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Review

Modern strategies for C–H functionalization of heteroarenes with alternative coupling partners

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SUMMARY

Heteroarenes containing oxygen, nitrogen, and/or sulfur are important in numerous aspects of chemistry and everyday life. C–H functionalization of heteroarenes represents the fastest and most atom-economical approach for the synthesis of complex molecules. This strategy avoids the requirement of *de novo* synthesis and is beneficial for the late-stage modification of structurally complex molecules. Although early protocols for C–H functionalization using organic halides (I, Br, and Cl) as coupling partners remain in active use today, a range of modern strategies allows the cleavage of less reactive C–Het (F, O, S, N, and P) and C–C bonds to form essential links to the feedstock chemicals, highlighting their renewable and sustainable features. This review focuses on modern strategies for the C–H functionalization of heteroarenes with these alternative coupling partners. Most of the transformations can be achieved through catalytic processes. Some non-catalytic strategies involving new reagents and techniques are also introduced.

INTRODUCTION

Heteroaromatics are important components of pharmaceuticals and play vital roles in pharmacological function.[1–4] The virtual exploratory heterocyclic library (VEHICLe) is a complete set of heteroaromatic ring systems. Of the 2,461 drug molecules extracted from the MDL drug data report (MDDR) (Symyx Technologies), there were over 1,000 occurrences of VEHICLe rings. The FDA orange book has arranged the top 10 heteroaromatic rings shown in Figure 1 from small molecule drugs in descending frequency. Therefore, the development of efficient strategies for the atom-economical, streamlined synthesis of these molecules is of commercial value. Many well-known classical methods are now available by *de novo* construction, but changing the substituent groups used in these methods typically needs considerable synthetic effort.

Over the past decade, atom- and step-economical C–H functionalization strategies have attracted the attention of many research groups in both academic and industrial sectors. [5] Reflecting the ubiquity of heteroarenes, strategies that enable late-stage modification of these molecules by directed functionalization of their C–H bonds have become highly desirable. Significant progress has been made in the C–H functionalization of heteroarenes, typically involving four types of coupling partners (Figure 2). The most common method involves the reaction of organic halides (I, Br, and Cl) with an extensive choice of heteroarenes in the presence of a transition metal (TM) (path I).[6,7] Heteroaromatic C–H bonds can be transformed into C (heteroaryl)-C (aryl) bonds with a range of organometallic reagents (Mg, Zn, B, Si, Sn, etc.) (path II). Although high conversions and selectivities can be obtained by these methods, the substrates should be preprepared from sustainable chemical

The bigger picture

The abundance of the heteroaryl structural motif in drugs, in natural products, and in material science has made the strategy of C–H functionalization of heteroarenes a priority of synthetic chemists. Compared with the widely used organic halides (I, Br, and Cl) as coupling partners, the cleavage of less reactive C–Het (F, O, S, N, and P) and C–C bonds in C–H functionalization of heteroarenes allows to construct complex molecules from simple, readily available feedstocks. This review article broadly describes strategies for C–H functionalization of heteroarenes with these alternative coupling partners emerging over the last decade. Selected examples of this approach include (1) heteroarylation of C–F bonds, (2) heteroarylation of C–O bonds, (3) heteroarylation of C–S bonds, (4) heteroarylation of C–N bonds, (5) heteroarylation of C–P bonds, and (6) heteroarylation of C–C bonds.

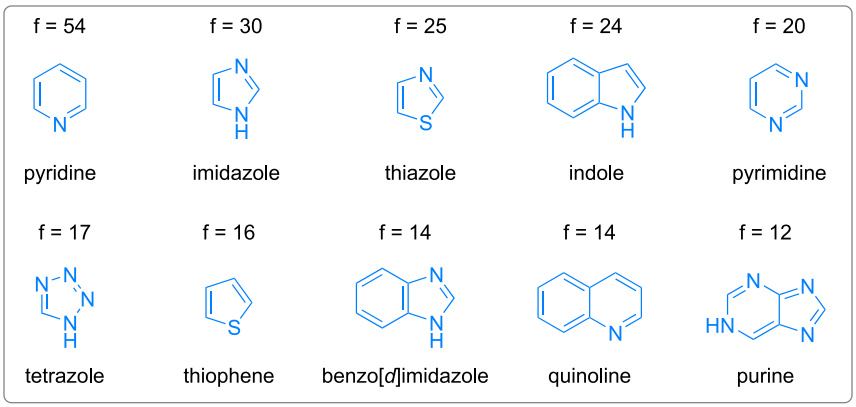

Figure 1. Structures of the most frequent heteroaryl motifs in small molecule drugs

feedstocks. The direct method for C–H functionalization of heteroarenes through cleavage of the less reactive chemical bonds has also reached impressive levels of sophistication and efficiency during the past decade. Among them, oxidative C–H/C–H coupling reactions to build C-heteroaryl bonds have been widely studied and summarized (path III).[8] Due to the ubiquitous C–Het (F, O, S, N, and P) and C–C bonds in organic compounds, modern strategies based on the activation of these chemical bonds for the C–H functionalization of heteroarenes have become highly desirable (path IV). Such coupling partners are classified as alternatives in this review. Although substantial evolution has been achieved in this area, a systematic review on the C–H functionalization of heteroarenes with these alternative coupling partners has not yet been conducted.

The goal of this review is to support researchers regarding key areas of modern strategies that have been developed for the direct C–H functionalization of heteroarenes over cleavage of unreactive chemical bonds. Such transformations pose challenges ostensibly due to the high energetic cost of breaking these chemical bonds and the deactivation of metal catalysts in the presence of strong coordination heteroatoms. Two general strategies have been employed to overcome these difficulties: catalyst activation and substrate activation (Figure 3). Catalyst activation involves the development of more reactive catalytic systems. For example, the unique properties of nickel catalysts facilitate the activation of these inert C–Het and C–C bonds to couple with heteroarenes. The substrate activation approach introduces directing groups or reagents to overcome the inherent stability of unreactive chemical bonds. Typically, these two strategies can be used together, enabling high selectivity and functional group tolerance in the direct C–H functionalization of heteroarenes with milder reaction conditions. The well-known approach for substrate activation via the preformation of aryl sulfonates (e.g., OTf and OTs) using phenols shows comparable reactivities with the corresponding aryl halides, which will not be defined in detail with the exception of noting that they are closely associated. Based on understanding from the seminal works, the reaction pathways for cleavage of these chemical bonds mainly include oxidative addition with TM catalysts, TM-catalyzed β-X elimination, and radical-induced processes. The C–H bond cleavage events in heteroarenes mainly involves C–H metalation and functionalization and Minisci-type reactions.[9] These reactions can be achieved using a variety of transition-metal catalysts and some organocatalysts in the photoredox process. Some non-catalytic modern strategies using new reagents and techniques are also introduced in this article. This topic is categorized as follows: (1) heteroarylation of C–F

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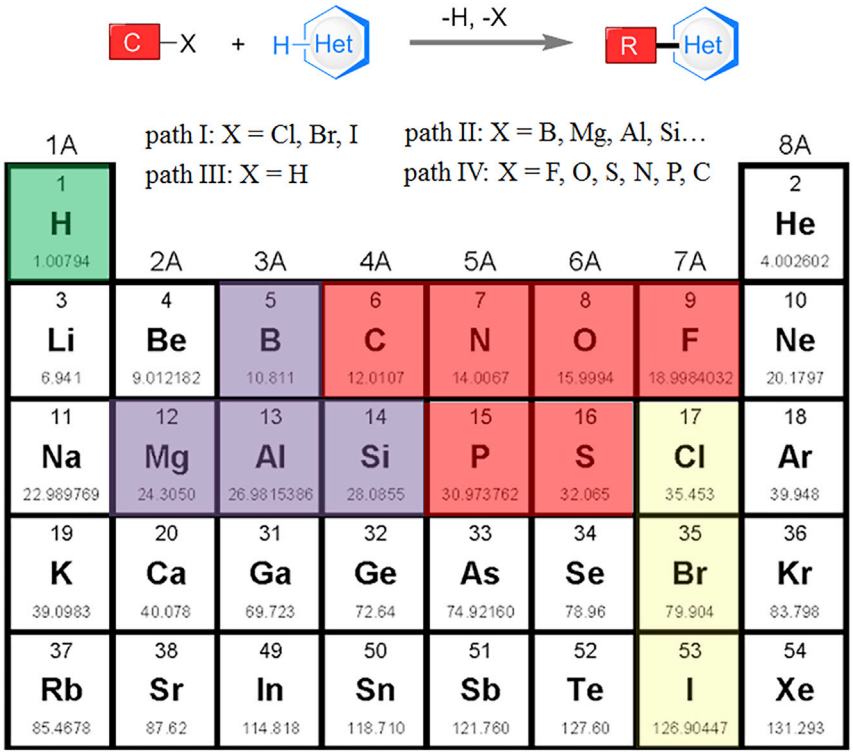


Figure 2. C–H functionalization of heteroarenes through cleavage of C–X bonds

bonds, (2) heteroarylation of C–O bonds, (3) heteroarylation of C–S bonds, (4) heteroarylation of C–N bonds, (5) heteroarylation of C–P bonds, and (6) heteroarylation of C–C bonds. Moreover, the discovery and development of the reactions, the limitations and scopes of these approaches, and the mechanistic pathways are highlighted.

HETEROARYLATION OF C–F BONDS

Due to the exceptional chemical and biological properties of fluorinated organic compounds, they are considered as important motifs in pharmaceuticals and agrochemistry.[10] Organofluorine chemistry has rapidly developed in modern years, since the demand for these compounds has promptly increased. Conventional approaches for the synthesis of fluorinated compounds predominantly focus on the formation of new C–F bonds. Recently, increased attention toward facile access to complex fluorinated compounds has turned to selective C–F bond cleavage of poly- or perfluorinated molecules. Functionalization of C–F bonds typically involves coupling polyfluorinated arenes with aryl nucleophiles such as Grignard reagents, zinc, boronic acids, or tin reagents. Some elegant catalytic manifolds have been developed for the C–H functionalization of heteroarenes via the selective cleavage of C–F bonds in fluoroarenes and fluoroalkenes. In these reactions, C–F bond cleavage primarily occurs through oxidative addition of C–F bonds in the presence of TM catalysts, radical-induced defluorination, and β-F elimination.

Fluoroarenes

Seminal work by Lu and Shen in 2013 described the palladium-catalyzed cross-coupling of polyfluoroarenes and benzoxazoles via sequential C–F/C–H activation for the first time (Scheme 1A).[11] The installation of a 2-pyridinyl substituent in

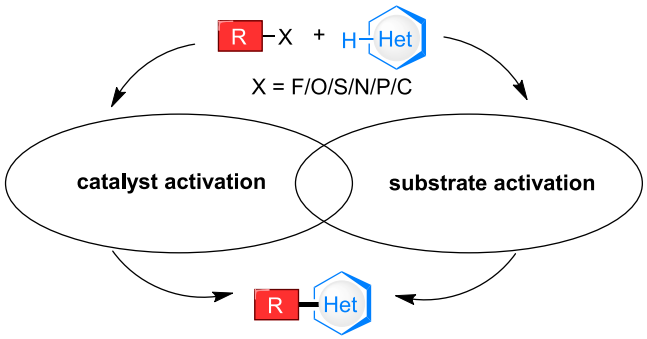


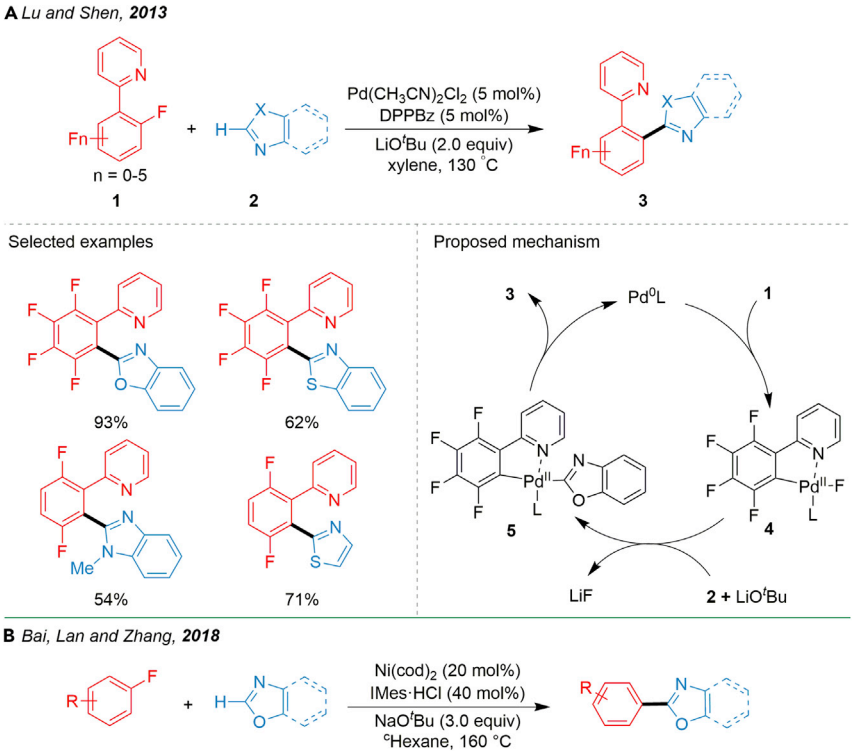
Figure 3. General strategies

substrates as a directing group to assist palladium-catalyzed selective C–F bond activation is the key to this accomplishment. The reaction proceeds at first, and Pd(0) species undergo oxidative addition to the C–F bond of fluoroarene **1** to afford cyclometalated intermediate **4**. Further C–H activation of heteroarene **2** with the assistance of LiO^tBu, and transmetalation to provide intermediate **5**, affords the final product **3** through reductive elimination with regeneration of Pd(0) species for the next catalytic cycle. Later work by Bai, Lan, and Zhang extended the scope of C–F bond functionalization of inactivated aryl fluorides with oxazoles as coupling partners under nickel catalysis (Scheme 1B).[12] In the absence of a directing group, the nickel (0) species can undergo oxidative addition to fluoroarene, accordingly promoting the subsequent heteroarylation.

The emerging field of photochemistry has offered new possibilities for the functionalization of C–F bonds under mild conditions. In 2016, Weaver and coworkers reported an efficient approach for defluorinative heteroarylation of polyfluoroarenes **6** with heteroarenes **7** using an Ir-photocatalyst, blue light, and an amine (Scheme 2).[13] Both *N*-containing heterocycles and electron-rich arenes could be functionalized in this reaction, showing unconventional Minisci selectivity. From a mechanistic perspective, an electron adds to the low-lying LUMO of the perfluoroarene, resulting in an unstable radical anion **9**, which undergoes fluoride extrusion to generate perfluoroaryl radical **10**. Subsequent addition of radical **10** to the π systems of **7** results in radical species **11**. Final oxidation and rearomatization through either SET (**12**) or deprotonation (**12′**) provides coupling products **8**. In this transformation, only polyfluorinated arenes could be employed in C–F functionalization because the LUMO (π* orbital) decreases in energy as the degree of fluorination increases; yet, the rate of C–F bonds fragmentation increases.[14]

Fluoroalkenes

Fluoroalkenes are considered as advantaged structural motifs and have been extensively found in pharmaceutical chemistry.[15,16] In 2015, Loh and Feng first described an Rh-catalyzed vinylic C–F bond heteroarylation of *gem*-difluoroalkenes **13** in which substrates **14**, including indoles and pyrroles with N-directing groups, were used as coupling partners (Scheme 3A).[17] Treatment of easily prepared aryl- and alkyl-substituted *gem*-difluoroalkenes as electrophiles with heteroarenes, delivers a highly efficient and operationally simple introduction of α-fluoroalkenyl motifs onto the heteroarenes to access product **15** under oxidant-free conditions. Mechanistic studies revealed that rhodium-catalyzed β-F elimination was a key step during the transformation. Due to the requirement of rhodium catalysts, the improvement of earth-abundant metal catalysts for the earlier mentioned transformations is highly desirable. The following year, a related cobalt-catalyzed defluorinative



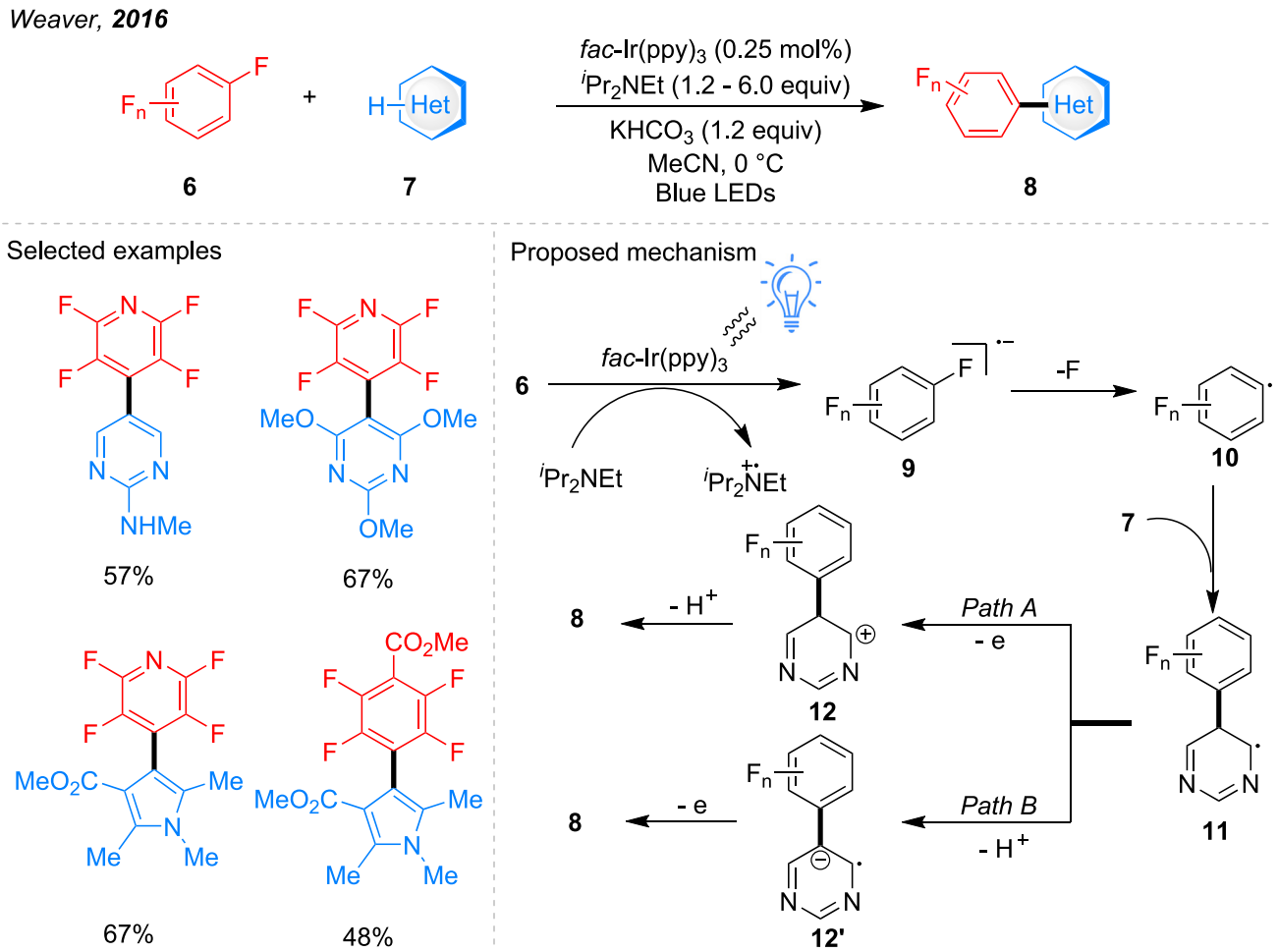
Scheme 1. TM-catalyzed defluorinative heteroarylation of fluoroarenes

functionalization was uncovered by the Li group in which a series of Z-alkenyl fluorides were produced under mild and redox-neutral conditions (Scheme 3B).[18] In 2017, Loh and Feng also found that manganese catalysts could also be used in this C–F/C–H coupling reaction (Scheme 3C).[19] Interestingly, this strategy has emerged for the synthesis of monofluoroalkenes with predominant unusual *E*-selectivity, which serves as complement to the existing protocols to access these molecular architectures.

In addition to vinylic C–F bond heteroarylation, the functionalization of allylic C–F bonds was also realized. In 2017, the Ackermann group showed manganese(I)-catalyzed allylic C–F heteroarylation between a variety of perfluoroalkenes and (hetero) arenes bearing pyridyl groups (Scheme 4).[20] The scope of the reaction is very high with respect to both coupling partners, and a variety of indoles and pyrroles can undergo C–H perfluoroalkenylation. Notably, high positional-, diastereo-, and chemoselectivities were observed in (per)fluoro alkenylation and allylation reactions. Complete computational and experimental studies were conducted to investigate the mechanism in which β-F elimination was a key step. Meanwhile, the same group further explored the use of cobalt salts as catalysts for similar transformations under mild reaction conditions.[21]

HETEROARYLATION OF C–O BONDS

Phenol and alcohol derivatives are important starting materials used to construct numerous value-added chemicals, such as pharmaceuticals and resins. To explore new reactivities and efficient transformations, many synthetic chemists have been engaged and have devoted enormous effort for the functionalization of C–O bonds in recent decades.[22] Although the replacement of aryl halides with phenols may lead

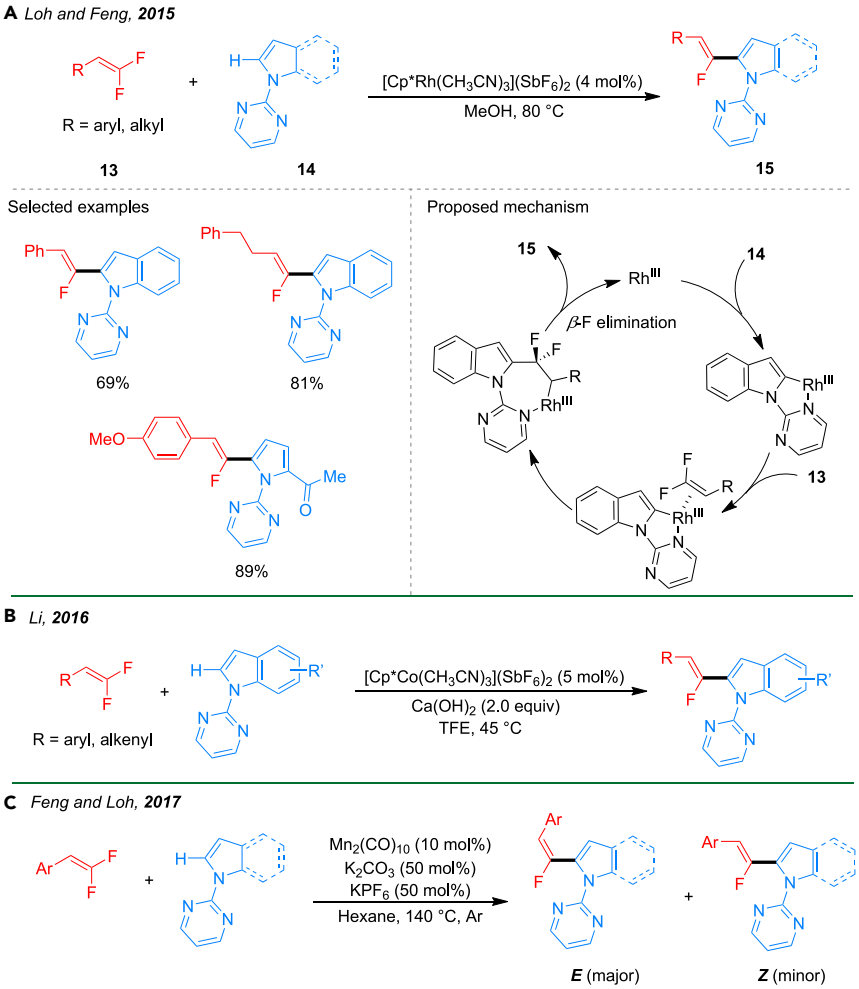


Scheme 2. Photocatalyzed defluorinative heteroarylation of polyfluoroarenes

to more cost-effective and environmental-friendly methods, initial studies are limited to using activated phenols such as triflates and tosylates for cross-coupling reactions under transition-metal catalysis. Recently, aryl ethers and carboxylates were employed for cross-coupling reactions by C–O bond activation, which has attracted significant attention in organic synthesis. In the field of aliphatic C–O bonds, some elegant approaches have been established for the direct heteroarylation of alcohols by the SET process instead of the traditional Friedel-Crafts-type alkylation of alcohols with aromatic rings with the requirement of some Lewis acids. From this perspective, C–O/C–H coupling reactions have delivered new synthetic routes toward heteroarylation products. Based on the diverse class of substrates, this topic can be classified into heteroarylation of aromatic C–O bonds (phenol esters and ethers), vinylic C–O bonds (enol derivatives), allylic C–O bonds (allylic alcohols and derivatives), and aliphatic C–O bonds (alcohols and oxalate salts). The cleavage of C–O in this transformation proceeds through the oxidative addition of C–O bonds in the presence of TM catalysts, nucleophilic aromatic substitution, β-O elimination, and radical-induced deoxygenation.

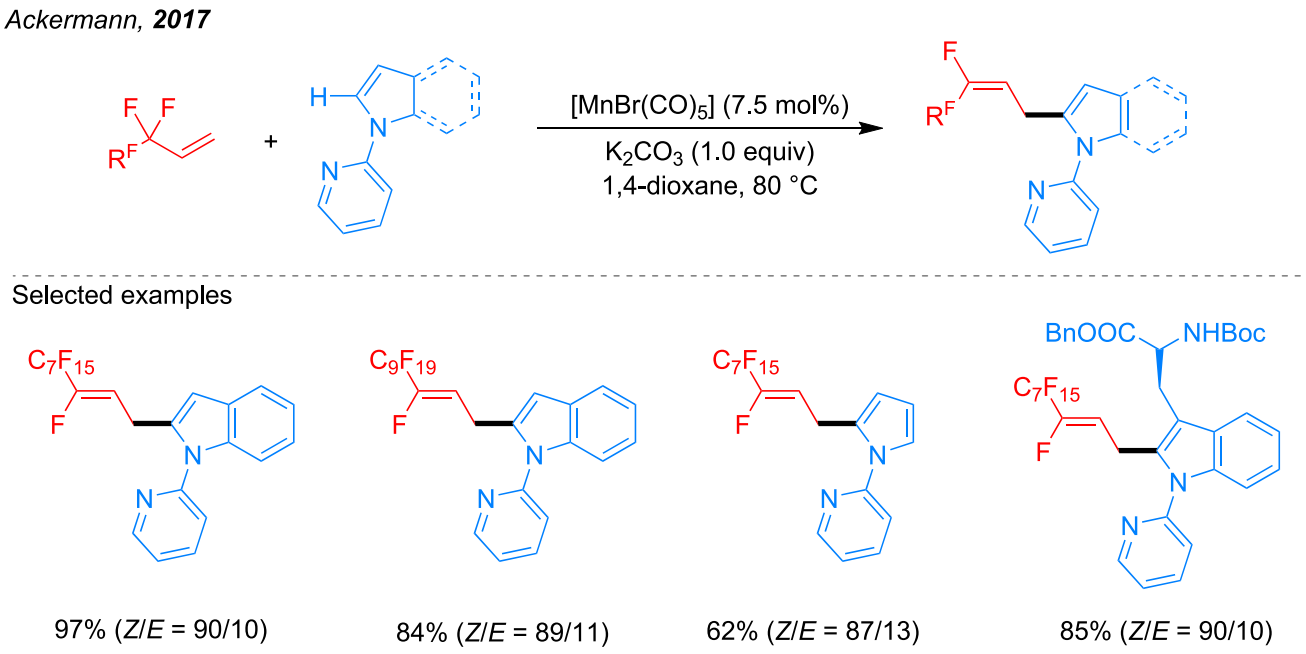
Phenol esters

Wenkert and coworkers first reported a nickel-catalyzed cross-coupling of aryl ethers with the Grignard reagent via C–O bond cleavage in 1979.[23] The nickel catalyst was



Scheme 3. TM-catalyzed defluorinative heteroarylation of gem-difluoroalkenes

found to be a superior catalyst for activating inert C(aryl)-O bonds. In 2012, Itami and coworkers reported pioneering work on C–O/C–H coupling between phenol derivatives **16** and azoles **17** under Ni-catalysis (Scheme 5A).[24] The use of catalytic $Ni(cod)_2$ together with 1,2-bis-(dicyclohexylphosphino)ethane (dcype) as a ligand and Cs_2CO_3 as a base is important for the accomplishment of this coupling process. A wide range of protected phenol-derived pivalates and triflates were suitable substrates under the developed system. Based on this discovery, the swift identification of novel biologically active compounds by late-stage functionalization of naturally occurring structures can be accessed. Importantly, the isolation of arylnickel(II) pivalate **19** confirmed by X-ray analysis supports a catalytic cycle involving C–O bond oxidative addition, C–H nickelation, and final reductive elimination. In addition, it also provides insights into the strong ligand effect in this coupling reaction (Scheme 5B).[25] The effect of the base was further studied with the help of computational experiments.[26] Azole C–H activation was accomplished by the catalysis of **20** generated through C–O bond oxidative addition in the absence of Cs_2CO_3, which requires overcoming the ΔG = 34.7 kcal/mol barrier. Alternatively, when Cs_2CO_3 was present, cluster complex **21** was formed with the release of ΔG = 36.1 kcal/mol. During the C–H activation of azole **17**, the formed weak Cs—heteroatom(azole) bond increases the acidity of the C–H bond, which is responsible for the dramatically reduced barrier of C–H activation.



Scheme 4. Mn-catalyzed allylic C–F bond heteroarylation

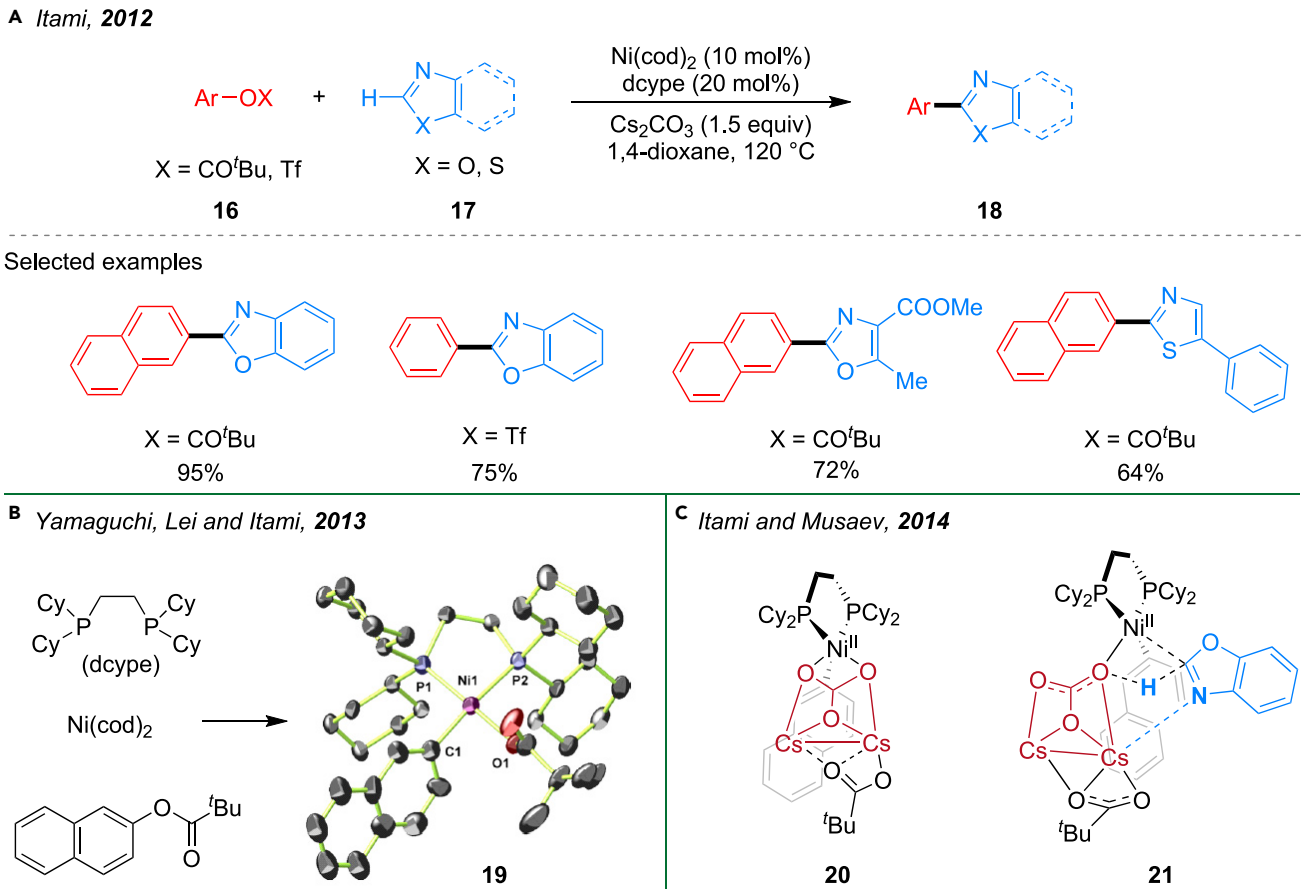
Ethers

Compared with aryl pivalates and carbamates, aryl ethers with C–OMe bonds have higher dissociation energy. An early example by Tsuchimoto and coworkers disclosed an indium-catalyzed S_NAr reaction for the construction of heteroaryl–heteroaryl bonds using thiophene ethers as electrophiles with indole derivatives as nucleophiles (Scheme 6).[27] Soft metal salts with non-coordinating counterions were selected as good candidates to facilitate this transformation. In addition to $In(OTf)_3$, other hard Lewis acids involving $In(ONf)_3$, AgOTf, and $Bi(OTf)_3$ were also investigated as alternative catalysts to attain the anticipated products. Meanwhile, the authors provided two plausible pathways to explain the mechanistic details of this reaction. The deuterium experiments indicated that the two different allylindium complexes that were generated during this catalytic route were attacked by heteroaromatic rings with high π-electron density in which the indium metal served as an electron-withdrawing moiety to improve the electrophilicity of the thiophene rings.

In 2018, Zhao and Ong further disclosed that aryl methyl ethers can also be employed as coupling partners via C–O activation using a catalytic amount of $Ni(cod)_2$ and IPr (1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene) ligand employed for heteroarene C–H activation (Scheme 7).[28] The use of sterically demanding o-tolylMgBr is a key success in both C–O and C–H activation. This procedure is highly effective in a wide range of substrate scopes with anisoles, naphthyl methyl ethers, and a variety of other heteroarenes. However, aryl methyl ethers containing withdrawing groups are not appropriate for this catalysis due to their possible interaction with Grignard reagents. The synergistic effect of nickel and Grignard reagent is driving for C–O bond cleavage acquired by detailed mechanistic studies, and the sterically demanding Grignard reagent is crucial to avoid the byproducts in this transformation.

Enol derivatives

TM-catalyzed Mizoroki-Heck reaction is an expedient synthetic method for the construction of alkenyl-substituted arenes from simple arylboronic acids. Different from

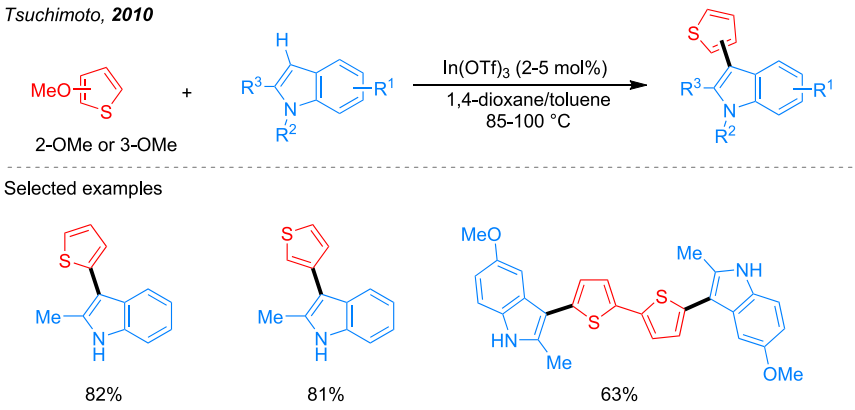


Scheme 5. Nickel-catalyzed coupling of phenol derivatives with N-heteroarenes involving C–O/C–H activation

this traditional process, Itami and Yamaguchi disclosed the cross-coupling between enol derivatives and heteroarenes through C–O/C–H activation using the developed Ni/dcype catalytic system to build alkenyl-substituted products (Scheme 8A).[29] Enol derivatives, including styryl pivalate and carbamate, could be utilized to couple with benzoxazoles and oxazoles, and in most cases, the styryl carbamates exhibited greater reactivity than the related pivalates. However, benzothiazole was not compatible with the developed conditions. Later, the same research group explored nickel-catalyzed vinylic C–O heteroarylation using imidazole derivatives as one of the partners (Scheme 8B).[30] Instead of using dcype, a new dcypt (3,4-bis(dicyclohexylphosphino)thiophene) ligand was employed in this reaction. Positively, the phenol derivatives were also compatible with imidazoles in this developed catalytic approach.

Allylic alcohols and derivatives

TM-catalyzed C–H allylation has been intensively studied over the last decade, emerging as a powerful tool to build C–C bonds.[31] In 2014, Glorius and coworkers reported an efficient cocatalyzed C–H allylation of indoles with allyl carbonate by N-pyrimidin-2-yl directing group (Scheme 9A).[32] It is noted that the use of Co(III) catalyst in this reaction showed excellent turnover number (up to 2,200) at room temperature. Instead of using the preactivated allyl carbonate, Matsunaga and Kanai later found that many nonactivated allyl alcohols could be employed in the C2-allylation of indoles and pyrrole directly in the presence of a cationic Co catalyst

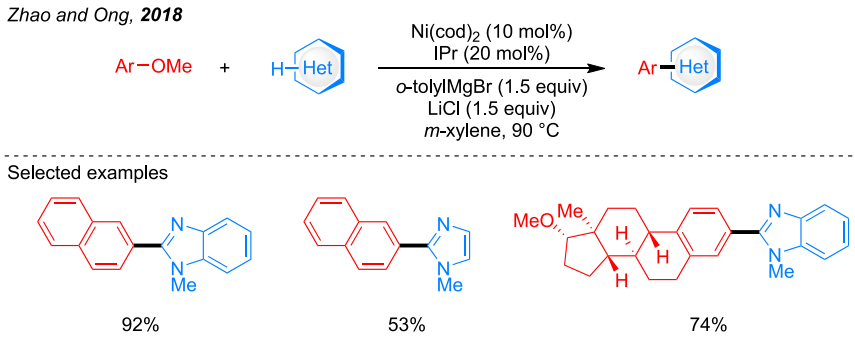


Scheme 6. In-catalyzed the construction of heteroaryl–heteroaryl bond via C–O/C–H cleavage

(Scheme 9B).[33] Mechanistic investigations have revealed that the δ-selective substitution reaction proceeded by C–H metalation and the addition of a C=C bond, with subsequent β-OH elimination. Using dioxolanones as coupling partners, the Ackermann group further developed the Mn(I)-catalyzed C–H allylation with indoles (Scheme 9C).[34] Remarkably, the C–H activation manifold was tolerant of air and water. In addition, indole C–H allylation has also been successfully applied in bioorthogonal late-stage diversification of structurally complex peptides. In 2018, Ackermann and coworkers uncovered cobalt-catalyzed C–H allylation of tryptophan-containing peptides, compatibility with various functional groups, and excellent regioselectivity (Scheme 9D).[35] Combined with olefin metathesis and hydrogenation, a library of structurally complex cyclic peptides was obtained. Furthermore, free stapled peptides were generated via traceless removal of the pyridyl directing group.

Alcohols

Direct functionalization of alcohol C–O bonds can be considered the most challenging but sustainable route for the synthesis of high-value products and for late-stage functionalization of pharmaceuticals and biomolecules. In 2015, the MacMillan group developed a general method by using alcohols **22** as simple alkylating agents, allowing prompt late-stage derivatization of heteroarenes **23** through the successful merger of photoredox and hydrogen atom transfer (HAT) catalysis 24 (Scheme 10A).[36] These authors achieved the alkylation of a wide range of heterocycles, such as isoquinolines, quinolines, phthalazines, phenanthridines, and pyridines, with methanol and higher alcohols. The importance of multicatalytic approach has been described via late-stage functionalization of medicinal agents such as fasudil and milrinone. The mechanism relies on dual photoredox and HAT catalytic methods to accomplish spin-center shift (SCS) elimination from vital radical intermediates **26**. α-Hydroxyalkyl radical addition takes place on heteroarenes followed by subsequent deprotonation, giving intermediate **26**. This species can rapidly undergo SCS elimination of water to afford intermediate **27**, which further promotes reduction and protonation to yield desired product 25. In 2017, the Li group explored a similar transformation for alkylation of quinolines, pyridines, and phenanthridines with an additional rationalized reaction system (Scheme 10B).[37] The direct generation of α-hydroxyalkyl radicals from the corresponding alcohols can also be realized in the presence of ultraviolet radiation. Similarly, Scaiano and Barriault also described the photochemical reaction in which protonated heterocycles undergo direct excitation and alcohols/ethers participate as suitable alkylating agents (Scheme 10C).[38] Although the above-mentioned methods require no photocatalyst, they have the practical disadvantage of necessitating ultraviolet light.



Scheme 7. Nickel-catalyzed cross-coupling of aryl methyl ethers and heteroarenes

Oxalate salts

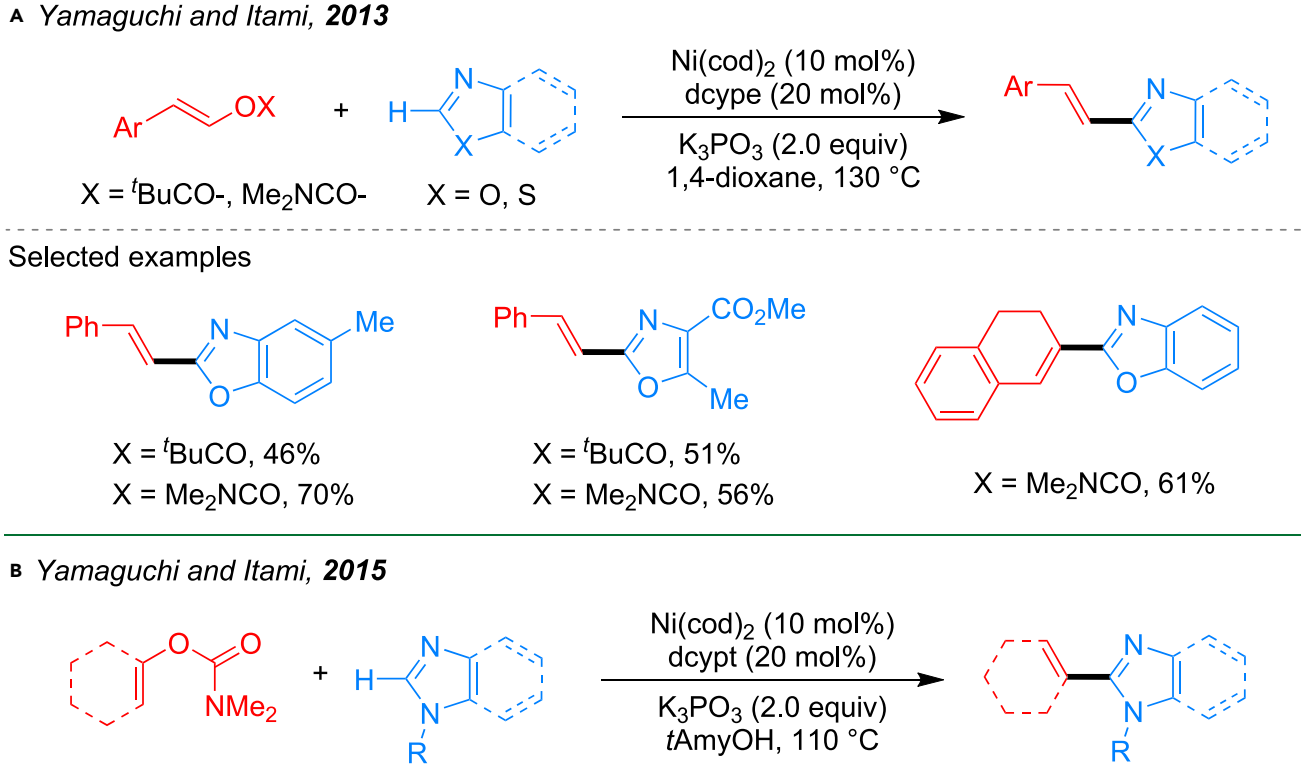
Despite these advances, the introduction of tertiary carbons and the formation of quaternary centers for the functionalization of heteroarenes by Minisci methods are limited in the literature. Recently, Overman and coworkers reported C–O bond heteroarylation using *tert*-alkyl oxalate salts resulting from the related alcohols through Minisci processes (Scheme 11).[39] Compared with the tertiary half esters of oxalic acids, the corresponding salts are relatively stable and could be kept for prolonged periods at room temperature. Moreover, they are considerably easier to oxidize than the related oxalic acids as based on cyclic voltammetry data. This reaction has a broad scope of heterocycles and tertiary alcohol derivatives, which can originate from either the thermal activation or photochemical process. In most cases, the visible light exhibited greater reactivity than the thermal conditions. The shorter reaction time and milder conditions of the Minisci reaction result from a synergistic arrangement of effectual excited-state quenching of chain propagation and photocatalyst.

HETEROARYLATION OF C–S BONDS

Organosulfurs have played a crucial role in organic chemistry for the construction of unusual vital chemical structures.[40] Prominently, among the organosulfurs, those containing S(II), S(IV), and S(VI) centers have been investigated for more than a hundred years. In addition to the long list of sulfur-based reactions in chemical textbooks, there has been continued attention devoted to cross-couplings using organosulfur compounds through cleavage of sulfur atoms. This section aims to cover the expansions of C–H functionalization of heteroarenes through cleavage of C–S bonds over the past decade. Based on the valency of sulfur atoms, this section is considered to include C–S(VI) bonds (sulfonyl chlorides, sulfonic anhydrides, sulfonyl hydrazides, sulfones, and sulfoxonium ylides), C–S(IV) bonds (sulfonates), and C–S(II) bonds (sulfides). The C–S cleavage process in these desulfitative heteroarylation occurs mainly through extrusion of SO_2, C–S bond transition-metal insertion, and radical-induced desulfitation.

Sulfonyl chlorides

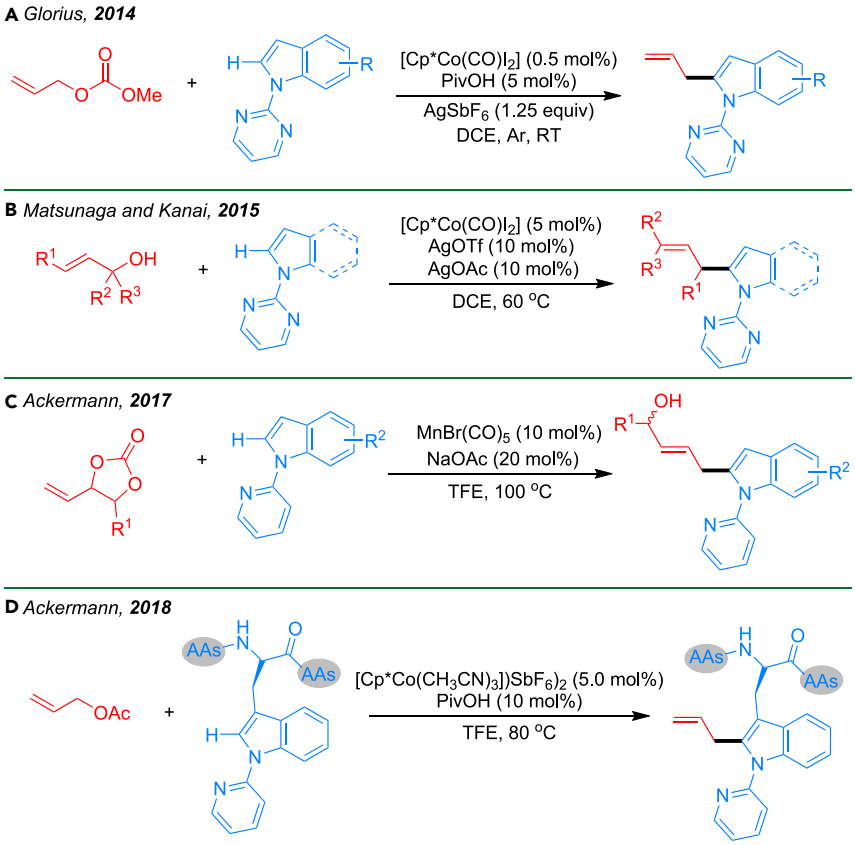
In 2011, the Cheng group established a Pd-catalyzed desulfitative functionalization of the C–H bond of oxazole using aromatic sulfonyl chlorides 28 for the first time (Scheme 12A).[41] The reaction shows a broad scope, including substrates bearing C–Br bonds. The copper salt addition is crucial for the reactivity and simplified its use by the formation of cuprate derivatives **31** via an electrophilic attack of CuI to the oxazole C–H bond. Then Cu/Pd exchange arises to form Pd(II) species 32, which undergoes oxidative addition of sulfonyl chlorides 28 to Pd(II) species, forming Pd(IV) intermediate **33**. Further extrusion of SO_2 provides species **34**, which



Scheme 8. Ni-catalyzed C–O/C–H coupling of enol derivatives with N-heteroarenes

undergoes reductive elimination to deliver products **30** and an active Pd(II) catalyst. In 2013, Jafarpour et al. uncovered palladium-catalyzed desulfitative coupling reactions of arenesulfonyl chlorides with readily available coumarins, constructing the α-position C–C bond (Scheme 12B).[42] Doucet's group in 2014 also deliberated a Pd-catalyzed β-selective desulfitative arylation of thiophenes with arenesulfonyl chlorides in the absence of copper salt (Scheme 12C).[43] In addition, the same group using palladium catalyst and arenesulfonyl chlorides, explored other heteroarenes, such as pyrroles, indoles, and furans, as coupling partners.[44]

As early as 1994, Kamigata and coworkers published seminal work on the perfluoroalkylation of heteroarenes using perfluorosulfonyl chlorides enabled by ruthenium(II) catalysis under thermal conditions.[45] The emerging field of photoredox chemistry has offered new possibilities for using fluorosulfonyl chlorides to realize heteroarylation under mild conditions. In 2011, the MacMillan group demonstrated that the trifluoromethylation of heteroarenes could be achieved via a single-electron pathway using conveniently available trifluoromethylsulfonyl chloride (**35**) as a trifluoromethyl source in the presence of $Ru(phen)_3Cl_2$ under irradiation with household light (Scheme 13A).[46] The trifluoromethyl moiety could be assembled on diverse heteroarenes **36** involving pyrroles, furans, thiophenes, pyridines, pyrazines, pyrimidines, pyrones, and electron-rich arenes with high efficiency and regioselectivity. Importantly, this method could be allowed for the preparation of drug analogs by late-stage trifluoromethylation of some biologically active molecules. Mechanistically, compound **35** was converted into the stabilized trifluoromethyl radical via a single-electron-transfer reduction process with oxidation of [Ru(II)] to the [Ru(III)] complex. Subsequently, the trifluoromethyl radical was added to the electron-rich position of heteroarenes **36**, giving new radical intermediates. Then the radical



Scheme 9. TM-catalyzed C–H allylation of heteroarenes using allylic alcohols and derivatives

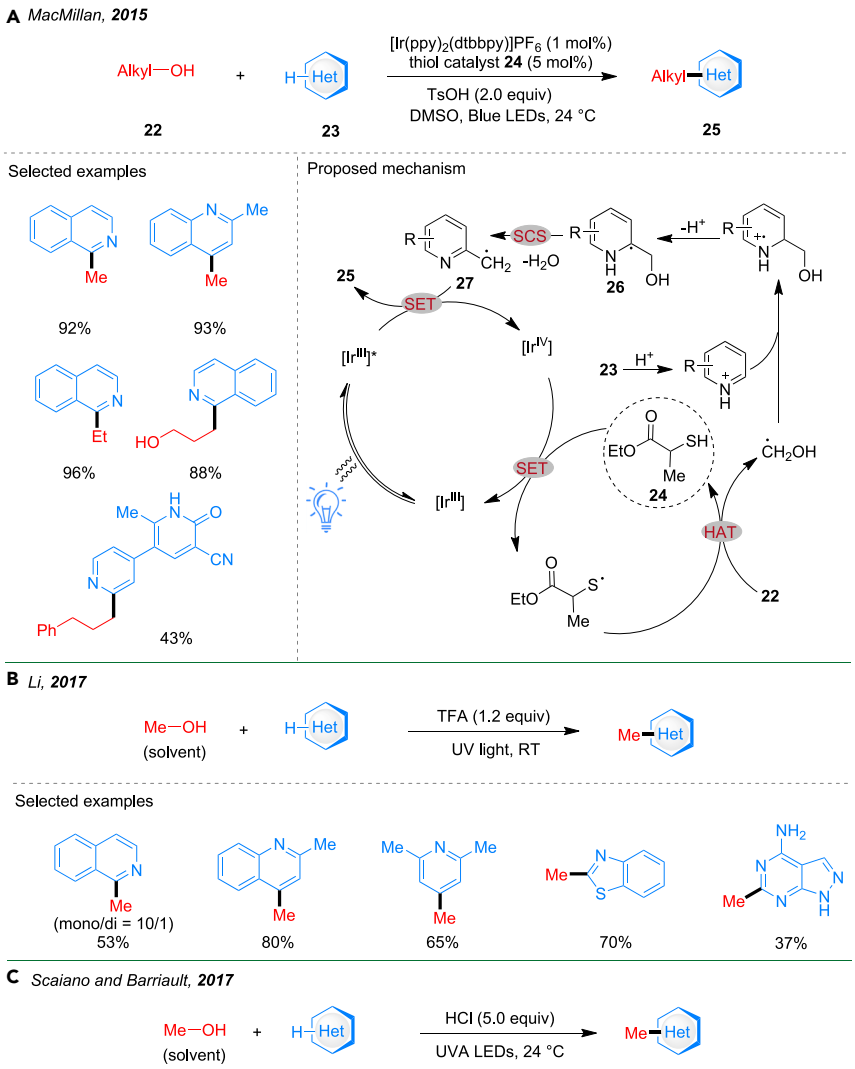
intermediates with reductive potential could be oxidized to cation species by the [Ru(III)] complex to fulfill the catalytic cycle and further transformed into the desired products **37** through base-promoted deprotonation. Recently, Nguyen and Luo also explored a similar chemical transformation electrochemically by sequentially performing redox events at the cathode and anode (Scheme 13B).[47]

Sulfonic anhydrides

Trifluoromethanesulfonic anhydride (**38**, Tf_2O) is an attractive and practical trifluoromethylation reagent due to its inexpensive cost and abundant chemical properties. Qing and coworkers reported for the first time the direct trifluoromethylation of heteroarenes using Tf_2O as a trifluoromethyl source by merging photoredox catalysis and pyridine activation (Scheme 14).[48] The key success of this reaction is the *in situ* formation of pyridinium complex 41 from the reaction of Tf_2O and pyridine. The mechanism is first started by photocatalyst excitation then pyridinium complex **41** formed from Tf_2O/pyridine undergoes single-electron reduction to yield radical species. The obtained radical anion facilitates the release of electrophilic CF_3 radicals and the addition of the resultant radical to heteroarene **39**, followed by oxidation and deprotonation to afford the final desired product **40**.

Sulfonyl hydrazides

In 2012, You and coworkers developed a palladium-catalyzed exciting desulfitative heteroarylation of heteroarenes **43** using arylsulfonyl hydrazides **42** (Scheme 15).[49] A series of heteroarenes, such as caffeines, purines, oxazoles, and thiazoles, could be coupled with arylsulfonyl hydrazides, smoothly affording variable bi(hetero)aryl

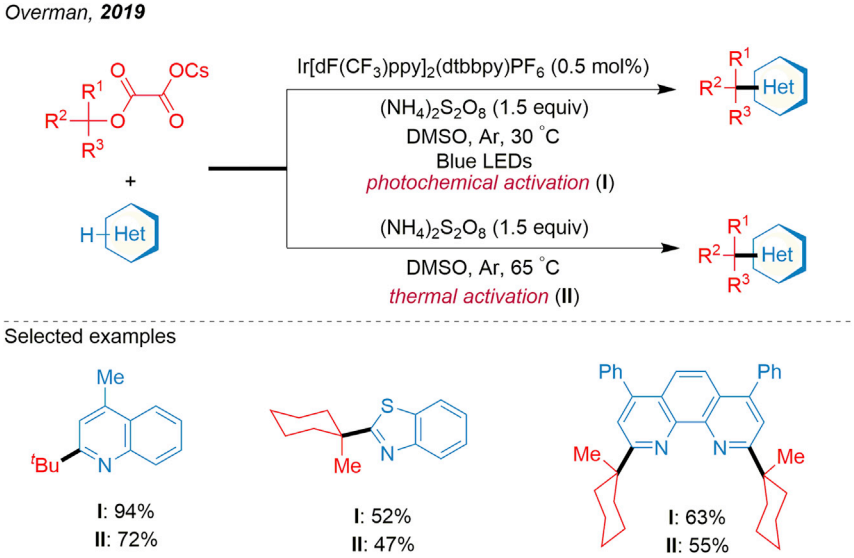


Scheme 10. Visible-light-induced alkylation of heteroaromatic C–H bonds using alcohols

compounds **44** under similar palladium-catalysis with copper-mediated conditions. PPh_3 dramatically improved the yield of the desired product, and copper salts could activate the heteroarenes affording the copper-heteroarene species, which underwent transmetalation with the aryl palladium complex to yield the important di(hetero)aryl palladium intermediate. Meanwhile, Wan and Li demonstrated that Phen·H_2O could be employed as an alternative ligand for this transformation.[50]

Sulfones

This illustrated that sulfone derivatives could be employed as versatile electrophiles for the straightforward formation of C–C bonds by a desulfonative strategy. In 2017, Curran and coworkers reported a palladium-catalyzed heteroarylation of oxazoles with benzylic sulfone derivatives prepared by direct palladium-catalyzed α-arylation of arylmethyl sulfones with aryl halides (Scheme 16).[51] The reactivity of the C(aryl)-S bond could be enhanced by assembling electron-withdrawing groups into phenyl rings. Diverse unsymmetric triarylmethanes could be attained in good yields through C–S/C–H bond cleavage catalyzed by the catalytic amount of Pd_2dba_3 associated with the dppp (1,3-bis(diphenylphosphino) propane) ligand and LiO^tBu in 1, 4-dioxane at 120°C.



Scheme 11. Introduction of tertiary substituents into heteroarenes using oxalate salts

Moreover, 1-phenylethyl sulfone also showed good performance, producing unsymmetric bisarylethanes under the optimized conditions.

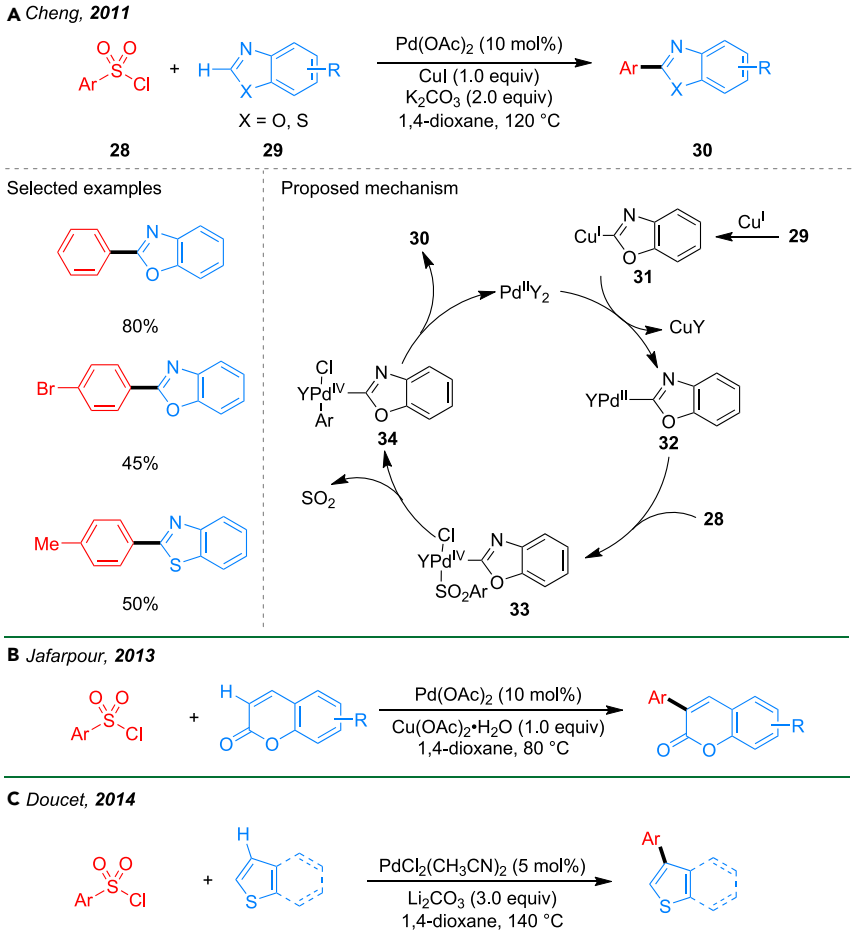
In addition, sulfone derivatives could be utilized in Minisci-type reactions via alkyl radical addition. By rational design of a variety of sulfone compounds 45, Li and coworkers demonstrated a redox-neutral and catalyst-free strategy to provoke alkyl radicals in the context of trifluoromethylation and general alkylation with heteroarenes **46** (Scheme 17).[52] The planned protocol was based on Norrish type I reactivity, whereas ultraviolet radiation prompts the homolysis of a ketone to produce two radical fragments. The authors reasoned that controlled decomposition of the sacrificial group from α-methyl-α-sulfone phenyl ketones **45** homolytically under light irradiation generates an unstable radical ($^{\cdot}SO_2R$), which further undergoes extrusion of SO_2 to obtain the desired reactive radical fragment $R^{\cdot}$. Finally, radical addition to heteroarenes **46** could produce the corresponding products **47** through the Minisci reaction pathway.

Sulfoxonium ylides

Sulfoxonium ylides are valuable motifs and are widely utilized as methylene surrogates in cyclopropanations, epoxidations, and aziridinations discovered by Corey, Johnson, and Chaykovsky in the 1960s. The intermolecular nucleophilic addition of sulfoxonium ylides with electron-deficient π-unsaturated systems, such as α, β-unsaturated compounds, carbonyls, and imines, could provide the corresponding cyclopropanes, epoxides, and aziridines. Recently, Kim's group reported an unprecedented alkylation of iminoamido heterocycles **49** with sulfoxonium ylides **48** (Scheme 18).[53] As a representative example, the trimethylsulfoxonium salt can be used as a methylating agent in aqueous conditions. The base, then ylide **51** participates in the nucleophilic addition with the imine function of **49**, producing intermediate **52**. The simultaneous protonation and E2 elimination of intermediate **52** under aqueous basic conditions delivers intermediate **53** and DMSO. The final protonation of **53** can provide desired product **50**.

Sulfinates

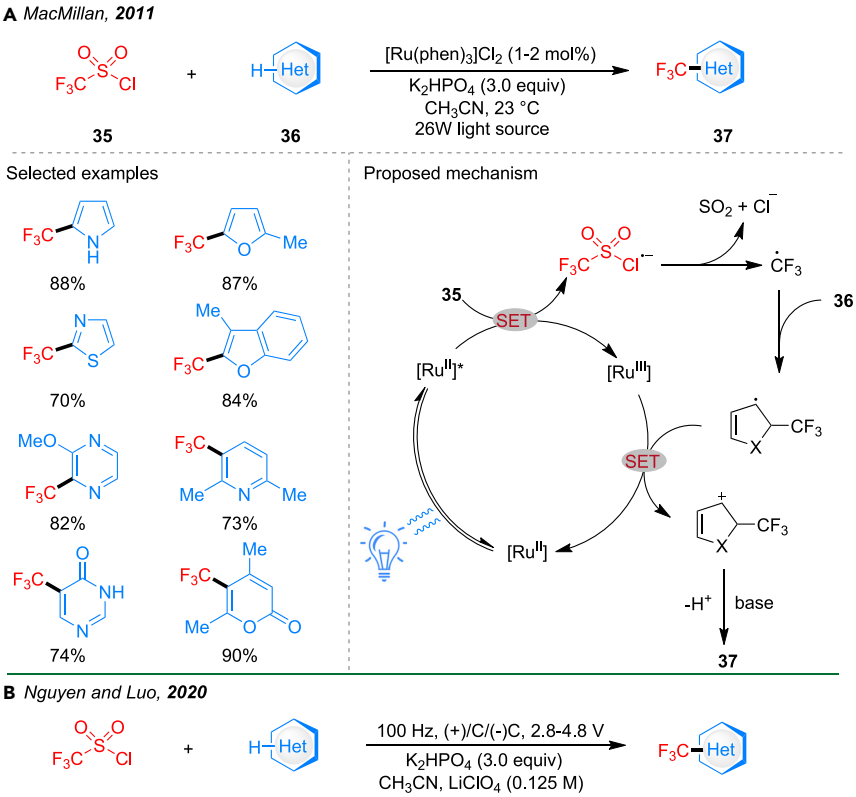
Air-stable and easily prepared sulfinate salts could be treated as electrophilic coupling partners for the development of coupling reactions with the liberation of SO_2 gas. The



Scheme 12. Palladium-catalyzed heteroarylation of benzoxazoles with arylsulfonyl chlorides

desulfitative C–H heteroarylation of heterocycles with sulfinate salts has been considered an effective method for the straightforward synthesis of aryl-heteroaryl moieties. In 2011, You and coworkers disclosed a palladium-catalyzed desulfitative heteroarylation of heteroarenes **55** with aryl sulfonates **54** (Scheme 19A).[54] Varieties of heteroarenes involving caffeines, oxazoles, thiazoles, 1,3,4-oxadiazoles, imidazoles, etc., were amenable to desulfitative heteroarylations at the C2 position. It was found that only copper salts were effective oxidants for this catalytic cycle, and other oxidants including O_2, benzoquinone, potassium persulfate, and silver salts were completely incapable of fulfilling this transformation. It was explained that the copper(I) species could facilitate the formation of an azole-copper intermediate that might transmetalate with the aryl palladium(II) intermediate formed through the desulfitative process producing the key intermediate, followed by reductive elimination to afford the heterocoupling products. In 2013, the Wang group also discovered that arylsulfinic acid could also be used as an electrophilic coupling partner for efficient microwave-accelerated direct palladium-catalyzed *N*-free indole C–H arylation (Scheme 19B).[55] The indoles can be selectively arylated at the C-2 position with the aid of $PdCl_2$ and AgOAc as the oxidant under acidic conditions.

Given the importance of trifluoromethylated organic molecules, the Baran group established a practical technique for the trifluoromethylation of medicinally applicable heterocycles using CF_3SO_2Na (Langlois reagent, a bench top stable, inexpensive solid) (Scheme 20A).[56] The reaction proceeds under noble metal-free conditions and can be

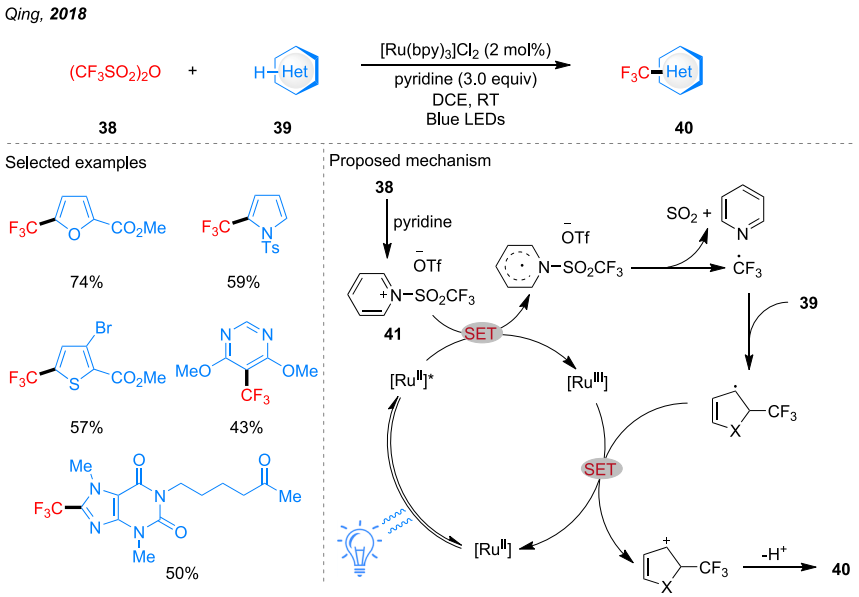


Scheme 13. Trifluoromethylation of heteroarenes using trifluoromethylsulfonyl chloride as trifluoromethyl source

applied directly to unprotected heteroarenes. Preliminary data have clearly explained that the regioselectivity of C–H trifluoromethylation can be fine-tuned simply by careful choice of solvents. Shortly after this work, they also invented a series of zinc sulphinate salts $(RSO_2)_2Zn$) with highly active counteraction for C–H of heterocycles (Scheme 20B).[57–59] Regiochemical comparisons suggested that the alkyl radical produced from these substances possessed nucleophilic properties. In 2014, the electrochemical transformation of the developed zinc sulfinate salts with diverse heterocyclic substrates was also reported, which is recalcitrant to conventional peroxide radical initiation conditions (Scheme 20C).[60] Notably, some of these reagents developed by the Baran group are currently commercially available from Sigma-Aldrich. In addition, Ackermann and coworkers recently developed the C–H trifluoromethylation of heteroarenes in the presence of Langlois reagent and merging of electrosynthesis and photoredox catalysis by avoiding the addition of chemical oxidants (Scheme 20D).[61] Such an electrophotochemical process could also be achieved in a flow setup.

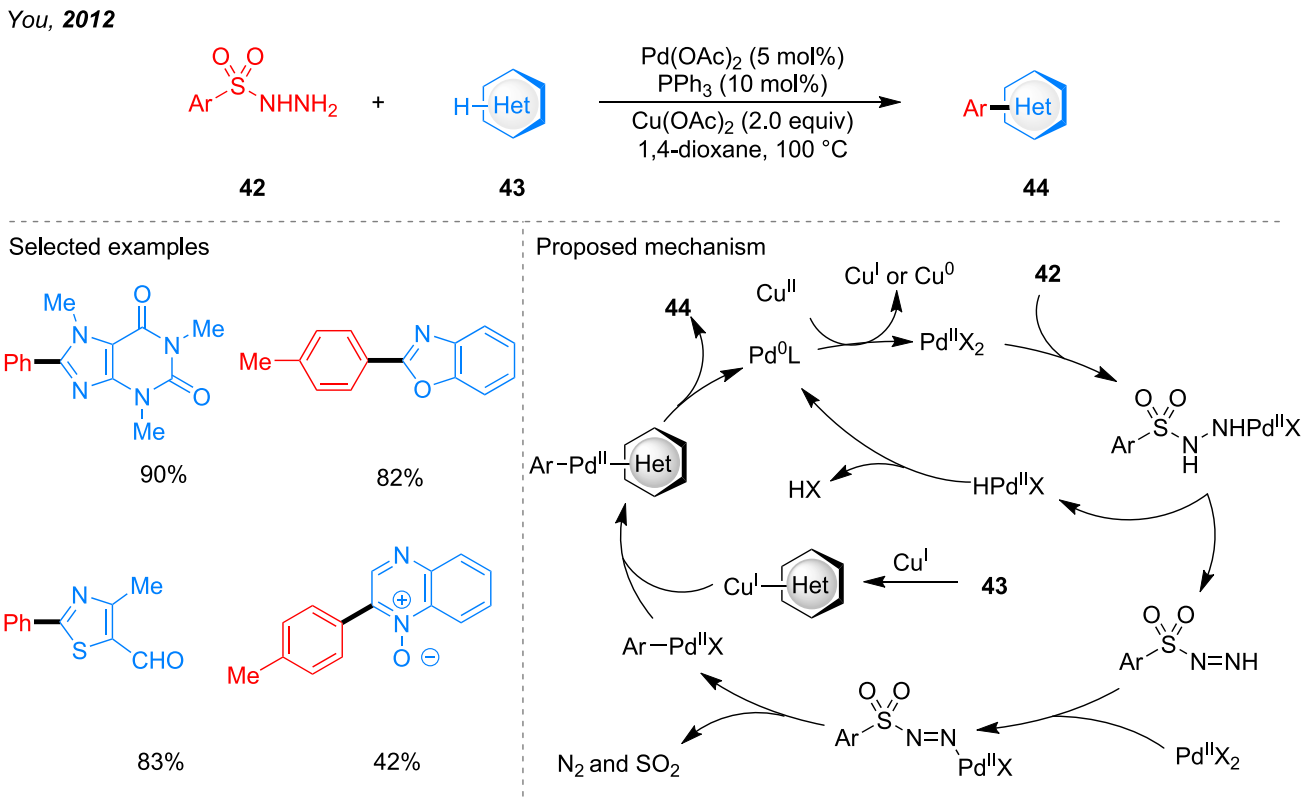
Sulfides

Compared with high-valent sulfur-containing compounds, the use of aryl sulfides as electrophiles in transition-metal-catalyzed cross-coupling reactions poses several challenges, including the breaking of inert C–S bonds and deactivation of catalysts by strong coordination. In 2015, Wang and coworkers reported a great approach that addressed this encounter for heteroarylation of aryl thioethers **57** with azoles **58** through C–S and C–H activation in which palladium salt and dcype ligand showed excellent reactivity (Scheme 21).[62] Several aryl methyl sulfides and diaryl sulfides having electron-rich and electron-poor sulfides could be used as coupling partners. A suggested mechanism covers

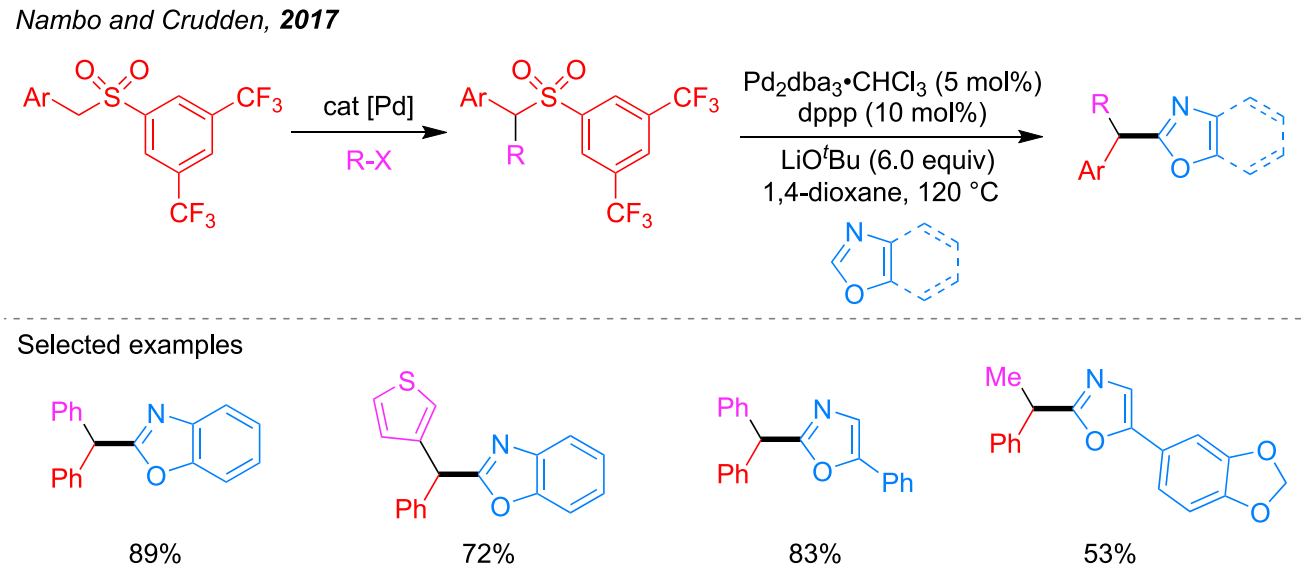


Scheme 14. Trifluoromethylation of heteroarenes using Tf_2O as the trifluoromethyl source

oxidative addition of C–SMe to Pd(0), generating a Pd(II) species 60 that undergoes C–H palladation with heteroarenes to form intermediate **61** under NaO^{t}Bu. Subsequent reductive elimination of **61** delivers the final products and active Pd(0) catalyst. Based



Scheme 15. Palladium-catalyzed heteroarylation of heteroarenes with arylsulfonyl hydrazides

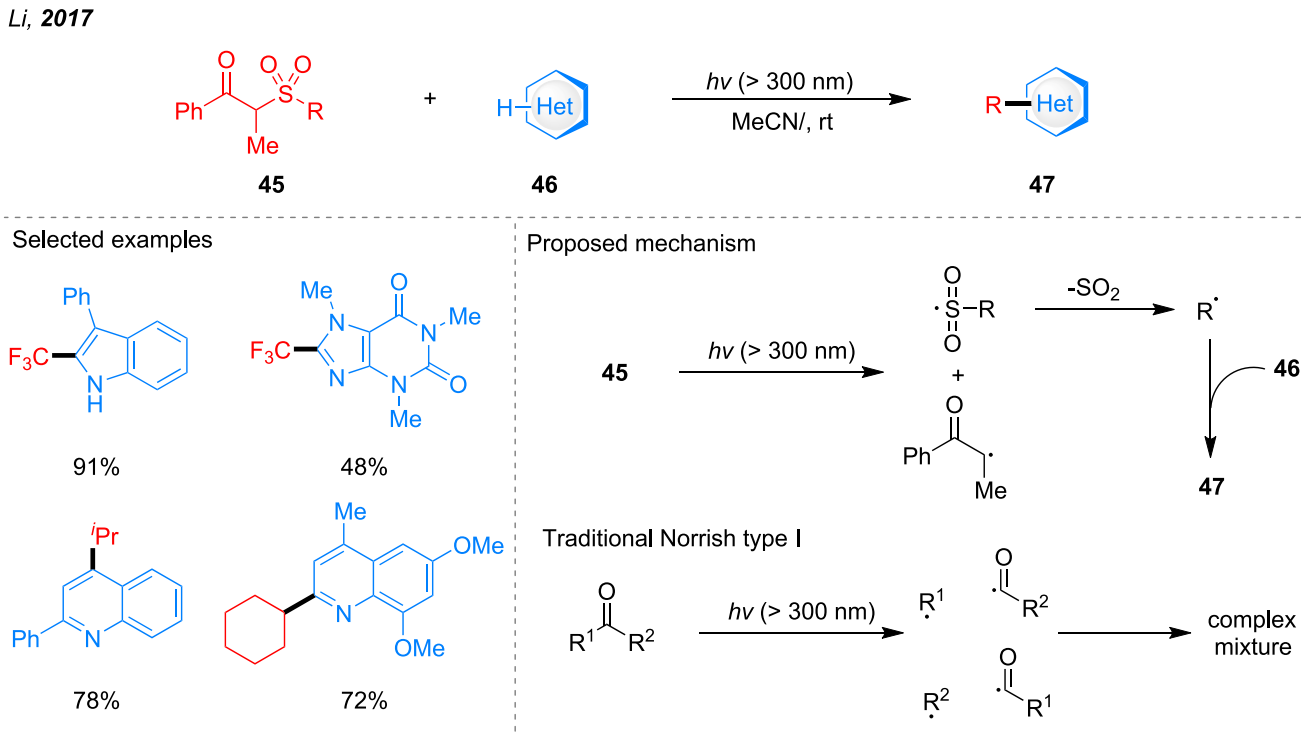


Scheme 16. Cross-couplings of sulfones and oxazoles under Pd-catalysis

on the developed catalytic system, C–Se bond heteroarylation of an aryl selenide with azoles could also be achieved.

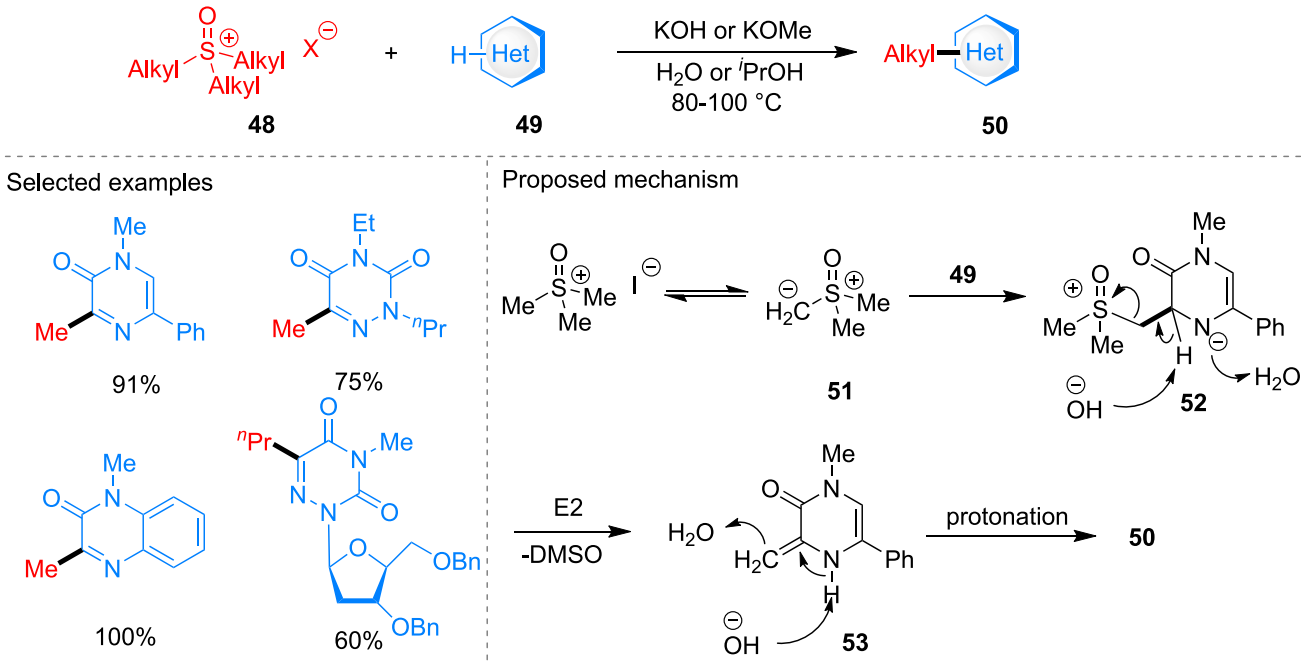
HETEROARYLATION OF C–N BONDS

Amines and their derivatives prominently feature in numerous biologically active natural products and drug molecules, and a range of methods exists for their



Scheme 17. Photoinduced C–H alkylation of heteroarenes using sulfone compounds

Kim, **2021**



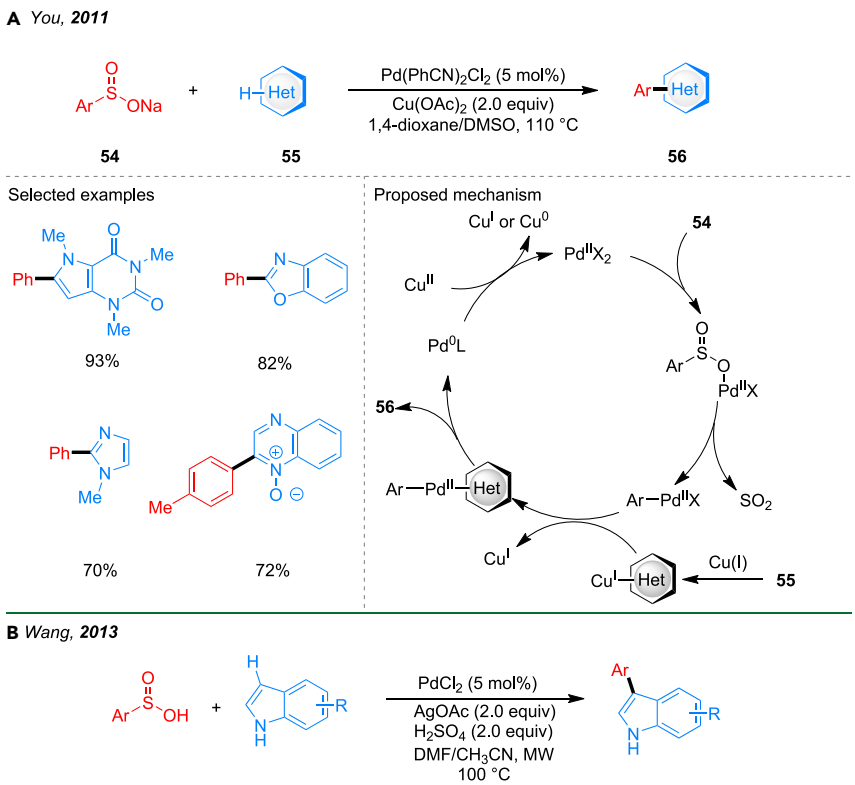
Scheme 18. C–H alkylation of iminoamido heterocycles with sulfoxonium ylides

synthesis. All of these features support the demand to exploit this functionality as a synthetic handle in C–N bond functionalization.[63,64] Some methods for C–H bond functionalization of heteroarenes have been reported recently via cleavage of C–N bonds in anilines and derivatives. The most abundant and inexpensive substrates, including aryldiazonium salts, arylhydrazines, aryltriazenes, and pyridinium salts were employed to build C-heteroaryl bonds by two-electron or one-electron pathways. The deaminative process in these reactions occurs mainly through TM insertion into C–N bonds and radical-induced deamination.

Aryldiazonium salts

Aryl diazonium salts are considered conveniently available aryl sources and can be easily prepared from simple aniline and its derivatives. Seminal works from the Sanford group have used aryl diazonium salts as a radical source for directed C–H arylation of arenes. In 2012, the Correia group uncovered the C–H functionalization of heteroaromatics such as indoles, benzofurans, and benzothiophenes with aryldiazonium tetrafluoroborates using a palladium catalyst (Scheme 21A).[65] The method does not involve the generation of radical intermediates. Schoenebeck and Timothy Noël in 2017 described a more efficient system for this transformation with low palladium catalyst loadings (0.5 mol % Pd) (Scheme 22B).[66] Mechanistic experiments and DFT calculations supported a Heck-Matsuda-type pathway, and the computed selectivities are in agreement with experiments in which indoles and benzofurans involve C-2 arylation and benzothiophenes for C-3 arylation. Based on these discoveries, Fairlamb and workers also extended this chemistry to produce C2-arylated tryptophan derivatives with aryldiazonium salts by palladium catalyst (Scheme 22C).[67] Moreover, the applicability of this procedure can also be extended to in the modification of peptides.

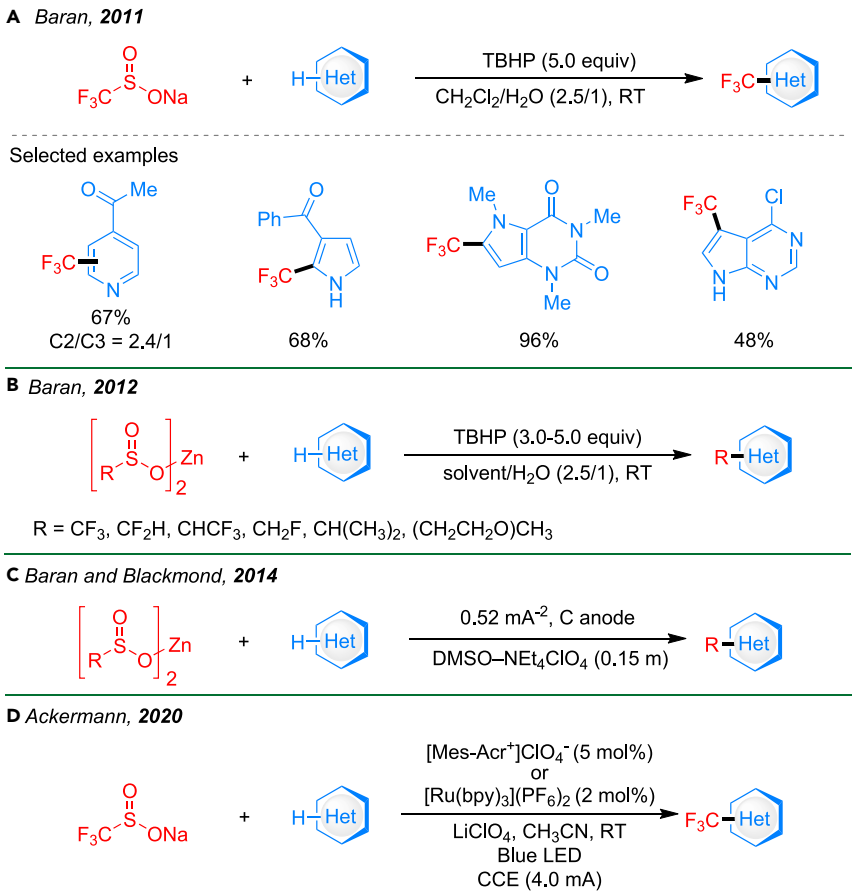
To synthesize aryl-heteroaryl compounds, the König group also applied a photochemical strategy to achieve C–N/C–H bond cross-coupling using aryl diazonium



Scheme 19. Desulfitative heteroarylation of heteroarenes with aryl sulfinates under Pd-catalysis

salts 62 and various electronically rich heteroarenes **63** (Scheme 23A).[68] This is one of the primary models of the application of photoredox catalysis for radical generation in C–H heteroarylation. Several aryl groups were introduced to the C2 position of furans, thiophenes, and pyrroles with excellent regioselectivity when subjected to eosin Y as the photoredox catalyst under irradiation with green light. Mechanistically, oxidative aryl diazonium salts **62** could be converted into aryl radical intermediates by the excited state of eosin Y. Subsequently, the aryl radical was accepted by **63** at the C2 position, forming a radical intermediate. Then, the authors suggested that two plausible pathways might be responsible for the generation of the desired products. (1) The reductive radicals were oxidized into corresponding cations, followed by deprotonation, resulting in aryl−heteroaryl compounds **64**. (2) The radical intermediates underwent sequential radical chain propagation with aryl diazonium salts and deprotonation to give desired products **64**. Later, the Xue group also disclosed a visible-light-driven reaction between aryl diazonium salts and electron-deficient heteroarenes involving pyridines, quinolones, pyrazines, pyridazines, thiazoles, and caffeines (Scheme 23B).[69] Such transformation could be achieved in water using the photoredox catalyst $[Ru(bpy)_3Cl_2]\cdot 6H_2O$ under mild acidic treatment. Radical chain propagation is proposed to occur during this transformation.

Instead of using a photoactivation step, Mandal and coworkers developed an alternative pathway to access C–N/C–H cross-coupling with aryl diazonium salts **65** and heteroarenes **66** enabled by the catalytic amount of phenalenyl-based compound **68** in which a range of heteroarenes, such as azoles, thiophene, furan, and pyridine, were neatly investigated (Scheme 24).[70] Treatment of compound **68** with KO^tBu can *in situ* generate a key phenalenyl-based radical anion intermediate **70** through complex **69**. Then, the aryl radical could be obtained from diazonium salts **65**

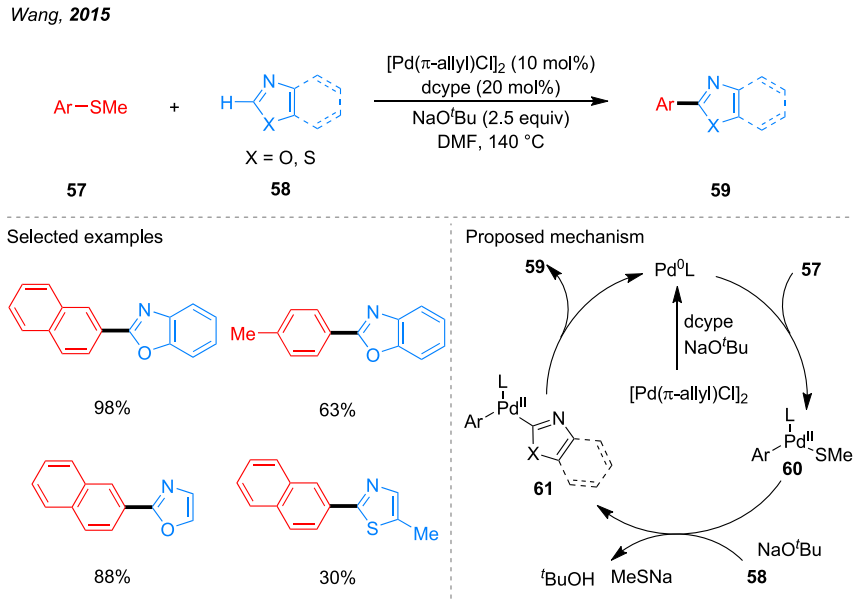


Scheme 20. Radical-induced desulfitative heteroarylation with sulfinates

through one-electron transfer from the singly occupied molecular orbital (SOMO) of active species **70**, which was accepted by heteroarenes **66**. Further SET and deprotonation can yield the desired products **67**.

Starting from aniline, the related aryl diazonium salt can be *in situ* generated. Based on this process, Martín and Carrillo developed a straightforward method for the C–N/C–H coupling of anilines **71** by excess heteroarenes **72** using a catalytic amount of ascorbic acid (**74**) as a radical initiator (Scheme 25A).[71] Aryl diazonium intermediate **75** was generated during the reaction by treatment with ^{t}BuONO reagent. Compound **75** could be converted into the aryl radical by SET from **74** to aryl diazonium through an inner-sphere pathway. Then the radical-mediated process and radical chain propagation provided desired products **73** with high efficiency. At the same time, Felpin and coworkers also achieved C–N/C–H bond cross-coupling directly from pyrroles and anilines under mild copper-catalyzed conditions in which $MeSO_3H$ and ^{t}BuONO were added for the *in situ* formation of aryl diazonium salts (Scheme 25B).[72] The addition of $CaCO_3$ as a buffer additive might suppress undesired acid-mediated azo compounds.

In 2019, Ito and coworkers postulated that a complementary method for agitation of piezoelectric materials through ball milling reduces aryl diazonium salts **76** with electron-rich heteroarenes **77** in which an easily available, inexpensive, and easy-to-handle $BaTiO_3$ nanoparticle was selected as the piezoelectric material (Scheme 26).[73] Although the reaction scope is less, simple thiophene, furan, and pyrroles



Scheme 21. Pd-catalyzed C–S/C–H bond heteroarylation of aryl thioethers with heterocycles

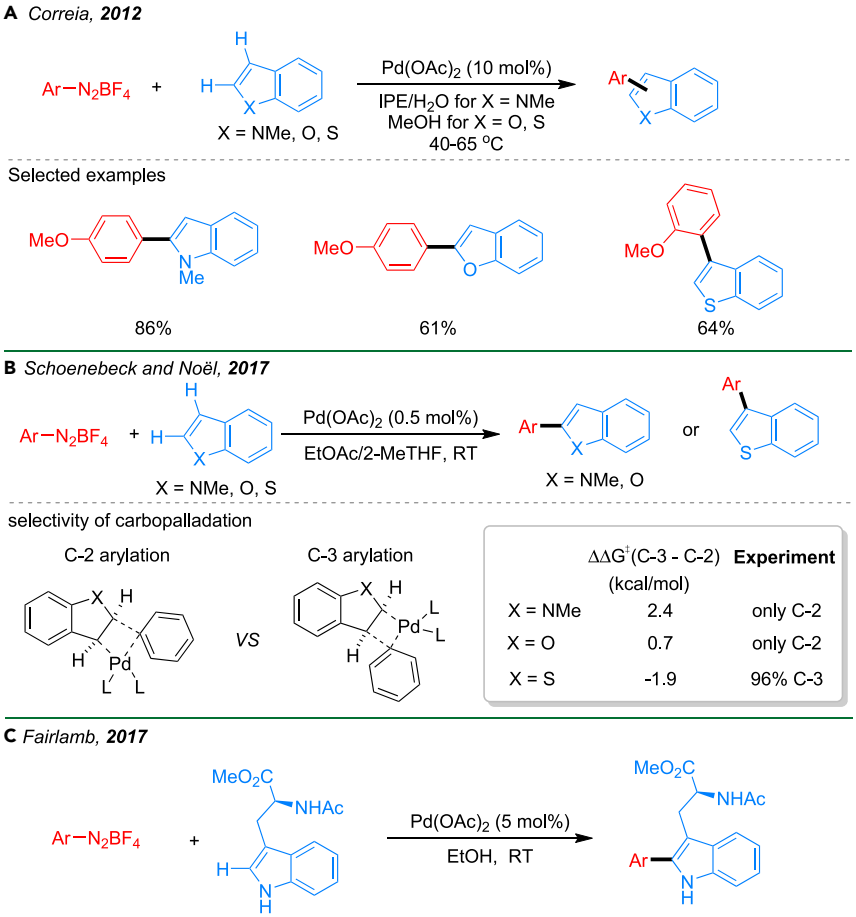
were functionalized well, and this reaction has suitable modularity by the mechanoredox method. In their postulated mechanism, the agitation of $BaTiO_3$ via ball milling generates a temporary electrochemical potential in response to mechanical impact. The temporary polarization should be sufficiently persistent to reduce aryl diazonium salts **76** through a SET mechanism analogous to the photoredox reaction to deliver the corresponding aryl radical. The addition of aryl radicals to **77** would afford a radical intermediate, which would be subsequently oxidized by the hole in the agitated $BaTiO_3$ to form a carbocation intermediate. Finally, deprotonation of carbocation species would lead to products **78**.

Arylhydrazines

Arylhydrazines could also be employed as alternative arylating reagents to access aryl−heteroaryl compounds. In 2013, Chen's group reported that indoles **80** could undergo C–H functionalization with arylhydrazines **79** under aerobic palladium-catalyzed conditions (Scheme 27).[74] Air was considered an oxidant superior to other oxidants, such as metal salts and benzoquinone. Mechanistically, the C–N bond might be activated by the coordination of the nitrogen atom to palladium (II), forming a three-membered palladium complex-**82**, and then another palladium (0) could insert into the C–N bond through oxidative addition leading to intermediate **83**, which was transformed into palladium complex **84**. Subsequently, complex 84 underwent direct C–H activation to generate diaryl palladium intermediate **85** and then reductive elimination to give anticipated products **81**. Moreover, the released palladium (0) returned to palladium (II) by the oxidation of oxygen gas.

Aryltriazenes

Mostly, secondary aliphatic amines such as pyrrolidine/morpholine with arenediazonium salts could be used for the efficient preparation of 1-aryltriazenes, and they can also be converted back to diazonium salts upon treatment with Brønsted or Lewis acids. In 2014, Wang and coworkers described a Pd-catalyzed C2 arylation of N-substituted indoles with 1-aryltriazenes for the preparation of 2-arylindoles (Scheme 28A).[75] Under the conditions of $BF_3{\cdot}OEt_2$ and $Pd(OAc)_2$, the N-substituted indoles reacted with 1-aryltriazenes in N,N-dimethylacetamide (DMAC) solvent to give the



Scheme 22. Pd-catalyzed C–N/C–H cross-coupling of aryl diazonium salts and heteroarenes

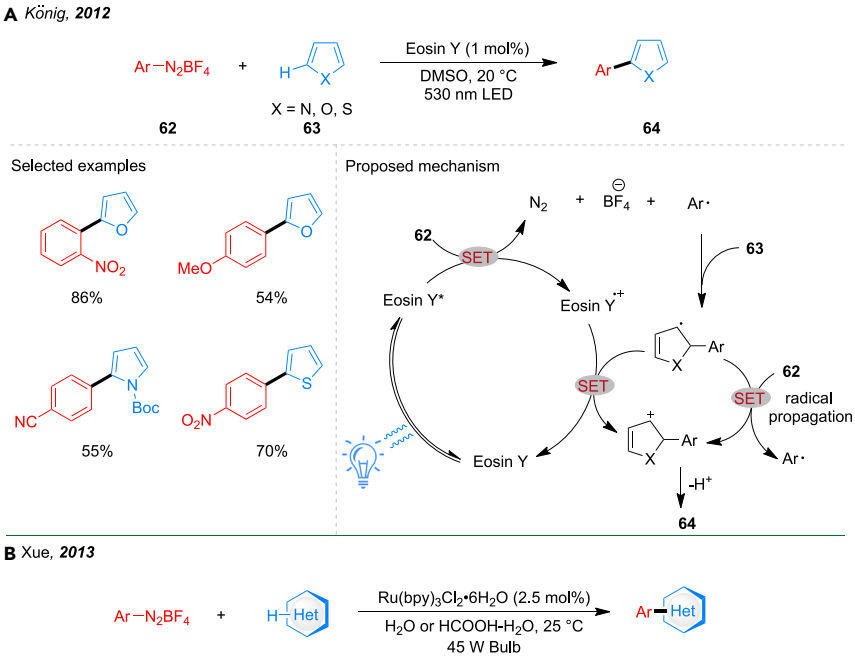
corresponding arylated indole in good to excellent yields. In addition to electron-rich heteroarenes, changing the coupling partners to azoles such as oxazoles was also reported under the combination of a palladium catalyst and stoichiometric copper salts (Scheme 28B).[76,77]

Arylammonium salts

Arylamines have been used for the preparation of aryltrimethylammonium salts and are widely available in nature and industry. Associated with the corresponding arylamines, ammonium salts show much higher C–N reactivity because of the strong C–N bond polarity and release of electronically neutral amines in the course of the reaction. In 2015, the Wang group outlined a general strategy for Pd-catalyzed cross-coupling between aryltrimethylammonium triflates **86** and heteroarenes **87** through C–N/C–H cleavage (Scheme 29).[78] A series of heteroarenes, including benzoxazole, thiazoles, oxazoles, and benzothiazole were investigated with compound **86**, affording desired coupling products **88** in reasonable to excellent yields. Mechanistic experiments suggested that the C–N bond oxidative addition in **86** affords Pd(II) species **89**. Further C–H palladation of **87** with **89** can form complex **90**, which finally endures reductive elimination to give targeted product **88**.

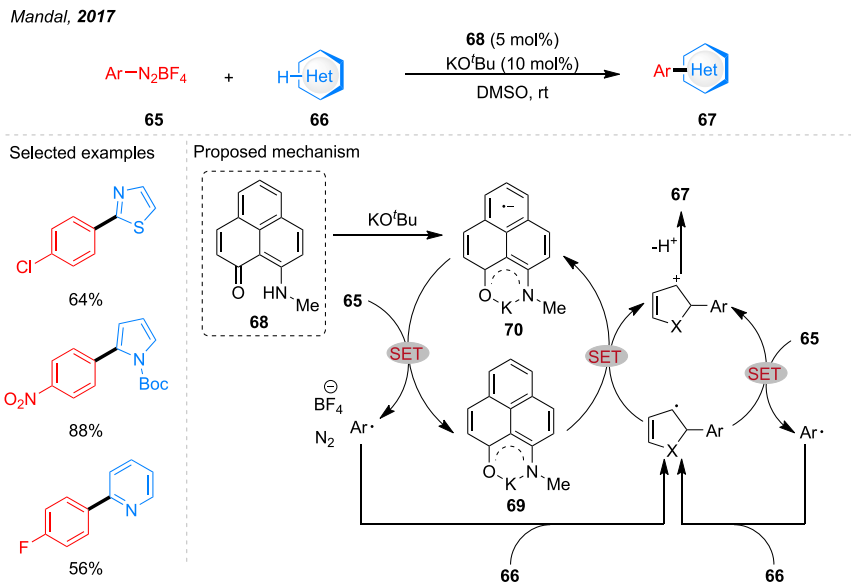
Pyridinium salts

Primary alkyl amines are considered unreactive substrates for the development of unique transformations. Pyridinium salts (also called Katritzky salts) derived from

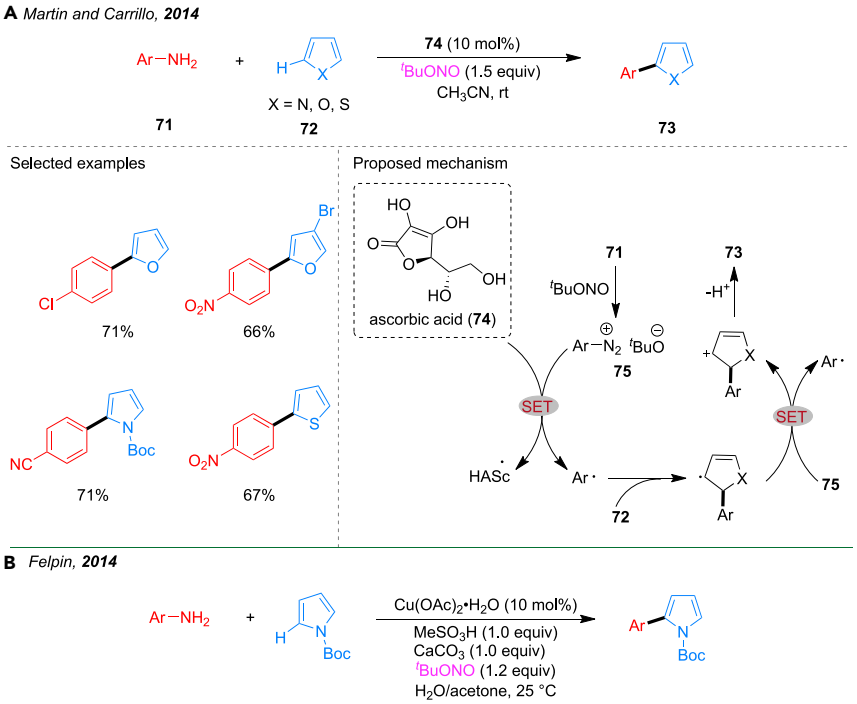


Scheme 23. Radical-induced C–N/C–H bond heteroarylation of aryl diazonium salts with heteroarenes

these primary alkyl amines exhibit high oxidative potential and have received remarkable attention in recent years.[79–81] In 2017, Glorius and coworkers found that Katritzky salts 91 could also undergo Minisci-type reactions under operationally mild and convenient photoredox catalytic conditions (Scheme 30A).[82] Katrizkyl salts with oxidative potential were deliberated as alkyl radical precursors, which could reduce and furnish deaminative alkyl radicals by the excited iridium complex. Subsequently, these nucleophilic alkyl radicals are trapped rapidly by diverse heterocycles

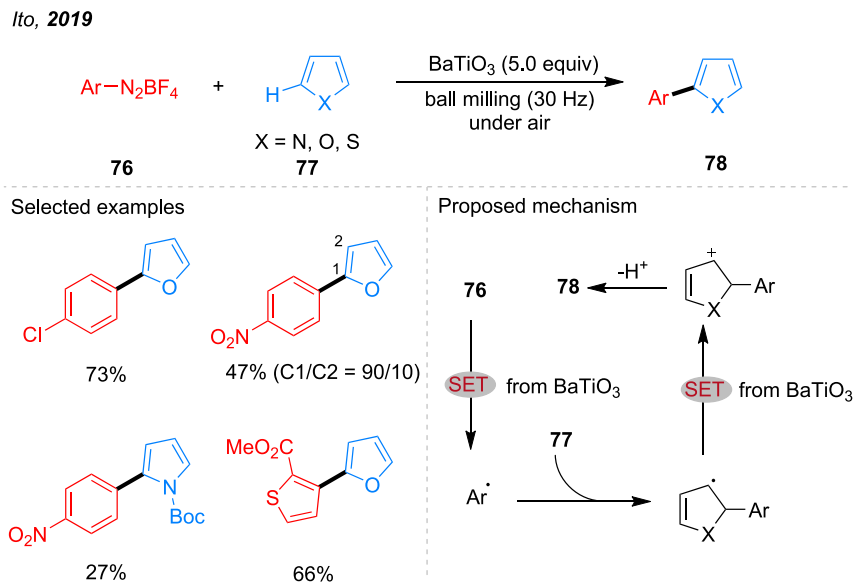


Scheme 24. C–N/C–H heteroarylation using aryl diazonium salts and heteroarenes under phenalenyl-based catalysis

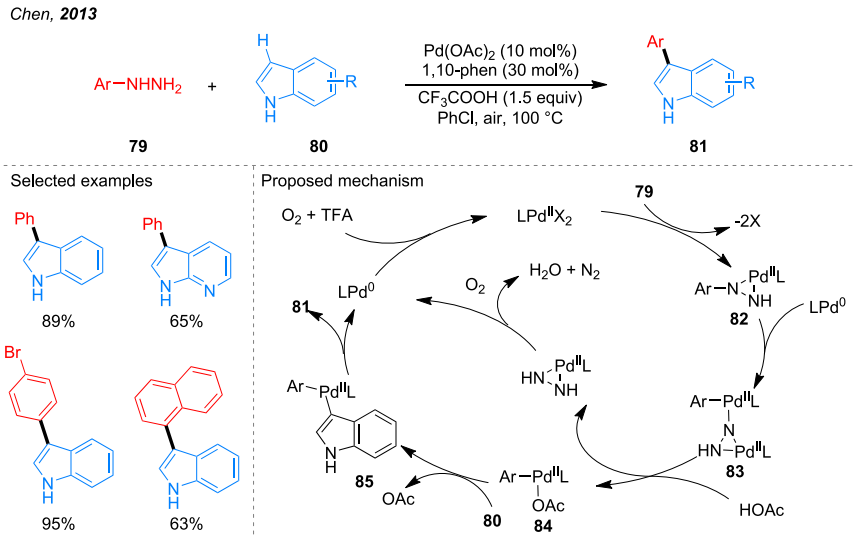


Scheme 25. Radical-mediated C–N/C–H bond heteroarylation of *in situ* formed aryl diazonium salts

92. Eventually, desired arylation products **93** were obtained, enabled by a familiar sequential oxidative SET process and deprotonation sequence. Both electron-deficient N-containing heterocycles and electron-rich indole derivatives were ideal radial acceptors, achieving highly chemo- and regioselective C–N bond arylations. Moreover, some amino acid-based Katritzky salts could also participate in these



Scheme 26. Mechanoredox arylation with aryl diazonium salts using mechanical force



Scheme 27. Pd-catalyzed C3-arylation of indoles using arylhydrazines

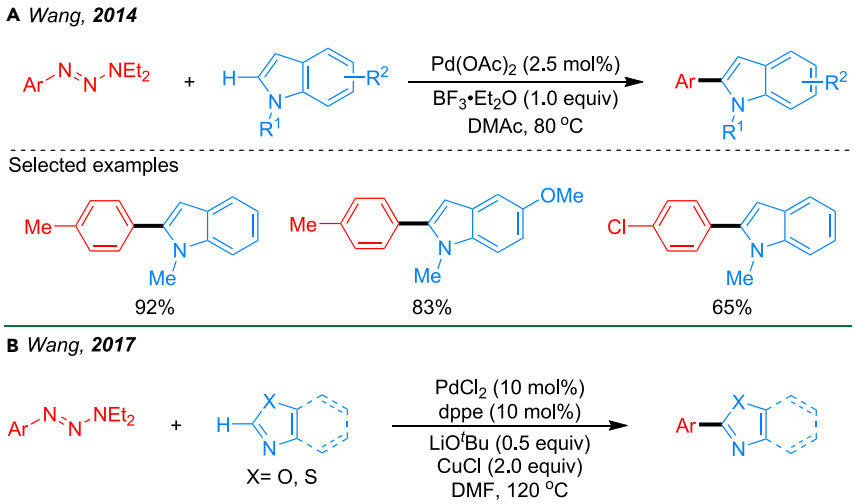
Minisci-type reactions, affording deaminative products. 2 years later, the same group developed a deaminative construction of C–C bonds based on photoexcitation of *in situ* produced electron-donor-acceptor (EDA) complex from electrophilic Katrizkyl salts and electron-rich heterocycles (Scheme 30B).[83] Mechanistic experiments and DFT calculations clarified the vital parts of EDA complexes. The alkyl radicals were released by the light excitation of EDA complexes 94, facilitating the sequential SET process and fragmentation sequence. Then, the alkyl radicals were captured, affording more stable and reductive potential radical intermediates. Subsequently, a radical chain process was triggered and furnished the desired products as well as active radical intermediates with the coordination of Katrizkyl salts to morpholine.

HETEROARYLATION OF C–P BONDS

The effect of phosphines on chemistry is broad, spanning organic, inorganic, organometallic, and analytical chemistry; materials science; and biochemistry.[84] Fine-tuning of the electronic and steric characteristics of phosphines has enabled a wide array of new TM-catalyzed constructs of C–heteroatoms and C–C bonds that have revolutionized organic synthesis. Phosphines have also emerged as efficient organocatalysts and reagents, further enhancing their effect on synthetic methodologies. As a challenging research topic, the extensive exploration of C–P bond activation has attracted wide attention in organic transformation. Over the last few years, extensive developments have realized the C–P bond functionalization of phosphine compounds. Some elegant catalytic manifolds have been developed for the C–P functionalization of heteroarenes via cleavage of C–P bonds in tertiary phosphines and phosphonium salts. The C–P cleavage process occurs by two primary mechanistic paths: (1) C–P bond undergoes oxidative addition with TM catalysts and (2) contractive carbon-carbon coupling occurs via P(V) intermediates.

Phosphines

The activation of C–P bonds in tertiary phosphines with transition metals is a fundamental reaction and an important and challenging research topic in both modern experimental and theoretical chemistry due to the solid interaction with metal catalysts and higher C–P bond energy of approximately 513 kJ/mol. Most of the early



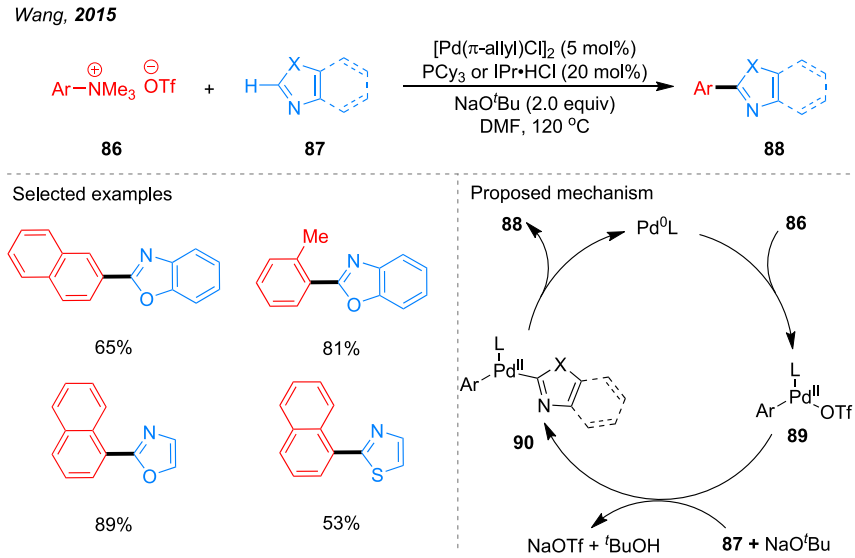
Scheme 28. Palladium-catalyzed C–N bond heteroarylation with aryltriazenes

examples concern the stoichiometric reactions between transition metals and phosphines to give stable phosphido complexes. In 2013, Yao and coworkers first discovered that triarylphosphines could serve as aryl sources for the construction of aryl–heteroaryl skeletons using azoles and indoles as coupling partners under oxidative palladium-catalyzed conditions (Scheme 31).[85] Cleavage of the C–P bond thermally initiated at high temperature. A variety of substituted triarylphosphines could be successfully employed, but the use of sterically hindered triarylphosphines with ortho-methyl groups is unsuccessful to afford the targeted product. Notably, the indoles could be phenylated at the C2 position to provide the anticipated product in 53% yield.

Phosphonium salts

As alternative platforms to transition-metal-catalyzed cross-couplings, phosphorus-mediated cross-coupling reactions through a central pentacoordinate P(V) species were developed in the absence of any metal catalyst. In 2018, McNally and Paton reported an effective approach to form bis-azine biaryls through bis-azine phosphonium salts from C–H precursors and then employed phosphorus-ligand coupling to construct the biaryl bond (Scheme 32).[86] The cross-couplings of heteroaryl phosphine with heteroarenes could be achieved based on P(V) intermediates. Initially, heteroaryl phosphine **97** could be prepared on a large scale when pyridine **95** was treated with reagent **96**. Then, another heteroarene coupling partner could attack the phosphine center, forming diheteroaryl phosphonium salts **98** with complete regiocontrol. Tf_2O and DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) were added to promote this process. Finally, desired diheteroaryl compounds **99** could be obtained under acidic conditions with diphenylphosphine oxide as a byproduct. Mechanistic experiments indicated that the rate of the coupling depended on the structure of the aryl groups attached to the phosphine atom, electron-withdrawing substituents promoted the coupling reactions, and electron-donating substituents retarded the rate of this reaction. Importantly, this approach can be applied to complex drug-like compounds with several reactive sites and polar functional groups and facilitates to convergent coupling of drug molecules and late-stage heteroarylation of pharmaceuticals.

Phosphonium salts were also investigated as redox-active species with a tendency for single-electron-transfer reactions. Paton and McNally recently disclosed a

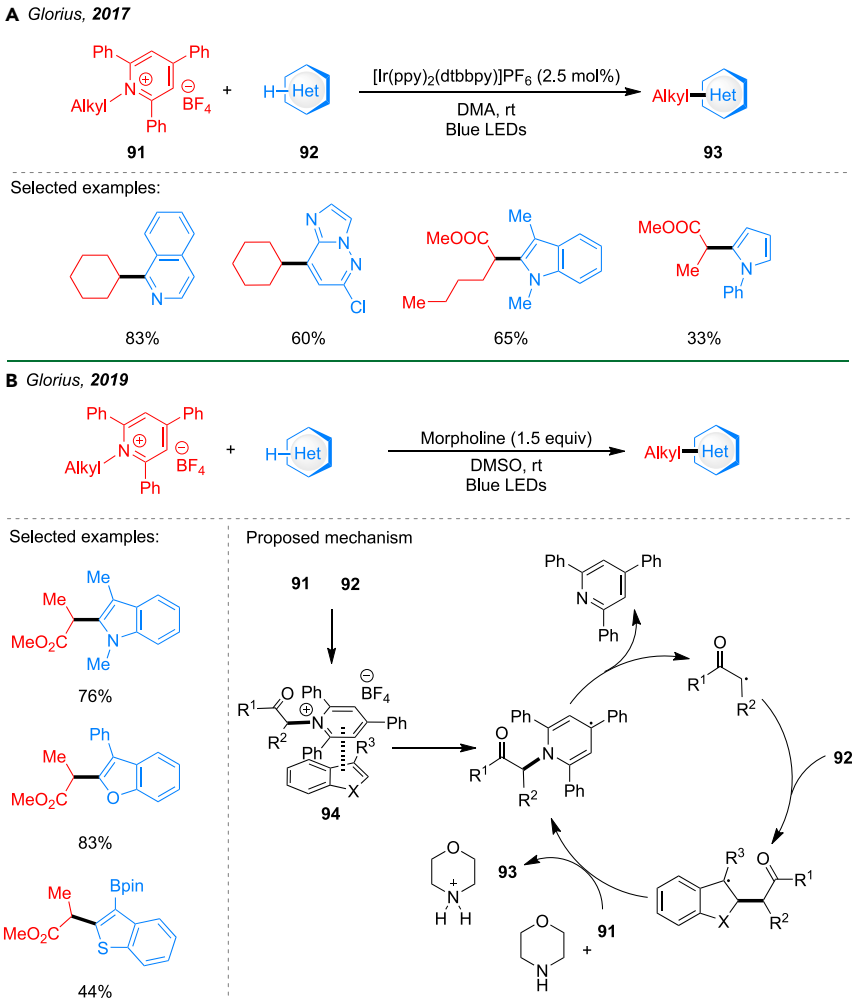


Scheme 29. C–N bond heteroarylation with arylammonium salts under Pd-catalysis

coupling of pyridine-pyridine between pyridyl phosphonium salts **100** and cyanopyridines **101** in the presence of B_2pin_2 as an electron-transfer species (Scheme 33).[87] The sensitive functional group was well tolerated under this reaction condition, and broad regio- and cross-selectivity were realized while forming a series of important 2,4′-bipyridines **102**. The cyano group at the 4-position in pyridine substrates is important for radical stabilization, which exhibits remarkably high regioselectivity at the C2 position during the coupling process. In addition to the cyano group, a phosphonate ester at the 4-position could also serve in this role, but aryl and ester substituents were not effective. Mechanistic studies revealed an unusual pathway wherein the phosphonium group was not expelled to form a pyridyl radical; however, a radical-radical coupling event between a boryl-stabilized cyanopyridine radical and boryl phosphonium pyridyl radical elucidates the C–C bond-forming step. In contrast, achieving cross-selectivity between two different pyridines is challenging in traditional Minisci-type addition, as pyridyl radicals can conceivably react at comparable rates with their radical precursors and coupling partners.

HETEROARYLATION OF C–C BONDS

Selective cleavage and functionalization of carbon-carbon single bonds has attracted numerous organometallic chemistry studies, not only for its essential scientific attractiveness but also for its potential utility in organic synthesis. Various chemists worldwide have intensively developed a range of protocols for the activation/cleavage of C–C bonds, and a significant amount of progress has been made in this arena during the past few decades.[88–90] In recent years, there have been significant and impressive developments in heteroarylation of C–C bonds. In these transformations, substrates with C–C bonds have been cleaved to form new carbon-carbon bonds using diverse heteroarenes, which leads to a rapid increase in molecular complexity. Successful substrates typically rely upon strategies involving moieties such as carboxylic acids, carboxylic anhydrides, amides, esters, alcohols, ketones, peroxides, and DHPS. The C–C cleavage process in these reactions occurs through four primary pathways: (1) decarboxylation, (2) decarbonylation, (3) TM-catalyzed oxidative addition of C–C bonds, and (4) C–C cleavage by radical induction.

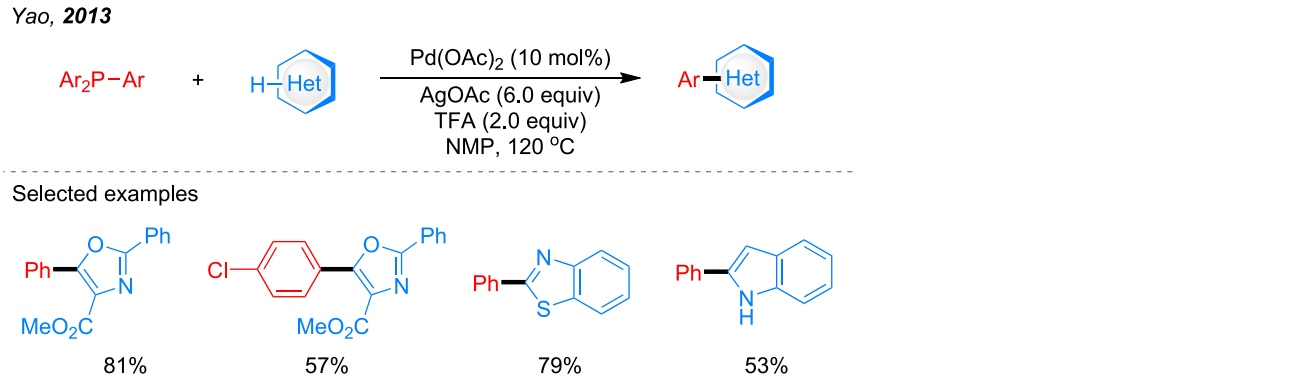


Scheme 30. Visible-light-induced C–N bond heteroarylation with Katritzky salts

Carboxylic acids

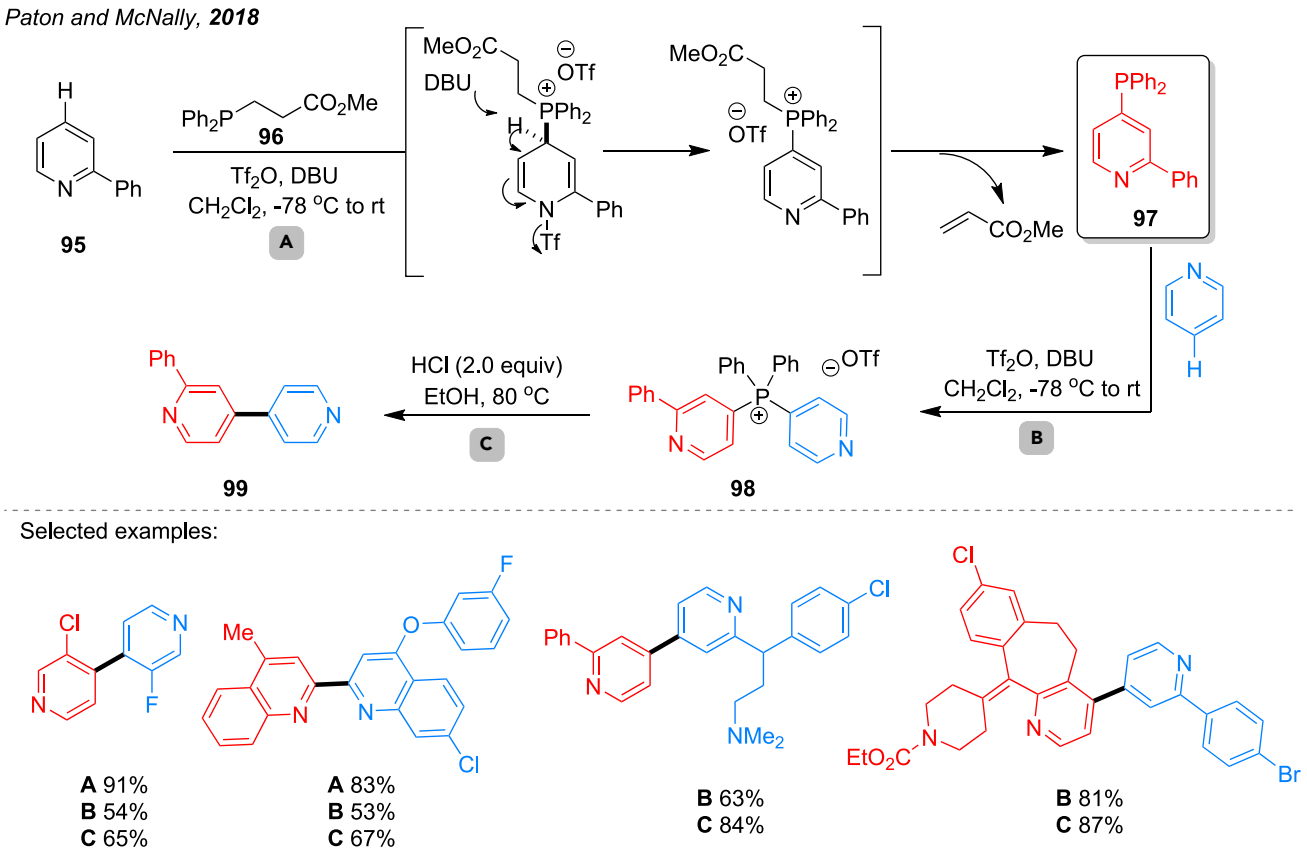
Carboxylate groups have served tremendously as versatile functional groups for the construction of carbon frameworks. Therefore, the direct decarboxylative C–H cross-coupling of heteroarenes in heteroarylation is a fast-growing topic. In 2009, Greaney and coworkers established a Pd-catalyzed, copper-mediated approach for the synthesis of 2,5-linked bisazoles **105** using thiazole carboxylic acids **103** and oxazoles **104** as substrates (Scheme 34).[91] Palladium was responsible for oxazole C–H arylation, and the decarboxylation of thiazole carboxylic acids was achieved by stoichiometric amounts of copper salts. These two catalytic cycles combined with the transmetalation of the oxazole-palladium complex with the thiazole-copper complex afforded a diheteroaryl-palladium intermediate, leading to the formation of the desired coupling products. The use of excess copper salt oxidizes Pd(0) to Pd(II), which participates in the next cycle.

Larrosa and coworkers developed a related decarboxylative reaction between aryl carboxylic acids and indoles under ligand-free palladium-catalysis in which Ag salts played the role of copper salts as additives (Scheme 35A).[92] The *N*-pivalic acyl-protected indoles are considered an elegant aryl source via regio- and chemoselective Pd-catalyzed C–H activation at the C3 position. The proposed mechanism

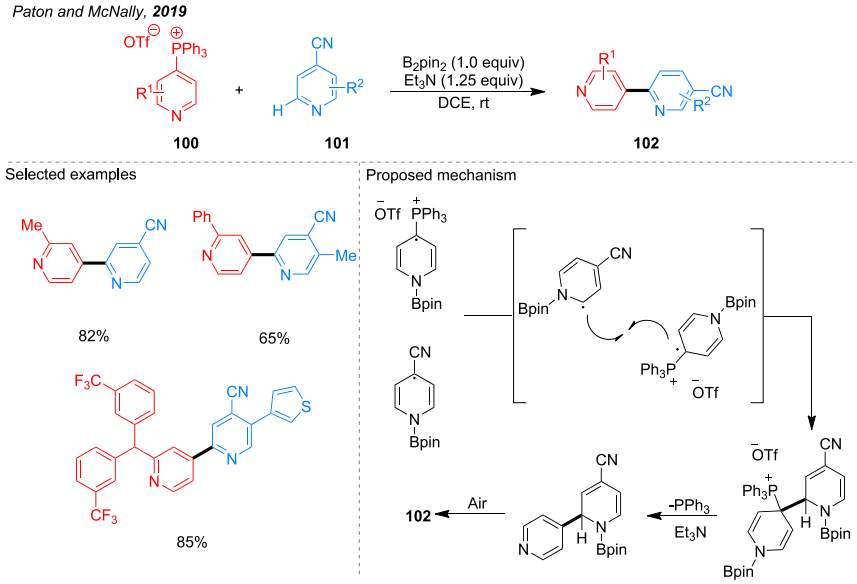


Scheme 31. Palladium-catalyzed C–P bond heteroarylation with arylphosphines

suggested that the silver salts played two important roles in this catalytic cycle as activators for the decarboxylation of aryl carboxylic acids and oxidants for the regeneration of Pd (II) species. Furthermore, the Su group extended this strategy for the coupling of ortho-substituted (hetero) aryl carboxylic acids bearing electron-rich or electron-deficient groups with thiophenes (Scheme 35B).[93] The authors also demonstrated that this coupling was accomplished by silver-mediated decarboxylation and palladium-catalytic procedures. Moreover, they further applied this method for the decarboxylative heteroarylation of aryl carboxylic acids with



Scheme 32. Phosphorus-mediated cross-coupling of heteroarenes toward biheteroaryl compounds

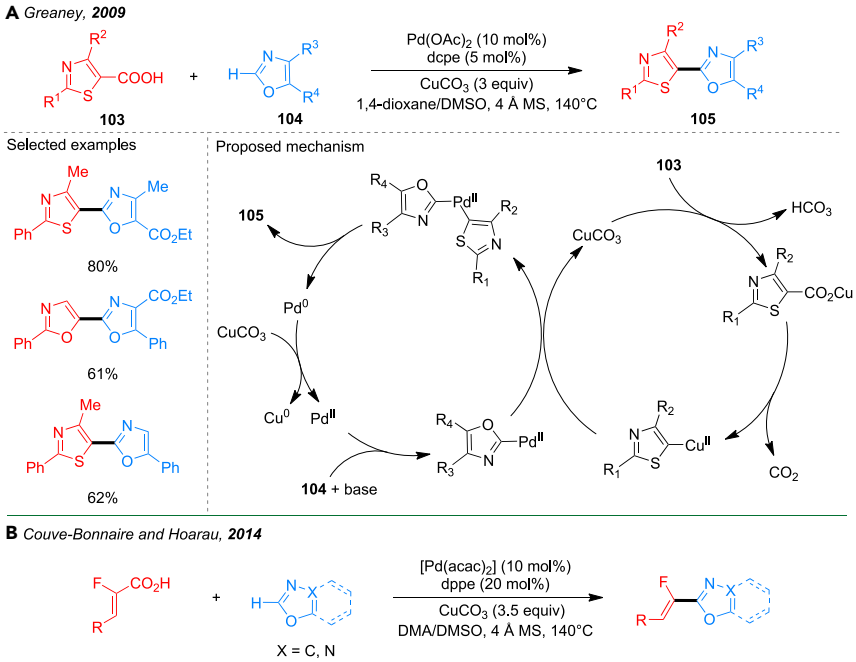


Scheme 33. Radical-radical coupling route for the construction of pyridine–pyridine structures via C–P/C–H cleavage

indoles[94] and furans[95] in the presence of palladium and silver salts. Tan and co-workers disclosed another Pd-catalyzed preparation of aryl–heteroaryl compounds using substituted aryl-derived carboxylic acids with thiazoles and oxazoles.[96] Different from the above-mentioned works, the authors described that palladium-catalyzed decarboxylation and C–H activation were involved during the procedure, and the silver salts merely acted as oxidant for the regeneration of palladium (II). Meanwhile, the Zhu group reported a chelation-assisted Pd-catalyzed C2-acylation of N-pyrimidinyl indoles with α-oxocarboxylic acids by a decarboxylative method (Scheme 33C).[97] $K_2S_2O_8$ served as a co-oxidant, dramatically improving the yield of the products, and the CO_2 gas was released through a palladium(II) complex.

Earth-abundant metal catalysts can also achieve decarboxylative coupling between carboxylic acids and heteroarenes. For example, the Ge group reported the cross-coupling between heteroarenes with α-oxoglyoxylic acids as acyl precursors by nickel catalysts with stoichiometric amounts of Ag salts (Scheme 36A).[98] In 2015, the Hoovera group reported bimetallic Ag/Cu catalysis for oxidative decarboxylative heteroarylation of 2-nitrobenzoic acids with benzoxazoles (Scheme 36B).[99,100] The copper salts in catalytic amounts served dual roles, including facilitating the decarboxylation of carboxylic acid and activation of heterocyclic C–H bond using oxygen as oxidant. Sun, Lu, and Li also established cobalt-catalyzed decarboxylation of α-oxoglyoxylic acids[101] and heteroaryl carboxylic acids[102] with heteroarenes (Scheme 35C).

Unlike the above-mentioned *ipso*-selective decarboxylative coupling reactions, Su et al. demonstrated that heteroaryl cycles 107 were introduced to the *ortho* position of carboxylic acids **106** by chelation-assisted rhodium-catalyzed C–H arylation and silver-mediated decarboxylation (Scheme 37A).[103] The diversity of functionality tolerated on both substrates was impressive, especially thiophenes bearing keto, formyl, ester, alkenyl, chloro, or bromo substituents, which could be smoothly converted to the corresponding products **108** in excellent yields. Among the selected aryl carboxylic acids, the installation of a functional group at the *ortho* position

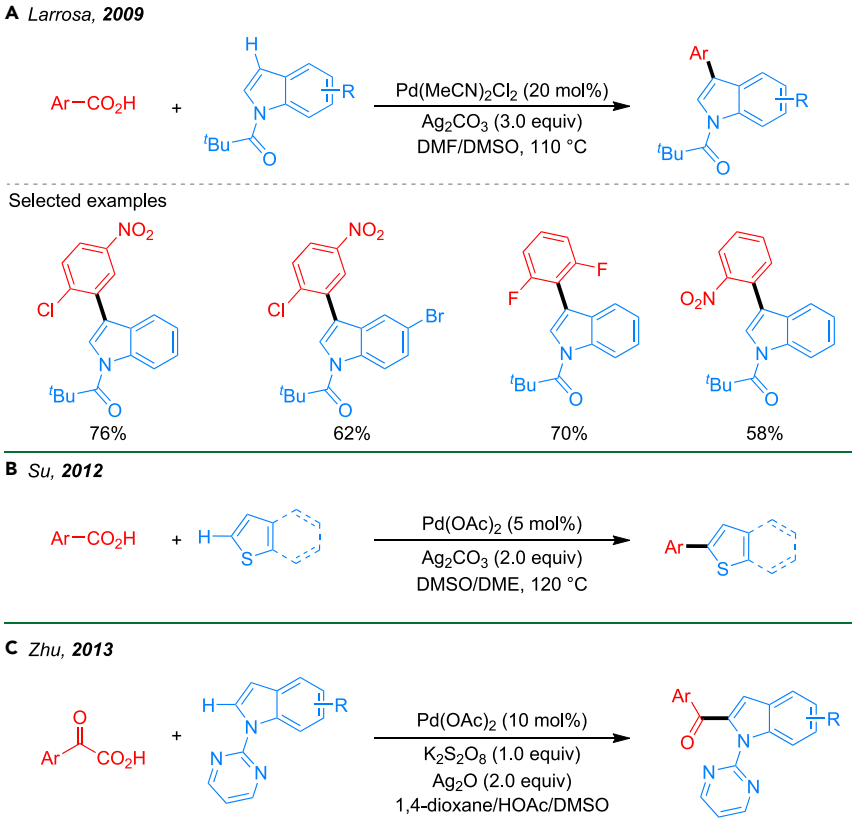


Scheme 34. Palladium-catalyzed, copper-mediated decarboxylative heteroarylation of carboxylic acids

produced higher reactivity. The proposed mechanism consists of two catalytic cycles involving rhodium-catalyzed carboxylic acid-directed *ortho* arylation and silver-catalyzed protodecarboxylation. The developed system can enable carboxylic acid-directed *ortho* arylation to occur prior to Ag-catalyzed decarboxylation. Meanwhile, the Lan and You group deliberated a related Rh-catalyzed decarboxylative C–H/C–H heteroarylation in which a series of heteroarenes, such as benzothiophene, benzofuran, thiazole, indolizine, and caffeine, were investigated effectively (Scheme 37B).[104]

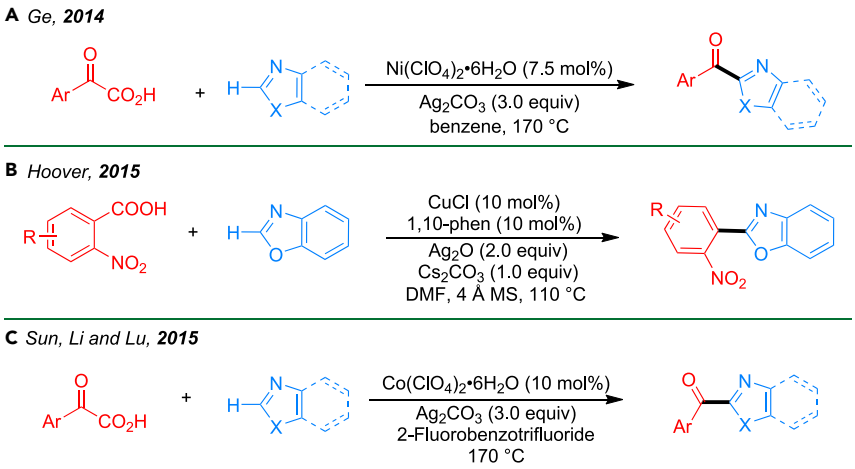
The Minisci reaction involves alkylation of heteroarenes from carboxylic acids; however, the harsh reaction conditions result in the formation of byproducts and thus limit the scope of the reaction. Alternatively, the classical silver/$K_2S_2O_8$-catalyzed reaction system was also suitable for the exploration of decarboxylative Minisci-type reactions. In 2014, Su and coworkers established a cross-coupling reaction of aryl carboxylic acids **109** and electron-deficient heteroarenes **110** via oxidative silver catalysis through a decarboxylative method (Scheme 38).[105] A higher temperature was essential to encourage the decarboxylation process of aryl carboxylic acids to generate carboxyl radicals, and excess amounts of heteroarene and trifluoroacetic acid (TFA) were required to promote radical addition. Although low regioselectivity was observed for most of the substrates, in the case of simple pyridine, there was a slight preference for the second position. Aryl radicals were then added to the aromatic rings, forming new radical intermediates, which were converted to aryl-(hetero)aryl compounds with sequential SET oxidation and rearomatization. Additionally, Qu and Guo reported a silver/$K_2S_2O_8$-catalyzed Minisci-type reaction of alkyl carboxylic acids with purine nucleosides with high regioselectivity at the C6 position.[106]

Radical-mediated Minisci-type reactions are an expedient approach for the synthesis of heteroaryl compounds through decarboxylation of aryl and alkyl carboxylic

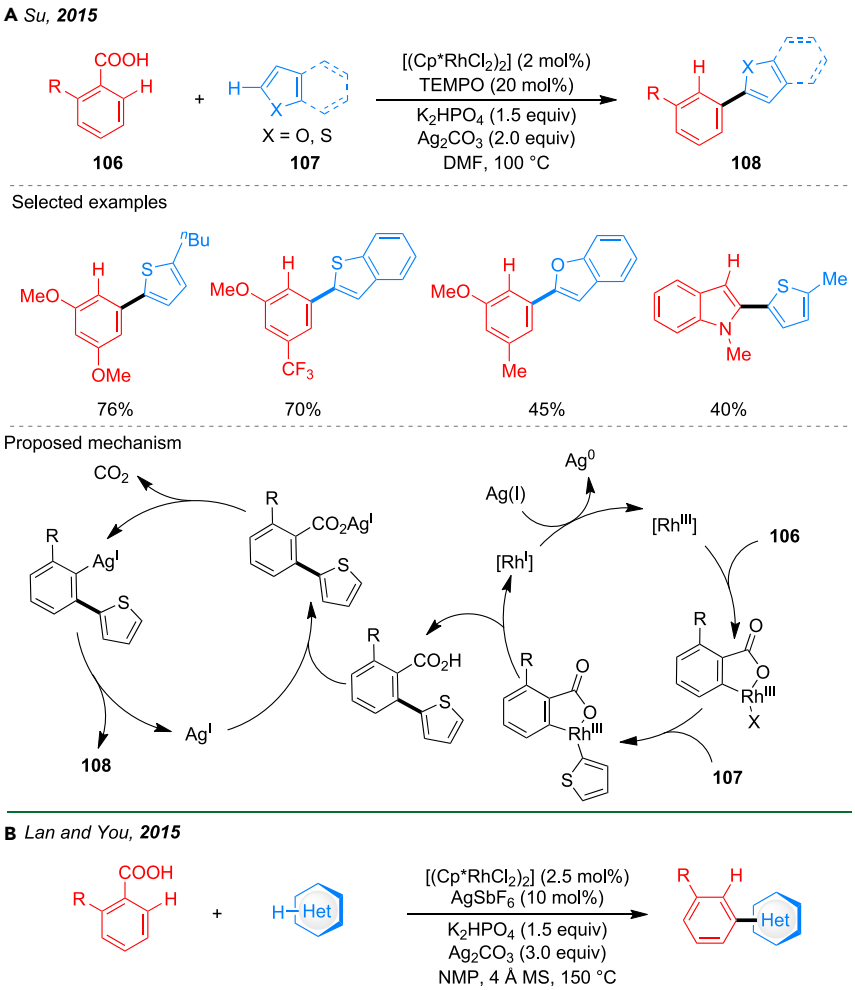


Scheme 35. Pd-catalyzed, silver-mediated decarboxylative heteroarylation of carboxylic acids

acids. In 2015, Glorius and coworkers demonstrated that the Minisci reaction of alkyl carboxylic acids **112** with variable heteroarenes **113** could be realized under photo-induced conditions instead of using silver salts (Scheme 39A).[107] Photoexcitation of the Ir catalyst with visible light produced a reductive potential Ir(III) complex that could be oxidized into an Ir(IV) complex by $(NH_4)_2S_2O_8$ with the generation of sulfate radical anions, which could promote the generation of alkyl radicals from **112** via a



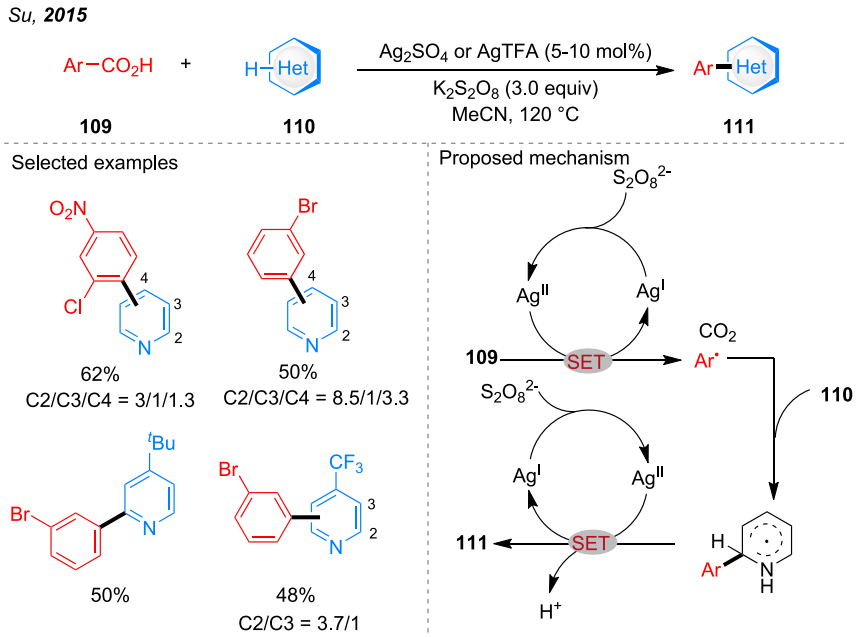
Scheme 36. Nickel-catalyzed decarboxylative heteroarylation of carboxylic acids



Scheme 37. The C–H/C–H cross-coupling decarboxylative heteroarylation under Rh-catalysis

HAT process. Then, the formed alkyl radical was captured by **113**, resulting in a radical intermediate, followed by SET oxidation of the Ir(IV) complex or a radical chain propagation process, with deprotonation affording the coupling products. 1 year later, Genovino and Frenette disclosed a superior visible-light-induced reaction system realizing the Minisci reaction of alkyl carboxylic acids with a wider range of heterocycles in the presence of the photoredox catalyst MesAcr as well as bis(trifluoroacetoxy)iodo benzene (PIFA) as an oxidant (Scheme 39B).[108]

Due to its low price, friendliness in handling and availability in large quantities, TFA is the most attractive trifluoromethylation reagent. The major challenge behind this transformation is the formation of trifluoroacetate radicals under mild conditions, which further undergo rapid extrusion of CO_2 to afford the expected CF_3 radical. Due to the higher oxidation potential, the realization of trifluoroacetate radicals from TFA requires high temperatures and strong oxidants.[109,110] The Su and Li group in 2017 described a photoinduced catalytic process to facilitate decarboxylative C–H trifluoromethylation of (hetero)arenes with TFA and used $Na_2S_2O_8$ in a catalytic amount as an oxidant. Rh-modified TiO_2 nanoparticles were used as a photocatalyst in which H_2 release was considered an important driving force for this transformation (Scheme 40A).[111] First, the photogenerated hole in the valence



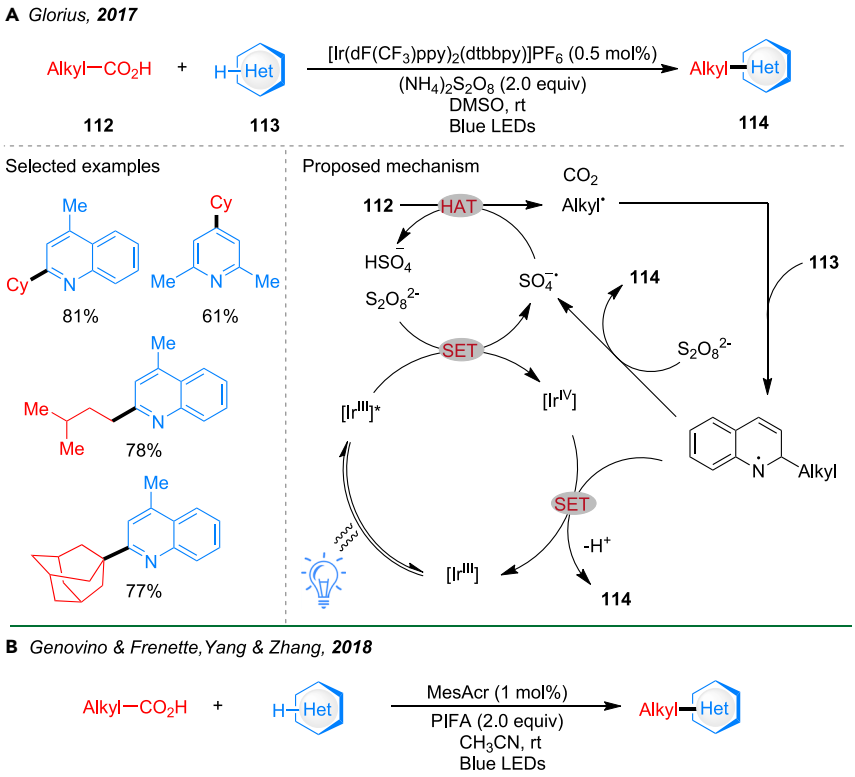
Scheme 38. Silver-mediated decarboxylative heteroarylation of carboxylic acids

band of TiO_2 assists the oxidation of TFA, which leads to a swift decarboxylation process to form the required trifluoromethyl radical along with carbon dioxide and protons. The obtained trifluoromethyl radical was rapidly captured by heteroarenes to produce trifluoromethyl-heteroarene radical. Last, the trifluoromethyl-heteroarene radical undergoes oxidation via a single-electron-transfer method, and subsequent deprotonation affords the final desired trifluoromethylated heteroarenes. Recently, the Jin group also uncovered a practical method for Minisci-type perfluoroalkylation of heteroarenes with TFA and the related carboxylic acids by photoredox catalysis with diaryl sulfoxide (Scheme 40B).[112]

Carboxylic esters

In 2012, Yamaguchi and Itami recognized the first nickel/dcype catalytic system for decarbonylative C–H biaryl coupling of azoles **116** with aryl esters **117** (Scheme 41A).[113] The advantage of this newly established transformation is that the use of highly expensive metal catalysts or silver- or copper-based stoichiometric oxidants is not required. This decarbonylative reaction could be applied for the formal synthesis of muscoride A. A catalytic cycle involving Ni(0), Ni(II), and again Ni(0) was described involving oxidative addition of Ni(0) to C(acyl)-O bond of esters to provide complex **118**. CO migrates onto the Ni center, delivering heteroaryl−Ni(II) complex **119**, and diazole C–H activation is promoted by the base, affording heteroaryl−Ni(II)-diazole complex **120**, with sequential reductive elimination yielding the diheteroaryl skeletons. Moreover, during the exploration of direct C–H alkenylation of diazoles with enol derivatives, Itami and Yamaguchi also applied this nickel-catalyzed strategy for the decarboxylative alkenylation of diazoles using alkenyl esters as alkenyl motifs (Scheme 41B).[29]

In addition to phenolic esters, carboxylic acids can be converted into redox-active *N*-hydroxyphthalimide (NHPI) esters as radical precursors for radical-mediated reactions. In 2017, the Fu group reported that NHPI esters **121** derived from amino acids and peptides could couple with *N*-containing heteroarenes **122**, delivering a series

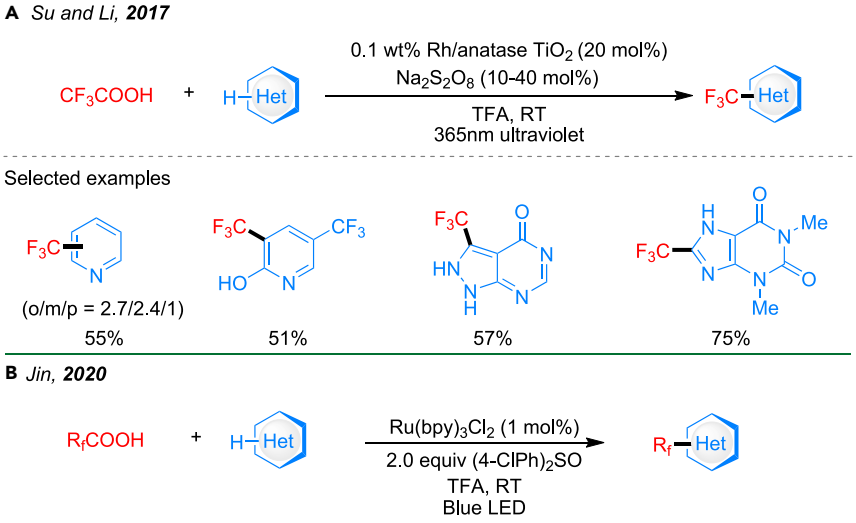


Scheme 39. Photoinduced decarboxylative heteroarylation of carboxylic acids

of Minisci-type products by irradiation with visible light under an Ir-photocatalyst as well as in the presence of racemic phosphoric acid **124** (Scheme 42A).[114] Moreover, the same group disclosed an alternative visible-light-mediated coupling of *N*-heteroarenes with *N*-hydroxyphthalimide esters using a stoichiometric amount of TFA or a catalytic amount of $In(OTf)_2$ as a cocatalyst.[115] The next year, Phipps and coworkers achieved the enantioselective variant using NHPI esters **125** with pyridines or quinolones (Scheme 42B).[116] Chiral phosphoric acid **127** was selected as the cocatalyst, which assembled the radical nucleophile and pyridinium counterion via hydrogen-bonding interactions. The N–H motifs of these radicals derived from redox-active esters via the decarboxylation process played important roles in this interaction. Radical addition onto protonated heteroarenes might be reversible, and both the relative energy of intermediate **128** and the deprotonation barrier of **129** determined the enantioselectivity of products **126**.

Carboxylic amides

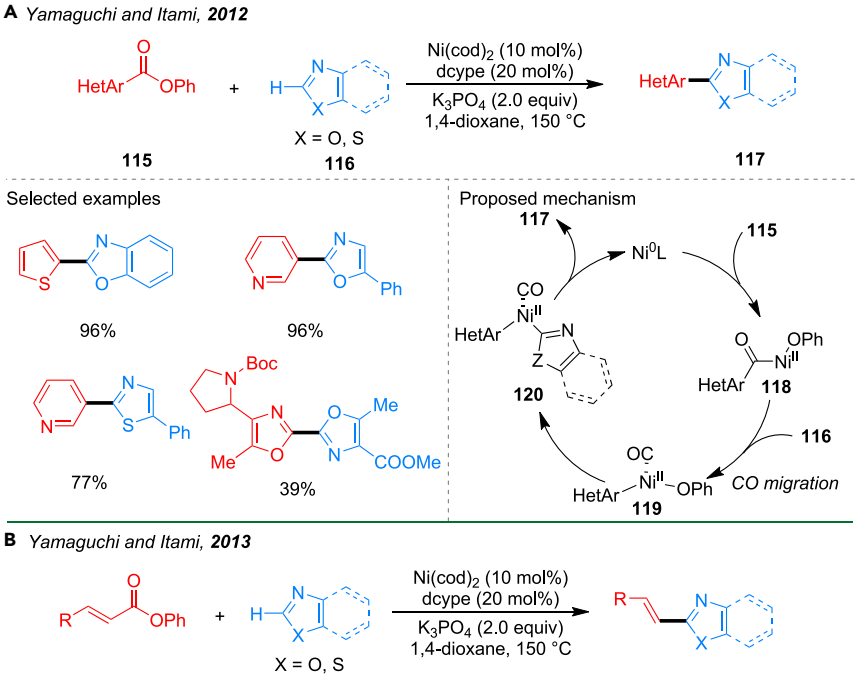
Amides are among the most abundant and important functional moieties present in natural and artificial chemicals, due to the resonance of amides, amides are stable and have poor electrophilicity. In 2017, Zeng et al. reported rhodium-catalyzed C–H functionalization of indoles utilizing N-acylsaccharins as coupling partners through C–N cleavage and decarbonylation (Scheme 43A).[117] The sustainability of functional groups such as esters, formyls, and vinyls and employing removable directing groups are highlights of this reaction. Later, Zhou et al. also reported a palladium-catalyzed, copper-mediated decarbonylative heteroarylation of benzamides with heteroarenes (Scheme 43B).[118] Varieties of heteroarenes involving oxazoles, thiazoles, imidazoles, and oxadiazoles can easily couple with benzamides affording aryl—heteroaryl compounds.



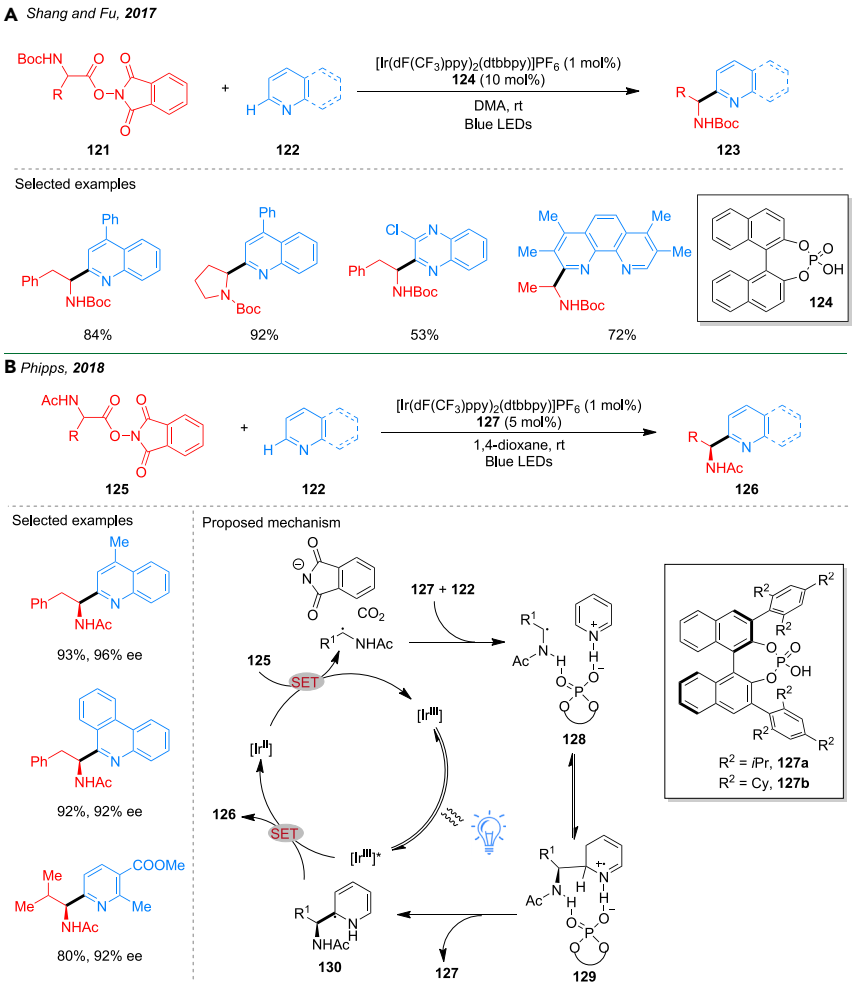
Scheme 40. Photoinduced decarboxylative heteroarylation of TFA

Carboxylic anhydrides

Based on decarboxylation of carboxylic anhydrides, Zhang et al. established an Rh-catalyzed system for the chelation-assisted decarboxylative arylation of *N*-pyrimidyl indoles with aryl carboxylic acids in the presence of $(^tBuCO)_2O$ (Scheme 44A).[119] *In-situ*-generated anhydrides **131** from aryl carboxylic acids and $(^tBuCO)_2O$ were the active precursors that could react with the five-membered rhodacyle complex accessed from pyrimidine-induced C–H activation. In 2019, the Shi group extended this reaction to use a P(III)-directing group, realizing C7-functionalization of indoles with excellent regioselectivity (Scheme 44B).[120] C7 arylation, alkenylation,



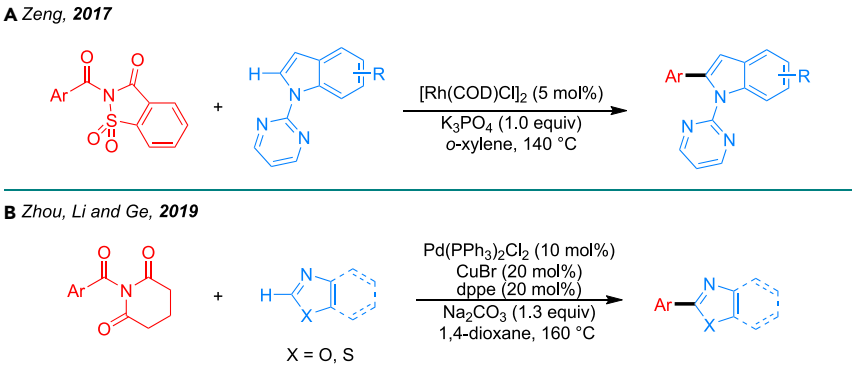
Scheme 41. Nickel-catalyzed decarboxylative heteroarylation of esters



Scheme 42. Visible-light-driven decarboxylative Minisci-type reaction of amino-acid-derived redox-active esters with heteroarenes

methylation, and acylation of variable indoles could be achieved when the reactions were conducted with different coupling partners. Cinnamic acids were added directly for the C7-alkenylation of indoles through the *in situ* formation of anhydrides from cinnamic acids with Boc_2O or methacrylic anhydride.

Very recently, Hong and Szostak reported the straightforward decarbonylative heteroarylation of universal carboxylic acids through acyl C–O/C–H coupling under bimetallic cooperative catalysis (Scheme 45).[121] This catalytic approach exploits the copper and palladium catalyst cooperatively under a decarbonylative procedure, which facilitates the highly chemoselective construction of essential heterobiaryl motifs **133**. The developed procedure for heterobiaryls offers huge advantage in the domain of organic synthesis by coupling carboxylic acids **131** with heteroarenes **132** in the absence of directing groups or prefunctionalizations. To gain mechanistic insights into the bimetallic decarbonylative process, extensive experimental and computational studies were effectively conducted. The transmetalation of the palladium(II) intermediate generated by oxidative addition/decarbonylation with copper-aryl species is the key step for this catalytic cycle.



Scheme 43. TM-catalyzed decarbonylative heteroarylation of amides

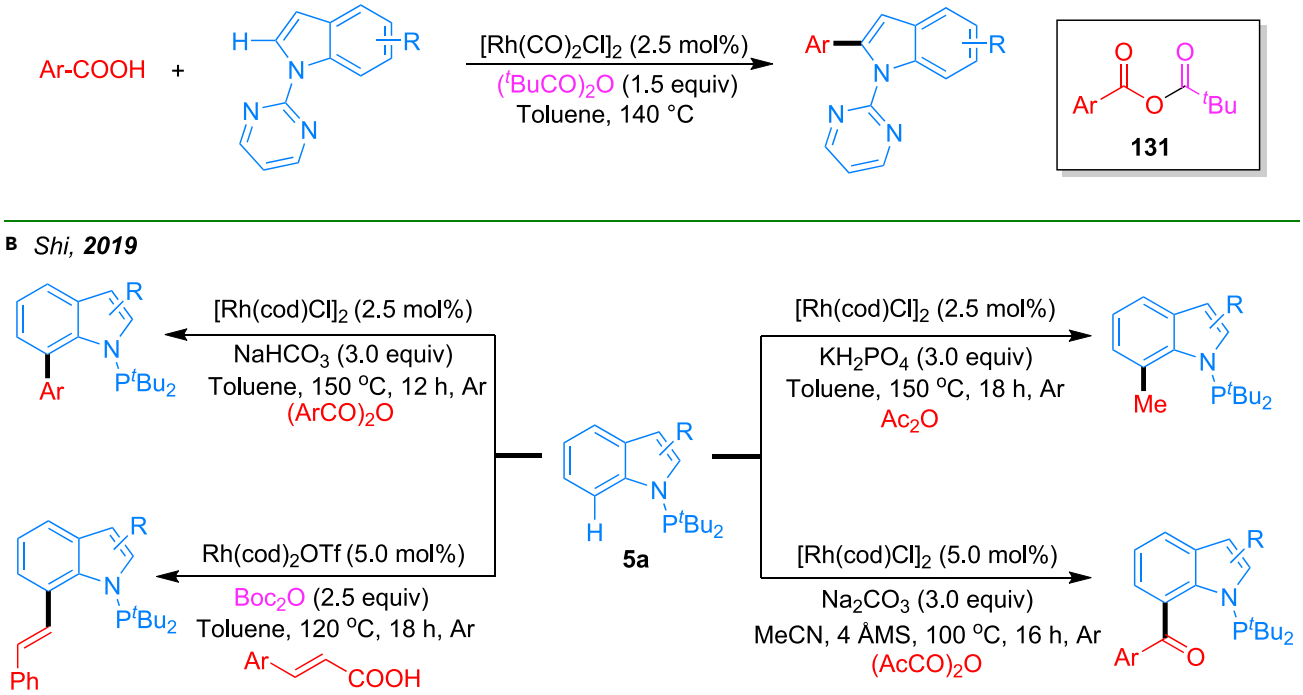
Trifluoroacetic anhydride (**134**) represents an attractive source of CF_3 due to its ready accessibility and low cost, but minimal applications toward this end have been explored. In 2015, Stephenson and coworkers reported Minisci-type trifluoromethylation of heteroarenes **135** using **134** as a CF_3 source assisted by a Ru photocatalyst (Scheme 46).[122] Pyridine *N*-oxide was a key additive for this transformation, which could afford N-acyloxypyridinium salt 137 *in situ* with **134**. This intermediate easily undergoes reductive decarboxylation to produce CF_3 radicals by single-electron reduction from the photoredox catalyst, similar to N-acyloxyphthalimides. Further addition of CF_3 species to heteroarenes through the Minisci-type pathway could produce final products **136**. Further investigation by the same group found that the use of 4-phenyl-pyridine *N*-oxide performed better.[123] Moreover, the modified photochemical reaction system was not limited to trifluoromethylation, and perfluoroalkylation could also be achieved with the replacement of perfluoroalkyl anhydrides with **134**.

Alcohols

As mentioned earlier, alcohols could be used as surrogates for alkyl radicals in Minisci-type reactions proceeding through formal C–O bond cleavage. In addition, secondary alcohols have also been reported for C–C/C–H coupling with heteroarenes by TM catalysts. In 2019, Yu and coworkers described a rhodium-catalyzed direct heteroarylation of indoles **138** with **139** through cleavage of the C–C bond (Scheme 47).[124] Based on the substrate activation strategy, the installation of directing groups in the substrates can overcome the inherent stability of the C–C bond in alcohols. In the catalytic cycle, the formation of a stable metal complex intermediate is a key factor in smooth C–C bond activation of alcohols via β-O elimination and subsequent transformations. Without preactivation of the starting materials, this reaction provides a tool for the prompt synthesis of biheteroaryls **140**.

Peroxides

Peresters and diacyl peroxides are readily available from carboxylic acids and represent a type of activation of the corresponding carboxylic acids. In 2014, Dirocco and coworkers found that several organic peroxides, including **141** and **141′**, could serve as alkyl reagents for radical-mediated C–H functionalization of N-heteroarenes **142**, especially the transformation of small and unstable alkyl radicals, i.e., Me, Et, and ^{c}Pr, into heteroarenes with the assistance of visible-light catalysis (Scheme 48A).[125] As a precursor of methyl radicals, *tert*-butylperacetate (**141a**) was employed in the late-stage functionalization of many medicinal and agrochemical compounds.

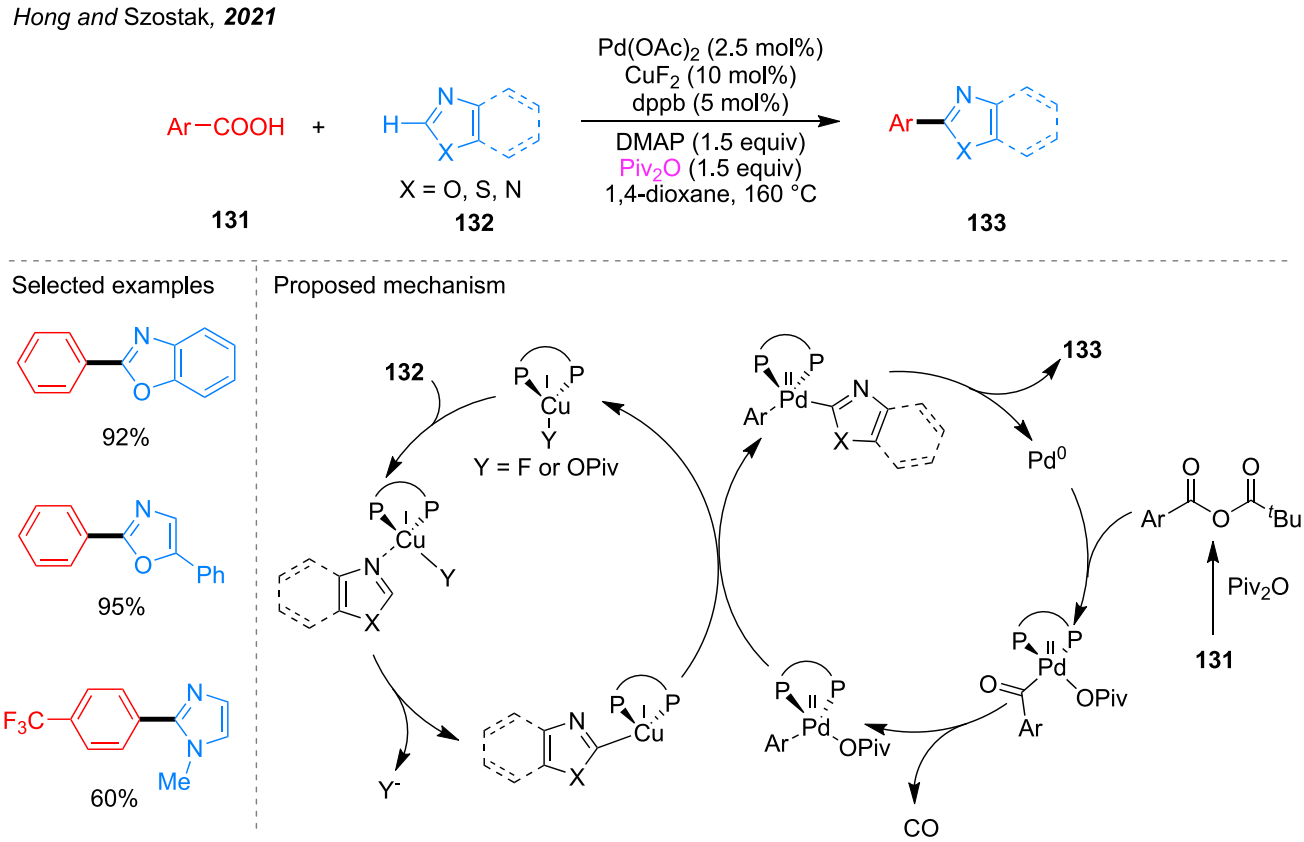


Scheme 44. Rhodium-catalyzed decarbonylative heteroarylation of *in situ* formed carboxylic anhydrides

Mechanistically, the photoinduced Ir catalyst reduces peroxides 141a to a greater extent than fragmentation β-scission to yield methyl radicals. The methyl radical is further added to protonated heteroarenes, and deprotonation and rearomatization with the help of the Ir (IV) complex affords the final product. Instead of using a photocatalyst, the Bao group also uncovered iron-catalyzed C–H alkylation of benzothiazoles with alkyl diacyl peroxides and alkyl tertbutyl peresters through a Minisci-type process (Scheme 48B).[126]

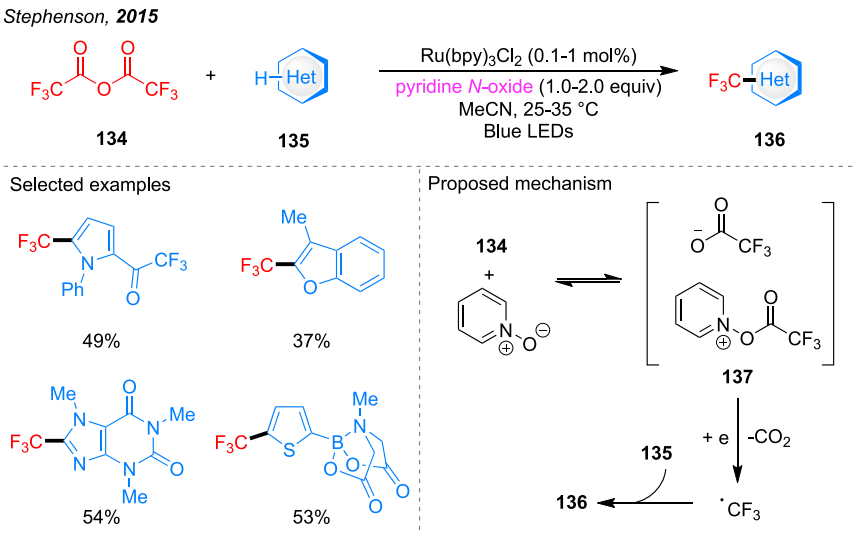
Alkyl-1,4-dihydropyridines (DHPs)

Alkyl-DHPs can be easily synthesized from aldehyde derivatives, which provides alkyl motifs exploited in selective radical-mediated coupling reactions. Compared with alkyl aldehydes, DHPs require harsh reaction conditions to realize certain transformations; DHPs normally take part in such reactions under related mild conditions. In 2017, Molander and coworkers established a convenient oxidative reaction system for the direct C–H alkylation of heterocycles **145** with alkyl-DHPs **144** using a strong oxidant ($Na_2S_2O_8$) under mild acidic conditions (Scheme 49A).[127] The formation of secondary alkyl radicals is the major part of the scope, however, the primary alkyl radicals were also observed with the help of heteroatom stabilization. The use of sodium persulfate as an oxidant and stoichiometric TFA could effectively facilitate the Minisci-type reaction to offer good yield at room temperature. This method could be effective for late-stage functionalization of pharmaceuticals and numerous natural products. In the proposed mechanism, SET oxidation of **144** by $Na_2S_2O_8$ first initiates the alkyl radical; furthermore, the substrate undergoes radical addition, forming a dearomatized intermediate, likely through a radical chain process. Despite this advance, the developed reaction system requires stoichiometric $Na_2S_2O_8$, making it incompatible with readily oxidizable functionalities. To solve this issue,

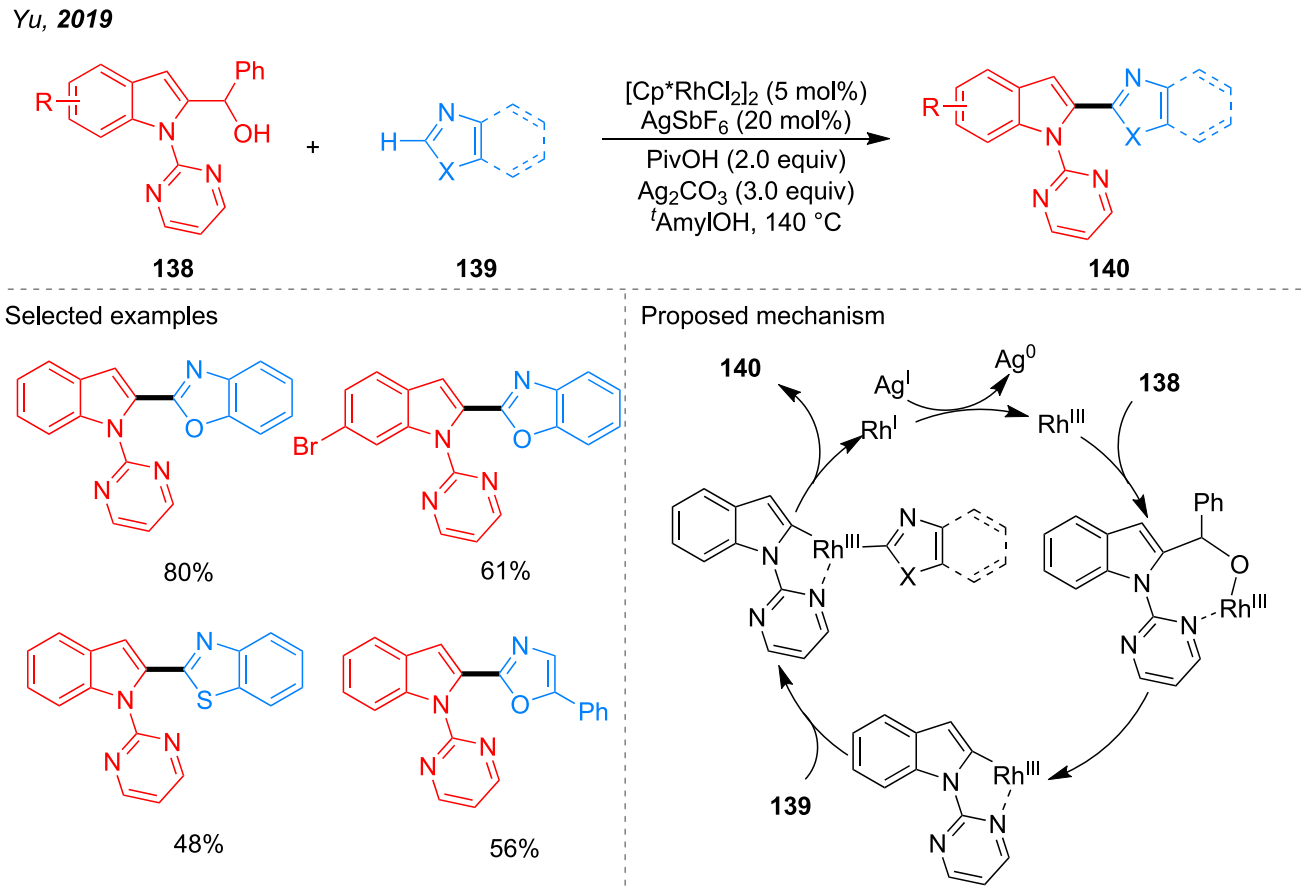


Scheme 45. Palladium-catalyzed decarbonylative heteroarylation of *in situ* formed carboxylic anhydrides

Wang and coworkers further reported a method using molecular oxygen as an oxidant for the direct Minisci C–H alkylation of N-heteroarenes under visible-light-mediated alkyl-DHPs at room temperature (Scheme 49B).[128] Due to mild reaction conditions and excellent functional group tolerance, nitrogen-containing



Scheme 46. Radical trifluoromethylation of heteroarenes with TFAA

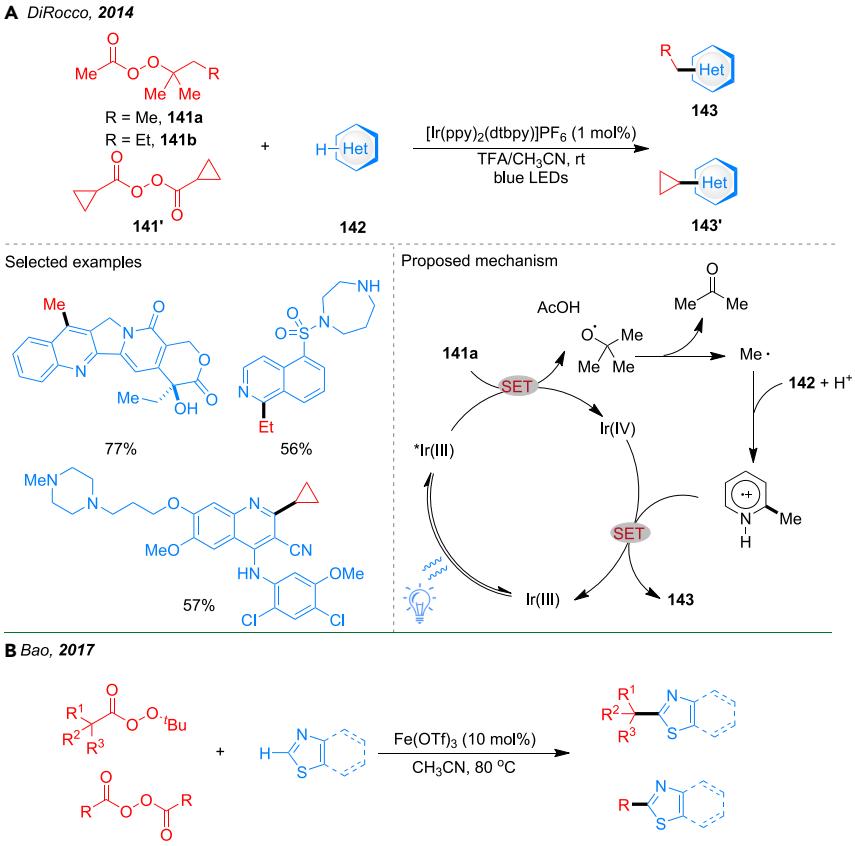


Scheme 47. The direct heteroarylation of indoles by Rh-catalysis via alcohol C–C bond cleavage

drugs and complex natural products are highly convenient for late-stage functionalization.

In addition to alkyl-DHPs, acyl-substituent compounds **147** could also be used as radical precursors. In 2019, the Melchiorre group reported an unusual model of radical C–H hydroxyalkylation of heteroarenes **148**, including isoquinolines and quinolones with substrates **147**, thus avoiding the need for external oxidants (Scheme 50).[129] Essential natural products and active pharmaceutical ingredients have effectively participated in late-stage functionalization due to the high functional group tolerance of this reaction condition. Instead of the typical Minisci-type acylated products, the oxidative Minisci-type reaction opens exclusive reactivity, which leads to hydroxyalkylated heteroarenes **149**. Mechanistic examinations revealed that activated acyl-DHPs **147*** could behave as strong SET reductants and successfully generate nucleophilic acyl radicals, however, without an external oxidant, they led to hydroxyalkylated adducts through a radical-mediated SCS as a vital step.

The visible-light Minisci-type reaction also offers unique opportunities to achieve smooth and clean functionalization of complex molecules by unlocking site-specific reactivities under milder reaction conditions. Using alkyl-DHPs **150** as coupling partners, Chen and Wang recently developed an expedient and largely applicable method for late-stage alteration of peptides **151** through radical-mediated selective C–H alkylation of histidine residues under visible-light-promoted

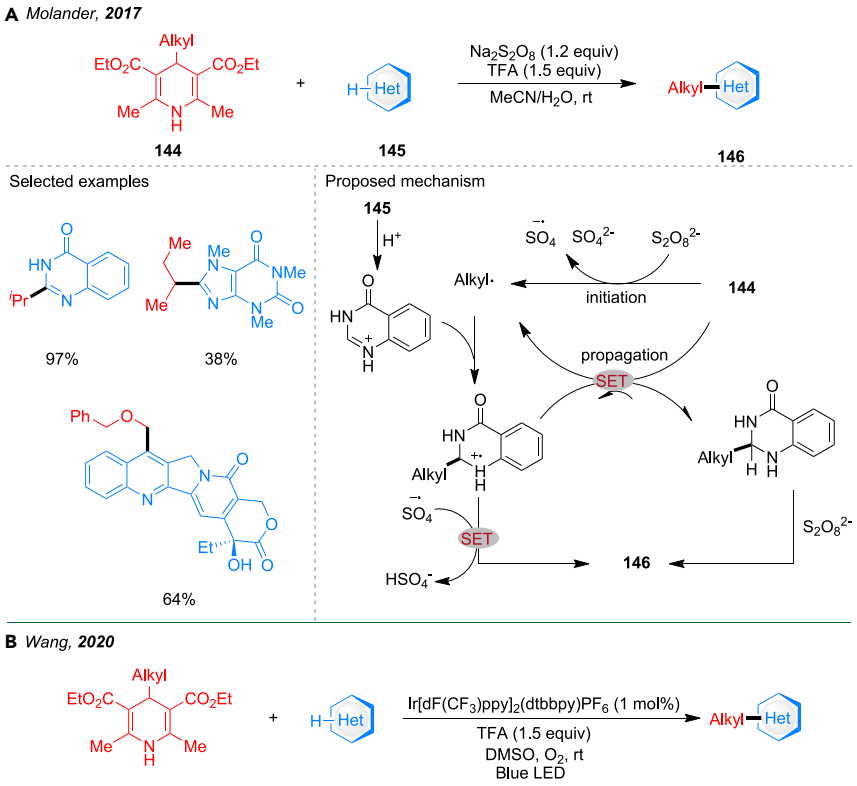


Scheme 48. Radical-mediated C–H functionalization of heteroarenes using organic peroxides as alkyl sources

conditions (Scheme 51).[130] A series of essential peptide drugs, small proteins, and complex natural products were investigated to provide products **152**, showing an exceptionally broad scope. Mechanistic studies of the reaction indicate that reagent **150** plays unprecedented roles as both an alkyl radical donor and oxidant. The exclusion of strong external oxidants is critical to suppress oxidation of peptide substrates.

CONCLUSION AND OUTLOOK

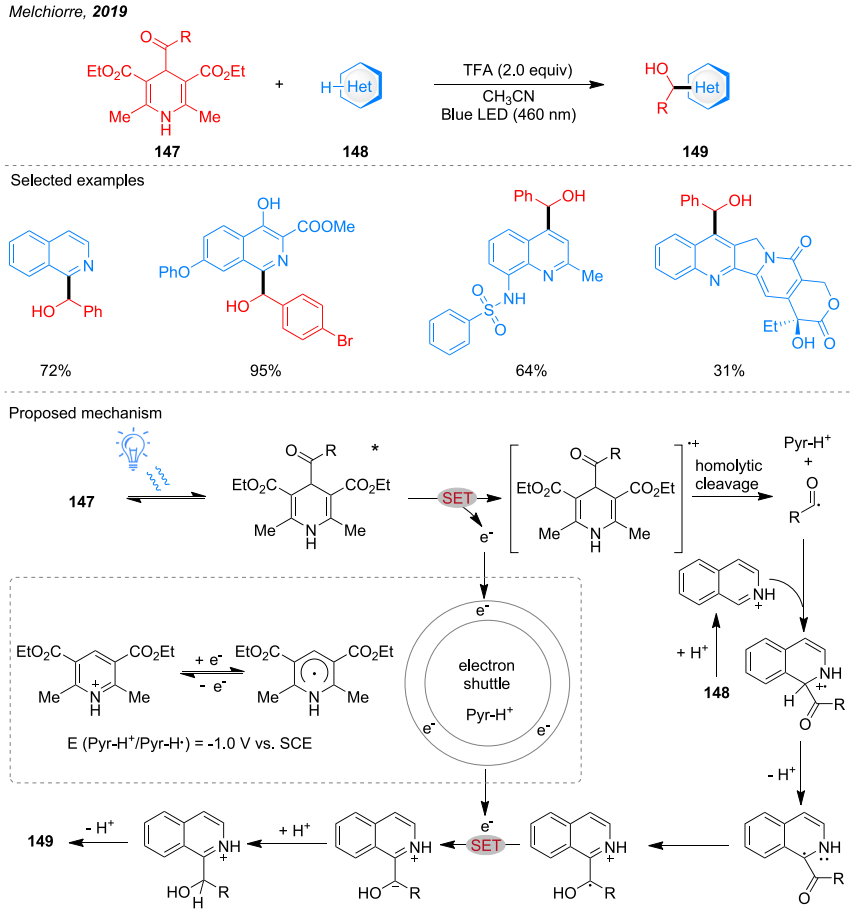
Based on the diversity and quantity of materials introduced in this review article, abundant advancements have been made in the C–H functionalization of heteroarenes through the cleavage of unreactive C–Het (F, O, S, N, and P) and C–C bonds over the past decades. As detailed in this review, these reactions utilize readily available heterocyclic substrates such as indoles, pyridines, quinolones, thiazoles, and imidazoles, which are the most extensively utilized in medicinal chemistry. Alternative coupling partners such as esters, ethers, amines, alcohols, and carboxylic acids, among other prevalent organic molecules that found in nature, are highly appropriate, and the development of a straightforward method for converting them will always be desirable. Although TM catalysts have greatly enhanced the capacity for C–H functionalization of heteroarenes using these readily available feedstocks, significant synthetic challenges remain in this domain. Innovative and efficient ways to cleave these unreactive chemical bonds have been a constant motive either in two-electron or one-electron pathways. Certainly, TM catalysis involving nickel,



Scheme 49. Oxidative C–H alkylation of heterocycles using alkyl-DHPs as alkyl sources

palladium, and rhodium is considered a great facilitating approach, which leads to challenging inert chemical bond activation. Radical-induced protocols involving photoredox catalysis will definitely afford further innovations in the near future, providing a surge of attention within the synthetic community. Therefore, further expansion of the current methods and increasing development of novel transformations are highly desirable.

The C–H functionalization of heteroarenes using simple feedstocks under direct activation of C–OH, C–SH, C–NH_2, and C–COOH still offers a difficult challenge because of the kinetic and thermodynamic stability of these denoted chemical bonds. Moreover, owing to the presence of multiple C–H bonds in heteroarenes, the acquisition of site-selectivity is a long-standing task. For example, much effort has been devoted to the C–H functionalization of indoles and quinolones at the pyrrole or pyridine core, whereas accessing their benzene backbones remains difficult. In addition to this, for attaining stereoselective transformations, various methods conferred in this review offer the possibility to realize stereocenters through the addition of prochiral radicals; however, controlling the absolute stereochemistry in particular centers is a long-standing challenge. To date, only one example has been accessed, in this case by the Phipps group: they accomplished an enantioselective Minisci reaction by merging chiral phosphoric acids and photoredox catalysis. Furthermore, the utility of the developed methods with respect to late-stage modifications of complex molecules, such as drugs, natural products, peptides, and even proteins will have widespread effects across the synthetic community. Ultimately, a better mechanistic understanding of the inert bond activation process would lead to the design and discovery of better catalytic systems that could offer great opportunities in organic synthesis.



Scheme 50. Visible-light-driven C–H hydroxyalkylation of heteroarenes with acyl-DHPs under acidic conditions

In conclusion, the increasing number of reports on the C–H functionalization of heteroarenes with alternative coupling partners demonstrates the importance of this topic. We hope that this review will not only show the most exciting new developments over the last decade but also provide a valuable guide to the respective researchers wishing to enhance the advancement of synthetic chemistry, particularly in pharmaceutical and natural product research.

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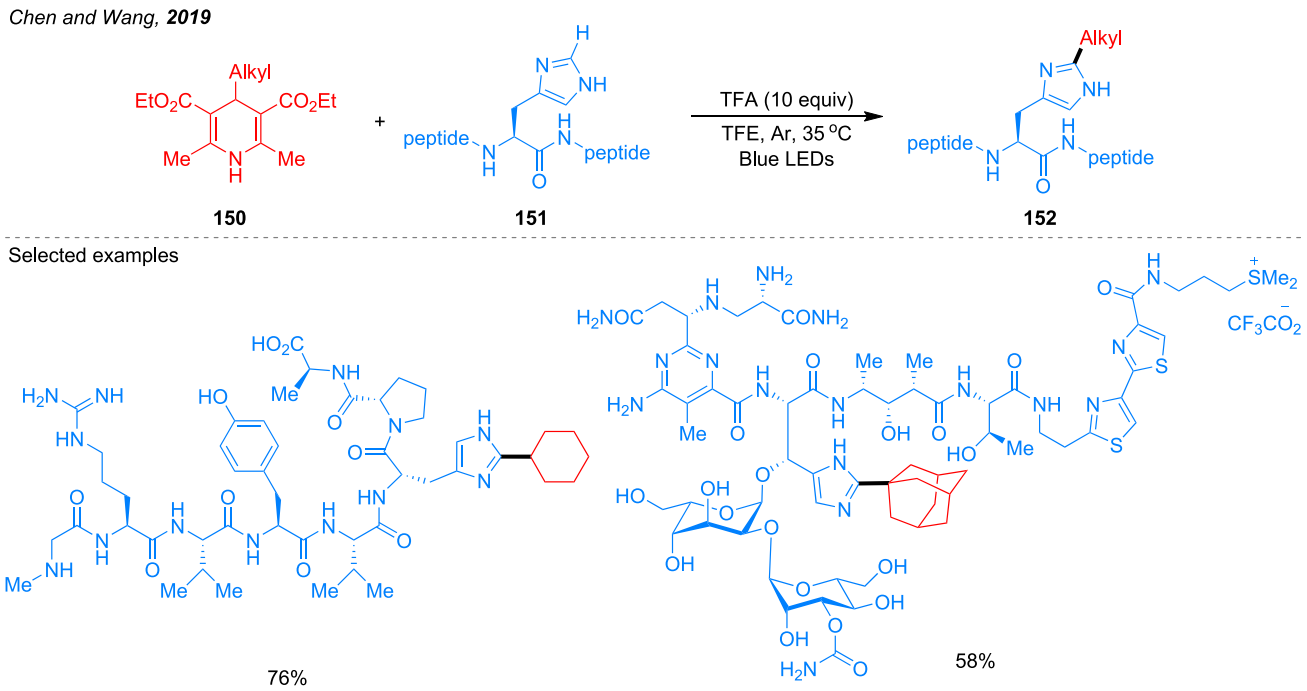
AUTHOR CONTRIBUTIONS

Z.S. proposed the topic and revised the manuscript. B.Z. and B.P. collected the literature and wrote the manuscript.



Scheme 51. Radical-mediated late-stage functionalization of peptides and complex bioactive molecules using alkyl-DHPs as alkyl sources

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