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Recent advances in radical-based C–N bond formation *via* photo-/electrochemistry

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The employment of nitrogen sources with free N–H bonds for amination is considered to be most straightforward and desirable, especially when the C–N bonds are prepared from N–H bonds and non-functionalized carbon sources, such as C–H bonds and C–C double/triple bonds, since this obviates the needs for the pre-installation of reactive groups in the starting materials and leads to a high atom and step economy. Recently, radical chemistry has been resuscitated owing to its great value in organic synthesis, and notable advances have been made in the direct use of N–H bonds for radical-based C–N bond formation with photo-/electrotechniques. Apart from the well-studied N-radical species addition pathway, radical-mediated aminations also proceed through N-atom nucleophilic addition, C-/N-radical cross-coupling, and a hydrogen-atom transfer (HAT) process. This review highlights the recent advances in this area with emphasis on the related reaction mechanisms.

Key learning points
(1) Direct use of N–H bonds for C–N bond construction.
(2) Advances made in radical-mediated amination in photocatalytic and/or electronic methods.
(3) Mechanism details involved in radical-mediated amination.
(4) Scopes and limitations.
(5) The challenges and trends in this area.

1. Introduction

Structures containing C–N bonds are quite prevalent in the field of natural products, pharmaceutical agents, materials, synthetic intermediates, as well as coordination groups. Therefore, development of more convenient and mild amination strategies to install an amino group into a C–H bond has become one of the hottest research goals in synthetic chemistry.[1] The cross-dehydrohalogenative coupling of C–H/N–X (X = halide, pseudo-halide) bonds or C–X/N–H bonds constitute the state-of-the-art techniques, including the transition-metal catalyzed Buchwald–Hartwig amination and Ullman amination, for building C–N bonds. However, as it requires the introduction of a functional group before amination, cross-dehydrohalogenative coupling is considered to have low atom-efficiency in view of green chemistry.

Recently, cross-dehydrogenative coupling (CDC) has become an appealing technique, and it can avert the need for pre-installation of a reactive group in either of the coupling precursors, thus leading to atom and step economy in chemical synthesis. Accordingly, CDC amination, namely using substrates without pre-functionalized C–H bonds and N–H bonds for cross-coupling, is acknowledged as one of the most straightforward and step-economical approaches toward C–N bond formation. With limited but notable advances, reviews on transition-metal-mediated CDC amination have been reported by Patureau[2] in 2014 and updated by Chang[3] in 2016. Generally, transition-metal catalytic CDC aminations rely on the use of directing groups to facilitate C–H metalation followed by reaction with aminating agents. It's undoubtedly clear that the need for removal of these attached groups after amination makes this strategy practically compromised. On the other hand, in direct C–H amination without the assistance of chelation, the substrate scope is mostly restrained to the acidic C–H bonds to allow C–H activation although some cases have managed to overcome these limitations and shown the direct conversion of N–H bonds and inert C–H bonds into C–N bonds *via* metal-nitrenoid species.[4] Apart from metal chemistry, direct oxidative

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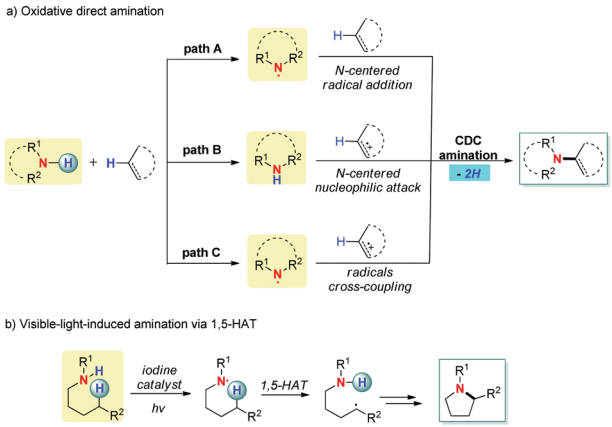

Scheme 1 Applying N–H bond for C–N bond formation.

C–H amination mediated by hypervalent iodine agents has also been achieved by the research groups of Antonchick, Deboef, and Chang, *etc.*[5]

Radical chemistry is undergoing a revival in interest in organic synthesis owing to its inherently advantageous properties, and it has provided alternative avenues to C–N bond construction. Among these, much progress has been made on photocatalytic amination in the past. Moreover, remarkable achievements in electrochemical amination have recently been witnessed. These oxidative direct aminations involve radical intermediates and can be summed up as proceeding through an N-radical addition (Scheme 1a, path A), N-atom nucleophilic addition (Scheme 1a, path B), and radicals cross-coupling (Scheme 1a, path C) without the assistance of metal-chelation, which enriches the methodology of C–N bond formation and broadens the substrate scope to some extent. Besides, the recently modified Hofmann–Löffler-type amination using iodine catalysis or reagents under visible-light irradiation has significantly contributed to the construction of intramolecular C–N bonds directly from N–H bonds and remote C(sp^3)–H bonds (Scheme 1b).

This review mainly highlights the recent advances in radical-based C–N bond formation from the photo-/electrochemically mediated reactions between N–H bonds with diverse C–H bonds, and also includes several examples of C–N bond construction with internal carbon triple bonds and tetra-substituted C=C double bonds without available C–H bonds. Specific emphasis is placed on the reaction mechanism with an aim to stimulate the interest of researchers on developing more practical and versatile amination protocols. Metal-coordinated amination involving radical intermediates has been documented in another review.[6] Except for the modified Hofmann–Löffler-type amination, direct C–H amination enabled only by hypervalent iodine agents in the absence of light irradiation will not be discussed herein. After a survey of the existing literature, radical-involved amination reactions with the employment of N–H bonds were classified into the categories of: N-radical species addition, N-atom nucleophilic addition, radicals cross-coupling, and hydrogen-atom transfer (HAT) according to their different reaction modes. Within these scaffolds, literally conceptional CDC aminations were included.

2. C–N bond formation *via* N-radical species addition

One practical method to forge C–N bonds is through N-radical species addition to unsaturated C–C bonds. Recently burgeoning interest in visible-light photoredox catalysis has provided a number of approaches for C–N bond formation, which typically proceed through the addition of a N-radical species generated from the reductive cleavage of weak N–X (X = N, O, S, Cl, and Br) bonds *via* a single-electron-transfer (SET) process. Photocatalytic amination through breaking the N–X bonds was comprehensively summarized by Zhang,[6] Xiao,[7] and Kärkäs,[8] respectively. Unlike the readily reductive cleavage of N–X bonds, direct scission of the strong N–H bonds to generate N-radical species is challenging

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owing to its higher bond dissociation energy and so it often requires harsh reaction conditions or strong stoichiometric oxidants.

In most cases realizing the utilization of N–H bonds, the aminating agents used for providing N-radical species often possess relatively lower pK_a values to ensure their effective oxidation. Also, electron-deficient functional groups, such as –Ts adjacent to N-atom, could favor the stability of the resulting N-radical species, which has led to the generation of amidyl or sulfonamidyl radicals being much common in the application of N–H bond scission to C–N bond construction.

2.1 Radical addition to C–C double/triple bonds

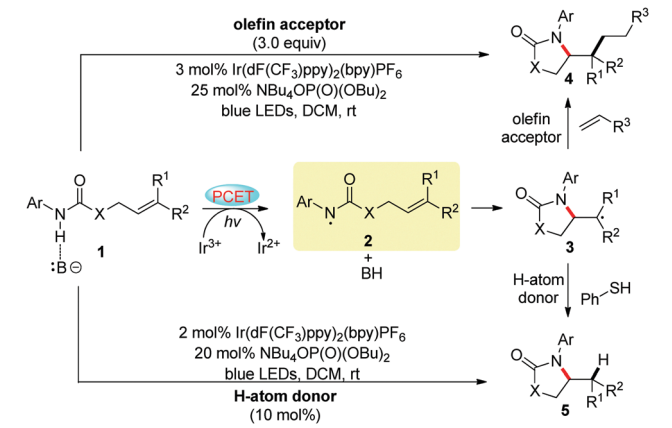
Amidyl radical addition. In the past few years, Knowles' group advanced a systematic platform based on concerted proton-coupled electron-transfer (PCET) catalysis for the formation of N-radical species to facilitate the following C–N bond construction or other transformations. In PCET-enabled CDC amination reactions, the formation of a discrete hydrogen bond complex between the N–H bonds of the substrate and the Brønsted base prior to the electron-transfer step is required to modulate the redox potential of the substrate, thus enabling homolytic activation of the strong N–H bonds under mild oxidative conditions.

In 2015, Knowles' group sequentially demonstrated the carboamination and hydroamination[9] of an alkene with a remote amidyl substituent through the dual action of a mild photo-oxidant and a catalytic Brønsted base (Scheme 2). In these reactions, it was proposed that the N–H bond of **1** first interacts with the weak Brønsted base to form an intermolecular H-bond, which decreases the potential requirements for the electron-transfer process to enable the mild one-electron oxidation by [Ir] species to produce the amidyl radical **2**. Then, the intermediate **2** undergoes intramolecular cycloaddition to the pendant alkene to construct a new C–N bond with a nascent C-centered radical **3**. Subsequently, the nucleophilic radical **3** is intercepted by an electrophilic olefin acceptor to give the carbonamination product **4** after a tandem electron- and proton-transfer process. On the other hand, the radical **3** could also abstract a H-atom from thiophenol to furnish the hydroamination product **5**, while the oxidized thiophenol could then undergo electron reduction by the reduced form of [Ir] species and protonation by the conjugate acid of the Brønsted base to complete the catalytic cycle.

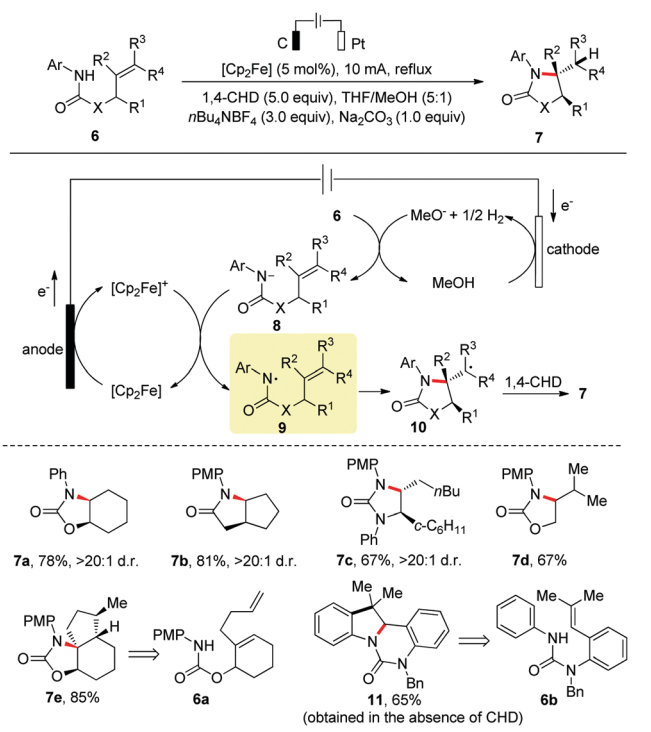
Recently, Knowles and coworkers employed PCET-enabled N-radical formation for the selective alkylation of remote C(sp^3)–H bonds after a nascent amidyl radical-engaging 1,5-HAT process, which was simultaneously disclosed by Rovis's group.[8] Therefore, N-radical formation from the strong N–H bond by concerted PCET activation is supposed to be an optimistic reaction mode in organic synthesis. Also, it is promising to expand a broader scope of N–H bond-containing substrates by searching for appropriate oxidant/base systems.

The revived electrochemical oxidation reaction involving a radical process presents an environmentally friendly alternative to traditional synthetic methods due to the lower production of waste and the high tolerance of the functional groups. In the field of electronic C–N bond formation from unactivated C–H and N–H bonds, a series of achievements have been made by Xu's group. In 2016, Xu and coworkers reported an electrocatalytic olefin hydroamination reaction by utilizing the cheap organometallic ferrocene ([Cp_2Fe]) as the redox catalyst, which obviated the requirements for a stoichiometric strong oxidant and/or expensive metal catalyst (Scheme 3).[10] According to the controlled cyclic voltammetry experiments with a selected substrate **6** and [Cp_2Fe] in a solvent of MeOH with or without THF, no electron-transfer process occurred just in MeOH, suggesting the importance of the less polar media to the reaction success.

The transformation was proposed to begin with the anodic oxidation of [Cp_2Fe] to [Cp_2Fe]$^+$ and the concomitant cathodic



Scheme 2 PCET-mediated amination of alkenes.



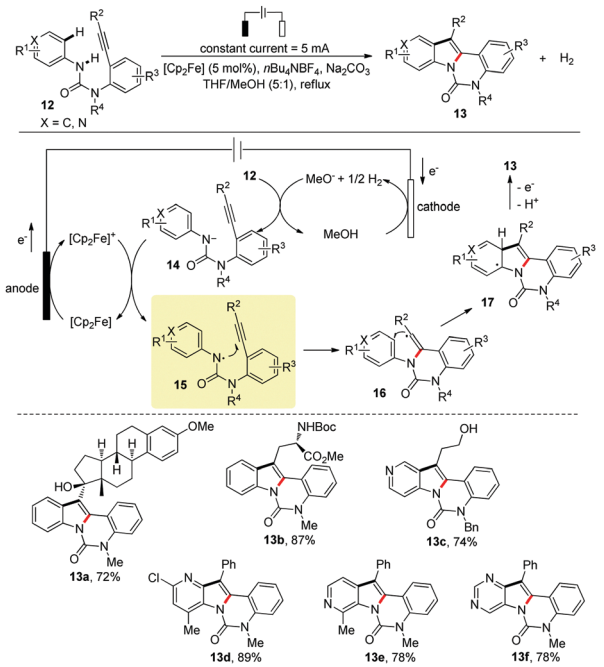
Scheme 3 Electrocatalytic hydroamination of alkenes.

reduction of MeOH to MeO^- and H_2 by applying an electric current. Then critically, MeO^- deprotonated substrate **6** to afford its conjugate base **8**, which represented a better electron donor than the neutral precursor, which was rapidly oxidized by $[Cp_2Fe]^+$ to give the key amidyl radical **9**, along with the regeneration of the catalyst $[Cp_2Fe]$. The formed radical **9** cyclizes onto the linked alkene to furnish the final hydroaminated product **7**, followed by 1,4-CHD donating a hydrogen atom to the intermediate **10**. To illustrate the wide substrate scope of the electronic method, a series of diverse carbamates, ureas, and amides were screened under the standard electrocatalytic conditions, providing good to high reaction efficiency. Interestingly, the generated amidyl radical from **6a** could trigger a tandem cyclization to construct the polycyclic heterocycle **7e** in an 85% yield. Moreover, exposing substrate **6b** to electrolysis conditions in the absence of the H-atom donor CHD finally managed to afford the indoline **11** after an oxidative termination.

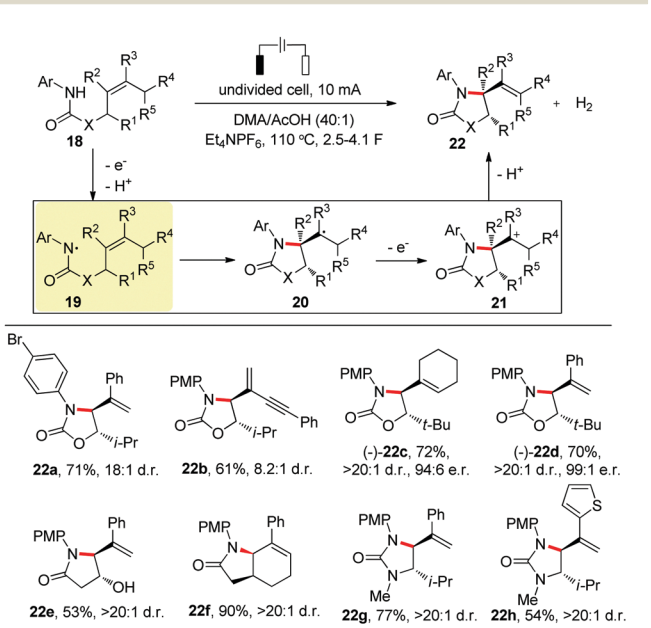
In the same year, Xu and coworkers applied a similar strategy, namely the formation of an N-radical by the electrocatalytic oxidation of N–H bond after deprotonation, to the synthesis of highly functionalized (aza)indoles through C–H/N–H functionalization of (hetero)arylamines with tethered alkynes (Scheme 4).[11] The inexpensive ferrocene ($[Cp_2Fe]$) still served as the redox catalyst to initiate the reaction with anodic oxidation and cathodic reduction, affording $[Cp_2Fe]^+$, MeO^-, and H_2, respectively. Then, the SET process between $[Cp_2Fe]^+$ and the deprotonated **14** produced the electron-deficient N-radical **15** and regenerated $[Cp_2Fe]$. Based on density functional theory (DFT) studies, the radical intermediate **15** was engaged in 6-*exo-dig* cyclization followed by a subsequent radical cyclization to give the delocalized radical **17**. After electronic and protonic donation, the final product **13** was delivered. The scope of the reaction was quite general, which was supported by testing a large number of substrates bearing various peripheral substituents. In addition, various kinds of functional groups were well tolerated in these electrolysis conditions, including the acid/base-sensitive chiral Boc-amino ester (**13b**). Notably, the method was applicable to the late-stage modification of ethinyl estradiol to furnish the indole-containing product (**13a**). Moreover, a wide range of challenging 4-, 5-, and 6-azaindoles (**13c–13f**) could be prepared *via* this electrochemical cyclization in moderate to high yields.

In 2017, substrate **18** with a similar structure to substrate **1** was adopted by Xu's group to the aza-Wacker type cyclization in electrochemistry, wherein the N-centered radical **19** was generated by direct anodic oxidation of the amidyl N–H bond tethered to a polysubstituted alkene moiety (Scheme 5).[12] A C-centered radical **20** could then be readily formed by intramolecular cyclization of radical **19** with the alkenyl group. Instead of being reduced through H-abstraction, the intermediate **20** was further oxidized after donating one electron, leading to its derived cation **21**. After the loss of a proton, the final N-heterocyclic product **22** was delivered. Under acidic and highly thermal conditions, this electrosynthetic method succeeded in achieving the intramolecular oxidative amination of the challenging tri/tetra-substituted alkenes in the absence of a metal catalyst, and was compatible with a wide range of carbamate (**22a–22b**), amide (**22e–22f**), and urea (**22g–22h**) substrates. Especially, subjecting enantio-enriched substrates to the standard electrolysis conditions could result in the stereoselective amination products (−)-**22c** and (−)-**22d** without any loss of enantioselectivity.

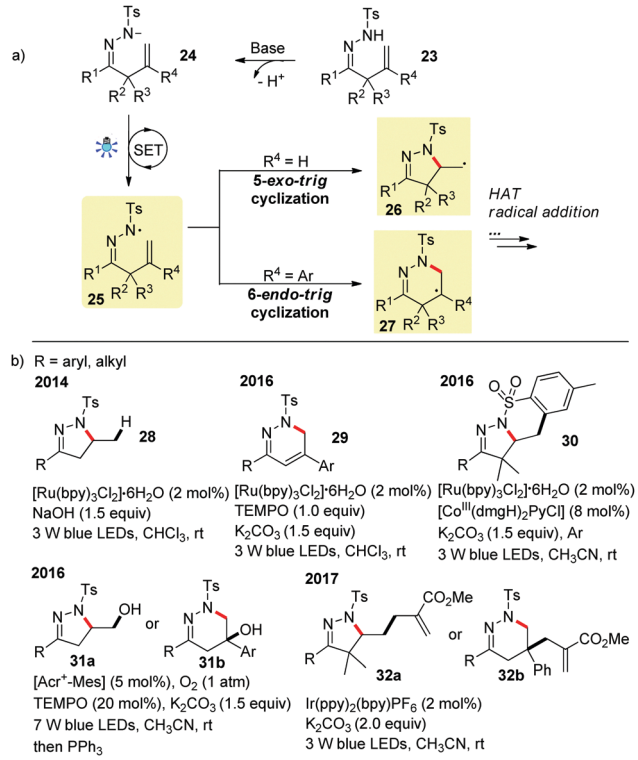
Hydrazonyl radical addition. The acidic N–H bonds of β,γ-unsaturated hydrozones represent another kind of readily available aminating sources for direct N-radicals formation.



Scheme 4 Electrochemical synthesis of functionalized (aza)indoles.



Scheme 5 Electronic intramolecular amination of tri-/tetra-substituted alkenes.

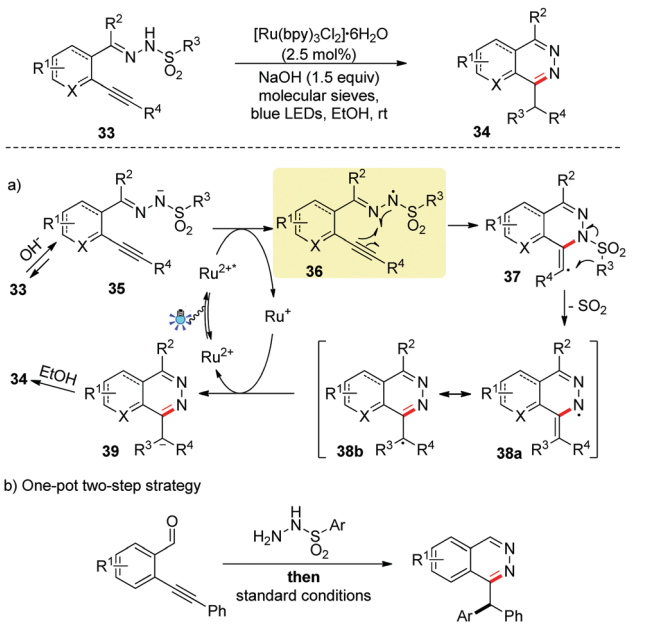


Scheme 6 Applying a hydrazonyl radical for C–N bond formation in photochemistry.

In this area, Xiao's group made much representative progress by manipulating the generated hydrozonyl radical **25** for the synthesis of various dihydropyrazoles or dihydropyridazines in a photochemical manner (Scheme 6a). In these transformations, the crucial radical intermediate **25** was generated not from direct oxidation of the neutral N–H bonds of substrate **23**, but from the single-electron oxidation of the deprotonated anionic species **24** under basic conditions instead. Subsequently, the N-radical **25** could participate in 5-*exo-trig* or 6-*endo-trig* radical cyclization to the tethered alkenes, to access the corresponding intermediates **26** and **27** depending on the substituent R^4, which then undergo further transformations, such as HAT and radical addition, to provide five-/six-membered final products.

In 2014, the first research on the above N–H bond activation mode was developed for the intramolecular hydroamination of β,γ-unsaturated hydrozones (Scheme 6b).[13] The desired product **28** resulted from the radical intermediate **26** through the abstraction of a hydrogen from the solvent $CHCl_3$, which was demonstrated by a deuterium-labeling experiment in $CDCl_3$. The C-centered radical **26** was successfully intercepted by TEMPO to give the related oxyaminated product, strongly indicating the involvement of radical species. In their subsequent work in 2016, Xiao's group this time changed the R^4 of substrate **23** into aromatic groups for the photocatalytic synthesis of 1,6-dihydropyridazines **29**, which was facilitated by a TEMPO-mediated HAT process.[14] Therein, they proved that N-radical **25** with R^4 = Ar preferred 6-*endo* cyclization over the 5-*exo* cyclization pathway due to the lower activation free energy as calculated by DFT. Following this, Xiao and coworkers managed to expand the strategy of the deprotonated oxidative activation of N–H bonds in β,γ-unsaturated hydrozones to other cascade transformations by subtly tuning the reaction conditions, *e.g.*, the synthesis of dihydropyrazole-fused benzosultams **30** through the addition of radical **26** to the phenyl ring of the pendant –Ts group;[15] synthesis of –OH functionalized pyrazoline **31a** or pyridazine **31b** by O_2 trapping the intermediate **26** or **27**;[16] and the synthesis of **32a** or **32b** *via* radical **26** or **27** added to allyl sulfones.[17]

In independent work in 2016, Belmont and coworkers developed a photoredox hydroamination reaction followed by a Smiles rearrangement to obtain highly diversified phthalazine derivatives **34** from alkynyl-substituted arylsulfonohydrazones **33** under basic conditions (Scheme 7),[18] wherein the way to activate the N–H bond of the substrate for the generation of the key N-radical was similar to that in Xiao's work. To examine the reaction scope, they modified the substituted moieties of the substrate **33**. Based on cyclic voltammetry and fluorescence experiments, they proposed that the excited state of Ru^{2+} (Ru^{2+*}) was reduced by the deprotonated sulfonohydrazone **35** rather than its neutral precursor **33**. Meanwhile, the N-centered radical **36** was produced and cyclized onto the alkynyl substituent to give the vinylic radical **37**, which could engage in a radical Smiles rearrangement to yield the balanced phthalazine radicals **38a** and **38b** with the extrusion of SO_2. After that, the ground-state of photocatalyst Ru^{2+} was regenerated from Ru^+ species by donating an electron to the phthalazine radical. Also, the resulting anionic species **39** was protonated or deuterated by the solvent, delivering the final product **34**. In addition, the researchers determined the quantum yield of this transformation as Φ = 0.33, indicating that a radical chain propagation

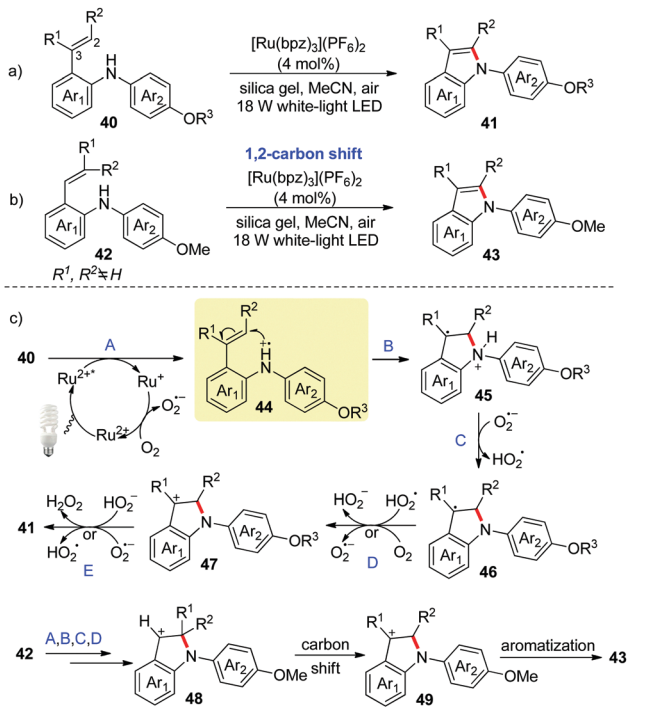


Scheme 7 Visible-light-enabled access to phthalazine derivatives in an amination/Smiles cascade.

process was excluded in the reaction. Furthermore, they attempted to realize the hydroamination and Smiles rearrangement sequence in a one-pot strategy to prepare substrate **33** *in situ* from the corresponding aldehydes and sulfonylhydrazides, which turned out to be equally effective compared to the two-step procedure (Scheme 7b).

Aminium radical cation addition. Alkene amination with the electrophilic addition of an aminium radical cation is also an attractive approach to C–N bond construction. In photochemistry, the critical aminium radical cation intermediate is often generated by a single-electron-transfer process between an aminating source and an excited photocatalyst, and is then prone to be further converted into an α-amino radical or iminium ion causing the desired C–N bond formation competitively and in a challenging process. As representatives, the independent research groups of Zheng and Knowles developed notable photocatalytic direct amination reactions with aminium radical cations that resulted from the oxidation of N–H bonds.

For example, in 2012, Zheng's laboratory disclosed how styryl diarylamines **40** were able to directly participate in C–N bond formation under photoredox conditions, in which *N*-arylindoles **41** were prepared under irradiation from an 18 W white-light LED at room temperature and air atmosphere (Scheme 8).[19] The reaction scope was quite general with various electron-donating and electron-withdrawing substituents on the Ar_1. Most of the functional groups, such as alkenes, arenes, and furans, contained in the styrene moiety were well tolerated under the circumstance of C2 being monosubstituted. While the C2 position was fully occupied, the indole products **43** were obtained in moderate yields *via* a 1,2-carbon shift process (Scheme 8b).

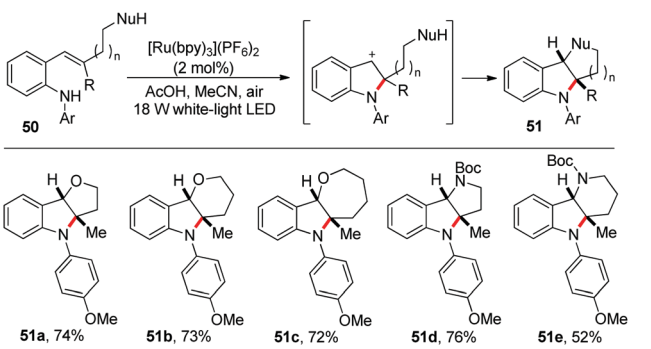


Scheme 8 Photocatalytic C–N bond formation for the preparation of *N*-arylindoles.

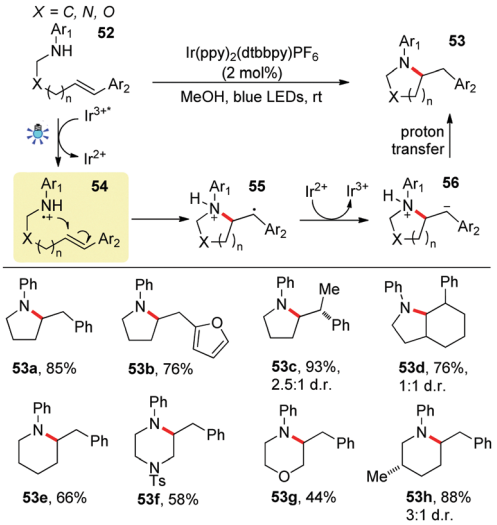
However, substituent groups on the Ar_2 were restricted to *para*-alkoxys to facilitate oxidation, *e.g.*, **42** bearing two methyl groups at the C2 position failed to form the expected methyl-migration product. As depicted in Scheme 8c, the proposed mechanism was presumed to be *via* oxidation of the styryl aniline **40** by Ru^{2+}* to form the key aminium radical cation **44**, followed by electrophilic addition to the attached alkene to afford the benzylic radical **45**. After release of a proton, the resulting radical **46** was further oxidized into its corresponding benzylic cation **47** and then aromatized to the final indole derivative *via* deprotonation. As for substrate **42**, it proceeded through the same transformations to generate the corresponding benzylic carbocation **48**, which was then engaged in a 1,2-carbon shift and aromatization to deliver the product **43**.

Thereafter, the authors expanded the usage of the important benzylic carbocation intermediate to other transformations (Scheme 9),[20] such as incorporating a remote nucleophilic functional groups, such as –OH or –NHBoc, at the C2 position of the styrl anilines **50** to attack the benzylic carbocation, which was obtained under a similar photocatalytic system as that for the synthesis of fused *N*-arylindolines **51**.

In 2014, Knowles' group reported a novel photoredox protocol for the intramolecular anti-Markovnikov hydroamination of (hetero)styrenes for the construction of five-/six-membered *N*-aryl heterocycles **53** under pretty mild conditions, which represented a rare direct C–N bond formation by using aminium radical cations stemming from simple secondary anilines (Scheme 10).[21] The authors proposed that the reaction began with the one-electron oxidation of aniline **52** by the excited state of the photocatalyst Ir^{3+} (Ir^{3+}*) to yield the requisite aminium intermediate **54**, which was further demonstrated by luminescence quenching assays. The following sequence of the intramolecular olefin addition of **54**, the one-electron reduction of **55**, and the proton transfer of **56** furnished the desired product. A number of substrates bearing various substituents on the aniline and styrene moieties were compatible with this method, giving cyclization products, including heterocylic and fused bicyclic ones in good yields. However, the application of this protocol to intermolecular couplings of C–H and N–H bonds was unsuccessful, probably due to the fact that the bimolecular C–N bond formation failed to compete with the favorable



Scheme 9 Visible-light-initiated tandem reactions for the synthesis of fused *N*-arylindolines.



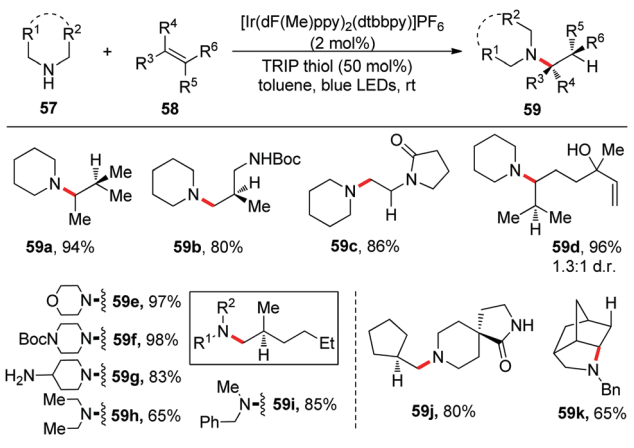
Scheme 10 Photocatalytic intramolecular hydroamination of olefin with aminium radical cations.

electron back-transfer from the reduced Ir^{2+} to **54**, as the authors supposed.

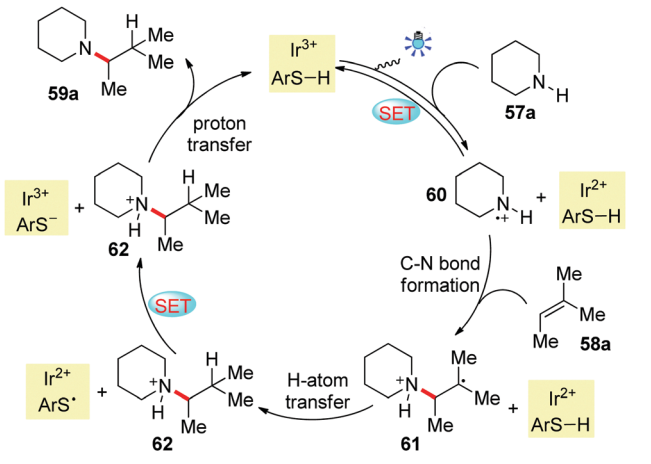
With their continuous research on olefin amination chemistry, Knowles' group recently realized the formidable intermolecular anti-Markovnikov hydroamination of unactivated alkenes **58** with secondary alkyl amines **57** that proceeded through a photocatalytic aminium radical cation intermediate (Scheme 11),[22] which had been challenging to achieve with metal-catalyzed and other methods. The approach was highlighted by its absolute atom-economic, redox-neutral environment and broad functional group tolerance under significantly simple and mild reaction conditions. Using piperidine as the amine source, various patterns of olefins, including terminal and di-/tri-/tetra-substituted internal ones as well as silyl enol ether and electron-rich styrene, were able to be hydroaminated in generally high yields (**59a–59d**). Notably, the aminium cation radical preferred to add to the more electron-rich trisubstituted internal C=C bond when two electronically differentiated alkenes existed in the same substrate (**59d**). Then, numerous cyclic and acyclic secondary alkyl amines, even more structurally complex and sterically demanding, were found to be viable aminating partners (**59e–59i**). Specifically, this direct hydroamination protocol was also feasible for intramolecular C–N bond formation (**59k**). Nevertheless, it was not suitable for aromatic amines, α-amino acids, or tetramethylpiperidine.

According to the Stern–Volmer experiments, piperidine **57a** could efficiently quench the excited state of the photocatalyst Ir^{3+} (Ir^{3+}*) to give the corresponding piperidine radical cation derivative **60** (Scheme 12), which then underwent intermolecular addition to an olefin acceptor, such as **58a**, to facilitate a new C–N bond formation and the adjacent alkyl radical **61**. Distinguished from the intramolecular amination in Scheme 10, herein the reduction of the nascent alkyl radical **61** occurred through H-atom transfer by the thiol cocatalyst rather than by a one-electron transfer process with Ir^{2+}, furnishing a closed-shell ammonium ion **62** and a transient thiyl radical. Subsequently, the electron-transfer process occurred between the thiyl radical and Ir^{2+} species, leading to the formation of thiolate and regeneration of the photocatalyst Ir^{3+}. Finally, the resulting thiolate deprotonates the closed-shell ammonium ion intermediate **62** to provide the desired tertiary amine product **59a**. Based upon the measurement of the potential values, the tertiary amine products could be potentially oxidized by the excited Ir^{3+}*. However, high yields were still achieved in these amination reactions without further decomposition of the formed products. The authors postulated this might result from the protective action of the thiol cocatalyst by reducing any α-amino radicals that caused oxidation of the tertiary amines.

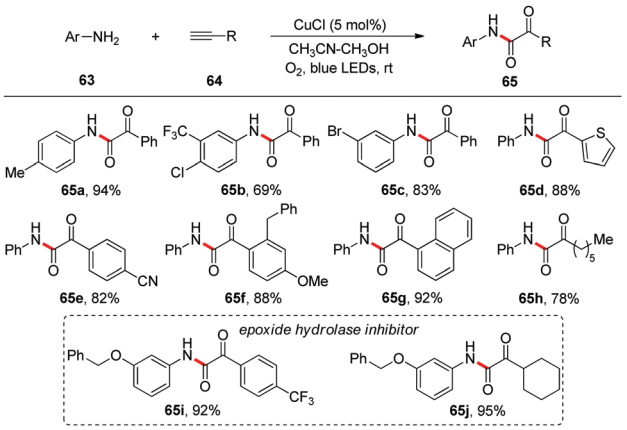
In the aforementioned reactions of photocatalyzed C–N bond formation, the employed photoredox catalysis was typically used to harvest visible-light. Lately, a new photo-activation paradigm has been emerging, wherein the transition-metal-based photocatalysis not only undergoes photoexcitation during the reaction, but also is engaged directly in bond-formation/cleavage processes. There is a growing body of work, contributed by Fu, Hwang, and Kobayashi, *etc.*,[23] in photoinduced C–N coupling



Scheme 11 Photocatalytic intermolecular hydroamination of unactivated olefin with secondary alkyl amines.



Scheme 12 Mechanism of the photocatalytic intermolecular hydroamination of olefin with a secondary alkyl amine.



Scheme 13 Photoinduced CuCl-catalyzed oxidative C–N coupling of anilines with terminal alkynes.

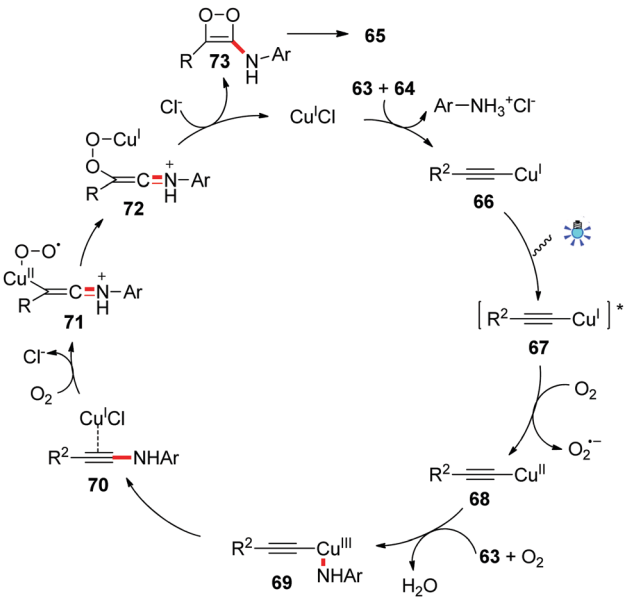
reactions *via* copper-based photocatalysts involving an unconventional photocatalytic methodology. For instance, Hwang's group developed a green synthetic process for preparing α-ketoamides *via* visible-light-initiated CuCl-catalyzed direct oxidative C–N bond formation without the need for a ligand or base (Scheme 13).[24] Using O_2 as an oxidant, the method was highly atomic efficient and could be applied to a wide range of alkynes and anilines with good functional groups tolerance. In particular, biologically epoxide hydrolase inhibitors were also able to be prepared with high yields in a single step from commercially available substrates by using this strategy.

Based on mechanistic studies, the reaction was proposed, as shown in Scheme 14, to initially involve the formation of Cu^{I} phenylacetilyde **66**, which then reached its excited state **67** with blue LED irradiation. The following SET process between **67** and O_2 led to the formation of a superoxide and electron-deficient Cu^{II} complex **68**. Subsequently, the latter reacted with the aniline radical species to yield Cu^{III} complex **69**. Next, this underwent reductive elimination to form the Cu^{I}-coordinated ynamine **70**, which readily reacts with O_2 to generate the Cu^{II} peroxo complex **71**, followed by isomerization into **72**. Then, the regeneration of the catalyst CuCl *via* Cl^- attack indicated the closure of a single catalytic cycle, accompanied by formation of the intermediate **73**. Finally, the ring opening of **73** delivered the desired product **65**.

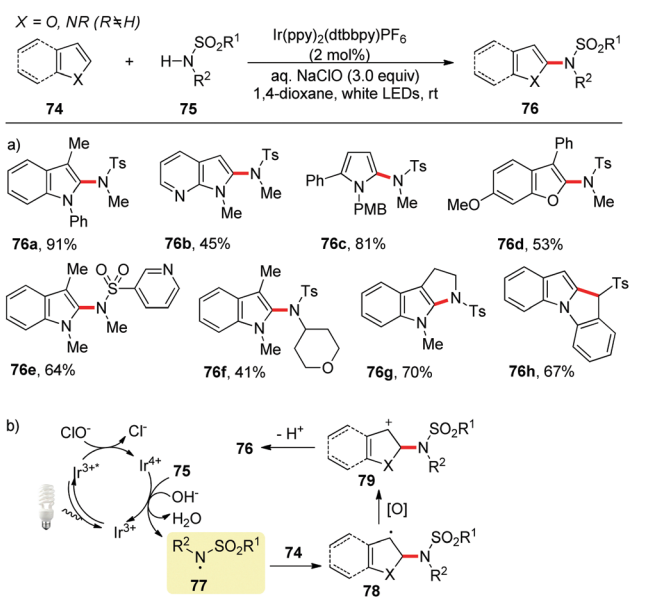
2.2 Radical species addition to aromatic rings

In the early years, valuable approaches to the direct oxidative amination of non-functionalized arenes using iodine-based reagents were disclosed by DeBoef, Chang, and Antonchick, *etc.*, wherein the amino sources were sulfonamides, phthalimides, and so on. With the development of photoredox chemistry, new synthetic routes emerged for the direct amination of simple arenes with N–H bonds of sulfonamides and phthalimides.

In 2016, Yu and coworkers demonstrated the direct oxidative C–H amidation of heteroarenes with sulfonamides by using bleach (aqueous NaClO solution) as an external oxidant under visible-light-irradiation (Scheme 15).[25] In these reactions, the key N-radicals were straightforwardly generated from the oxidative scission of N–H bonds of the sulfonamide. A large number of heteroarenes **74**, such as indoles, pyroles, and benzodurans, could engage in the amidation with *N*-methyl-*para*-toluenesulfonamide in good to high yields, generally affording the regioselectively C2-amidated products (**76a–76d**). Using 1,3-dimethyl-1*H*-indole as the model substrate, the scope of the sulfonamide coupling partners **75** were also examined and could give the products in moderate yields (**76e–76f**). The R^1 substituent of the sulfonyl moiety was extended to phenyl, benzyl, *n*-pentyl, cyclopropyl, styryl, and even heterocylic groups, while the R^2 linked to the



Scheme 14 Mechanism for the photo-initiated CuCl-catalyzed C–N coupling of anilines with terminal alkynes.

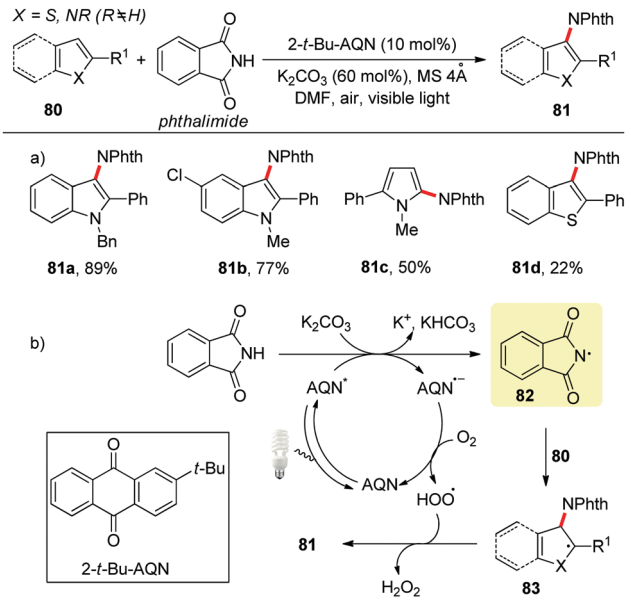


Scheme 15 Visible-light-induced direct C–H amidation of heteroarenes with sulfonamides.

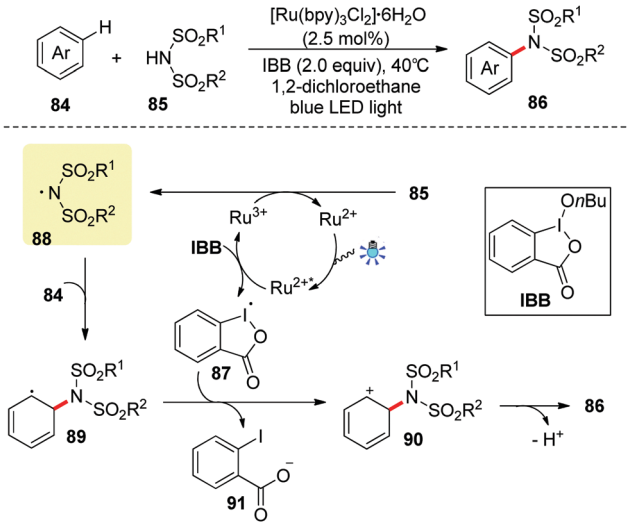
amide part was compatible with phenyl, benzyl, and various alkyl substituents, such as ether, carbamate, phenol ether, benzofuran, and olefin. Furthermore, the application of this protocol to the intramolecular C2-amidative cyclization of indoles was able to build hetercycle-fused 2-amidated indole derivatives (**76g**, **76h**) in 50–80% yields. Based on the fluorescence quenching experiments and Stern–Volmer analysis, the excited state of Ir^{3+} (Ir^{3+}*) was oxidatively quenched by NaClO to Ir^{4+}, which then directly oxidized sulfonamide **75** into the N-radical **77** with the assistance of a base, accompanied with closure of the photocatalytic cycle. The resulting radical **77** was then added onto the heteroarene **74** to give the radical intermediate **78**, which was further oxidized into the corresponding cationic **79** and then delivered the final product **76** after deprotonation.

Later in 2017, Itoh's group reported a similar cross-dehydrogenative C–H amination of heteroarenes with phthalimide under metal-free photo-oxidative conditions, featuring the organic 2-*tert*-butylanthraquinone (2-*t*-Bu-AQN) as the photocatalyst and aerobic oxygen as the sole oxidant (Scheme 16).[26] Numerous heteroarenes, including diversely substituted indoles, pyrroles, and benzo[*b*]thiophene, were accommodated under the standard reaction conditions (**81a–81d**). In light of several control experiments, the authors postulated that the N-radical **82** was derived from the deprotonation of phthalimide and following electron transfer to the excited AQN*. Then, the resulting $AQN^{\bullet -}$ was oxidized into AQN to complete the catalytic cycle. On the other hand, the final product **81** was produced by the N-radical **82** engaging in the sequences of radical addition, one-electron oxidation, and aromatization.

In the same year, Itami's group reported the photocatalytic dehydrogenative C–H imidation of arenes **84** with the simple and commonly available sulfonimides **85** serving as aminating reagents (Scheme 17).[27] As the authors suggested, the external



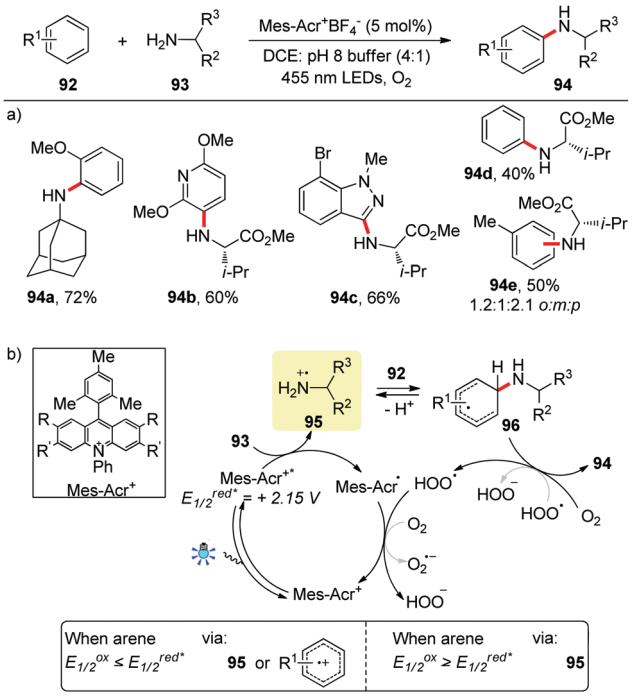
Scheme 16 Visible-light-mediated C–H amination of indoles.



Scheme 17 Direct C–H imidation of arenes with sulfonimide in electrochemistry.

hypervalent iodine-based oxidant 1-butoxy-1λ^3-benzo[*d*][1,2]iodaoxol-3(1*H*)-one (IBB) was able to oxidize the excited state of photocatalyst (Ru^{2+}*) to form Ru^{3+} along with an iodine radical intermediate **87**. The crucial imidyl radical **88**, generated from the oxidation of sulfonimide **85** by Ru^{3+}, was added to arene **84** to afford a new C–N bond with an adjacent C-radical. Subsequently, an electron-transfer process between **89** and **87** furnished the cationic intermediate **90**, which eventually aromatized to give the desired C–H imidation product **86**. The scope of the coupling partners was quite general, in which sulfonimides bearing various substituents and arenes, including polycyclic and heterocyclic ones, reacted efficiently.

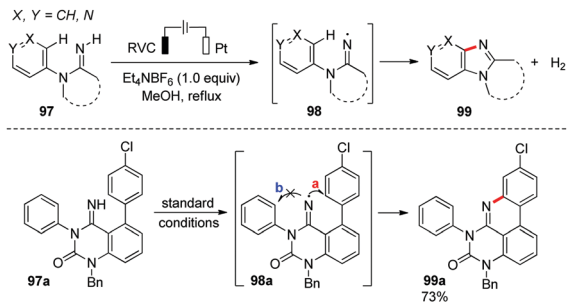
Remarkably, the N–H bonds of aliphatic amines could even be applied in the direct amination of arenes. Very recently, Nicewicz's research group demonstrated the challenging intermolecular (hetero)aryl C–N bond formation with primary aliphatic amines *via* an acridinium photoredox catalysis under the conditions of a phosphate buffer (pH = 8) and aerobic atmosphere (Scheme 18).[28] The method was compatible with a wide range of electron-rich (hetero)aromatics and primary amines, including amino acids and more complex amines. Based on Stern–Volmer fluorescence quenching experiments, both amines and electron-rich arenes could quench the excited photocatalyst, suggesting the oxidized amine radical cation and arene radical cation were both potentially reactive intermediates. However, the less electron-rich benzene and toluene, unable to be oxidized by the excited photocatalyst, still underwent successful amination and afforded corresponding aniline products in 40% and 50% yields, respectively (**94d**, **94e**), wherein the reaction pathway involving the arene radical cation was excluded. Therefore, the authors proposed that the amine radical cation **95**, derived from the oxidation of the primary amine by the Mes-Acr^+*, was the key intermediate for the insufficiently electron-rich arenes (Scheme 18b), which was then added to the arene to form a cyclohexadienyl radical intermediate **96** that could be rearomatized by oxygen to form the final product.



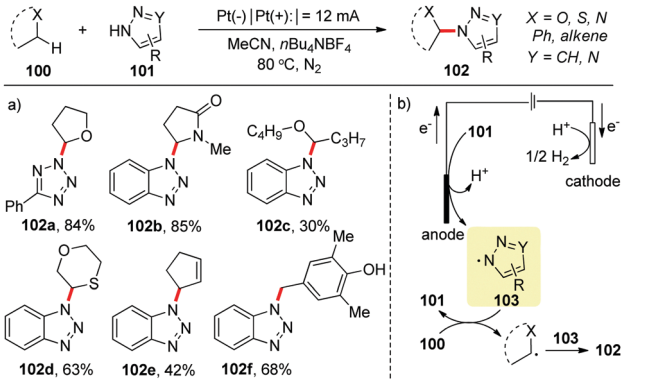
Scheme 18 Photocatalytic aryl C–H amination using primary aliphatic amines.

As for the electron-rich arenes, both the amine radical cation and arene radical cation were possible intermediates, and indeed the latter reaction pathway is discussed in the next section.

Electrochemistry, characterized as being metal and reagent free, was also applied to the direct C–H/N–H cross-coupling for aromatic C–N construction. As depicted in Scheme 19, Xu's group recently reported a sustainable approach to access the amidinyl radical intermediate **98** *via* the anodic N–H bond cleavage of substrate **97**,[29] which was followed by intramolecular cyclization onto (hetero)arenes and rearomatization to give a diverse range of functionalized tetracyclic benzimidazoles or pyridoimidazoles **99** in a high-efficiency process. In addition, the authors chose **97a**, which possessed two potential cyclization sites at the same substrate, as a sample to examine the cyclization tendency of the amidinyl radical. As a result, the 6-*endo-trig* cyclization (path a) of amidinyl radical **98a** took precedence over the alternative five-membered-ring formation



Scheme 19 Anodic N–H bond cleavage for aromatic C–H bond functionalization.



Scheme 20 Electronic intermolecular oxidative C(sp^3)–H/N–H cross-coupling.

(path b), which was further confirmed by density functional theory (DFT) calculations.

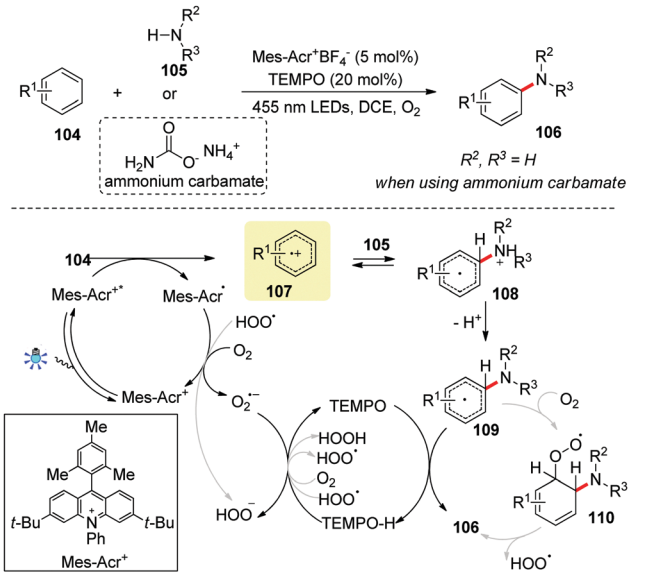
N–H/C(sp^3)–H cross-coupling. Apart from the above achievements of C(sp^2)–H direct amination, the strategy of C–H/N–H cross-coupling *via* a N-radical intermediate has also been applied to the amination of C(sp^3)–H bonds. As a limited example, Lei and coworkers recently developed an electrooxidative method for the intermolecular C(sp^3)–H/N–H cross-coupling under metal- and oxidant-free conditions (Scheme 20).[30] The reactive C(sp^3)–H bonds of benzylic, allylic, and those adjacent to O, S, and N atoms were smoothly aminated in this protocol. Therein, N–H bonds of azoles were oxidized into the critical N-radical intermediate **103** *via* a SET process and subsequent hydrogen transfer on the surface of the electrode. Afterwards, the N-radical intermediate **103** reacted with **100** to afford the desired product **102**.

3. CDC amination *via* N-atom nucleophilic addition

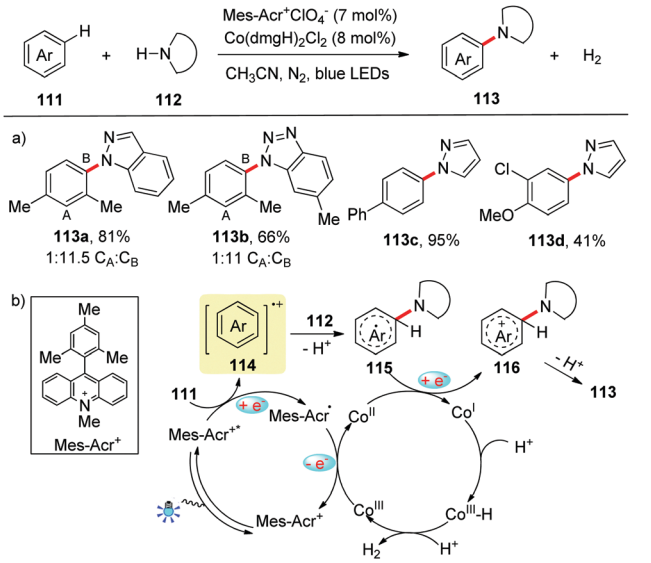
In the previous section, C–N bond formation proceeding through N-radicals addition relied on the oxidation of N–H coupling partners to generate the reactive key N-radical intermediate. On the contrary, CDC amination in the N-atom nucleophilic pathway is facilitated by direct oxidation of the other coupling partner, namely the C–H parts, to form the important cationic or radical-cationic intermediate, while the N–H parts usually work as nucleophiles during the formation of new C–N bonds.

3.1 Aromatic C(sp^2)–H bonds amination

According to preceding literature, (hetero)aromatic rings are able to be directly oxidized into their corresponding radical-cationic intermediates by photo- and/or electrotechniques, which are then attacked by proper nucleophiles, such as –NHR, –OR, and –CN$^-$. In the electrocatalytic amination involving the arene cation radical intermediate, it's rare as yet to utilize an aminating source bearing a naked N–H bond as a nucleophile. However, in this regard, notable progress has been made *via* photoredox catalysis in recent years, in which the strong nucleophilic azoles usually serve as aminating sources.



Scheme 21 Site-selective aromatic C–H amination *via* photoredox catalysis.



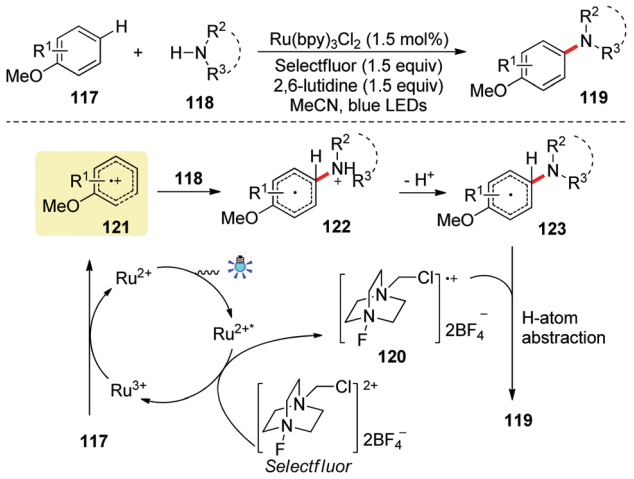
Scheme 22 Photoinduced oxidant-free C–H amination of arenes with azoles.

Among these, pioneering research on photocatalytic site-selective aromatic C–H amination was reported by Nicewicz's group in 2015,[31] using an organic acridinium salt as the photocatalyst and O_2 as the terminal oxidant with the assistance of a catalytic amount of TEMPO (Scheme 21). The acridinium photocatalyst (Mes-Acr$^+$) with highly positive reductive potentials after excitation by visible-light (E_{red}* = +2.20 and +2.09 V *vs.* SCE, respectively) was able to oxidize the arene substrate **104** into the crucial arene cation radical **107**, which could be subsequently attacked by the aminating nucleophile **105**. The resulting cation radical **108** delivered its radical derivate **109** after deprotonation. Sequential aromatization *via* hydrogen abstraction by TEMPO furnished the desired amination product **106**. Alternatively, the radical **109** could be trapped by O_2 to form the peroxyl radical **110**, which then yielded the product **106** by the internal elimination of $HO_2^\bullet$. To finish the photocatalytic cycle, the ground-state of Mes-Acr$^+$ was regenerated by the reduced Mes-Acr$^\bullet$ donating an electron to O_2 or $HO_2^\bullet$. Also, the TEMPO could be released *via* a hydrogen-atom-transfer process between TEMPO-H with reactive O-radicals, such as $O_2^{\bullet-}$ and $HO_2^\bullet$. The authors investigated a variety of (hetero)arenes or even more complicated drug-like structures containing diverse functional groups, such as ether, MOM–, TBS–, and halogens, affording the corresponding aminated products in moderate to good yields. Meanwhile, numerous N-heterocyclic nucleophiles, including pyrazoles, 1,2,3-/1,2,4-triazole, tetrazole, imidazole, and benzimidazole, were suitable substrates to couple with arenes in this elegant CDC amination protocol. Especially, using the commercially available ammonium carbamate $H_4N^+H_2NCO_2^-$ as a nitrogen source to react with (hetero)arenes was able to directly provide anilines in this photocatalytic sequence.

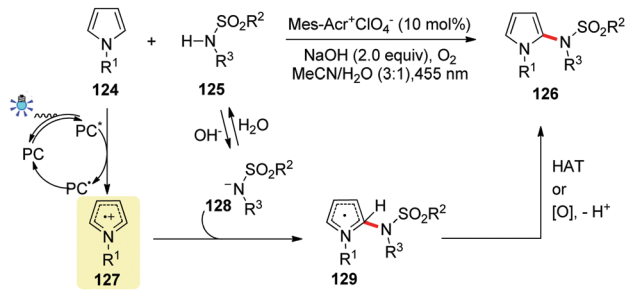
Subsequently, the oxidative C–H/N–H cross-coupling between arenes and azoles was also realized with other photocatalytic systems. In 2017, the laboratory of Lei developed a dual catalyst system, namely a combination of a Mes-Acr$^+$ photocatalyst with a $Co(dmgH)_2Cl_2$ cocatalyst, for the synthesis of *N*-arylazoles from arenes and azoles in the absence of any sacrificial oxidant, with H_2 released as the only by-product (Scheme 22).[32] A variety of alkyl-substituted benzenes as well as biphenyl and anisole derivatives were well tolerated under the oxidant-free conditions (**113a–113d**), which would otherwise be oxidatively functionalized at the benzylic C(sp^3)–H position through a benzyl radical intermediate stemming from the originally produced benzene radical cation. Based on KIE (kinetic isotope effect) experiments and a kinetic study, the authors reasoned that the transformation began with the oxidation of **111** by the photo-excited state of Mes-Acr$^+$ (Mes-Acr$^+$*), generating Mes-Acr$^\bullet$ and the important radical cation **114**. The Mes-Acr$^+$ then could be regenerated by Mes-Acr$^\bullet$ donating an electron to the Co^{III} catalyst. On the other hand, the radial cation **114** was attacked by the nucleophile **112** to form the intermediate **115**, which then underwent a single-electron transfer with Co^{II} to form cation **116**. Finally, the desired *N*-aryl product **113** resulted from the deprotonation of cation **116**.

Simultaneously, Pandey and coworkers disclosed an alternative route to the selective C(sp^2)–H amination of various anisoles with azoles under visible-light irradiation, wherein $Ru(bpy)_3Cl_2$ served as a photocatalyst and Selectfluor acted as an external oxidant.[33] The proposed reaction mechanism is outlined in Scheme 23. The Selectfluor was able to quench the excited Ru^{2+}* to form the Ru^{3+} and the Selectfluor radical cation **120**. Then, the oxidative Ru^{3+} obtained an electron from the electron-rich anisoles **117** to finish the photoredox cycle and generate the key aromatic radical cation **121**, which reacted with the nucleophile **118** to provide the intermediate **122**. After the sequence of deprotonation by 2,6-lutidine and H-atom abstraction by the Selectfluor radical **120**, the final product **119** was delivered.

Heterocyclic arenes, such as pyrroles and thiophenes, can also be directly aminated *via* a radical cation intermediate.



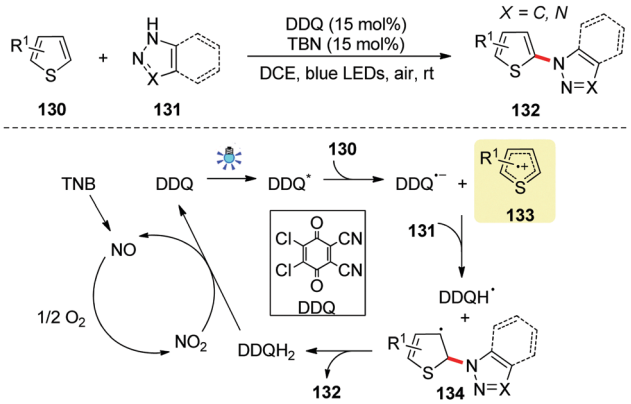
Scheme 23 Selective C–H amination of arenes *via* photoredox catalysis.



Scheme 24 Direct C–H sulfonamidation of pyrroles by visible-light photoredox catalysis.

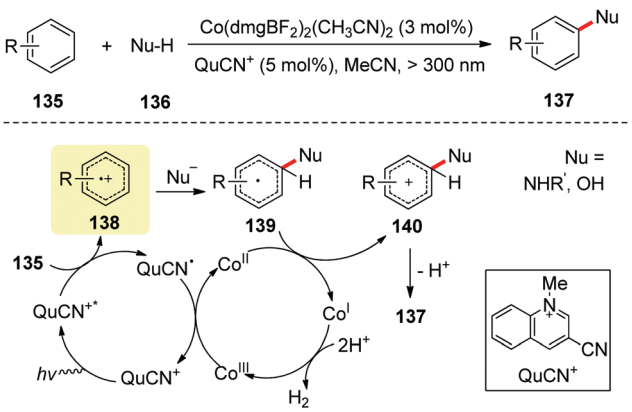
In 2016, König's group reported the oxidative C(sp^2)–H sulfonamidation of pyrroles by photoredox catalysis (Scheme 24).[34] The *N*-substituted pyrrole (*e.g.*, *N*-methylpyrrole, E_{ox} = 1.20 V *vs.* SCE) could be readily oxidized by the excited organic photocatalyst into the corresponding radical cation **127**. Meanwhile, the sulfonamide **125** was partly deprotonated by NaOH into the anionic **128**, which reacted as a nucleophile with the intermediate **127** to generate **129**. Subsequently, the desired product **126** was afforded through H-atom abstraction by $O_2^{\bullet-}$ or alternatively through further oxidation and deprotonation steps. On the other hand, the photocatalytic C2-amination of thiophenes with azoles was presented by Lei's group in 2017, utilizing DDQ as an organic photocatalyst, *tert*-butyl nitrite (TBN) as the electron-transfer mediator, and O_2 as the terminal oxidant (Scheme 25).[35] Under the irradiation of visible-light, DDQ was excited to its triplet state with a high oxidation potential (E_{red} = 3.18 V *vs.* SCE), which could directly oxidize thiophene **130** into the critical radical cation intermediate **133**. The final product **132** was formed after the sequence of nucleophilic addition and further oxidation. To regenerate DDQ, $DDQH_2$ was oxidized by reaction with TBN *via* NO_2, while TBN was then regenerated by O_2.

In addition to the commonly used azoles, the simple and largely commercial agent ammonia has also been employed as a compatible nucleophile in CDC amination. In 2016, Wu and



Scheme 25 DDQ-mediated C2-amination of thiophenes in photochemistry.

Tung demonstrated a photocatalytic hydrogen-evolution cross-coupling for aromatic C–H amination and hydroxylation through a combination of photocatalysis and cobalt catalysis without any external oxidants, wherein anilines were directly prepared from benzenes and ammonia, and phenols from benzenes and water, respectively (Scheme 26).[36] Control experiments revealed that the photocatalyst, cobalt catalyst, and light irradiation were essential for the aryl amination. In these reactions, onium $QuCN^+ClO_4^-$ or $QuH^+ClO_4^-$ (E_{red}* = 2.72 and 2.46 V *vs.* SCE, respectively) was used as the photocatalyst, of which the excited state was extremely oxidative to accept an electron from benzene (E_{ox} = 2.48 V *vs.* SCE), thus leading to $QuCN^{\bullet}$ and the crucial benzene radical cation intermediate **138**. The former could be oxidized by the Co^{III} catalyst to regenerate the photocatalyst $QuCN^+$, while the latter reacted with anionic nucleophiles to form the intermediate **139**. Then, **139** donated an electron to Co^{II} to give Co^{I} and cationic **140** which afforded the final product **137** after deprotonation. To complete the cobalt catalytic cycle, the Co^{I} might reduce two protons derived from X–H and aryl C–H into a H_2 molecule to revert back to Co^{III}. According to the measured oxidation potentials, product **137** was expected to quench the excited state of QuH^{+}* and lead to further functionalization. However, mono-aminated/hydroxylated benzene was still the only product and no other multi-amino/hydroxybenzene



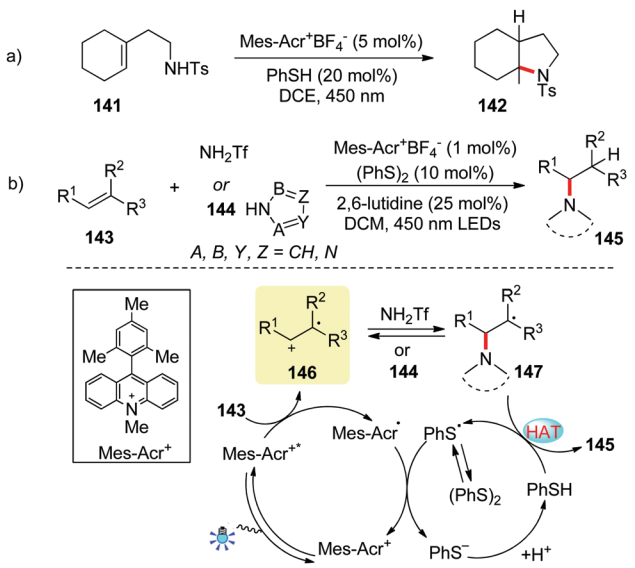
Scheme 26 Photocatalytic benzene C–H amination and hydroxylation with hydrogen-evolution.

was observed even after prolonged irradiation. The authors assumed this was presumably due to the pair of the product **137** radical cation and QuCN• that underwent rapid back-electron transfer to return to the starting material.

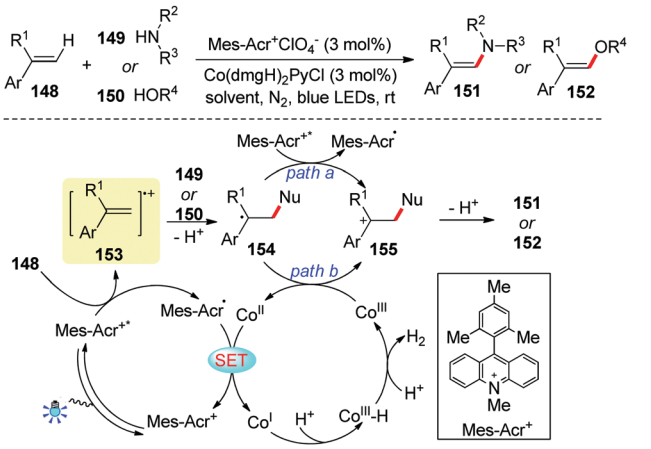
3.2 Olefinic C(sp^2)–H bond amination

Alkenes are usually used as radical acceptors to react with various nascent radicals to provide radical addition products. However, being analogous to aromatic C(sp^2)–H amination in the last section, the direct nucleophilic amination of olefinic C(sp^2)–H bonds proceeds through the straightforward oxidation of C=C double bonds into the pivotal radical cation intermediates, followed by addition with suitable nucleophiles.

The research group of Nicewicz recently devoted a significant body of work to the diverse anti-Markovnikov hydrofunctionalization of alkenes, such as hydroalkoxylation and hydrocarboxylation, by using an acridinium photocatalyst, in which nucleophiles could regioselectively add to the less-substituted position of alkene radical cations to give a more stable C-radical β to the nucleo-center. On the basis of previous research on the intramolecular anti-Markovnikov hydroamination of alkenes, which employed Mes-Acr$^+$BF$_4^-$ as a photocatalyst and thiophenol as a hydrogen-atom donor (Scheme 27a),[37] Nicewicz's group later developed the intermolecular anti-Markovnikov hydroamination of styrenes and aliphatic alkenes by switching the thiophenol cocatalyst to phenyl disulfide.[38] Therein, triflylamide (NH_2Tf) and heterocyclic azoles were utilized as qualified nitrogen nucleophiles to prepare diverse phenethylamine derivatives (Scheme 27b). In line with their reported work in the nucleophilic functionalization of alkenes, the authors proposed that the key step for the reaction was the single-electron oxidation of substrate **143** by the excited Mes-Acr$^+$*, thus leading to the formation of the important olefinic radical cation **146**. Then, nucleophilic NH_2Tf or **144** underwent reversible addition to the less-substituted site



Scheme 27 Anti-Markovnikov hydroamination of alkenes by a two-component organic photoredox system.



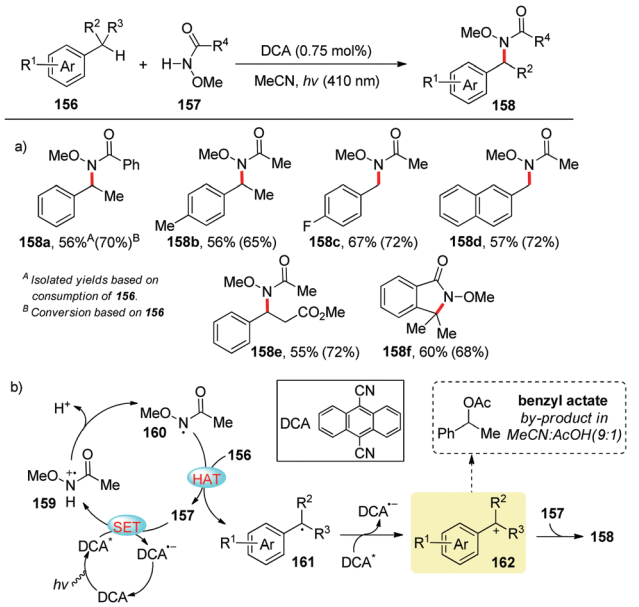
Scheme 28 Photocatalytic dehydrogenative cross-coupling of alkenes with alcohols *via* dual catalysis.

of **146** to result in the tertiary C-radical **147**, which reacted presumably with thiophenol to give the final product **145**. The authors assumed the putative HAT donor thiophenol came from protonation of the thiyl anion, which was generated through the oxidation of Mes-Acr• by PhS• to reset the ground-state of Mes-Acr$^+$, while the PhS• stemmed from homolysis of the S–S bond of $(PhS)_2$, probably by either light or energy transfer from Mes-Acr$^+$*.

In 2017, Lei's group also achieved the photocatalytic CDC amination of alkenes with azoles through a dual catalyst system in the absence of an oxidant, by which the C–H/O–H cross-coupling of alkenes with alcohols was enabled as well (Scheme 28).[39] In these reactions, the combination of Mes-Acr$^+$ClO$_4^-$ as a photocatalyst and the cobalt cocatalyst Co(dmgH)$_2$PyCl as an acceptor of two electrons led to radical alkenylation by the detection of H_2 evolution on GC-TCD. The SET process between alkene **148** and the excited Mes-Acr$^+$* was considered to constitute the key initial step of the reaction, generating Mes-Acr• and the alkene radical cation **153**. Subsequently, the nucleophile **149** or **150** reacts with the intermediate **153** against the "Markovnikov Rules" to form the stabilized radical **154**, which was further oxidized into the corresponding cation **155** by Mes-Acr$^+$* or Co^{III}, furnishing the final product after deprotonation. The resulting Co^{II} was reduced by Mes-Acr• to give Co^I, followed by protonation and H_2 evolution to regenerate the Co^{III} species.

3.3 Benzylic C(sp^3)–H bond amination

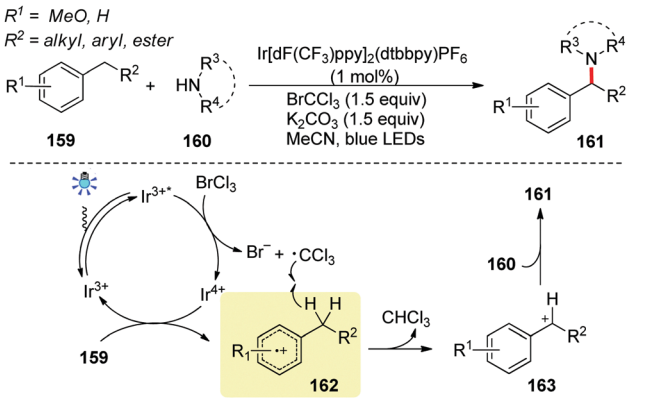
In the early years, most of the successful C(sp^3)–H amination reactions were realized by utilizing transition-metal catalysis or hypervalent iodine reagents. As a new methodology for the C(sp^3)–H amination, Pandey and coworkers developed a visible-light-catalyzed cross-dehydrogenative protocol for the selective C–N bond formation under metal- and external-oxidant-free conditions (Scheme 29).[40] The authors employed DCA (9,10-dicyanoanthracene) to absorb the visible-light (410 nm) that was obtained by irradiating a 450 W Hanovia medium pressure lamp with a CuSO$_4$:NH$_4$ solution filter. Using *N*-methoxyamides as the amino sources, a wide range of alkyl aryls participated in



Scheme 29 Photocatalytic benzylic C–H amination by dehydrogenative cross-coupling.

the desired intra-/intermolecular C(sp^3)–H amination reactions with good tolerance to the functional groups. Mechanistically, the SET process between **157** and DCA* gave rise to the *N*-methoxyamide radical cation **159**, which was then deprotonated to deliver the N-radical intermediate **160**. Afterwards, the benzylic H-abstraction from substrate **156** led to the regeneration of **157** and formation of benzylic C-radical **161**. Then, the cation **162**, resulted from the oxidation of **161**, and underwent a reaction with **158** to furnish the C–H aminated product **158**. Circumstantial control experiments supported the putative intermediates generated during the amination reaction. The existence of the N-radical **160** was concluded from the dimeric product of **157**, while the benzylic radical **161** was directly trapped by TEMPO. To gain evidence of the benzylic cation **162**, the authors carried out the reaction in a mixture of MeCN : AcOH (9 : 1), which produced the aminated product in diminished yield along with 10% of benzyl acetate.

As mentioned in Scheme 22, arenes bearing available benzylic C(sp^3)–H bonds are prone to be functionalized at the benzylic position *via* the preliminary arene radical cation intermediate under oxidative conditions. In 2016, Pandey's group reported a visible-light-mediated intermolecular benzylic C(sp^3)–H bond amination with different strong nucleophilic aozle derivatives, such as imidazole, benzotriazole, benzimidazole, and tetrazole, in moderate to good yields.[41] Control experiments confirmed the necessity of a visible-light, photocatalyst and oxidative quencher in these reactions. The authors proposed the reaction mechanism as presented in Scheme 30. Upon irradiation by blue LEDs, the Ir^{3+} photocatalyst reached its excited state and then donated an electron to $BrCCl_3$, giving the trichloromethyl radical $^{\bullet}CCl_3$ and the strong oxidative Ir^{4+} species. Then, the latter species accepted an electron from the electron-rich arene **159** to form the important radical cation intermediate **162**, along with the



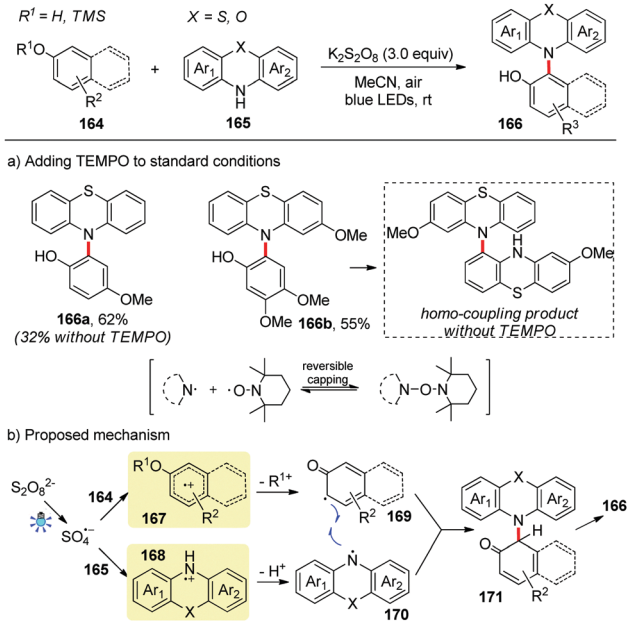
Scheme 30 Benzylic C–H amination *via* visible-light photoredox catalysis.

regeneration of the Ir^{3+} photocatalyst. Afterward, the radical $^{\bullet}CCl_3$ could abstract a H-atom from the benzylic C(sp^3)–H of intermediate **162** to form the cationic **163**, which then reacted with the azole nucleophile **160** to deliver the desired aminating adduct **161**. Moreover, it was feasible to capture the cationic **163** with moisture to prepare the corresponding carbonyl compounds by the further oxidation of the *in situ* generated alcohol intermediate in this protocol.

4. CDC amination *via* radical cross-coupling

To date, cross-dehydrogenative amination in a radical–radical coupling pattern has been limited, presumably because it is challenging to provide suitable reaction conditions for the simultaneous generation of both C-radical and N-radical species. Furthermore, the formed C-radical and N-radical in the same reaction mixture are supposed to obey the principle of the persistent radical effect (PRE) to yield the expected C–N cross-coupling product rather than a homo-coupling one.

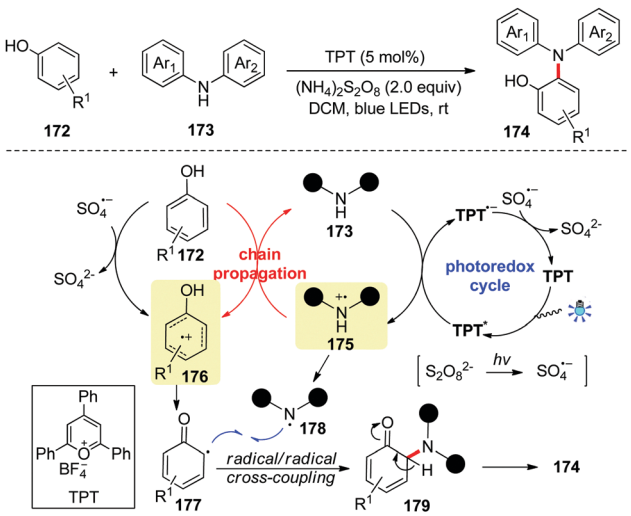
In 2016, Xia's group disclosed a visible-light-mediated CDC amination for intermolecular aryl C–N bond formation from phenols and phenothiazines at ambient temperature using $K_2S_2O_8$ as the external oxidant (Scheme 31).[42] A wide range of *ortho*-aminated phenols were prepared with moderate to excellent efficiency in this protocol. The need for a photocatalyst was averted in these reactions probably due to the inherent photophysical properties of phenothiazines to absorb visible-light to promote a possible energy-transfer process. It's notable that instead of halting the amination process or trapping any intermediates, the addition of the radical scavenger TEMPO could even dramatically improve the yield of product (**166a**). Moreover, the reaction mixture of phenol and 2-methoxylphenothiazine, which only afforded the unstable C–C homo-coupling product under standard conditions, was able to yield the desired C–N cross-coupling product when TEMPO was added (**166b**). Based on the documented literature, the authors attributed these results to the important role of TEMPO in covalently and reversibly prolonging the lifetime of the transient N-radical. During the reaction, the external oxidant $K_2S_2O_8$ was competent



Scheme 31 Visible-light-promoted CDC amination of phenols and phenothiazines.

to oxidize both phenol and phenothiazine under light irradiation to give the essential C-radical **169** and N-radical **170**, respectively. Then, the radical–radical cross-coupling process occurred to furnish **171**, which could be isomerized into the desired product **166**.

However, acyclic diarylamines could not be accommodated with this photocatalyst-free amination approach as they were incapable of absorbing light yet possessed higher oxidation potential values. Aiming to address this challenge, the same group subsequently developed a nonmetallic oxidative system to facilitate the CDC amination of phenols with acyclic diarylamines under benign conditions by employing the organic 2,4,6-triphenylpyrylium (TPT) photocatalyst (Scheme 32).[43] The method was applicable to various electron-rich acyclic diarylamines as well

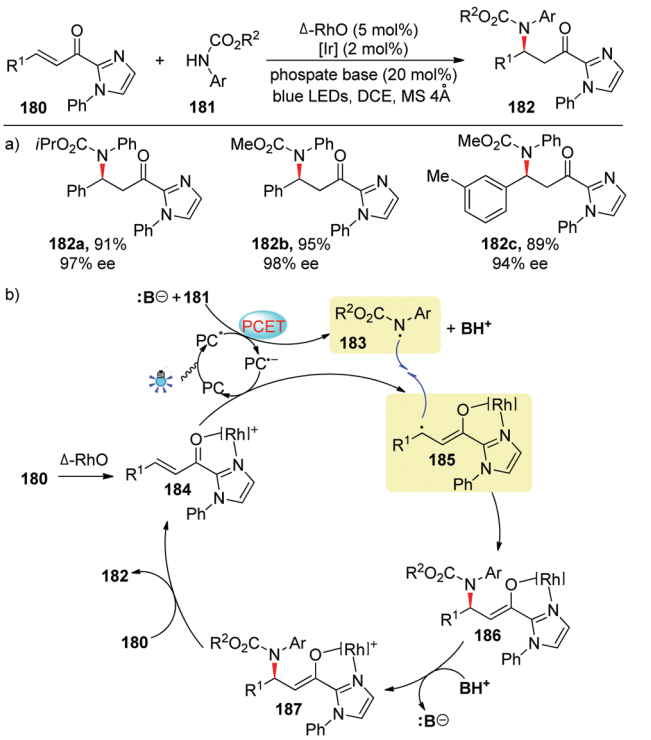


Scheme 32 Visible-light-mediated CDC amination of phenols and acyclic diarylamines.

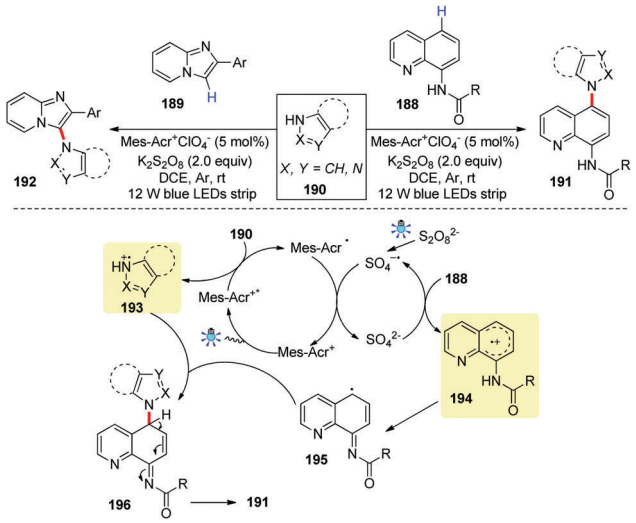
as phenols, including the complex (+)-δ-tocopherol. The authors conducted a series of experiments, such as electron paramagnetic resonance (EPR), Stern–Volmer quenching experiments, and quantum yield determination, to probe the mechanistic information.

According to the results, the amine **173** was able to quench the excited state of TPT, providing $TPT^{\bullet -}$ and the aminium radical cation **175**. As the determined quantum yield (Φ = 19) indicates the radical chain propagation process, the author proposed it might occur between phenol **172** and intermediate **175** to form the phenol radical cation **176** and to regenerate amine **173**. An alternative pathway to the formation of **176** was through the oxidation of **172** by persulfate. Eventually, the N-radical **178** would cross-couple with **177** to furnish the desired product **174**. Furthermore, cyclic phenothiazines substituted with electron-deficient groups, which required a prolonged reaction time in the previous amination strategy, could react in a much shorter time without compromising the high yields of products in this protocol.

The conjugate amination of α,β-unsaturated carbonyl compounds was a principle strategy to build the useful β-amino carbonyl blocks. However, it was not readily available neither *via* nucleophilic addition of nitrogen agents nor radical addition of the electron-deficient N-radicals. In 2017, Meggers and coworkers presented a new route to the selective β-amination of α,β-unsaturated 2-acyl imidazoles **180** with *N*-aryl carbamates **181** in high yields and excellent enantioselectivities through PCET-enabled N–H activation followed by stereocontrolled radical–radical coupling, using a photoredox catalyst in combination with a chiral-at-rhodium Lewis acid and weak phosphate base (Scheme 33).[44] As discussed in Section 2.1



Scheme 33 Enantioselective amination *via* the PCET process followed by stereocontrolled radicals cross-coupling.



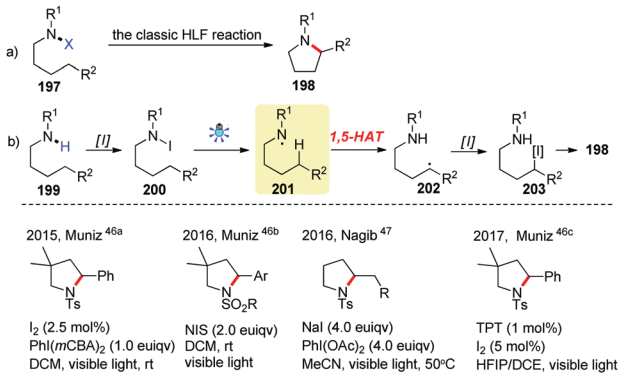
Scheme 34 Selective C–H amination of heteroarenes with azoles *via* an organic photoredox system.

of this review, the catalytic amount of photocatalyst and phosphate base utilized in the PCET strategy was intended to transform the N–H bond into the corresponding N-radical. Meanwhile, the Rh catalyst used in these reactions, which had been extensively researched by the authors, was not only for N,O-bidentate coordination to **180** to facilitate its reduction, but also for control of the stereoselectivity during the radicals cross-coupling. The authors proposed the reaction mechanism as detailed in Scheme 33b. The PC* induced a PCET process, converting the activated **181** by phosphate base into the carbamoyl N-radical **183**. The reduced $PC^{\bullet -}$ then donated an electron to the Rh-bound substrate **184** to regenerate the PC and provide the Rh enolate radical intermediate **185**. Subsequently, the radical-coupling partners of **183** and **185** were combined to form the C–N bond of **186**. Alternative mechanistic pathways *via* the addition of N-radical **183** or carbamate anions to the Rh-coordinated substrate **184** were discussed and precluded in accordance with the experiment results.

Very recently, Adimurthy and coworkers reported the visible-light-promoted regioselective C–H amination of heteroarenes with azoles by organic acridinium photoredox catalysis at room temperature (Scheme 34).[45] A wide range of quinoline amides **188** and imidazopyridines **189** were reported as competent substrates, and were aminated respectively at the C5 and C3 positions with a good tolerance of functional groups. Choosing **188** as a model coupling partner, the authors proposed that the reaction proceeded through the radical species cross-coupling of **193** and **195** under visible-light irradiation.

5. CDC amination of C(sp^3)–H bonds *via* HAT

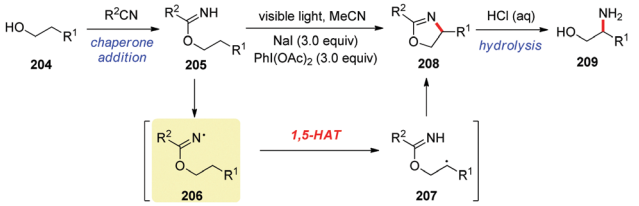
Although ubiquitous, aliphatic C(sp^3)–H bonds are often robust and show insufficient reactivity and selectivity. The direct functionalization of such inert C–H bonds has motivated researchers



Scheme 35 HAT-mediated intramolecular C–N bond formation.

to develop versatile approaches for their activation and utilization, among which hydrogen-atom transfer (HAT) is considered a unique strategy to activate the remote C(sp^3)–H bonds. The classic Hofmann–Loffler–Freytag (HLF) reaction involving 1,5-HAT has been a valuable method to synthesize five-membered N-heterocyclics (Scheme 35a). To avoid the pre-halogenation of N–H bonds and to modify the originally harsh reaction conditions, much advancement has recently been made for the direct construction of intramolecular C–N bonds from C–H/N–H bonds by using an iodine-type catalysis or reagents under visible-light irradiation (Scheme 35b).[46,47] These modifications concluded avoiding the use of sublimed iodine or a high loading of strong oxidative hypervalent iodine agents. In these modified HLF reactions, the key N-radical **201** used for the subsequent 1,5-HAT process was generated not from the direct oxidative cleavage of N–H bonds of **199**, but from the light-initiated collapsing of the *in situ*-formed N–I bonds of **200**. After the 1,5-HAT process, an alkyl radical **202** was delivered and then incorporated with iodine agents to form an iodinated intermediate **203**, which could engage in intramolecular nucleophilic substitution to afford the final product **198** through nitrogen attacking the intermediary C–I bond. Most recently, apart from the synthesis of pyrrolidines, the HAT strategy has also been applied to prepare other N-heterocyclic molecules, such as piperidines,[48] in a CDC amination fashion.

Although the above sp^3 N-centered radicals constitute the major body of works in HAT-mediated C–N bond formation, the use of sp^2 N-centered radicals in the HAT strategy has also been implemented. For instance, Nevado's group recently reported aliphatic C–H amination *via* a 1,5-HAT process of an iminyl radical generated from the photoinduced sp^2 N–O bond cleavage of oximes.[49] Furthermore, the sp^2 N–H bonds of imines were directly used for the generation of iminyl radicals after donation of a hydrogen atom. In 2017, Nagib's group employed a radical relay chaperone strategy for facilitating the selective βC–H amination of alcohols **204** to prepare β-amino alcohols **209** (Scheme 36),[50] wherein the imidate-based chaperone **205** served as a traceless director to access the crucial iminyl radical **206** under triiodide-mediated conditions. After the 1,5-HAT process, the intermediate **206** was converted to the ensuing alkyl radical **207**, which would readily afford C–H aminated oxazoline



Scheme 36 Selective βC–H amination of alcohols *via* the iminyl-radical-initiated HAT process.

208 through *in situ* iodination and N-displacement or through radical cyclization and subsequent oxidation. Moreover, the acidic hydrolysis of crude **208** could directly yield free β-amino alcohols **209**.

6. Conclusions

The reactions summarized in this tutorial review have enabled direct C–N bond construction from inactivated C–H/N–H coupling partners, facilitated by photocatalytic or electronic techniques under mild conditions. In comparison with the well-established cross-dehydrohalogenative routes, they are quite appealing in terms of atom and step economy. Various C–H bonds, including those contained in complex molecules as well as the robust aliphatic C(sp^3)–H ones, can be efficiently introduced with amino functionality with secondary amines even in the presence of labile functional groups. In particular, the literally conceptional CDC amination, releasing the aminated product and H_2 gas, has been achieved in some cases by dual catalysis in the absence of an external oxidant. Furthermore, as highlighted in this review, the radical species engaged in these transformations have expanded the mechanistic scaffolds to nucleophilic addition, radicals cross-coupling, and hydrogen-atom transfer beyond the familiar N-radical species addition.

Although notable advances have been achieved in this area, challenges as well as opportunities still remain: (1) the amino substrates that provide N–H bonds are greatly limited to the secondary amides, carbamates, sulfonamides, diaryl amines, and azoles. Extremely scarce examples have been realized involving the utilization of primary amines or secondary alkyl amines, which makes the application of more convenient amino sources desirable; (2) the aliphatic C(sp^3)–H amination is characterized in the reactive benzylic position or α-H to a hetero atom, and HAT-induced amination specifies the functionalization at the remote δ-H to a nitrogen. It's important to explore more extensive and versatile C(sp^3)–H amination; (3) high enantioselectivity as well as selective amination at a specific position on the aromatic ring are hardly accessible in these simple radical-involved reactions.

In the near future, further efforts in this area may rely on the development of novel catalytic system, such as a combination of different catalysis to broaden the substrate scope. Also, detailed mechanistic studies for the transformation are necessary to elucidate the activation mode during the reaction, which could conversely inspire the design of new reaction modes, thus leading to a wider substrate scope. Moreover, applying diverse chiral catalysts to coordinate with radical intermediates could potentially help to address the issue of lacking selectivities. It's anticipated that further investigation will eventually make the CDC amination protocol become one of the most valuable methods for C–N bond construction.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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