Recent Advances in Photocatalytic C–N Bond Coupling Reactions

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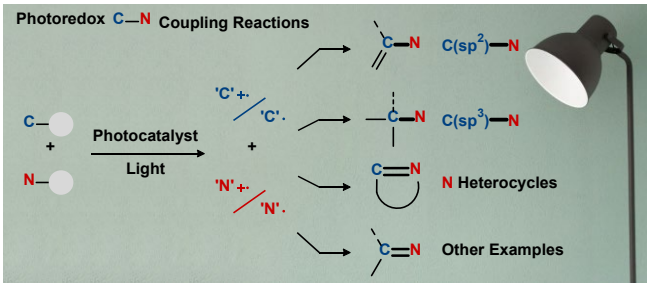

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Abstract Catalytic C–N bonds formation is one of the major research topics in synthetic chemistry owing to the ubiquity of amino groups in natural products, synthetic intermediates and pharmaceutical agents. Paralleling with the well-established metal-catalyzed C–N bond coupling protocols, photocatalytic reactions have recently emerged as one of the efficient and selective alternatives for C–N bonds construction. In this short review, recent progress of photocatalytic C–N bonds coupling reactions starting from 2012 to 2020 (Feb) are summarized.

Key words photochemistry, C–N cross coupling, amination, radical, visible light

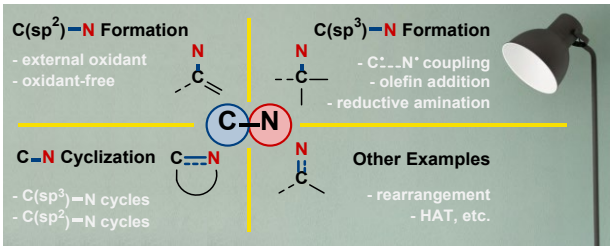
1. Introduction

Due to the ubiquity of carbon–nitrogen bonds in functional materials, natural products and pharmaceutical agents, development of efficient and selective methodologies for facile construction of carbon–nitrogen bonds remains a major research topic in synthetic chemistry.[1] While the traditional C–N bonds formation approaches often require forcing conditions and tedious synthetic steps, metal-mediated C–N bond formation has enabled a powerful synthetic platform with regard to efficiency and applicability.[2] Ever since the seminal reports by Ullmann and Goldberg on the Cu-catalyzed amination of aryl halides,[3] major breakthroughs have been accomplished. Most notable works include Buchwald-Hartwig coupling and Chan-Evans-Lam coupling reactions, which have now become "household" protocols for C–N bond coupling reactions.[4] Despite these great accomplishments, development for more sustainable and easily scalable protocols is still in demand. One of the viable approaches to construct C–N bonds is the direct functionalization of hydrocarbon substrates by C–H insertion or C–H activation.[5]

A newly emerging strategy in direct C–H amination is to employ photoredox catalysis. Upon photoirradiation, the photocatalyst may effect the formation of organoradical species via a single-electron transfer pathway. The radical would react with coupling partners to furnish aminated products.[6] Indeed, the integration of light energy with chemical transformations emulate photosynthesis in the natural systems for chemical synthesis. Photons can be regarded as traceless reagents, which can reduce the concomitant by-products and simplify the work-up procedures. The photocatalytic reactions allow organic transformations to occur at milder conditions with manageable set-up cost.[7] Photocatalytic reactions are likely to be a promising platform for practical C–N coupling reactions.

In the field of C–N coupling by photoredox catalysis, a good diversity of Ru/Ir-based polypyridyl complexes and organic dyes are available as photoredox catalysts to match the redox potentials of various substrates.[8] This chemistry can be ameliorated with the help of air or oxygen as terminal oxidant.

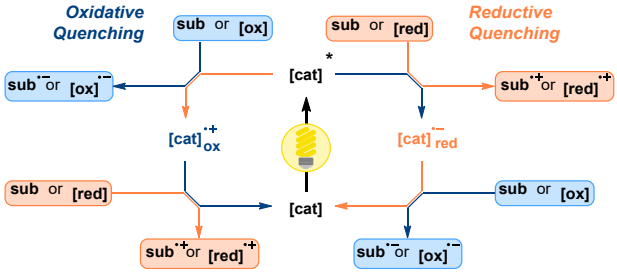
Photochemical aminations are usually categorized according to the nucleophiles used or the reaction types involved.[9] In this short review, we herein summarize the recent progress of photocatalytic C–N bond coupling reactions according to the nature of the C–N bond formed (Scheme 1).



Scheme 1 The scope of this short review

1.1 General Mechanisms for Photoredox Catalysis

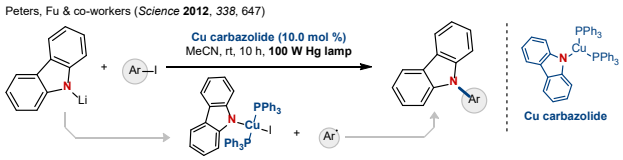
Most photoredox reactions are initiated by irradiation of the photocatalyst [cat] to generate an excited state photocatalyst [cat*]. The cat* would then react by donating an electron to the substrate [sub] or an oxidant [ox]. Alternatively, it may accept an electron from sub or a reductant [red]. The oxidized $[cat]^{\bullet+}$ and reduced $[cat]^{\bullet-}$ would react with either the substrate, reaction intermediate or an external redox-active reagent to regenerate the active catalyst (Scheme 2).



Scheme 2 General mechanisms for photoredox catalysis

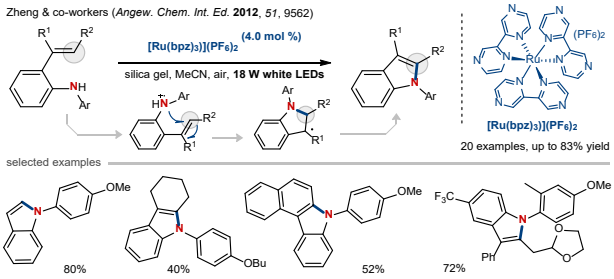
1.2 Pioneering Works

In 2012, the research groups of Fu and Peters pioneered the photoinduced Ullmann C–N coupling reaction catalyzed by the copper carbazolide catalyst (Scheme 3).[10] Lithium carbazolides were used to couple with aryl iodide leading to the C–N bonds formation. Experimental studies suggested that a carbon-based radical is involved for the copper-mediated C–N bond formation is ensured. This work demonstrated the possibilities for photoinduced C–N bond formations and pioneered further development, including *N*-arylation and *N*-alkylation reactions.



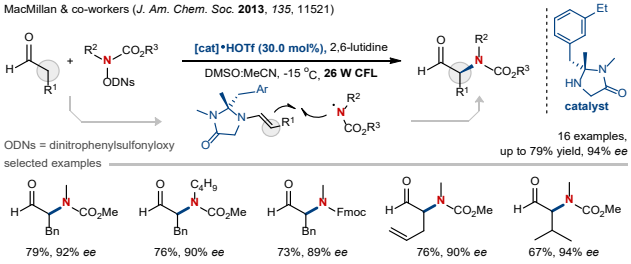
Scheme 3 Cu-catalyzed photoinduced Ullmann C–N coupling

Another inspiring work was reported by Zheng's group. A cascade aromatization of styryl anilines to the tethered alkene was achieved with $[Ru(bpz)_3(PF_6)_2]$ catalyst under an 18 W white LEDs irradiation (Scheme 4).[11] The N-centered radical cation generated from styryl anilines would undergo electrophilic addition to the tethered alkene. The following aromatization or C–C bond migration would give the indole products.



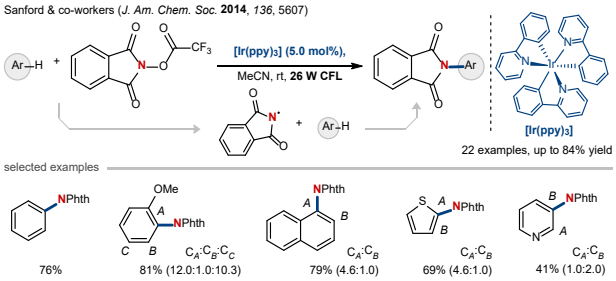
Scheme 4 Photocatalytic oxidative C–N aromatization

In 2013, the MacMillan and co-workers developed the enantioselective amidation of enamines by the combination of photoredox and organocatalysis (Scheme 5).[12] Dinitrophenylsulfonyloxy (ODNs) group was employed as a traceless activation handle to generate N-centered radicals. Enantioselective α-addition to the in situ formed chiral enamines would then give the *N*-substituted α-amino aldehyde product. The incorporation of chiral organocatalyst enables this reaction to be one of the few examples generating enantioenriched C–N coupling products.



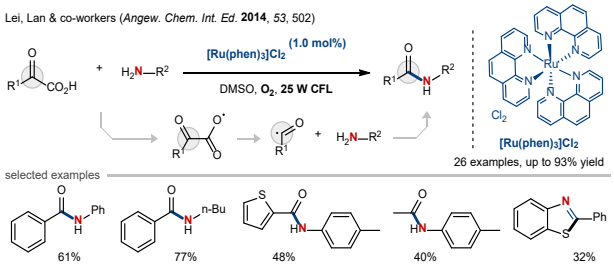
Scheme 5 Photoredox enantioselective α-amination of alkedhydes

Sanford and co-workers also explored the reactivity of *N*-acyloxyphthalimides under visible light to generate phthalimide radicals to add on arenes (Scheme 6).[13] The N-centered radical is generated without excessive amount of oxidant under mild conditions. A broad substrate scope was presented, including a meta selective C–H amination of pyridine derivatives.



Scheme 6 C–H amination of arenes and heteroarenes by *N*-acyloxyphthalimides

A novel radical oxidative decarboxylative coupling of α-keto acids with amines was reported by Lei, Lan and co-workers (Scheme 7).[14] $[Ru(phen)_3]Cl_2$ was employed as the photocatalyst with oxygen as terminal oxidant. Detailed mechanistic studies revealed that a SET process between the excited photocatalyst and aniline played an important role, suggested that the decarboxylation was facile and irreversible.

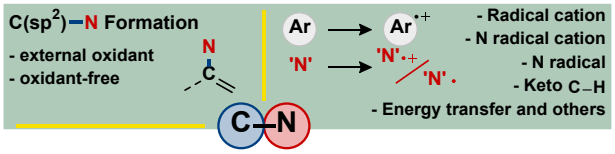


Scheme 7 Decarboxylative/Oxidative amidation of α-keto acids

These pioneering works showcased the concepts of photocatalytic C–N bond formations, including Cu-catalyzed coupling, cyclization, N-centered radical coupling and decarboxylative coupling.

2. C(sp^2)–N Bond Formation

Photocatalytic C(sp^2)–N bond formation can be categorized into oxidative amination and oxidant-free amination (Scheme 8). The coupling reactions are usually initiated by the generation of aryl radical cation, nitrogen radical cation or nitrogen radical. Some examples showed transition-metal mediated energy transfer as a key mechanistic step.

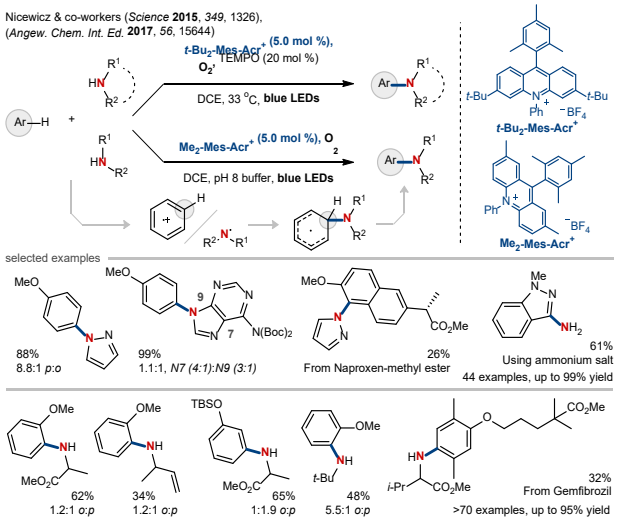


Scheme 8 Brief summary for photocatalytic C(sp^2)–N formations

2.1. Involving External Oxidant

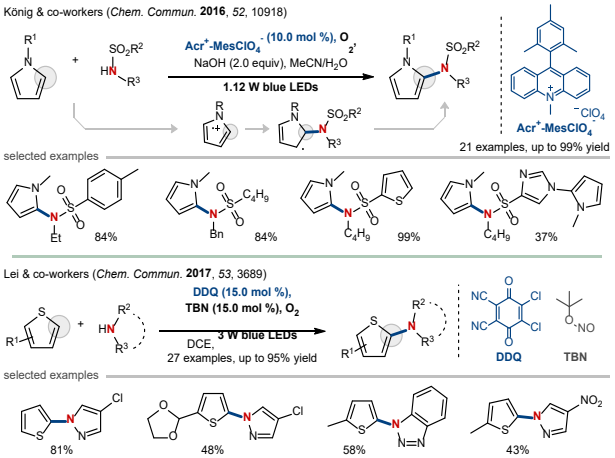
2.1.1. Aryl Radical Cation

In 2015, the research group of Nicewicz reported a visible-light-mediated arene C–H amination with azoles. The reaction was catalyzed by acridinium with TEMPO as the cocatalyst, using O_2 as terminal oxidant (Scheme 9). *para*-Selective C–N bond formation were achieved regardless of functionalities such as free alcohols, esters, halides and alkenes. This pioneering work offers an appealing approach for activation of arenes and site-selective arene C–H amination. In 2017, Nicewicz's group reported a comprehensive study for this reaction and extended the amination scope using primary amines.[15]



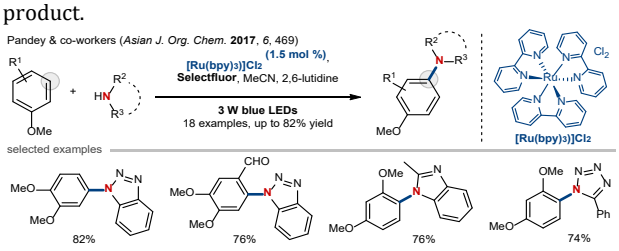
Scheme 9 Photoredox site-selective aryl C–H amination

The König's group developed the C2-seletive amination of pyrroles with sulfonamides for the synthesis of *N*-(2-pyrrole)-sulfonamide. They also reported the related amination reactions using carbamates, urea and other N-heterocycles. Lei and co-workers expanded the substrate scope to thiophenes by using 2,3-dichloro-5,6-dicyano-p-benzoquinone (DDQ) as catalyst and electron mediator *tert*-butyl nitrite (TBN) (Scheme 10).[16]



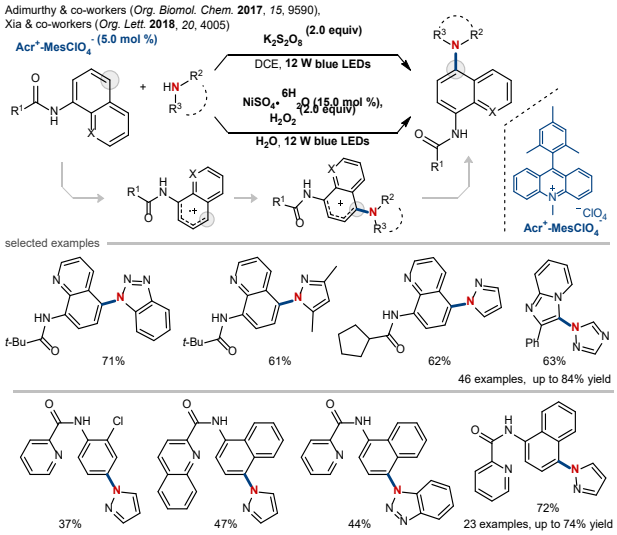
Scheme 10 C2-seletive amination of pyrroles and thiophenes

The use of external oxidants such as Selectfluor, H_2O_2, $K_2S_2O_8$, etc. were also reported in recent years. In 2017, Pandey and co-workers described the amination of some electron-rich arenes with various heteroaromatic amines, including imidazole, triazole, and tetrazole (Scheme 11).[17] The photoexcited Ru catalyst would undergo SET to generate an arene radical cation, which reacts with an amine nucleophile to give the C–N coupling product.



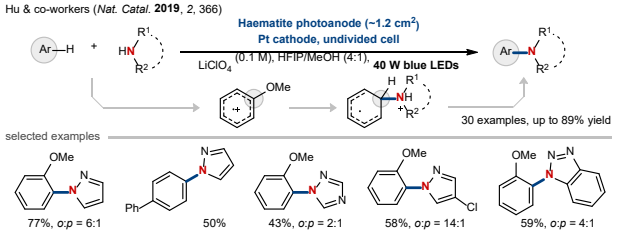
Scheme 11 Photocatalytic amination of arenes

Further developed by the Adimurthy's group, regioselective C–H amination of heteroarenes with heteroaromatic amines was achieved by using acridinium as photoredox catalyst with $K_2S_2O_8$ as oxidant. The Xia's group also reported the dual-catalyst C–N cross-coupling between arylamines and pyrazoles with [$NiSO_4 \cdot 6H_2O$] and acridinium catalyst. Both reactions are proposed to involve an aryl radical cation intermediate which reacts with the arylamines to give the C–N bond (Scheme 12).[18]



Scheme 12 Regioselective C–H amination of quinoline amides and imidazopyridines

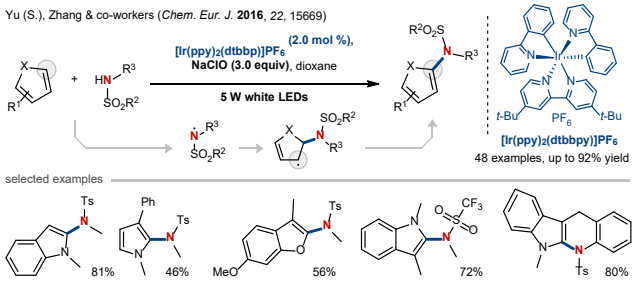
Recently, Hu and co-workers merged photocatalysis and electrocatalysis for non-directed arene C–H amination using haematite as photoanode (Scheme 13).[19] Under illumination, the photogenerated holes in haematite oxidized electron-rich arenes to radical cations, which further reacted with azoles to give the nitrogen heterocycles. An unusual ortho selectivity was achieved due to the hydrogen-bonding interaction between the hexafluoroisopropanol (HFIP) and the substrate. This photoelectrocatalytic amination also demonstrates potential applications for late-stage functionalization.



Scheme 13 Photoelectrocatalyrtic arene C–H amination

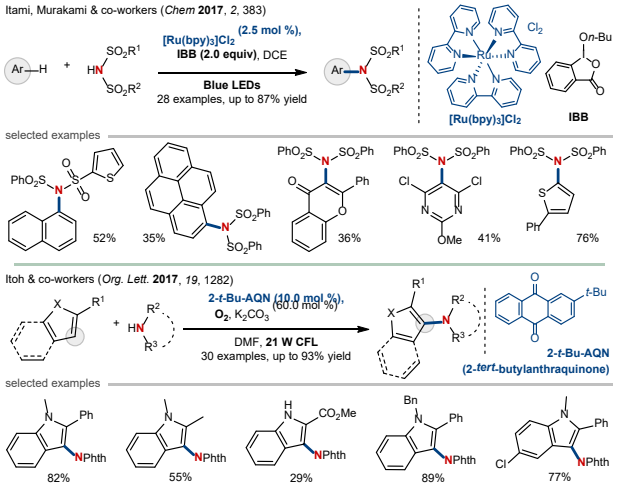
2.1.2.Nitrogen Radical and Radical Cation

Yu (S.), Zhang and co-workers developed an oxidative C–H amidation of heteroarenes with sulfonamides via N-centered radical. (Scheme 14).[20] With NaClO solution as oxidant, a variety of heteroarenes including indoles, pyrroles and benzofurans were amidated with up to 92% yield.



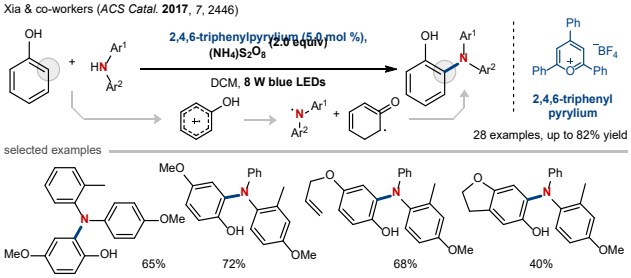
Scheme 14 Oxidative C–H amidation of heteroarenes with sulfonamides

Further development on direct arene amidations via N-centered radicals was reported by Itami, Murakami and co-workers. An equimolar C–H/N–H coupling of arenes and sulfonimides was presented using Ru photocatalyst and 1-butoxy-1λ3-benzo[*d*][1,2]iodaoxol-3(1*H*)-one (IBB) as oxidant. Itoh and co-workers also developed a similar cross-dehydrogenative C–H amination of indoles with phthalimide using oxygen as the external oxidant (Scheme 15).[21]



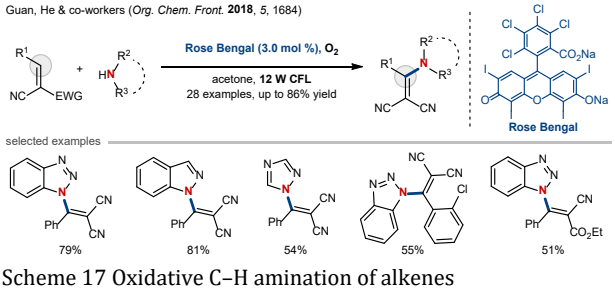
Scheme 15 Aromatic C–H amidation with sulfonamide and phthalimide

The Xia's group reported another cross-dehydrogenative amination reaction between phenols and acyclic diarylamines using persulfate as oxidant (Scheme 16).[22] The reaction was proposed to undergo a chain propagation pathway to generate a phenoxenium radical. Afterwards, a radical-radical cross-coupling reaction would furnish the product.



Scheme 16 Dehydrogenative amination of phenols

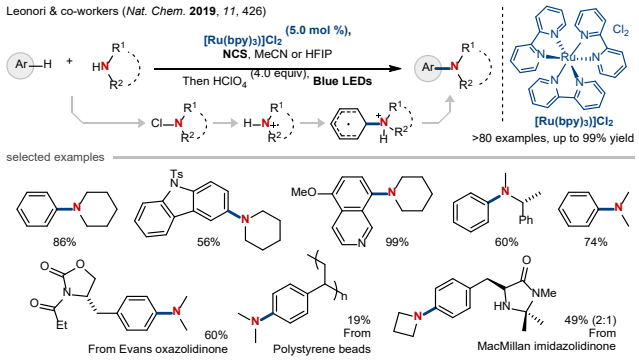
Further explored by Guan, He and co-workers, electron-poor alkenes were successfully coupled to azoles to form *N*-vinylazoles (Scheme 17).[23] Radical cation azole intermediates and the corresponding N-centered radicals were proposed to be the key species of this coupling reaction.



Scheme 17 Oxidative C–H amination of alkenes

Recently, Leonori's group developed a practical and regioselective amination of arenes using alkyl amines with [Ru(bpy)$_3$Cl$_2$] as photoredox catalyst with *N*-chlorosuccinimide (NCS) (Scheme 18).[24] The direct coupling of amines and arenes

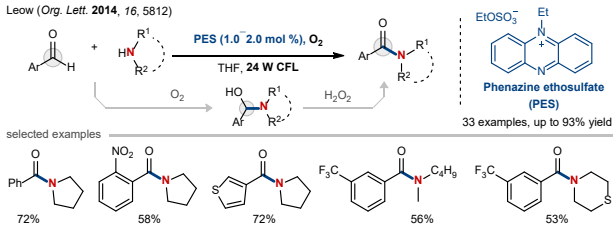
has been realized to a range of structurally diverse and complex substrates in multigram scale. Late-stage functionalization has also been applied to substituent such as peptides, chiral catalysts, polymers and organometallic complexes. Mechanistic studies revealed that the process starts with the in situ conversion of amine to *N*-chloroamine. Subsequent protonation and SET from the photocatalyst would generate the aminium radical and undergoes highly polarized addition to arenes.



Scheme 18 Regioselective amination of arenes with alkyl amines

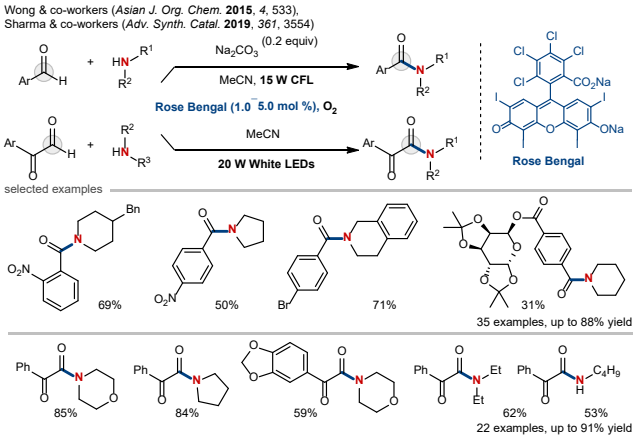
2.1.3.Keto C–H Amination

In 2014, Leow reported an amidation of aromatic aldehydes using phenazine ethosulfate as photocatalyst with O_2 as oxidant (Scheme 19).[25] The phenazinium cation is proposed to undergo an overall two-electron reduction to hydrophenazine and oxidized by oxygen to generate H_2O_2. The H_2O_2 formed would then oxidize the hemiaminal intermediate to give the amide product.



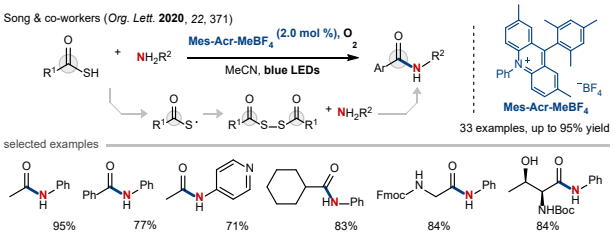
Scheme 19 Amidation of aromatic aldehydes

Wong and co-workers pursued a similar strategy for synthesis of tertiary amides, including examples of oligosaccharides and endoperoxide artemisinin. Sharma and co-workers extended the reaction scope to α-keto amides. This method is compatible with a large variety of α-keto aldehydes and primary/secondary aliphatic amines (Scheme 20).[26]



Scheme 20 Oxidative amidation of aldehydes and α-keto acids

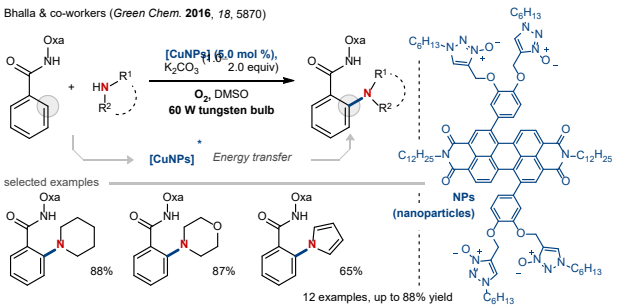
Recently, Song and co-workers utilized thioacetic acids as substrates for the visible light-induced amide bond formation (Scheme 21).[27] The reaction was triggered by the deprotonation of the thioacid with an amine, and a thioacid radical would be generated via single-electron transfer from the photocatalyst. Diradical coupling would generate a disulfide intermediate, followed by aminolysis to furnish the amide bond. This reaction offers an excellent synthetic approach to amides with high functional group tolerance.



Scheme 21 Oxidative amidation of thioacetic acids

2.1.4.Energy Transfer

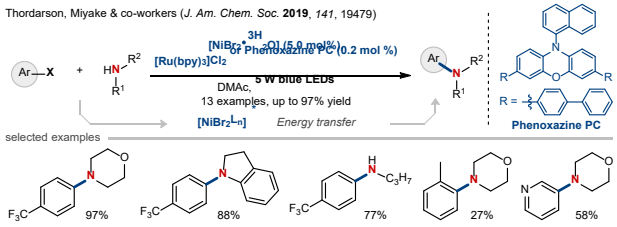
In 2016, the research group of Bhalla developed a regioselective amination using copper nanoparticles (CuNPs) (Scheme 22).[28] Supramolecular aggregates of triazole-appended perylene bisimide *N*-oxide are employed as reactors for the generation of copper nanoparticles (CuNPs). This nanoparticle exhibited photocatalytic activity for C–H amination under mild conditions. An energy transfer mechanism was proposed under the irradiation with a tungsten bulb at aerial conditions.



Scheme 22 Cu-nanoparticles mediated C–H amiantion

Recently, Miyake, Thorarson and co-workers presented a dual catalytic light-driven C–N cross coupling protocol using Ni(II) salt with a photocatalyst.[29] Results of a detailed mechanistic investigation are consistent with Förster-type energy transfer from the excited photocatalyst to Ni-amine

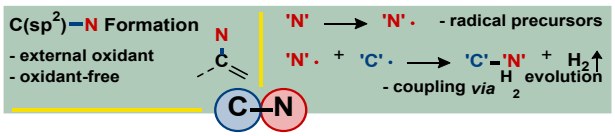
complexes. A diverse selection of amines and aryl halides reacted to produce the corresponding C–N coupled products (Scheme 23).



Scheme 23 Ni-amine complexes mediated C–H amiantion

2.2. Oxidant Free

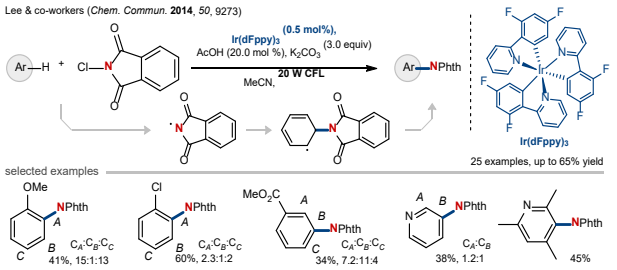
Photocatalytic C(sp^2)–N coupling usually involves the direct radical-radical coupling or radical addition to alkenes (Scheme 24).



Scheme 24 Brief summary for oxidant-free photocatalytic C(sp^2)–N formations

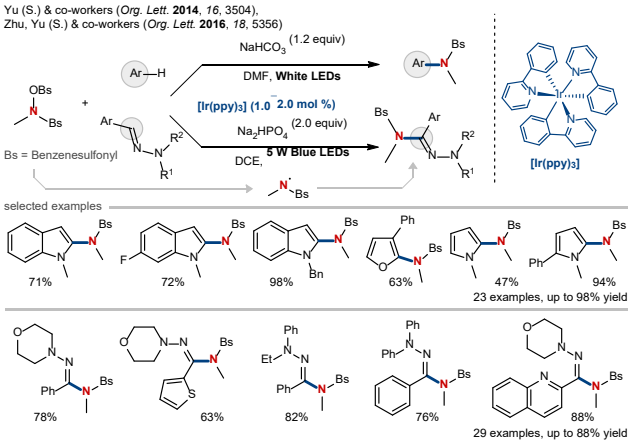
2.2.1. Nitrogen Radical Precursors

Lee and co-workers reported the use of *N*-chlorophthalimide as N-centered radical precursor for the C–H imidation of (hetero)arenes with Ir photocatalyst (Scheme 25).[30] This Minisci-type C–H functionalization is triggered by the reductive scission of the N–Cl bond using visible-light-photoredox catalyst under mild conditions.



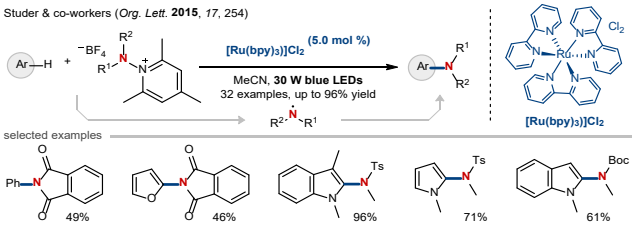
Scheme 25 C–H imidation of (hetero)arenes with *N*-chlorophthalimide

Yu (S.) and co-workers explored the use of other nitrogen radical precursors and found that hydroxylamine derivatives show excellent reactivity towards redox-neutral C–H amination of heteroarenes (Scheme 26). Regioselective C–N coupling was achieved for indoles, pyrroles and furans. In 2016, they extended this chemistry for the umpolung amidation of aldehyde-derived hydrazones. The corresponding hydrazonamides were formed in broad scope.[31]



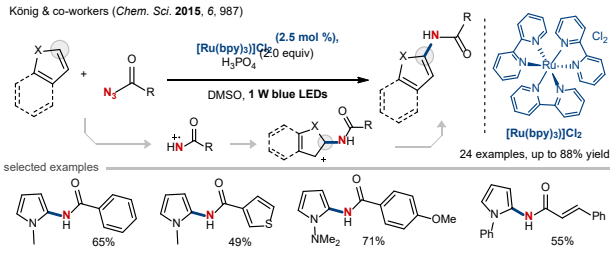
Scheme 26 Redox-neutral C–H amination of heteroarenes

In 2015 Studer and co-workers disclosed the use of *N*-aminopyridinium salts as N-centered radical precursors. Regioselective C–H amination of arenes and heteroarenes was achieved with [Ru(bpy$_3$)]Cl$_2$ as the catalyst (Scheme 27).[32] The excited photocatalyst reduces the pyridinium salt by SET and subsequent fragmentation would generate the N-centered radical for the C–N coupling.



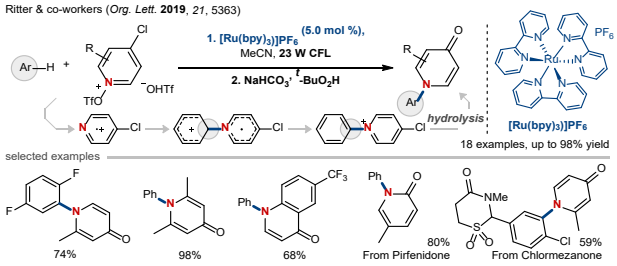
Scheme 27 Regioselective C–H amination of arenes and heteroarenes with aminopyridinium salts

König's group disclosed an oxidant-free C–H amidation of heteroarenes by using benzoyl azides (Scheme 28).[33] This reaction offers a mild protocol for photoredox C–N coupling with dinitrogen as the only by-product. Heterocycles including pyrroles, indoles, furan, benzofuran or thiophene were amidated in a single step.



Scheme 28 Amidation of heteroarenes with benzoyl azides

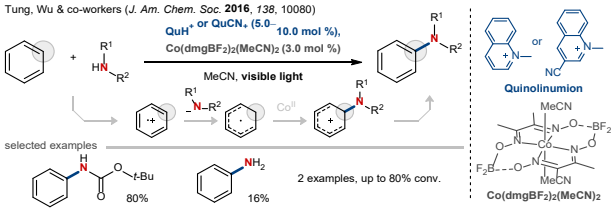
Recently, Ritter and co-workers developed an interesting C–H pyridonation reaction which successfully coupled 2- or 4-pyridones to arenes (Scheme 29).[34] The photoredox catalysis generates chloropyridinium radical cations for coupling to arenes to furnish the *N*-aryl-pyridone in excellent yields. Late-stage modification of natural compounds was also realized by this method.



Scheme 29 C–H pyridonation of arenes

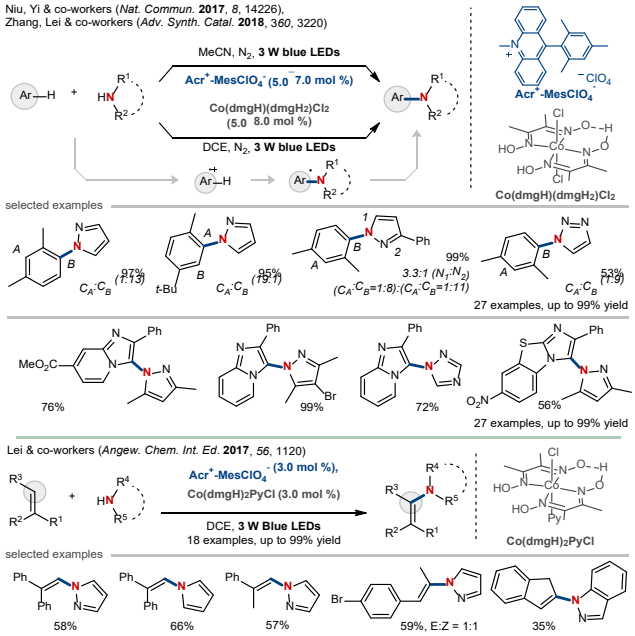
2.2.2.C–N Cross-Coupling via Hydrogen Evolution

In 2016, Tung, Wu and co-workers presented a blueprint of a dual catalyst system to produce aniline directly from benzene and ammonia (Scheme 30).[35] They developed the hydrogen-evolution cross-coupling reaction using the combination of a photocatalyst and a Co catalyst accompanied by liberation of hydrogen gas. In this design, the Co catalyst capture electrons from the substrates and/or reaction intermediates to reduce the protons eliminated from the C–H and N–H bonds into molecular hydrogen.



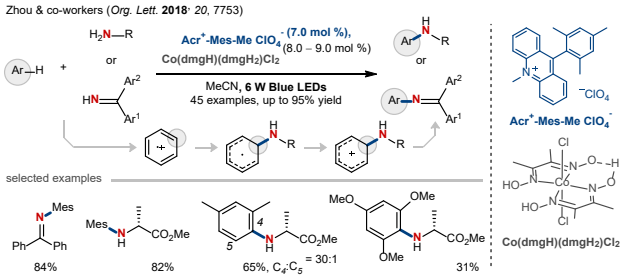
Scheme 30 Hydrogen-evolution cross-coupling of benzene and ammonia

This concept was further explored by Niu, Yi and co-worker. Selective C–H amination of arenes using heterocyclic azoles gives a wide range of *N*-arylazoles including biphenyls and anisoles. The scope was further expanded by Lei for the coupling of imidazo[1,2-α]pyridines with pyrazoles. Photocatalytic dehydrogenative cross-coupling of alkenes with azoles was also reported (Scheme 31).[36]



Scheme 31 C–H amination of arenes with heterocyclic azoles

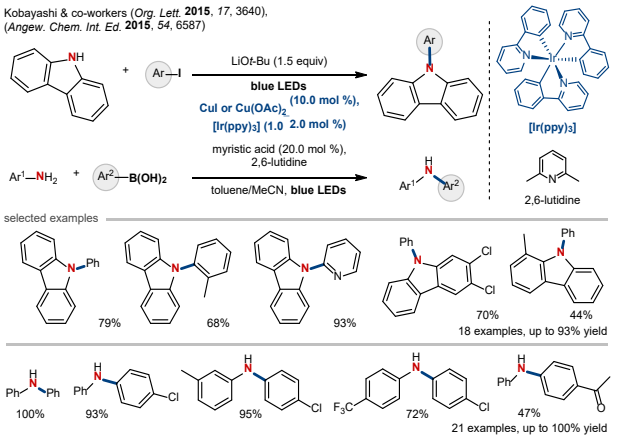
The Zhou's group also described the cooperative catalyst system for the C–H amination of arenes with concomitant generation of hydrogen. A variety of amines and hydrolytically unstable benzophenone imines were converted to the corresponding aromatic amines and triarylmethanimines (Scheme 32).[37]



Scheme 32 C–H amination of arenes with amine and imine

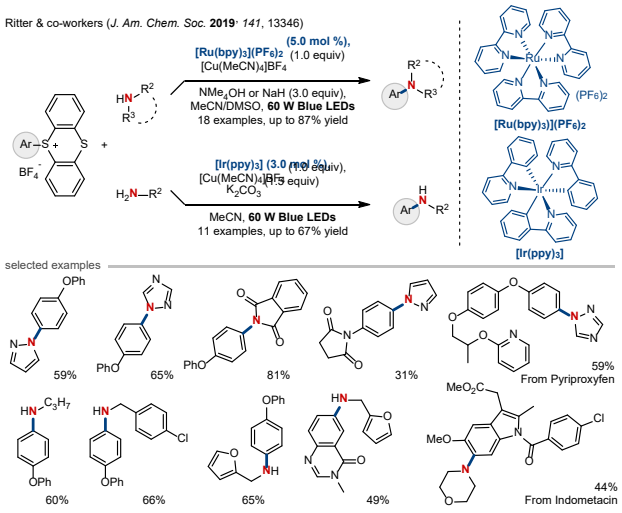
2.2.3.Other Examples

The Kobayashi's group significantly improved the Ullmann-type and Chan-Lam couplings under visible-light-mediated photoredox catalysis (Scheme 33).[38] Through the productive merger of copper and photoredox catalysis, the substrate scope was expanded under mild reaction conditions.



Scheme 33 *N*-arylation of aryl iodides and boronic acids

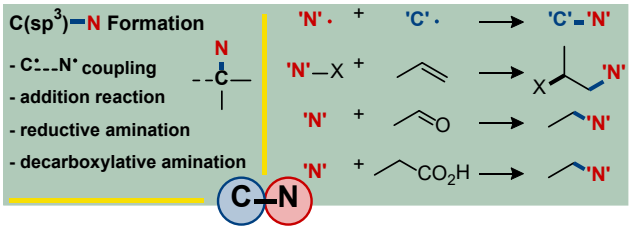
Recently, Ritter's groups reported a revolutionary site-selective late-stage diversification via aryl sulfonium salts. A set of four methods enables cross-coupling with a broad range of N-nucleophiles as well as N-containing heterocycles. The reaction was proposed to proceed via single electron reduction of the aryl thianthrenium, and sequent generation of an aryl radical, which can engage in the copper-mediated redox process for subsequent C–N reductive elimination from some high-valent copper species. (Scheme 34).[39]



Scheme 34 Site-selective late-stage diversification via aryl sulfonium salts

3. C(sp³)–N Bond Formation

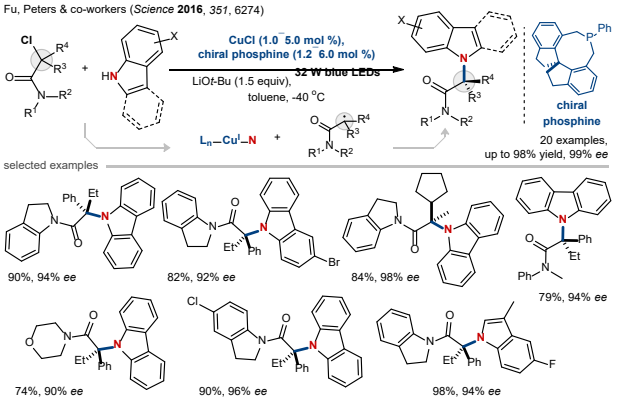
There are four major approaches for photocatalytic C(sp³)–N bond formations, including the direct radical-radical couplings, addition reactions to alkenes and reductive amination of carbonyl compounds (Scheme 35).



Scheme 35 Brief summary for photocatalytic C(sp³)–N formations

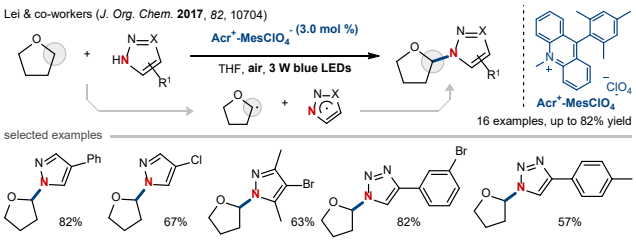
3.1. Direct Radical-Radical Coupling

In 2016, Fu, Peters and co-workers reported a groundbreaking visible-light-mediated asymmetric copper-catalyzed C–N coupling reaction (Scheme 36).[40] The combination of base-metal catalysis, chiral ligands and photoactivated conditions eanbled an enantioconvergent transformation of racemic starting materials to single enantiomeric products. Carbazole and α-halocarbonyl compounds were coupled in the presence of CuCl, a chiral phosphine ligand and Brønsted base under blue LEDs irradiation. This method ingeniously employed a single catalyst to achieve both photochemistry and enantioselective C–N bond construction.



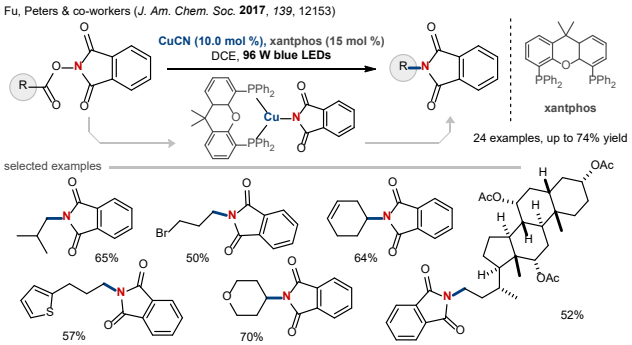
Scheme 36Cu-catalyzed asymmetric C–N coupling reaction

The Lei's group presented an oxidative amination of tetrahydrofurans with *N*-heterocyclic amines. The reaction was achieved by using acridinium as catalyst and oxygen as oxidant (Scheme 37).[41] The excited photocatalyst would undergo SET process with pyrazole to generate a N-centered radical for subsequent coupling reaction.



Scheme 37 Oxidative amination of tetrahydrofuran with *N*-heterocyclic amine

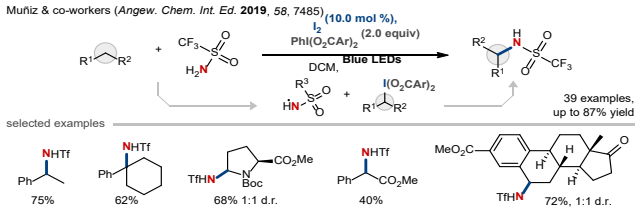
Fu, Peters and co-workers discovered an intramolecular decarboxylative C–N coupling of NHPI esters to give protected amines with copper catalyst under blue-LED irradiation (Scheme 38).[42] Copper species are engaged in both the photochemistry and the key bond-forming step, which occurs through out-of-cage coupling of an alkyl radical. This method provides an alternative to the Curtius rearrangement and the C–N bond formation is compatible with a wide range of functional groups.



Scheme 38 Cu-catalyzed intramolecular decarboxylative C–N coupling of NHPI esters

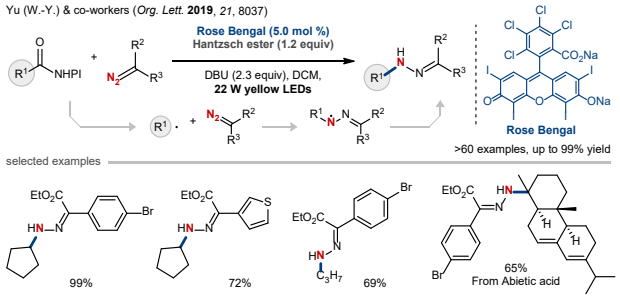
Muñiz and co-workers developed a direct amination of aliphatic C(sp³)–H bonds with triflamides under a unique iodine-catalyzed process (Scheme 39).[43] Surprisingly, secondary methylene positions are selectively functionalized over tertiary methine groups. A three-phase catalysis manifold involving the C–H iodination, alkyl iodide oxidation and amination by amidyl

radical was proposed. This work enables a new C–N bond process that complements the nitrene chemistry.



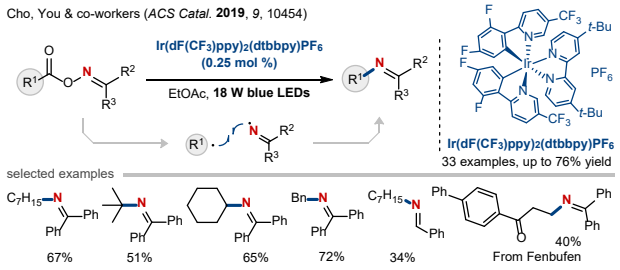
Scheme 39 Amination of C(sp^3)–H bonds with triflamides

Recently, our group reported a decarboxylative coupling of α-diazoacetates with *N*-hydroxyphthalimide esters (NHPI esters) (Scheme 40).[44] By employing Rose Bengal as a photocatalyst under yellow LEDs irradiation, we prepared successfully over 60 *N*-alkyl hydrazones. Mechanistic studies suggested Hantzsch ester serves as both electron donor and proton source for the reaction.



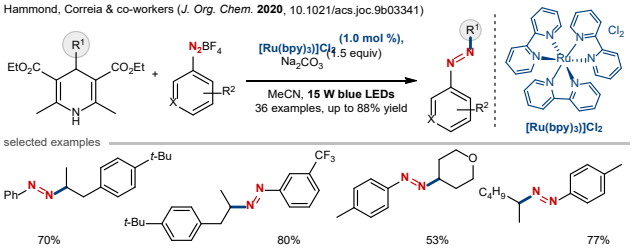
Scheme 40 Decarboxylative coupling of α-diazoacetates with NHPI esters

The reductive N–O bond cleavage for C–N bond coupling has been further studied by Cho, You and co-workers. The homolytic cleavage of oxime esters in the presence of an Ir complex produces acyloxy and iminyl radicals, which would undergo decarboxylative cross-coupling to give structurally diversified imines (Scheme 41).[45] DFT studies with photophysical and electrochemical measurements indicated the operation of a photocatalytic Dexter-type energy transfer pathway.



Scheme 41 Intramolecular decarboxylative C–N coupling

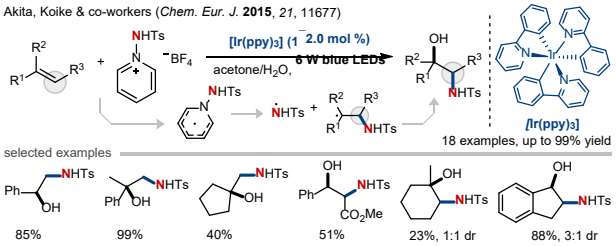
A similar formal deformylative C–N coupling reaction was presented by Hammond, Correia and co-workers (Scheme 42).[46] The procedure employs dihydropyridines for the generation of alkyl radicals, which then react with diazonium salts to afford the corresponding diazenes. Interestingly, no observed tautomerization of the diazenes to the corresponding arylhydrazones was observed.



Scheme 42 Decarboxylative coupling of diazonium salts with dihydropyridines

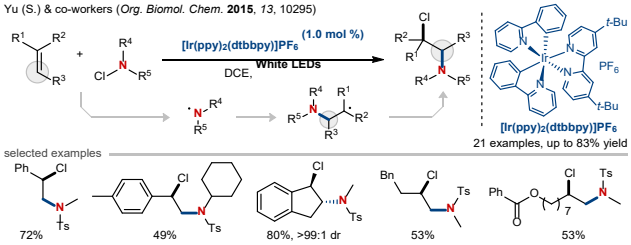
3.2. Addition Reactions to Alkene

In 2015, Akita, Koike and co-workers reported a regio-aminohydroxylation of alkenes by [Ir(ppy)$_3$] catalyst (Scheme 43).[47] *N*-Protected 1-aminopyridinium salts were used as amidyl radical precursors and vicinal aminoalcohols were successfully synthesized under mild conditions.



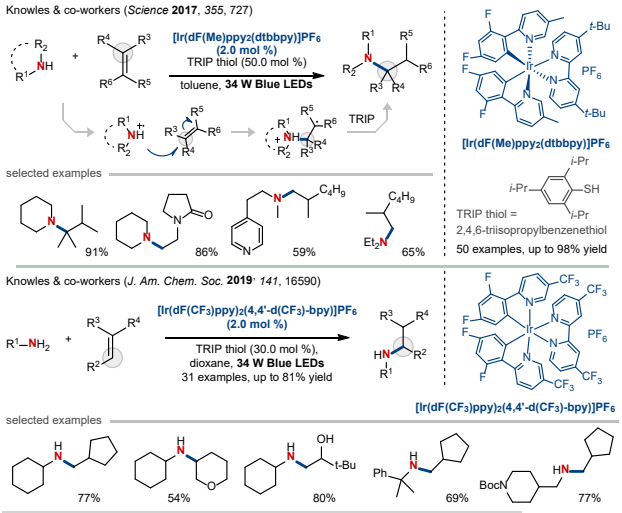
Scheme 43 Regio-aminohydroxylation of alkenes

Regioselective 1,2-chloramiantion of alkenes was also achieved by the Yu (S.)'s group (Scheme 44).[48] *N*-Chlorosulfonamides were used as both nitrogen and chlorine sources for the synthesis of vicinal haloamine derivatives.



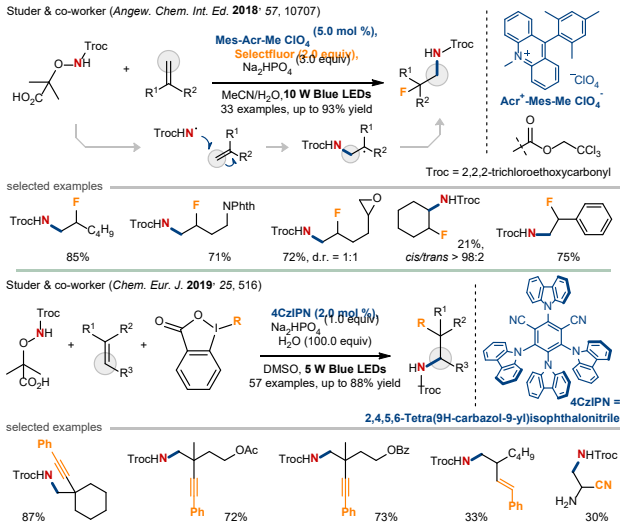
Scheme 44 Regioselective 1,2-chloramiantion of alkenes

In 2017, Knowles' group reported a catalytic protocol for efficient additions of secondary alkyl amines to a wide range of alkenes with complete anti-Markovnikov regioselectivity (Scheme 45).[49] The reaction is proposed to proceeds through a key aminium radical cation intermediate generated via electron transfer between the excited iridium photocatalyst and an amine substrate. This work offers a redox-neutral and atom-economical pathway for C–N bond formation with broad functional group tolerance. In 2019, they further expanded and optimized the reaction scope using [Ir(dF(CF$_3$)ppy)$_2$(4,4'-d(CF$_3$)-bpy)]PF$_6$ as catalyst.



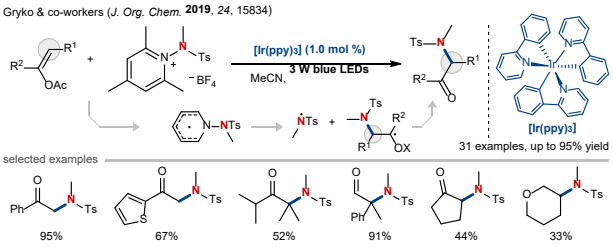
Scheme 45 Intramolecular hydroamiantion of alkenes

Studer and co-workers developed a three-component amido-fluorination of alkenes. α-Amido-oxy acids were used as a N-centered radical precursor with sequential CO_2 and aldehyde/ketone fragmentation. Radical addition to alkene would then occur and the adduct would be trapped by Selectfluor via fluorine-atom transfer. Recently, they present an 1,2-amidoalkynylation of unactivated alkenes using an organic photoredox catalyst (4CzIPN). Mechanistic studies were also performed to support the radical nature of these cascade reaction (Scheme 46).[50]



Scheme 46 Amidofluorination and amidoalkynylation of alkenes using α-amido-oxy acids

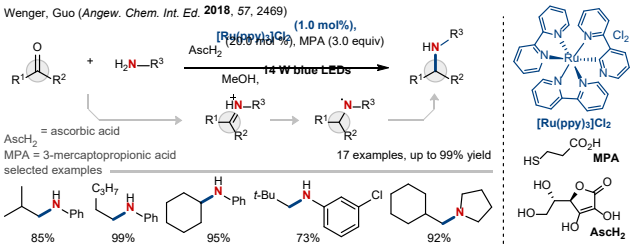
Recently, Gryko and co-workers expanded the use of *N*-aminopyridinium salts for the coupling of enol equivalents to give α-amino carbonyl compounds (Scheme 47).[51] *N*-aminopyridinium salts were reduced by Ir complex via SET to pyridyl radical for addition reaction to alkenes. Broad synthetic utility has been demonstrated, including functionalization of ketones, aldehydes, vinyl esters and 1,3-diketones.



Scheme 47 Amination of alkenes with *N*-aminopyridinium salts

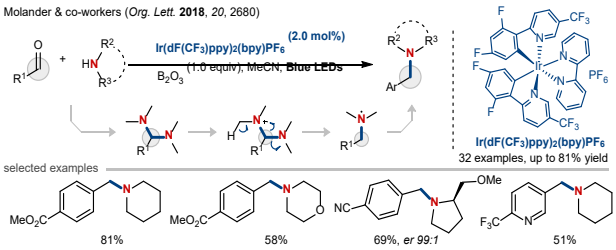
3.3. Reductive Amination of Carbonyl Compounds

Wenger and Guo unveiled a reductive amination of aldehydes and ketones with amines by $[Ru(bpy)_3]Cl_2$ photocatalyst (Scheme 48).[52] The reaction was triggered by the reduction of iminium ions with ascorbic acid to form a α-aminoalkyl radical intermediate. Subsequent hydrogen atom transfer reaction would furnish the reductive amination products.



Scheme 48 Reductive amination of aldehyde and ketones

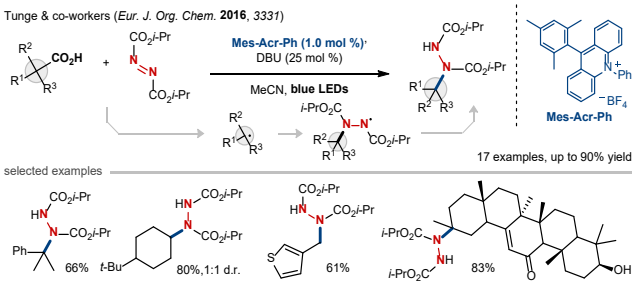
Molander and co-workers developed the reductive amination of aldehydes without an external hydrogen/hydride source via a distinct radical pathway (Scheme 49).[53] The generation of α-amino radicals is proposed to go through an aminal formation/oxidation/fragmentation pathway.



Scheme 49 Reductive amination of aldehydes

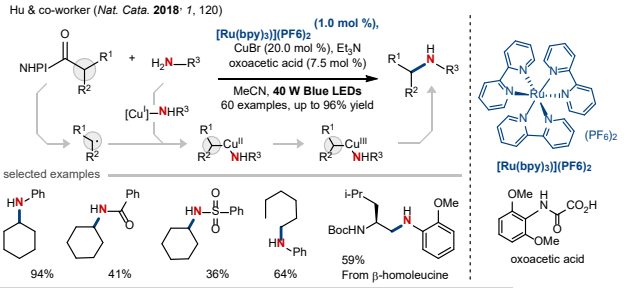
3.4. Decarboxylative Amination

In 2016, Tunge and co-workers reported a straightforward photocatalytic aminodecarboxylation of carboxylic acids for the synthesis of aliphatic amines using acridinium as photocatalyst (Scheme 50). The excited photocatalyst would trigger the radical decarboxylation to generate alkyl radicals. The radical would then be trapped by the azo compound and furnish the product. Guan, He and co-workers also presented a similar decarboxylative amination of inoline-2-carboxylic acids with Rose Bengal as photocatalyst.[54]



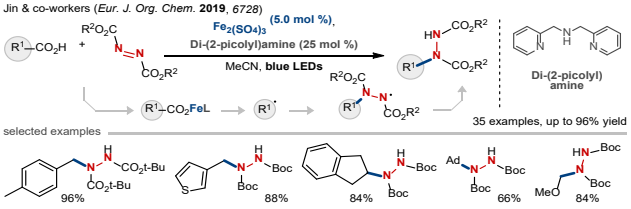
Scheme 50 Aminodecarboxylation of carboxylic acids

In 2018, the Hu's group presented a decarboxylative C–N coupling via synergetic photoredox and copper catalysis using redox-active ester with anilines. (Scheme 51).[55] In this work, the photoredox catalysis allows the use of NHPI esters to generate alkyl radicals, whereas copper catalysis enables the C–N cross-coupling. Rapid functionalization of amino acids, natural products and drugs was demonstrated.



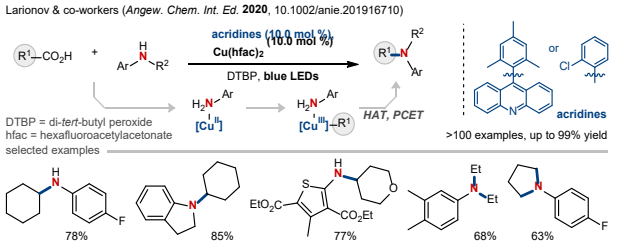
Scheme 51 Aminodecarboxylation of carboxylic acids

Jin's group developed an alternative protocol for the decarboxylative C–N coupling reaction using the iron catalyst prepared in situ by complexation of $Fe_2(SO_4)_3$ with di-(2-picolyl)amine ligand (Scheme 52).[56] Azodicarboxylates and carboxylic acids were successfully coupled to give aliphatic amines. The oxidation of Fe(II) back to Fe(III) by the electron-deficient radical intermediates is proposed to be the key process for the redox-neutral coupling reaction.



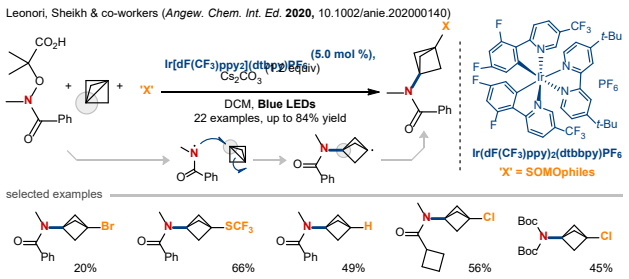
Scheme 52 Fe-catalyzed aminodecarboxylation of carboxylic acid

Larionov and co-workers expanded the scope of decarboxylative C–N coupling to anilines (Scheme 53). This dual catalytic system provides easy access to *N*-alkylated secondary and tertiary anilines, and *N*-heterocycles. Installation of metabolically robust deuterated methyl groups and tandem ring formation are also included. DFT study indicated the acridine-catalyzed photodecarboxylation would generate a Cu(III) intermediate and the reductive elimination and hydrogen atom abstraction would furnish the product.[57]



Scheme 53 Direct decarboxylative *N*-alkylation

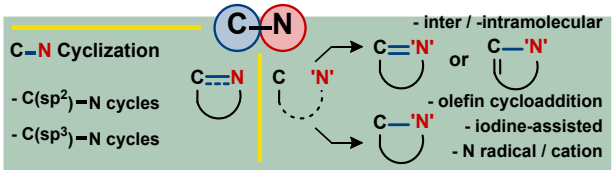
Recently, Leonori, Sheikh and co-workers presented a divergent strain-release amination of [1.1.1]propellane for the synthesis of functionalized bicyclo [1.1.1]pentylamines (Scheme 54).[58] N-centered radicals are showed to undergo strain-release reaction with [1.1.1]propellane, facilitated by the electrophilic nature of these open-shell intermediates. Strong polar effects in the transition-state would also enable the C–N bond formation/ring opening. This radical amino-functionalization provides application in medicinal chemistry programs as *p*-substituted aniline bio-isosteres.



Scheme 54 Strain-release amino-functionalization of [1.1.1]propellane

4. Cyclization Reactions

Photocatalytic C–N cyclization reactions are actually some of the earliest examples for visible-light mediated C–N bond constructions. They can be categorized by C(sp^2)–N heterocycles formations and C(sp^3)–N heterocycles formations (Scheme 55).

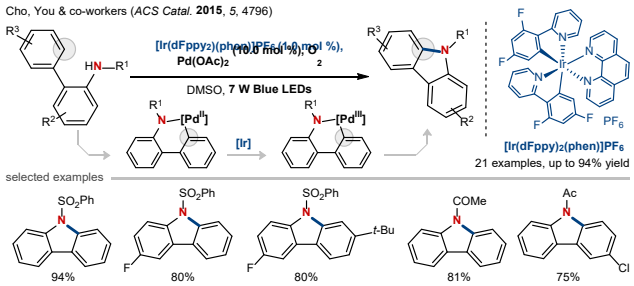


Scheme 55 Brief summary for photocatalytic C–N cyclization

4.1. C(sp^2)–N Heterocycles Formation

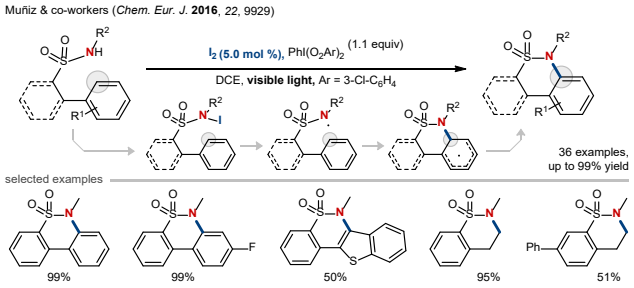
4.1.1. Intramolecular Cyclization

In 2015, Cho, You and co-workers developed a novel intramolecular C–N coupling reactions by merging Pd- and photoredox catalysis (Scheme 56).[59] Spectroscopic and electrochemical studies revealed that the reaction was initiated by the electron transfer from a palladacyclic intermediate to the photoexcited Ir catalyst. This will trigger reductive elimination in a Pd(III)-containing palladacycle to produce the carbazole. The Pd(I) can then be oxidized by O_2 to regenerate the active catalyst.



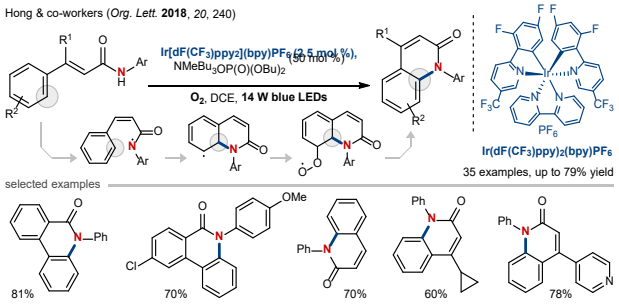
Scheme 56 Intramolecular C–N coupling reactions by Pd- and photoredox catalysis

The Muñiz's group utilized iodine as catalyst for the intramolecular C–H amination of arenes (Scheme 57).[60] The reaction starts from the *N*-iodination of the sulfonamide. Photolytically assisted homolysis of the N–I bond would generate the N-centered radical. Subsequent addition to the aromatic ring would furnish the product.



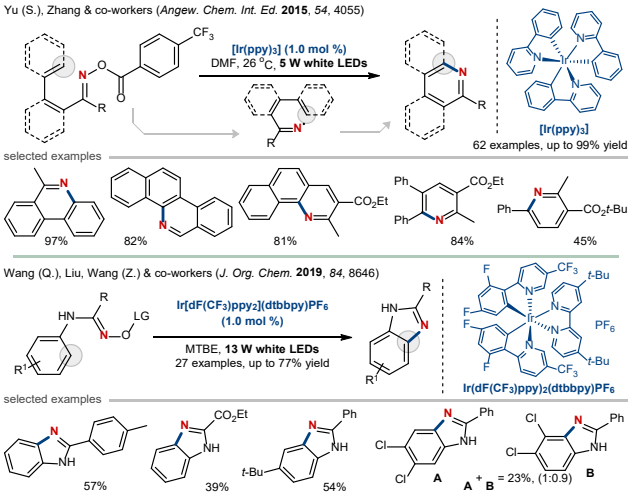
Scheme 57 Intramolecular C–H amination of arenes by iodine catalyst

Hong and co-workers presented an oxidative C–H amidation strategy for the synthesis of quinolinones (Scheme 58).[61] The reaction is triggered by the homolysis of N–H bond of the amide precusors via SET process to give an amidyl radical, which will lead to the intramolecular C–H amidation.



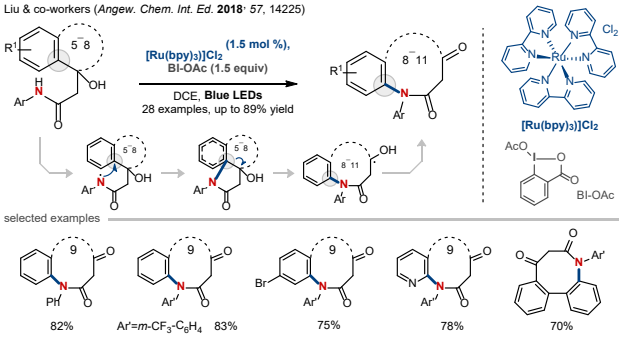
Scheme 58 Hydrogen atom transfer for phenanthridinones and quinolinones synthesis

Intramolecular C–N coupling was also achieved by visible-light-induced N–O bond cleavage to form iminyl- or amidinyl radicals. In 2015, Yu (S.), Zhang and co-workers reported a unified approach to pyridines, quinolines and phenanthrisines. The reaction is initiated by the reduction of acyl oxime to give an iminyl radical intermediate, which then underwent intramolecular homolytic aromatic substitution to give the product. A similar cyclization methodology was reported by Wang (Q.), Liu, Wang (Z.) and co-workers. Substituted benzimidazoles were synthesized with amidinyl radicals (Scheme 60).[62]



Scheme 59 Intramolecular C–N coupling by N–O bond cleavage

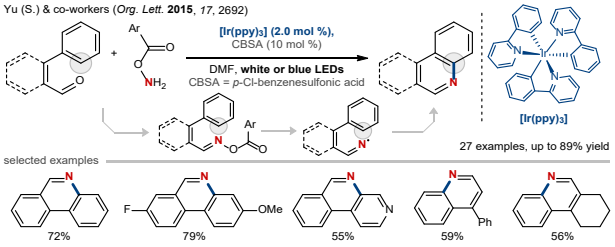
In 2018, the Liu's group reported an interesting photocatalytic C–N coupling reaction for the synthesis of medium-sized lactams (Scheme 61).[63] A remote radical (hetero)aryl migration from C to N under visible light condition enables the ring-expansion of 5–8-membered cyclic ketones to 8–11-membered lactams. Some 13–15-membered marcolactams can also be synthesized by an additional one-step manipulation. Mechanistic studies suggest an acid promoted amidyl radical was involved.



Scheme 60 Photocatalytic ring-expansion for medium-sized lactams synthesis

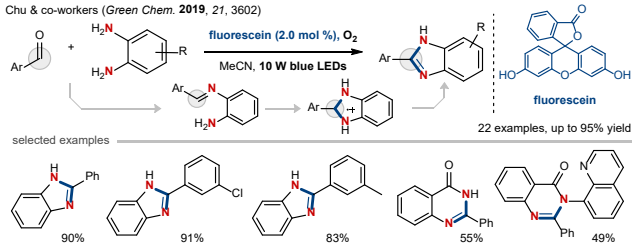
4.1.2.Intermolecular Cyclization

Yu (S.) and co-workers developed an intermolecular one-pot C–N coupling reactions of aldehydes and *O*-acyl hydroxylamine to give phenanthridines and quinolines (Scheme 62).[64] The in-situ reaction between aldehydes and *O*-acyl hydroxylamine would give *O*-acyl oxime for the generation of iminyl radicals. Further cyclization would then take place and furnish the desired aza-arenes.



Scheme 61 Intermolecular one-pot C–N coupling reactions of aldehydes and *O*-acyl hydroxylamine

The research group of Chu developed a fluorescein-catalyzed condensation cyclization for the synthesis of benzimidazoles (Scheme 63).[65] The reaction is initiated by the condensation reaction between aromatic aldehyde and *o*-phenylenediamine to form an imine intermediate. Subsequent intramolecular cyclization would furnish the product.

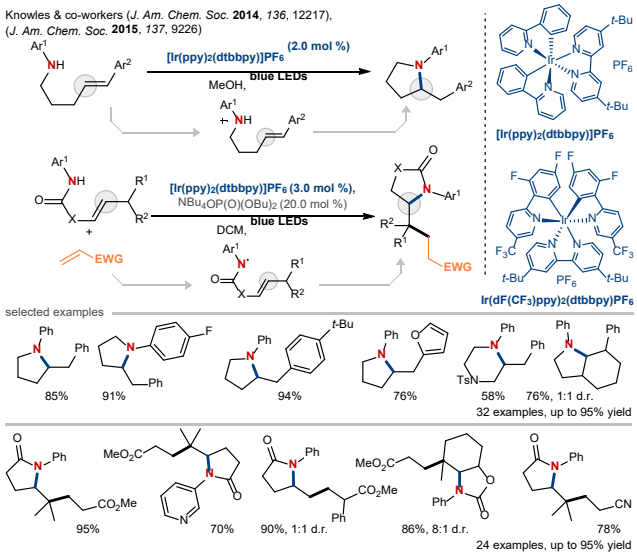


Scheme 62 Condensation cyclization of aromatic aldehydes and *o*-phenylenediamines

4.2. C(sp³)–N Heterocycles Formation

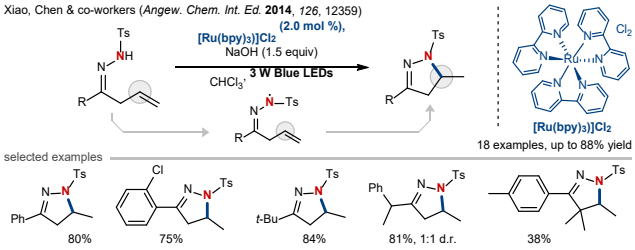
4.2.1. Alkene Cycloaddition

In 2014, Knowles' group reported the intramolecular anti-Markovnikov hydroamination of aryl alkenes to give *N*-aryl heterocycles. The reaction proceeded through sequential amine oxidation, turnover-limiting C–N bond formation and reduction of a carbon radical resulting in overall redox-neutral C(sp³)–N cyclization. This work also presents the use of aminium radical cations derived from simple amine to furnish the alkene hydroamination products. They further expanded this chemistry using a ternary catalyst system for the synthesis of γ-lactams (Scheme 64/63??). According to Knowles' studies, the reactive amidyl radical is generated via the concerted proton-coupled electron transfer (PCET) mediated by the iridium photocatalyst assisted by a weak phosphate base.[66] Recently, the same group further achieved the PCET-enabled alkene hydroamination reaction with *N*-alkyl amides using the iridium photocatalyst and a dialkyl phosphate base.[67]



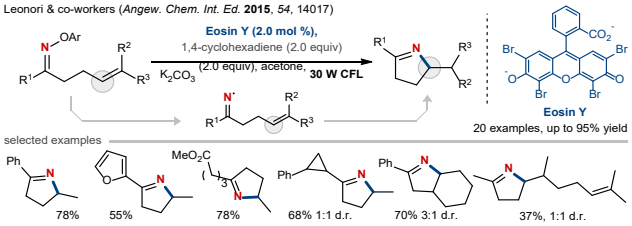
Scheme 63 Intramolecular hydroamination of alkenes

Xiao, Chen and co-workers reported another intramolecular hydroamination example using β,γ-unsaturated hydrazones. The photocatalytic generated N-centered hydrazonyl radicals would undergo alkene hydroamination and to give the corresponding 4,5-dihydropyrazoles in good yields (Scheme 65 /64??). The protocol involves deprotonation of an N–H bond and photocatalytic oxidation to an N-centered radical, thus obviating the need to prepare photolabile amine precursors or the use of external oxidant.[68]



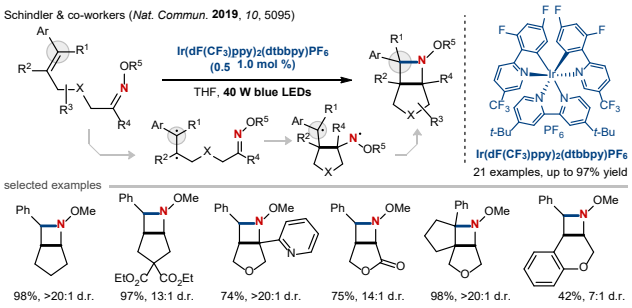
Scheme 64 Intramolecular hydroamination using β,γ-unsaturated hydrazones

Meanwhile, Leonori and co-workers developed the metal-free hydroamination of *O*-aryl oximes (Scheme 66/65???). This new class of *O*-aryl oximes enabled the formation of iminyl radicals owing to their low reduction potentials.[69]



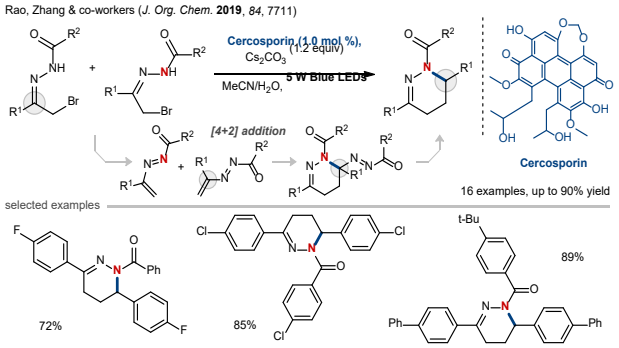
Scheme 65 Hydroamination and iminohydroxylation of *O*-aryl oximes

Schindler and co-workers disclosed an interesting visible-light mediated Paternò-Büchi reactions (Scheme 67/66???).[70] The Ir-catalyzed coupling of imines and alkenes under blue LEDs irradiation would furnish the functionalized azetidines. This approach relies on the selective activation of the alkene functionality upon energy transfer from a suitable photocatalyst to its corresponding triplet state. Overall, this work provides a novel strategy for [2+2] cycloaddition involving C–N bond formation.



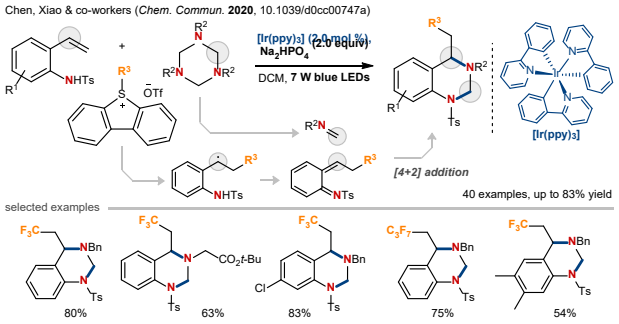
Scheme 66 Visible-light mediated Paternò-Büchi reactions

Rao, Zhang and co-workers discovered an interesting cercosporin-catalyzed [4+2] homocyclodimerizations of azoalkenes for the synthesis of 1,4,5,6-tetrahydropyridazine derivatives (Scheme 68/67???).[71] The reaction is initiated by reacting the α-halo hydrazone with a base to generate azoalkene. Azoalkene would undergo regioselective [4+2] cycloaddition to give a pyridazine intermediate. Attack of the OH radical at the acyl carbonyl group, followed by dinitrogen elimination, would generate the desired product.



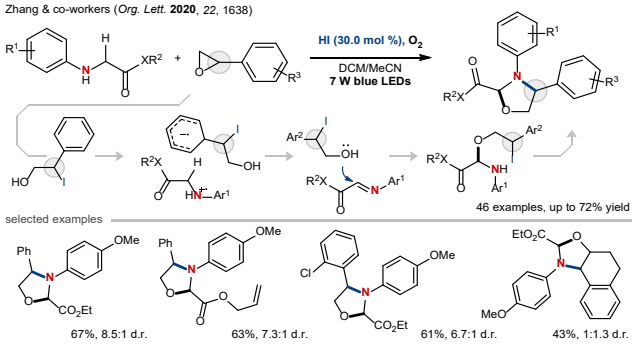
Scheme 67 [4+2] homocyclodimerizations of azoalkenes

Recently, Chen, Xiao and co-workers reported an inverse-electron-demand [4+2] cycloaddition of 2-vinylanilines with 1,3,5-triazinanes and Umemoto reagent to give perfluoroalkylated tetrahydroquinazolines (Scheme 69/68???).[72] The key intermediate to this reaction is proposed to be the photocatalytic radical-mediated generation of aza-*ortho*-quinone methides from 2-vinylanilines.



Scheme 68 Inverse-electron-demand [4+2] cycloaddition of 2-vinylanilines

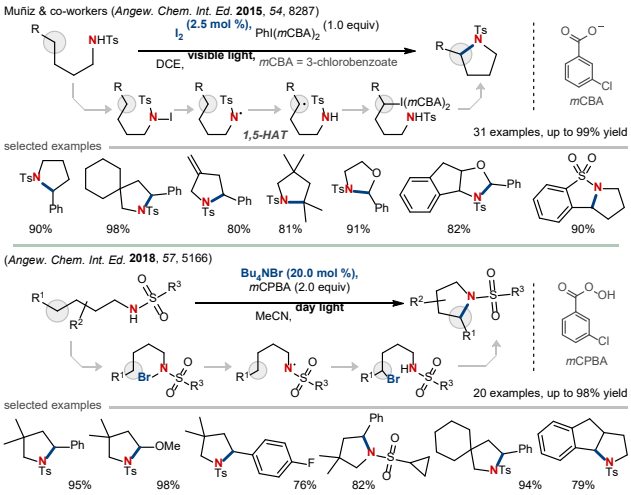
Another interesting C(sp^3)–N cyclization reaction was presented by Zhang and co-workers. An aerobic oxidative [2+3] cycloaddition reaction between glycine derivatives and styrene oxides catalyzed by hydroiodic acid was disclosed for the synthesis of 1,3-oxazolidines (Scheme 70/69???).[73] Mechanistic studies suggested that an electron donor-acceptor complex is formed between glycine derivatives and benzyl iodides is the key intermediate for this reaction.



Scheme 69 Aerobic oxidative [2+3] cycloaddition of glycine derivatives and styrene oxides

4.2.2.Iodine-Assisted Cyclization

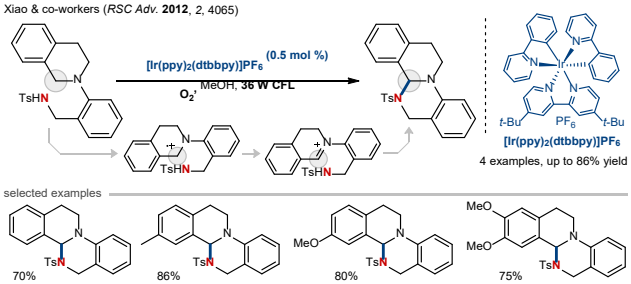
Muñiz and co-workers explored the Hofmann-Löffler type reaction using visible light. Direct oxidative amination of alkyl groups was achieved by iodine catalyst via the iodine(I/III) manifold. This reaction is applicable to all primary, secondary and tertiary C–H bonds to give the corresponding cyclized aminal products. In 2017, the same group further expanded the iodine-mediated intramolecular amination using 2,4,6-triphenylpyrylium tetrafluoroborate (TPT) photocatalyst. Following a computational study. The group also designed a bromine redox catalysis for aliphatic C–H amination. Under the photocatalytic conditions, the *N*-brominated tosylamide would be formed and subsequent homolysis would generate the N-centered radical. A kinetically preferred 1,5-H abstraction followed by bromide radical recombination gives the intermediary alkyl bromide. Final nucleophilic cyclization would furnish the product (Scheme 71).[74]



Scheme 70 Visible-light mediated Hofmann-Löffler type reaction

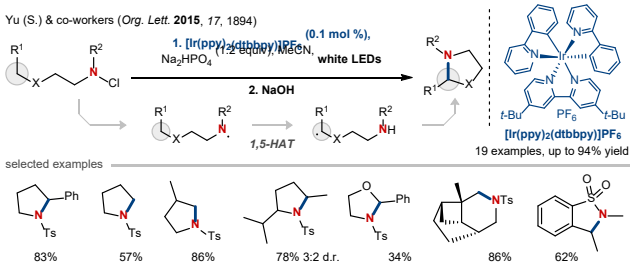
4.2.3.Nitrogen-Centered Radicals and Radical Cations

In 2012, Xiao and co-workers reported a simple C–N cyclization for the synthesis of isoquino[2,1-*a*]pyrimidines using Ir photocatalysts (Scheme 72/71???).[75] The reaction was believed to be initiated by the photooxidation to generate a nitrogen radical cation intermediate. Subsequent hydrogen atom abstraction would generate the cationic intermediate with a C=N bond. Intramolecular cyclization would then furnish the desired product.



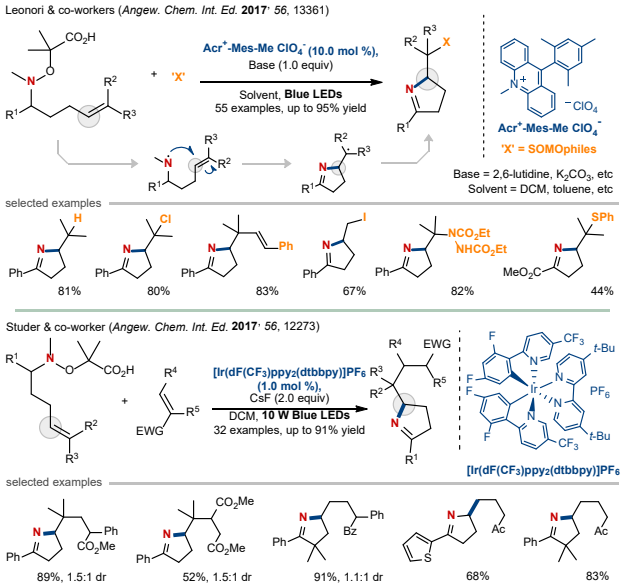
Scheme 71 C–N cyclization for isoquino[2,1-*a*]pyrimidines synthesis

Yu (S.) and co-workers presented a remote C–H amidation from through hydrogen atom transfer by nitrogen radical generated from *N*-chlorosulfonamides to give pyrrolidine derivatives (Scheme 73).[76] The excited photocatalyst is oxidatively quenched by *N*-chlorosulfonamide to generate a N-centered radical. An intramolecular 1,5-hydrogen atom transfer to generate a carbon-centered radical for the following cyclization reaction.



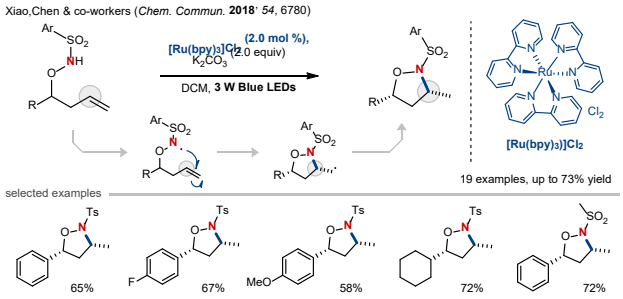
Scheme 72 C–H amidation with *N*-chlorosulfonamides

In 2017, Leonori's group developed a divergent platform for C–N coupling reaction for the synthesis of functionally diversified pyrrolines (Scheme 74). The reaction was proposed to involve the photoredox generation of iminyl radicals by oxidative SET of a traceless eletrophore and a subsequent cyclization with SOMOphiles. Studer and co-workers also developed the photoredox carboimination of alkene for pyrrolines synthesis. Intermolecular conjugate addition to a Michael acceptor, and a single-electron reduction was proposed to complete the functionalization.[77]



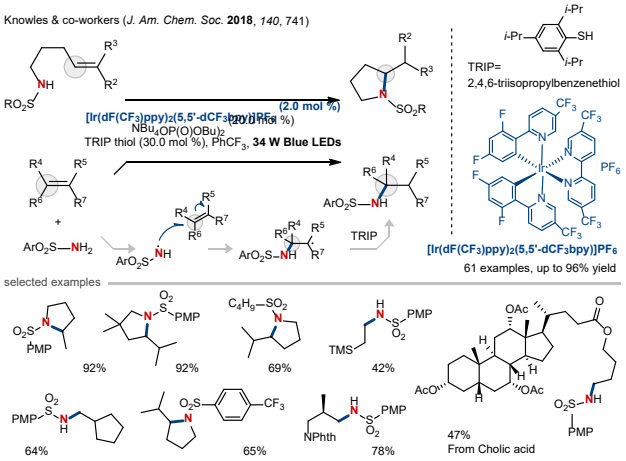
Scheme 73 Photoredox imino functionalization of alkenes

Sulfonamides can also serve as a N-centered radical precursor. Xiao, Chen and wo-workers presented an intramolecular alkene hydroamination of unsaturated sulfonamides to generate functionalized isoxazolidines (Scheme 75).[78] Hydroxylamine is firstly transformed into the sulfonamidyl radical via photocatalytic SET oxidation. Then an intramolecular radical 5-*exo*-trig cyclization, followed by trapping a hydrogen atom from $CHCl_3$ would furnish the product.



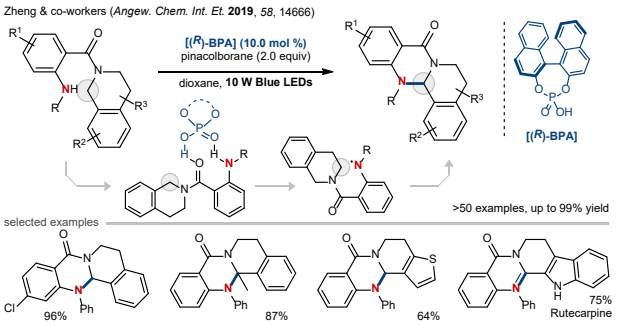
Scheme 74 Intramolecular alkene hydroamination of unsaturated sulfonamides

Knowles' group further developed the PCET enabled intramolecular anti-Markovnikov hydroamination of alkenes with sulfonamides (Scheme 76).[79] The reaction was catalyzed by an iridium photocatalyst, a dialkyl phosphate base, and a thio hydrogen atom donar. The N-centered sulfonamidyl radical is generated via proton-coupled electron transfer activation of the sulfonamide N–H bond. Anti-Markovnikov addition to alkene would furnish the new C–N bond and a vicinal carbon-centered radical. Further reduction by the thiol cocatalyst via HAT would generate the product.



Scheme 75 Intermolecular hydroamination of alkenes with sulfonamides

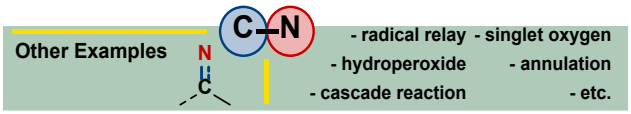
Zheng and co-workers reported a long-lived photoactive photoisomer complex for intramolecular C–N coupling reaction (Scheme 77).[80] More than 50 *N*-substituted polycyclic quinazolinones were synthesized using a catalytic amount of phosphoric acid [(*R*)-binol-phosphoric acid] and 2.0 equiv of pinacolborane as reducing agent. Initiated by the coordination of (*R*)-BPA to the starting material through hydrogen bonding, SET process can be induced to produce a N-centered radical. Followed by the intramolecular 1,6-HAT and the sequential interaction with peroxide radical, the polycyclic quinazolinone would be formed.



Scheme 76 Intramolecular C–N coupling by photoisomer complex

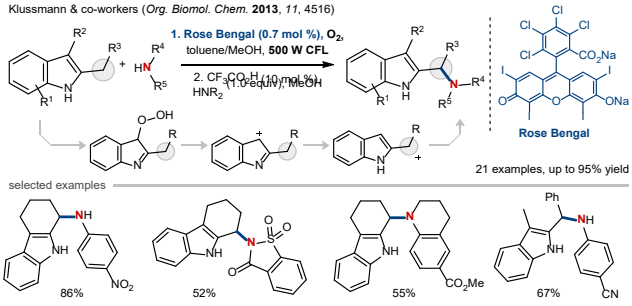
5. Other Examples

Examples involving rearrangements, annulations and other reaction manifolds were reported for visible-light-mediated C–N and C=N bonds formation (Scheme 78).



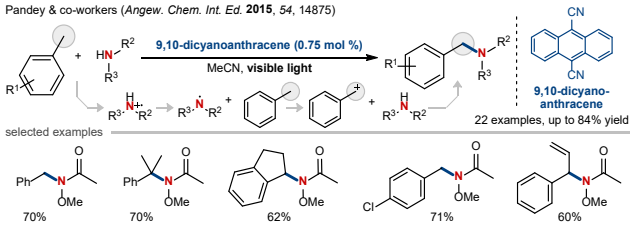
Scheme 77 Brief summary for other photocatalytic C–N coupling reaction

In 2013, Klussmann and co-workers reported the aerobic C–H amination of tetrahydrocarbazole via photochemically generated hydroperoxides with the use of oxygen and photocatalyst (Scheme 79).[81] The reaction is initiated by the acid-catalyzed tautomerization of the imine to the hydroperoxide enamine isomer. Protonation of the hydroperoxide would generate the allylic cation and react with the N-nucleophile to give the product.



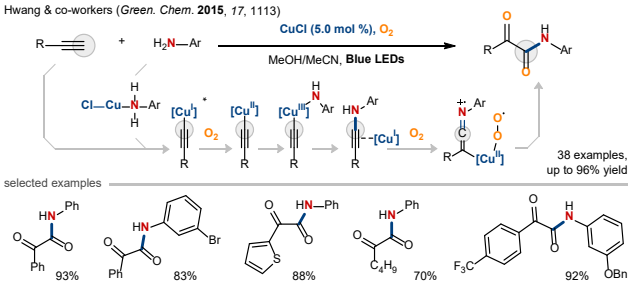
Scheme 78 Aerobic C–H amination of tetrahydrocarbazole

In 2015, Pandey and co-workers reported a cross-dehydrogenative benzylic C(sp^3)–H amination by employing 9,10-dicyanoanthracene (DCA) as photoredox catalyst (Scheme 80). This regioselective protocol covers a broad substrate scope requiring no external oxidant. [82] The key reaction process includes the generation of aminyl radical and benzylic cation from the DCA photocatalytic cycle.



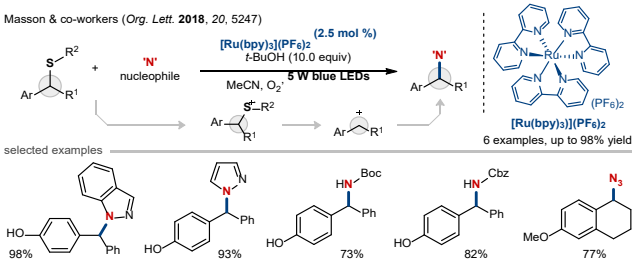
Scheme 79 Cross-dehydrogenative benzylic C(sp^3)–H amination

Hwang and co-workers reported a highly atom efficient oxidative C–N coupling reactions using alkynes and anilines (Scheme 81).[83] The reaction was induced by CuCl catalyst and oxygen was incorporated into the C ≡ C bond to give α-ketoamides. And the author proposed the reaction to start with the formation of Cu(I)-aniline complex. Upon the addition of phenylacetylene, Cu(I) phenylacetylide is preferentially formed. Photoexcitation of the Cu(I) species and the following SET to molecular oxygen would generate Cu(II) phenylacetylide. Nucleophilic addition of aniline to the Cu(II) species would generate the Cu(III) complex, subsequent reductive elimination would form the Cu(I)-coordinated ynamine complex. The reaction with molecular oxygen would afford the Cu(II) peroxo complex. Isomerization of the resulting Cu(II) peroxo complex to a Cu(I) species with concurrent formation of a C–O bond would furnish the product.



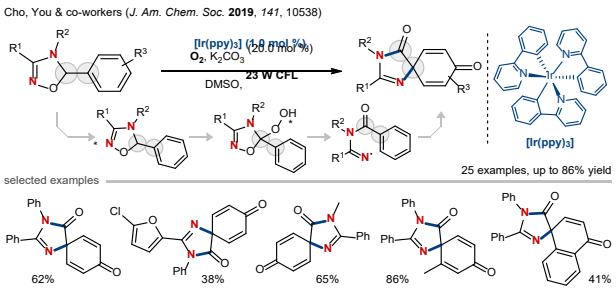
Scheme 80 Cu-catalyzed oxidative C–N coupling reactions using alkynes and anilines

The research group of Masson presented an interesting visible-light-mediated C–N bond coupling using benzylic thioethers (Scheme 82).[84] The reaction is triggered by the mesolytic cleavage of the C–S bond in the photoactivated thioether. Subsequent coupling with nitrogen nucleophile would furnish the C–N bond. The C–S bond cleavage was supported by several experimental proofs, including the complete loss of enantiomeric excess through the arylation of optically pure thioether.



Scheme 81 C–N Bond coupling of benzylic thioethers

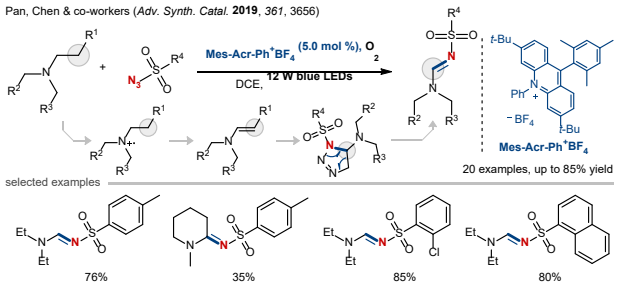
Recently, examples involving rearrangements, annulations and other reaction manifolds were reported for visible-light-mediated C–N and C=N bonds formation. Cho, You and co-workers presented a unique double functionalization of arenes facilitated by singlet oxygen (Scheme 83).[85] An insertion of the photoexcited singlet oxygen at the starting material would generate a hydroperoxyl species. Then a homolytic N–O bond cleavage would take place to generate an iminyl radical. An ipso attack on the N-centered radical would generate the spirocyclic species and eventually producing the product. *ortho*-Hydroperoxidation followed by a [1,3]-sigmatropic shift is also proposed.



Scheme 82 Double functionalization of arenes

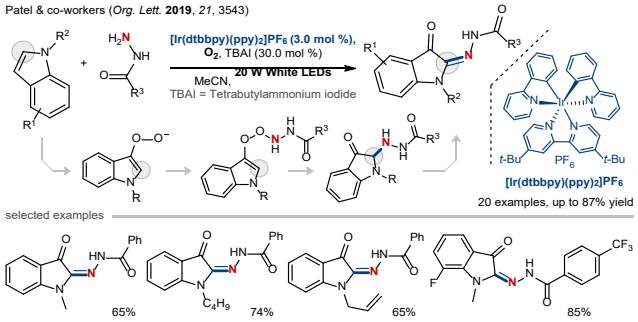
Other than the construction of C–N bonds, photoinduced C=N bonds formations were reported by Pan, Chen and co-workers. Tertiary amines were effectively coupled with sulfonyl azide to give amidine derivatives (Scheme 84).[86] The SET to the excited photocatalyst would generate a tertiary amine radical cation. Subsequent hydrogen radical abstraction by an oxygen

radical anion and double bond shift results in the formation of enamine intermediate. 1,3-Dipolar addition of sulfonyl azide, followed by the ring-opening reaction would furnish the product by releasing CH_2N_2.



Scheme 83 Photoinduced C=N bonds formations

The research group of Patel also developed a concomitant C3 oxidation and C2 amination of indoles using Ir photocatalyst. The reaction proceeds via the attack of a singlet oxygen at the C3 position of indoles, followed by the amination reaction using benzohydrazides at the C2 position to give difunctionalized indoles (Scheme 85).[87]



Scheme 84 Concomitant C3 oxidation and C2 amination of indoles

6. Conclusion and Outlook

Utilization of visible light by photocatalysis is a burgeoning field in contemporary organic synthesis. Through photocatalysis, highly reactive carbon radical and/or nitrogen radical can be generated for the subsequent C–N coupling reaction. With the judicious pairing of the starting materials and photocatalyst, conditions can be designed to tailor for C(sp^2)– and/or C(sp^3)–N bonds under mild conditions. This review showcases some important contributions in recent literature, and the examples are classified according to the bonding types, reaction modes for easy referencing for synthetic application.

With the current momentum of development, greater impact of photocatalytic C–N bond coupling reaction is foreseeable as in the late-stage modifications of natural products, large-scale synthesis and enantioselective C–N coupling reactions. Recent technological advances in flow chemistry is likely to popularize photocatalytic C–N coupling reactions in the industrial manufacturing settings. The merge of photocatalysis, flow chemistry and chiral synthesis will set the pharmaceutical industry for new wave of synthetic advances in sustainable synthesis.

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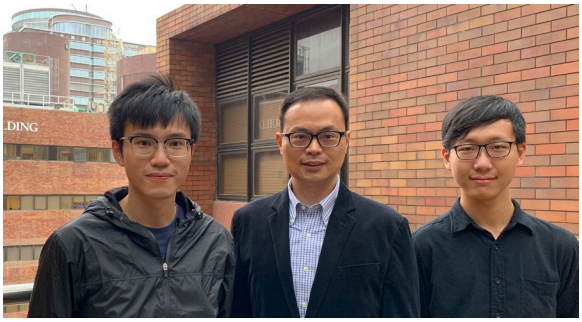
Biosketches



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