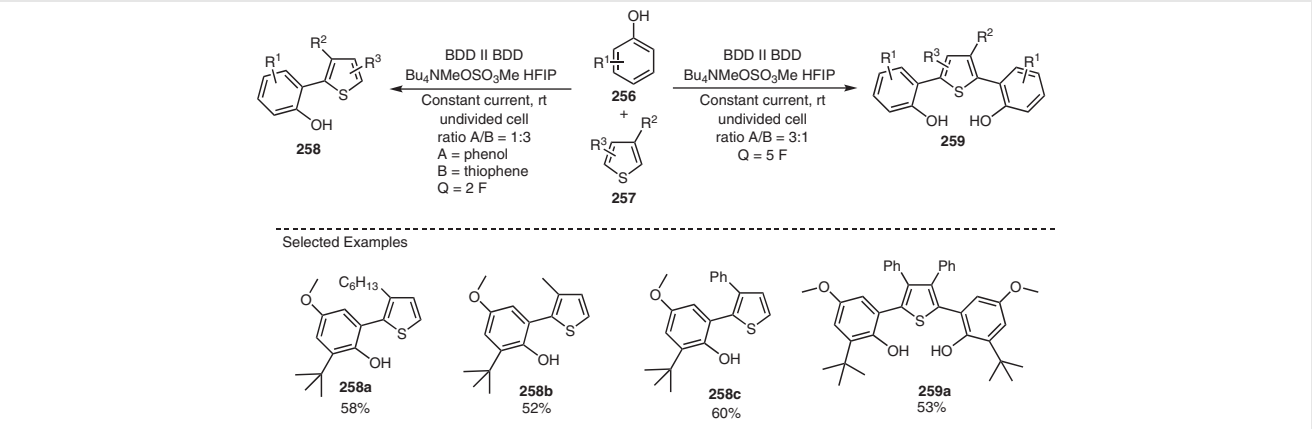
In 2016, Zhu and co-workers developed a novel methodology for the one-pot arylation of pyrroles with aryl halides using perylene-3,4:9,10-tetracarboxylic acid diimide (PDI) derivatives as redox mediators in 1-ethyl-3-methylimidazolium bis((trifluoromethyl)sulfonyl)imide [EMIM]NTf_2/DMSO mixture.[104] Though electron-rich and electron-poor arenes effectively coupled with pyrrole, reactions with other heteroanalogues such as furan, thiophene, and indole did not occur. The mechanism of the reaction is outlined in Scheme 50.



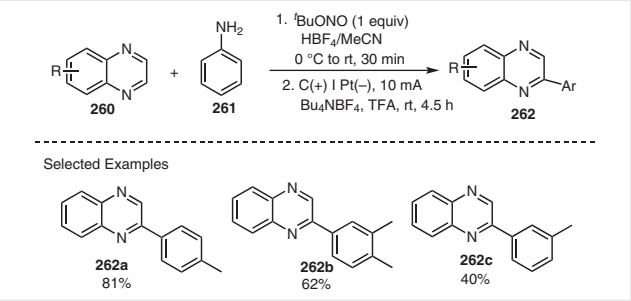
Scheme 50 Electroreductive coupling of phenols with arenes

Extending their previous studies, the Waldvogel group described an impressive application of electricity for arene coupling. In 2017, they demonstrated the C–C coupling between phenols and anilines at room temperature by electrochemical means.[105] A subsequent report further showed that this strategy could enable the regioselective C-2 arylation of thiophenes with phenols (Scheme 51).[106] A notable aspect of this method, besides the scalability and robustness, is its high selectivity as the desired C-2 or C-3 arylated products can be obtained by simply blocking the other position. Employing a three fold excess of thiophene and 2F of electricity with respect to phenols, the authors were able to synthesize a broad variety of 2-(2-hydroxyphenyl)thiophenes. Though no homocoupling was detected under the optimized conditions, partial polymerization of thiophenes could not be ruled out by the authors. The proposed mechanism involves the oxidation of phenol to a phenoxyl radical followed by nucleophilic attack by the thiophene. Subsequent oxidation then results in a cross-coupling product. In the same year, Charusin and co-workers reported C–C bond formation between aza-aromatics and nucleophilic arenes without any metal catalyst/base or leaving groups at room temperature.[107]

In 2019, Lei and co-workers reported the coupling between electron-deficient arenes and aryldiazonium salts using cathode reduction (Scheme 52).[108] The electrolysis was carried out in an undivided cell with a graphite anode and a Pt cathode electrode. The method showed good compatibility with a variety of aryldiazonium tetrafluoroborates and electron-deficient heteroarenes. In addition, one-pot arylation with diazonium salts generated in situ from anilines could also be achieved in good yield, with better results noted when using anilines having electron-donating groups rather than electron-deficient groups.



Scheme 51 Electrocatalyzed C–C coupling of thiophenes with phenols



Scheme 52 Electrolysis of electron-deficient arenes

3 Summary and Outlook

Over the past two decades, direct C–H arylation has become an important synthetic tool for molecular synthesis. 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 the development of pharmaceuticals and materials science applications. 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 toward efficient catalytic systems for sustainable development. Based on the 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 the future. Secondly, transition-metal-free coupling reactions offer simpler 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 polymerizations 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.

Conflict of Interest

The authors declare no conflict of interest.

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