Synthesis H. Zhang, A. Lei THIEME OPEN ACCESS Short Review

Electrochemical/Photochemical Aminations Based on Oxidative Cross-Coupling between C–H and N–H

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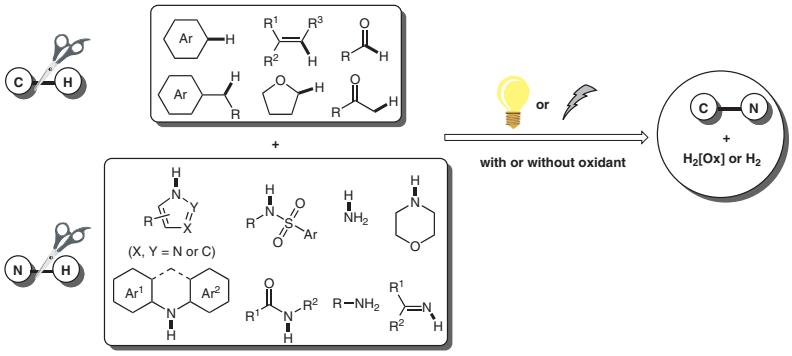
Dedicated to Professor Xiyan Lu on the occasion of his 90th birthday

Published as part of the *50 Years SYNTHESIS – Golden Anniversary Issue*



Received: 16.10.2018
Accepted: 18.10.2018
Published online: 15.11.2018
DOI: 10.1055/s-0037-1610380; Art ID: ss-2018-z0696-sr

Abstract The construction of nitrogen-containing molecules remains at the cutting edge of organic synthesis because of its wide application in various areas. Instead of prefunctionalized substrates, using free C–H and N–H bonds in the starting materials can supply a more sustainable avenue to the C–N bond-forming reactions. Compared with the well-developed transition-metal-catalyzed protocols, the strategy of introducing optical or electrical energy into reactions is fantastic and appealing. As a result, visible light or electricity mediated amination transformations have continued to develop over the past several years. In this short review, recent progress of carbon–nitrogen bond-forming reactions based on the oxidative cross coupling between C(sp^2, sp^3)–H and N–H are summarized.

Key words oxidative cross coupling, amination, C–H bond functionalization, electrochemistry, photochemistry

Heng Zhang received his Bachelor's degree (2000) and his Ph.D. (2005) from Wuhan. Upon completion of his graduate studies, he became a lecture of Wuhan University and was promoted to associate professor in 2009. He joined Prof. William D. Jones group (University of Rochester) as a visiting scholar from 2015 to 2016. His current research interests focus on physical organic chemistry.

Aiwen Lei obtained his Ph.D. (2000) under the supervision of Prof. Xiyan Lu at the Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences (CAS). He then moved to Pennsylvania State University, USA, and worked with Prof. Xumu Zhang as a postdoctoral fellow. He joined Stanford University (2003), working with Prof. James P. Collman as a research associate. He then became a full professor (2005) at the College of Chemistry and Molecular Sciences, Wuhan University, China. He was Fellow of the Royal Society of Chemistry, FRSC (2015). His research focuses on novel approaches and understanding of bond-formation processes.

1 Introduction

Nitrogen-containing molecules form the cornerstone of many disciplines including medicine, material science, and agrochemicals. As a result, relevant research on C–N bond-forming reactions remains at the cutting edge of organic synthesis. It is clear that transition-metal-catalyzed C–N bond-forming reactions have played an important role during the past several decades. The palladium-catalyzed Buchwald–Hartwig amination reactions, the copper catalyzed Chan–Evans–Lam coupling, and Ullmann type reactions have been extensively employed in the construction of various nitrogen-containing pharmaceuticals, organic optoelectronic materials, and so forth.[1] Despite the great accomplishments that have been achieved in this realm,

more efforts are still needed to make it sustainable and environmentally benign.

Prefunctionalized building blocks are normally the prerequisites of many C–N bond-forming protocols. However, this is a double-edged sword because the improvement of reactivity and selectivity is accompanied by a loss of atom economy. From the view point of retrosynthetic analysis, it is conspicuous that this obstacle can be overcome by the direct utilization of easily available 'C–H' and 'N–H' in the starting materials. Compared with the classical C–N coupling between electrophiles and nucleophiles, this idea is oxidative cross-coupling based on two nucleophiles: 'C–H' and 'N–H', which have been utilized extensively in bond formations.[2] Formally, two hydrogen atoms must be removed to drive the reaction to proceed and therefore sacrificial oxidant is usually required in this chemistry. Although this strategy has been successfully applied in transition-metal-catalyzed C–N bond-forming reactions, there remain some limitations; namely, the harsh reaction conditions required to compensate for the low reactivity of nonprefunctionalized substrates, and the low atom economy caused by the introduction of stoichiometric amount of oxidants.[3]

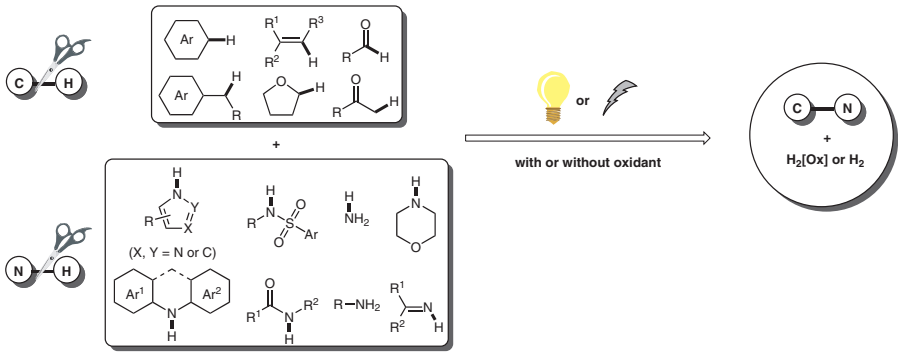
The involvement of visible light or electricity in chemical reactions is not a novel idea; indeed, the history of many reactions driven by visible light or electricity dates back to the early times of modern chemistry. In theory, the integration of optical or electrical energy with a chemical transformation can circumvent the restrictions of the second law of thermodynamics to make many unimaginably fantastic reactions feasible.

In addition, the renaissance of radical chemistry has drawn the attention of increasing numbers of chemists to the areas of electrosynthesis and photosynthesis.[4] Photons and electrons can be deemed as traceless reagents, which can not only reduce the concomitant by-product but also simplify the work up process. Moreover, the consumption of electricity or visible light can be negligible compared with the price of chemicals. Mild reaction conditions are characteristic features of these processes. The introduction of visible light or electricity can supply a promising avenue to the development of oxidative amination based on C–H/N–H.

For the visible-light-mediated aminations, many reported studies are based on photoredox catalysis. Ru/Ir-based polypyridyl complexes and organic dyes are frequently used photoredox catalysts, which supply many choices to match the needs of different substrates. Besides numerous chemical oxidants, air or oxygen can be employed as direct oxidant or terminal oxidant. This chemistry can be ameliorated with the help of dihydrogen producing catalyst, such as graphene-supported RuO_2 nanocomposite[5] or cobaloxime.[6] With this modification, sacrificial external oxidant can be omitted and dihydrogen is the sole side product. In some other cases, no photosensitizer is needed as the oxidant (DDQ, $K_2S_2O_8$, etc.) can be excited directly by visible light or the weak bond (C-I) can be broken just in the presence of visible light.

In principle, electrochemical oxidative cross coupling between C–H/N–H normally works in the anodic oxidation mode. Generally speaking, no external oxidant is needed and the surplus hydrogens are evolved in the form of dihydrogen. With the choice of appropriate anode, cathode and other reaction conditions, some transformations can be attained just through direct electrolysis. More flexible options can be provided if electrocatalytic amination is employed. Redox mediator (Br^-, I^-, etc.), transition-metal complexes are commonly used catalysts. Divided or undivided cells are another variable in the setup, with the more complex former being able to separate the reactive intermediates and avoid the reduction of transition-metal catalyst physically. Compared with the easily available constant-current electrolysis, constant potential electrolysis can control the activation of substrates and supply another way to inhibit the reduction of transition-metal catalyst.

Electrochemical or photochemical amination reactions established on the C–H and N–H nucleophiles are unquestionable hot topics nowadays. A case in point is the considerable research work summarized herein which has been published in the past one or two years, and many analogous works are reported nearly at the same time back to back.



Scheme 1 The scope of this short review

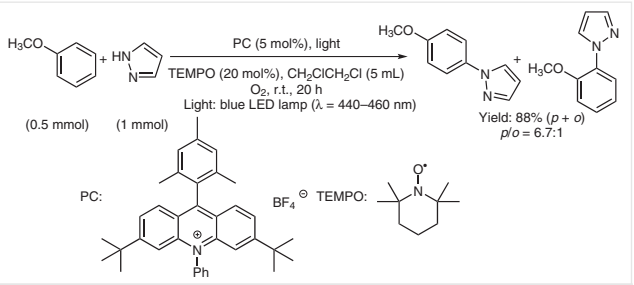
Many insightful reviews have been published on related domains or from different perspectives.[7] This short review concentrates on the C(sp^2, sp^3)–H/N–H oxidative cross-coupling reactions mediated by visible light or electricity (Scheme 1). The achievements of the past six years are reviewed, especially focusing on the latest progress.

2 C(sp^2)–H/N–H Oxidative Cross Coupling

2.1 Oxidative Cross Coupling between Aryl C(sp^2)–H and N–H

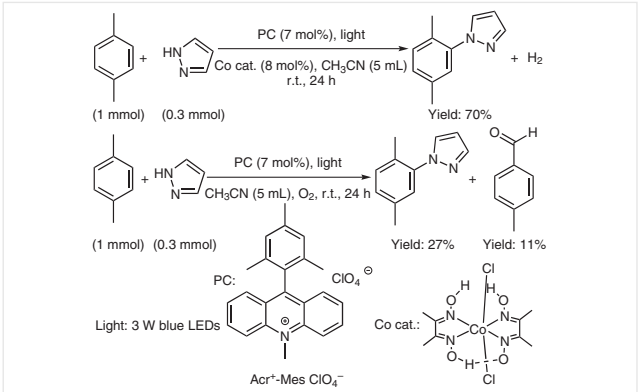
2.1.1 Azoles as N Nucleophiles

Photoinduced electron transfer is an efficient method to yield arene radical cations. In 2015, the Nicewicz group reported a pioneering work on a visible-light-mediated arene C–H amination reaction based on this strategy (Scheme 2).[8] Acridinium was chosen as the photoredox catalyst, 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) was the cocatalyst and dioxygen was the terminal oxidant. For substrates such as mesitylene or xylene, a stoichiometric amount of TEMPO and anaerobic conditions should be used to avoid the benzylic oxidation. Besides azoles, ammonium carbamate could also be used as nitrogen source for the synthesis of aniline. Regioisomers were observed for most of the transformations, which may be due to the complex interplay between electronic and steric effects.



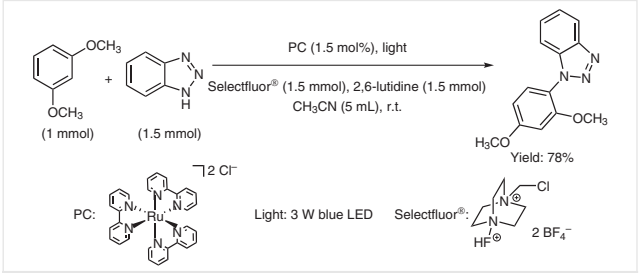
Scheme 2 Photochemical amination between arene and pyrazole

The oxidative cross coupling between electron-rich arenes and azoles were also realized based on photoredox catalysis (Scheme 3).[9] 9-Mesityl-10-methylacridinium perchlorate (Acr^+-$MesClO_4^-$) was used as the photoredox catalyst. No external oxidant was required in the presence of cobaloxime catalyst, which was proposed to replenish the photoredox catalyst, oxidize radical adduct intermediate and release dihydrogen. This assembly was superior to the combination of photoredox catalyst plus dioxygen because low yield and concomitant aldehyde formation were observed for the latter.



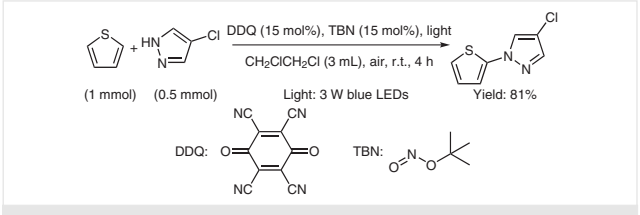
Scheme 3 Photochemical amination between arene and pyrazole with and without external oxidant

Pandey et al. reported the visible-light-mediated amination between electron-rich arenes and benzotriazole (Scheme 4).[10] In this case, Selectfluor was chosen as oxidant and 2,6-lutidine was used as base after screening. The delicate match between the Ru photoredox catalyst and the arenes was crucial for the success of this transformation.



Scheme 4 Photochemical amination between arene and benzotriazole

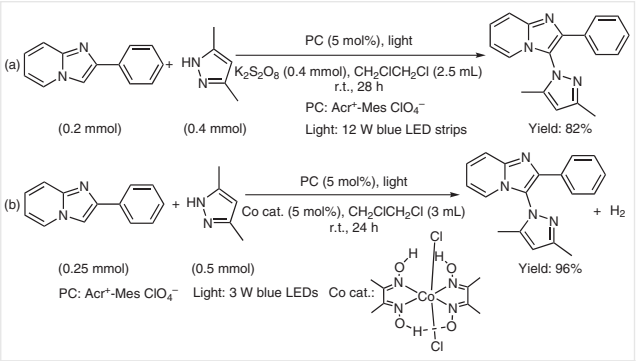
2,3-Dichloro-5,6-dicyano-*p*-benzoquinone (DDQ), a well-known organic oxidant, can also be used as photosensitizer. The Lei group realized the amination of thiophene by using a catalytic amount of DDQ and *tert*-butyl nitrite (TBN) (Scheme 5).[11] TBN could be considered as a bridge to connect DDQ and terminal oxidant O_2. The scope of the reaction with respect to nitrogen sources was limited to various azoles.



Scheme 5 Photochemical amination between thiophene and pyrazole

Heteroaryl C(sp^2)–H/N–H dehydrogenative cross coupling was reported with and without external oxidant in sequence. Acr^+-$MesClO_4^-$ was chosen as the photoredox cat-

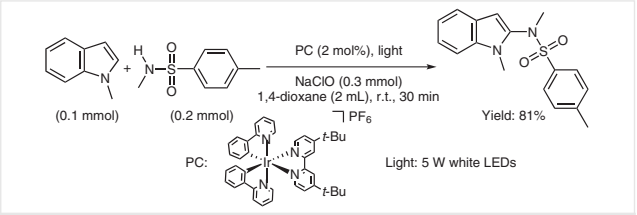
alyst for both works. Adimurthy and coworkers used $K_2S_2O_8$ as oxidant (Scheme 6a).[12] The cobaloxime catalyst was used by Lei, Zhang and coworkers to make this transformation external-oxidant free (Scheme 6b).[13] Both protocols were limited by the substrate scope of both heteroarenes and nitrogen sources.



Scheme 6 Photochemical amination between heteroarene and pyrazole with external oxidant (a) or with cobaloxime catalyst (b)

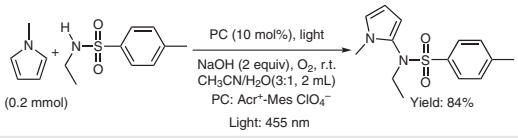
2.1.2 Sulfonamides/Sulfonimides as N Nucleophiles

By using $[Ir(ppy)_2(dtbbpy)]PF_6$ as photocatalyst and NaClO as oxidant, *N*-methylindole could be aminated with *N*-methylsulfonamide in only 30 minutes by Yu and Zhang et al. (Scheme 7).[14] According to the authors' proposal, an N-centered radical was the key reactive intermediate in the reaction, which was proved by trapping experiments using 2,6-di-*tert*-butyl-4-methylphenol (BHT). Although *N*-chlorosulfonamide can be formed when *N*-methylsulfonamide reacts with NaClO, control experiments demonstrated that *N*-chlorosulfonamide was not involved in the reaction pathway, which proposed that the N-centered radical did not originate from *N*-chlorosulfonamide.



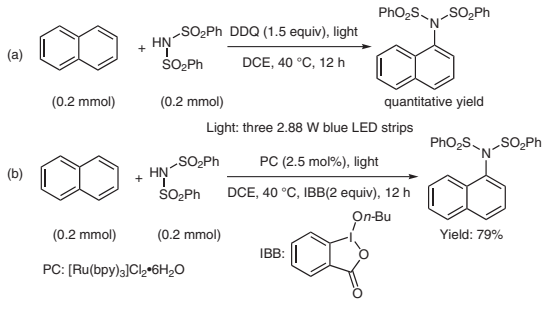
Scheme 7 Photochemical amination between indole and sulfonamide

Nearly at the same time, König et al. achieved the 2-amination of *N*-methylpyrrole by using Acr^+-$MesClO_4^-$ as photoredox catalyst and O_2 as oxidant (Scheme 8).[15] However, 5–20 equivalents of N-substituted pyrroles should be used to operate this transformation. However, the desired coupling product was not obtained when pyrrole was substituted with other heterocycles such as furan, thiophene and indole. The *N*-methylpyrrole radical cation was formed upon the oxidation by the excited state photoredox catalyst according to the proposed mechanism. *N*-Alkyl-substituted sulfonamide was deprotonated by sodium hydroxide to yield the corresponding anion nucleophile. The distinction between these two similar works may originate from the oxidizing ability of the excited-state photoredox catalysts.



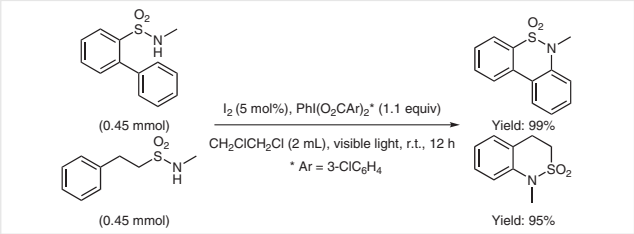
Scheme 8 Photochemical amination between pyrrole and sulfonamide

Aryl sulfonimidation was achieved by Itami and Murakami et al. using DDQ both as photosensitizer and as oxidant (Scheme 9a).[16] However, the substrate scope of the reaction with respect to arenes was quite limited, and it was postulated that unreactive arenes might be the quenchers of photoexcited DDQ. This transformation was developed by the same group using $[Ru(bpy)_3]Cl_2{\cdot}6H_2O$ as photoredox catalyst and a special hypervalent iodine reagent (IBB) as oxidant (Scheme 9b).[17] The superiority of this methodology was that only an equimolar amount of arene and sulfonamide were needed. Cyclic voltammetry (CV) experiments illustrated that an N-centered radical was generated upon oxidation by Ru photoredox catalyst. The addition of the N-centered radical to the arene and the following oxidation and deprotonation could yield the target cross-coupling product.



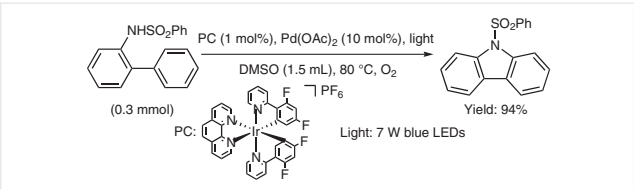
Scheme 9 Photochemical amination between naphthalene and sulfonimide with different photosensitizers

Cyclic sulfonamides were synthesized through intramolecular aryl C–H functionalization by the Muñiz group (Scheme 10).[18] This methodology was also compatible with silicon-tethered arenes, which could be removed easily by treatment with $^tBu_4NF$ under mild conditions. Based on the proposed mechanism, an N-centered radical was generated upon irradiation of the N-I intermediate formed in situ. The addition of the N-centered radical and the following single-electron oxidation and deprotonation gave the target product.



Scheme 10 Intramolecular aryl C(sp^2)–H/N–H amination mediated by visible light

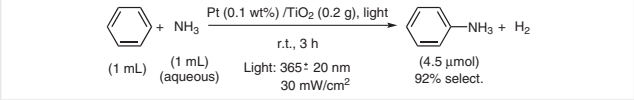
The photoredox and transition-metal catalysis were integrated in the intramolecular C–H amination for the synthesis of carbazoles (Scheme 11).[19] The substrate scope could be extended from sulfonamides to acetamides. According to the proposed mechanism, both the C–H and N–H activation process were achieved by Pd catalyst. The photoredox catalyst took part in the following product-forming step, which may be run through Pd(III)/Pd(I) or Pd(IV)/Pd(II) cycle.



Scheme 11 Preparation of carbazole by photoredox and Pd catalysis

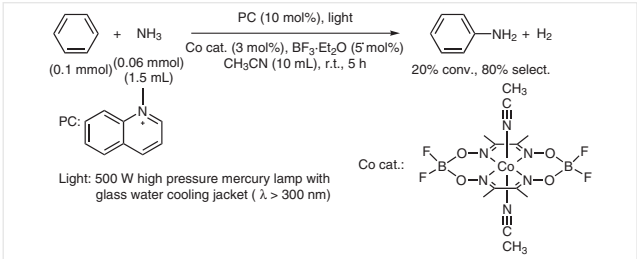
2.1.3 NH_3 as N Nucleophile

The classical procedures for the preparation of anilines are nitration and subsequent reduction, which runs counter to the idea of sustainable chemistry because relatively large amounts of byproduct are formed. In 2010, Yoshida et al. reported a direct aniline synthesis from benzene and ammonia using Pt/TiO_2 as photocatalyst with dihydrogen evolution at the same time (Scheme 12).[20] Later, the same group carried out a mechanistic study of this process.[21] Ammonia was oxidized by the photoinduced hole on the TiO_2 surface to yield an amide radical ($^{\cdot}NH_2$), which was detected by electron paramagnetic resonance (EPR). Aniline was formed by subsequent addition and elimination steps. The dihydrogen was liberated through simultaneous proton reduction by the photo formed electron.



Scheme 12 Photosynthesis of aniline from benzene and ammonia

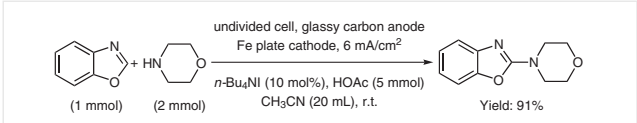
The same transformation was also realized by the Wu group in 2016 using organic photoredox catalyst QuH^+ (Scheme 13).[22] According to their proposal, a benzene radical cation was formed through single-electron oxidization by the excited-state photocatalyst, and ammonia was activated through the formation of $BF_3{\cdot}NH_3$, which was quite different to the mechanism proposed by Yoshida. Given that benzene (E_{ox} = 2.48 V vs. SCE) is not easily oxidized, the choice of a suitable photocatalyst QuH^+ [E_{red}(excited state) =2.46 V vs. SCE] insures the success of this methodology. No further amination occurred because of the rapid back-electron transfer.



Scheme 13 Photosynthesis aniline from benzene and ammonia

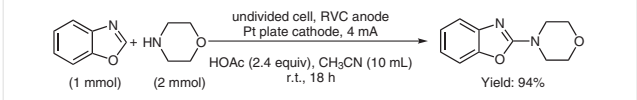
2.1.4 Morpholine as N Nucleophile

Zeng, Little and co-workers reported the electrochemical oxidative amination of benzoxazoles using iodide as electroredox catalyst (Scheme 14).[23] The reactions were carried out in an undivided electrolytic cell at constant current mode. HOAc acted both as ring-opening promoter of benzoxazole and as supporting electrolyte. The desired coupling product could still be obtained in 53% yield through direct electrolysis in the absence of halide. Besides morpholine, the N nucleophile substrates could be extended to both cyclic and acyclic secondary amines. However, primary amines and phthalimide were not compatible with this methodology.



Scheme 14 Electrochemical amination between benzoxazole and morpholine mediated by iodide

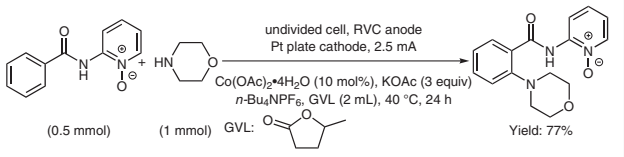
Very recently, the same reaction was also accomplished through direct electrolysis by the Ackermann group (Scheme 15).[24] A reticulated vitreous carbon (RVC) anode and a platinum plate cathode were employed. Cobalt catalyst was used in the initial screening, but later experimental



Scheme 15 Electrochemical amination between benzoxazole and morpholine

results indicated that it was not indispensable. Besides aryl C(sp^2)–H, benzylic C(sp^3)–H could also be aminated. The reaction was proposed to initiate through anodic oxidation of amine.

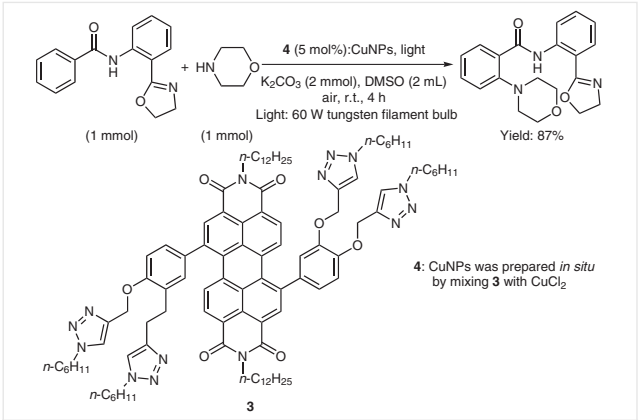
In an undivided cell, electrochemical amination was realized by the Ackermann group using a cobalt catalyst (Scheme 16).[25] An *N*,*O*-bidentate directing group was crucial for this methodology. No external oxidant was needed and dihydrogen was the only byproduct. The scope of nitrogen sources was restricted to the cyclic alkylamines. The proposed mechanism involved a Co(III)/Co(I) catalytic cycle which was based on the common organometallics notion. The anodic oxidation and cathodic reduction fulfilled the recycling of Co catalyst and dihydrogen evolution, respectively.



Scheme 16 Cobalt-catalyzed electrochemical amination between arene and morpholine

The directing group strategy was also applied by the Lei group to achieve a similar transformation at nearly the same time (Scheme 17).[26] *N*-(Quinolin-8-yl)carboxamide was installed as directing group in this case. No desired product could be obtained when an undivided cell was used, which may be because of reduction of Co at the cathode. According to an analogous mechanism, the regeneration of Co catalyst was attained through anodic oxidation.

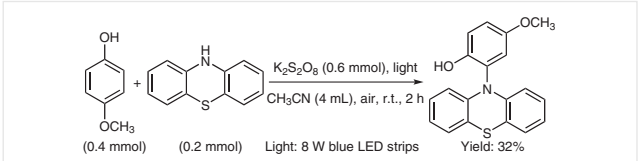
Besides the normally used organic and transition-metal photoredox catalysts, supramolecular ensembles of Cu nanoparticles can also be employed as photosensitizer in the C(sp^2)–H amination and alkynylation reactions (Scheme 18).[27] The supramolecular ensemble **4**:CuNPs was prepared in situ by mixing $CuCl_2$ and **3** (triazole-appended perylene bisimide derivative), in which **3** was oxidized to the *N*-oxide species **4**. The latter acted as both stabilizer of CuNPs and antenna to harvest light. Benzamide substituted with oxazoline as directing group was indispensable for this methodology. The authors also showed that the directing group can be easily removed through hydrolysis to yield the corresponding benzoic acid under alkaline conditions.



Scheme 18 Photochemical amination between arene and morpholine mediated by a supramolecular ensemble

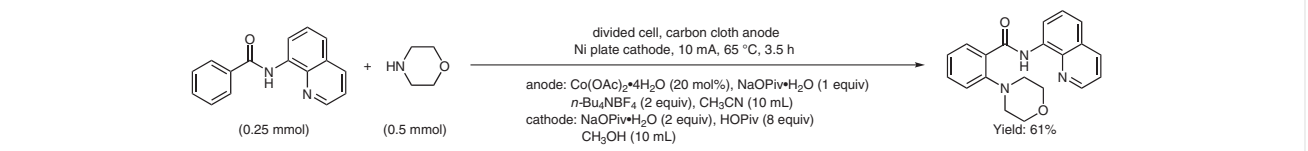
2.1.5 Diaryl Amines as N Nucleophiles

In 2016, the Xia group demonstrated the direct coupling between phenols and cyclic anilines mediated by visible light (Scheme 19).[28] No photocatalyst was needed because the oxidant ($K_2S_2O_8$) could be activated by visible light directly. Although dioxygen may not act as oxidant, the reaction could be promoted slightly in air atmosphere, which also simplified the operation. The relative low yield of the coupling product might be due to its decomposition and the oxidation of 4-methoxyphenol to 1,4-benzoquinone. Good to excellent yields could be obtained when other electron-rich phenols were employed. The authors proposed a C radical/N radical cross-coupling mechanism.



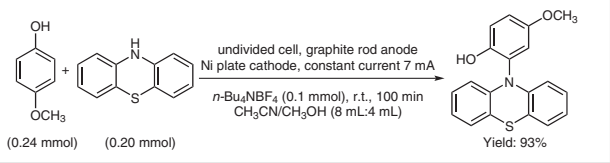
Scheme 19 Photochemical amination between phenol and phenothiazine

Two years later, the Lei group achieved the same transformation using direct electrolysis (Scheme 20).[29] No external oxidant was needed and dihydrogen was liberated. However, only 20% yields were obtained when phenothiazine was replaced with acyclic diaryl amines. According to the proposed mechanism, the phenothiazine was anodized



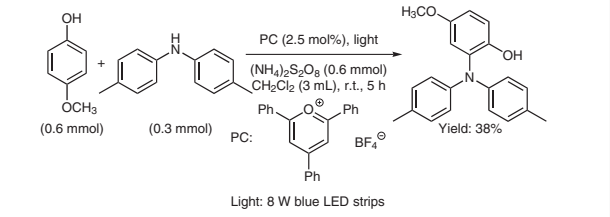
Scheme 17 Cobalt-catalyzed electrochemical amination between arene and morpholine

to its radical cation to initiate the reaction. Subsequent electrophilic addition to the phenol, oxidation and deprotonation gave the desired coupling product.



Scheme 20 Electrochemical amination between phenol and phenothiazine

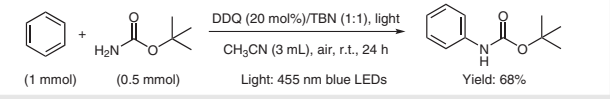
A little later, the substrate scope of N nucleophiles was enlarged to acyclic diaryl anilines by the Xia group (Scheme 21).[30] Although comparable yields could be obtained when acridinium was used, 2,4,6-triphenylpyrylium tetrafluoroborate was used as photoredox catalyst because of its easy preparation. One trick of this methodology was the choice of oxidant; ammonium persulfate was significantly superior to potassium persulfate. At least one electron-donating group should be installed in the aromatic ring because less than 5% yield was obtained when diphenylamine was tested. The mechanistic experiments still supported a C(radical)/N(radical) cross-coupling pathway.



Scheme 21 Photochemical amination between phenol and diaryl aniline

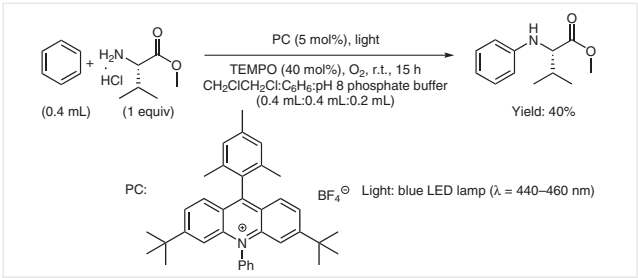
2.1.6 Primary Amines as N Nucleophiles

The combination of DDQ and TBN was also applied by König and co-workers to achieve benzene amination using $BocNH_2$ (Scheme 22).[31] According to the mechanistic studies, the reactivity of arenes can be divided into two categories: arenes that can form charge-transfer complexes with DDQ and those that cannot. More nucleophilic amines can react with the former, whereas the latter can react with various amines. However, the arenes (such as *N*-methylindole) and amines (such as aniline) that can react with DDQ directly are not suitable for this methodology.



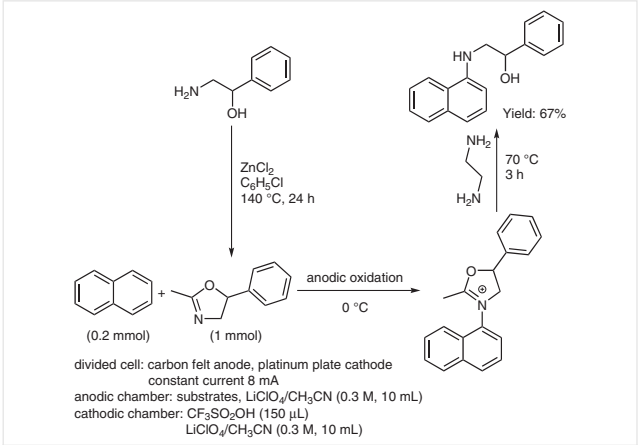
Scheme 22 Photochemical amination between benzene and $BocNH_2$

Acridinium photoredox catalyst was also used by the Nicewicz group to realize benzene amination with valine methyl ester hydrochloride (Scheme 23).[32] Although the oxidation of amine to its radical cation by the excited-state acridinium was proposed, the formation of an arene radical cation could not be precluded for the electron-rich arenes. Later, a predictive model was constructed by the same group to rationalize the regioselectivity of the aryl amination reactions based on the experimental results and on DFT calculations.[33]



Scheme 23 Photochemical amination between benzene and valine derivatives

The formal aryl amination using primary alkylamines was achieved by the Yoshida group by using a three-step process.[34] As shown in Scheme 24, 2-methyl-5-phenyloxazoline was first synthesized. Subsequent anodic oxidation resulted in the formation of a cationic intermediate, which could be treated with ethylenediamine to yield the target molecule.

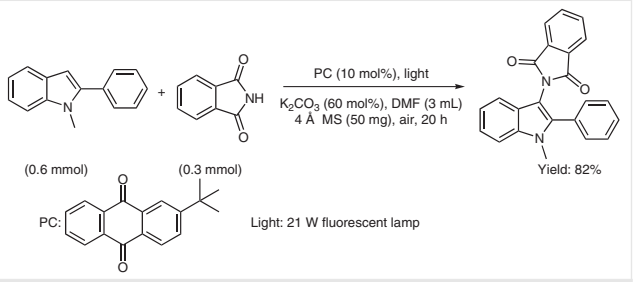


Scheme 24 Indirect electrosynthesis of aryl amine from arene and primary alkylamine

2.1.7 Imides as N Nucleophiles

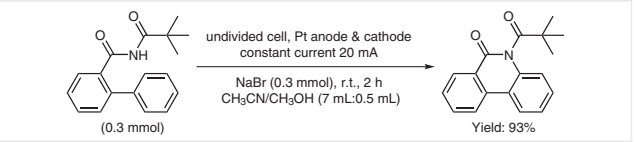
Amination of heteroarenes (indoles, pyrroles and benzothiophene) using phthalimide as N nucleophiles with a photoredox catalyst was reported by Itoh and co-workers (Scheme 25).[35] The reaction was inhibited in the presence of TEMPO, and the TEMPO adduct could be isolated. A plau-

sible mechanism may start with deprotonation of the phthalimide and then single-electron oxidation by the excited photoredox catalyst. The addition of the generated N-centered radical to arene and subsequent oxidation can result in the formation of the cross-coupling product. However, another possibility that the arenes quench the excited photoredox catalyst could not yet be excluded.



Scheme 25 Photochemical amination between heteroarene and phthalimide

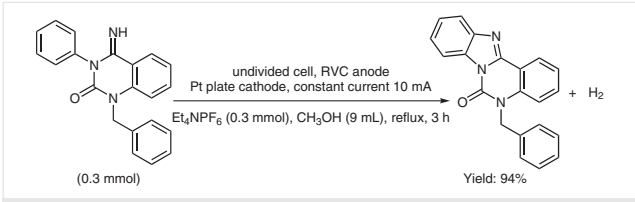
Intramolecular amination was realized through electrolysis using one equivalent of NaBr as redox mediator (Scheme 26).[36] After screening, pivaloxyloxy group (OPiv) was found the best substituent of the amide. The substrate was deprotonated with electrogenerated methoxide and then reacted with bromine to yield the N–Br species in situ. The *N*-acyloxy amidyl as the key intermediate was formed through N–Br bond homolytic cleavage. Subsequent radical addition, oxidation, and deprotonation would yield the target molecule.



Scheme 26 Intramolecular electrochemical amination to prepare lactam

2.1.8 Imines as N Nucleophiles

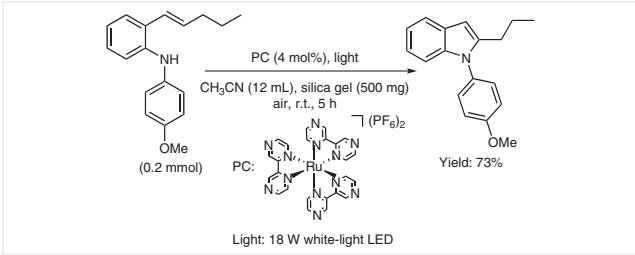
The Xu group synthesized tetracyclic benzimidazoles through intramolecular cyclization by direct electrolysis (Scheme 27).[37] This process was metal- and external-oxidant-free and the only byproduct was dihydrogen. Since this reaction was an anode oxidation process, the choice of anode material was crucial; no reaction occurred when Pt anode was used and the yields decreased significantly when the RVC anode was replaced with a graphite rod. Control experiments suggested that an N-centered radical was involved in the reaction pathway.



Scheme 27 Intramolecular electrochemical amination to prepare tetracyclic benzimidazole

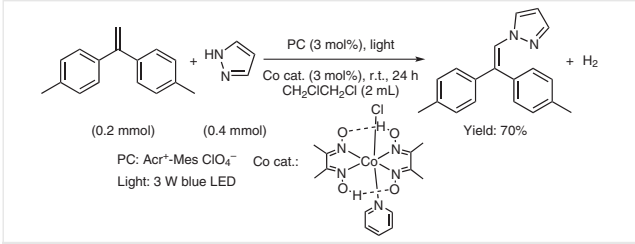
2.2 Oxidative Cross-Coupling between Vinyl C(sp^2)–H and N–H

In 2012, Zheng et al. reported the synthesis of *N*-arylindoles through the intramolecular C–H/N–H oxidative cross-coupling of styryl aniline (Scheme 28).[38] For the diarylamine substrates, one phenyl should be installed with a *p*-alkoxy group in order for the reaction to proceed. It is interesting to note that the involvement of silica gel increased the yield significantly, which was proposed to increase the solubility of dioxygen and supply protons. With elongation of the reaction time, the reaction can be enlarged to gram scale without a significant decrease in yield. As to the reaction mechanism, the replacement of Ru photocatalyst with tetraphenylporphyrin resulted in no formation of the target product, which indicated the absence of singlet oxygen in the reaction pathway.



Scheme 28 Intramolecular photochemical alkenyl C(sp^2)–H/N–H coupling to prepare *N*-arylindole

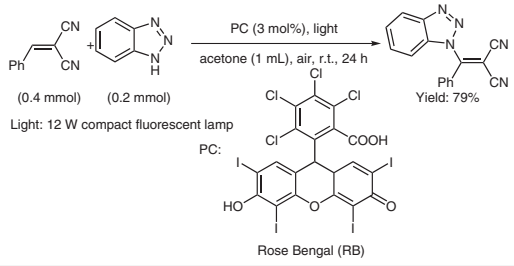
When a combination of Acr^+-$MesClO_4^-$ and cobaloxime catalyst was applied to alkenes and azoles, *N*-vinylazoles can be synthesized directly without external oxidant



Scheme 29 Photochemical amination between aryl alkene and pyrazole

(Scheme 29).[39] However, only aryl alkenes were reported and the N–H nucleophiles could not be extended to aniline, diphenylamine, and so forth.

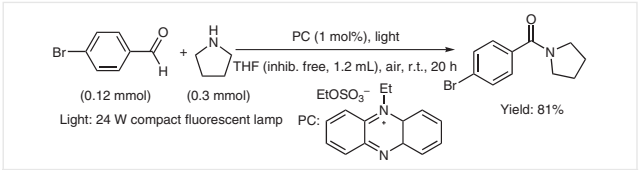
Recently, Guan and He et al. reported the synthesis of *N*-vinylazoles from cross coupling between electron-deficient alkenes and azoles (Scheme 30).[40] Rose Bengal (RB) was chosen as photoredox catalyst and air was used as oxidant. It is interesting to note that a compact fluorescent lamp (CFL) was superior to a green light-emitting diode (LED), which is normally to mate with RB. Although $^1O_2$ can be produced by RB through energy-transfer pathways, the possible involvement of singlet oxygen was eliminated because the reaction was not inhibited by singlet oxygen quencher, cysteine. When radical scavenger TEMPO or BHT was mixed in the reaction system, the reaction was inhibited, and high-resolution MS indicated the formation of radical species. Control experiments demonstrated the Michael addition between electron-deficient alkenes and azoles was not a possible pathway.



Scheme 30 Photochemical amination between electron-deficient alkene and benzotriazole

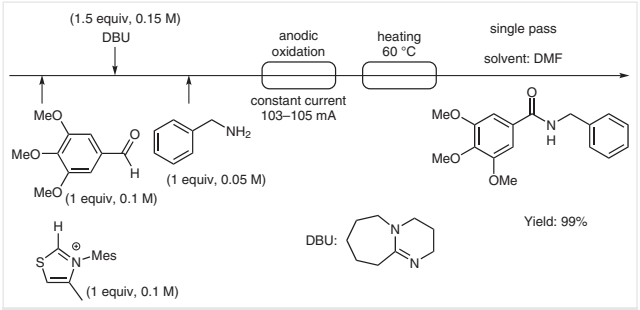
2.3 Oxidative Cross-Coupling between Aldehydic C(sp²)–H and N–H

The synthesis of amides can also be achieved by direct oxidative coupling between aldehyde and amine. Leow demonstrated this feasibility by using (hetero)aryl aldehydes and secondary amines (Scheme 31).[41] Various transition-metal and organic photoredox catalysts were tested, and phenazine ethosulfate was found to perform best. A negative effect was observed when the inhibitor was not removed from the solvent tetrahydrofuran (THF). However, only one acyclic secondary amine (^{n}BuNHMe) was reported with 56% isolated yield. According to the author's proposal, H_2O_2 was formed during the photocatalytic cycle and the amide was yielded through the oxidation of hemiaminal by H_2O_2. Besides acting as reactant, amine was oxidized to imine to finish the photocatalytic cycle; excess amines were therefore used in this transformation. It is interesting to note that the reductive amination product can also be prepared through photoredox catalysis between aromatic aldehydes and cyclic amines, as described by Molander et al.[42]



Scheme 31 Photochemical amide synthesis from aldehyde and amine

Having accomplished the oxidative esterification mediated by N-heterocyclic carbene using a microfluidic electrolysis cell, the Brown group applied the same strategy to prepare amide from aldehydes and amines (Scheme 32).[43] The key point to the success of this method was the formation of Breslow intermediate between aldehyde and the N-heterocyclic carbene formed in situ before mixing with amine. When the current was increased to 510 mA, the temperature of the heating chip was kept at 110 °C, the productivity of this system was as high as 2.5 g/h, which suggested the suitability of this methodology for scaling up. Various (hetero)aryl aldehydes and aliphatic or benzylic primary amines could be accommodated with good to excellent yields. Only one aliphatic aldehyde (n-$C_{12}H_{25}CHO$) was reported with 71% yield.



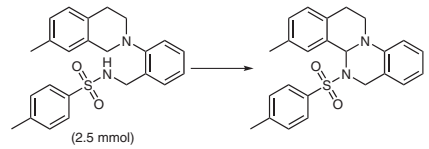
Scheme 32 Flow electrochemical amidation of aldehyde mediated by N-heterocyclic carbene

3 C(sp³)–H/N–H Oxidative Cross Coupling

3.1 Benzylic C(sp³)–H as C Nucleophiles

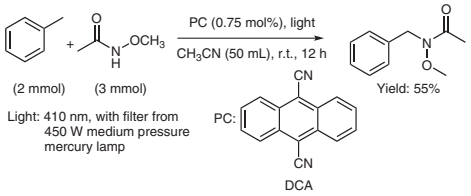
Isoquinolino[2,1-*a*]quinazoline derivatives were synthesized through intramolecular benzylic C(sp³)–H/N–H coupling by the Xiao group (Scheme 33).[44] Both transition-metal and organic photoredox catalysts could be successfully employed in the gram-scale preparation with good yields.

The benzylic C(sp³)–H amination using amide as N nucleophiles was reported by Pandey et al. (Scheme 34).[45] The amides must be methoxy substituted; no reaction occurred when N-phenylacetamide or diphenylamine was employed in this protocol. No clear decay of the photoredox catalyst 9,10-dicyanoanthracene (DCA) was observed after 12–15



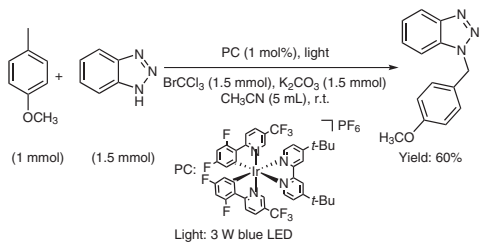
Scheme 33 Photochemical intramolecular benzylic C(sp^3)–H/N–H coupling

hours of photolysis. According to the results of control experiments, the benzylic carbocation and radical were probably involved in the reaction pathway.



Scheme 34 Photochemical amination between arene and amide

Later, the same group reported the benzylic C(sp^3)–H amination using benzotrizole as the N nucleophile (Scheme 35).[46] [Ir{dF(CF_3)ppy}$_2$(dtbpy)]PF_6 was the photoredox catalyst and $BrCCl_3$ was the oxidant. The scope of N nucleophiles was quite limited because pyrrole, $TsNH_2$, and $(Boc)_2NH$ were not compatible. A tentative proposed mechanism involved an oxidative quench of the excited Ir catalyst by $BrCCl_3$, which resulted in the formation of Ir(IV) and $^{\cdot}CCl_3$ radical. The arene radical cation was produced through the single-electron oxidation by Ir(IV). Then the benzylic carbocation was generated through hydrogen abstraction by $^{\cdot}CCl_3$ radical. The reaction between benzylic carbocation and N nucleophile could yield the target coupling product.

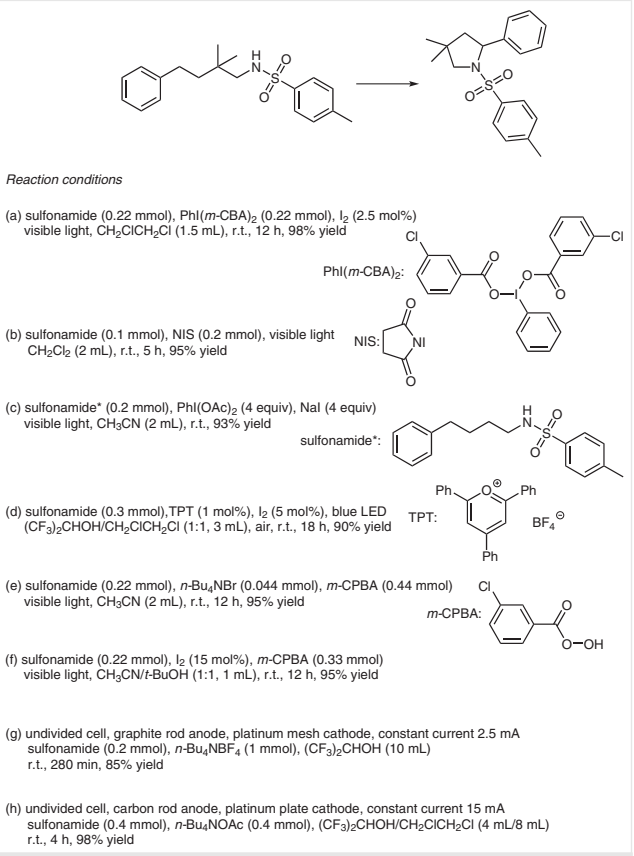


Scheme 35 Photochemical amination between arene and benzotrizole

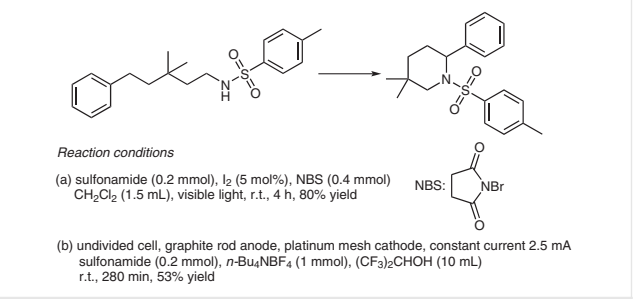
Hofmann–Löffler–Freytag reaction is a powerful method to the construction of pyrrolidines. However, harsh reaction conditions (high temperature, strong acid and base) are required for this transformation. The development of this reaction has been ongoing. For example, much milder reaction conditions could be employed when 1 equivalent of I_2 and 3 equivalents of PhI(OAc)$_2$ were used.[47] With the aid of visible light or electrolysis, Muñiz, Reiher, Nagib, Lei and coworkers improved this process prominently in recent several years. As shown in Scheme 36a, only 2.5 mol% I_2 was needed, and the key to the success was the choice of PhI(*m*CBA)$_2$ as iodine(III) reagent.[48] The loading of I_2 could be reduced to as low as 0.5 mol%. The screening of the visible-light wavelength illustrated that 400 nm was the optimum. Daylight was used in the end to simplify operations as no clear loss in yield occurred. As shown in Scheme 36b, *N*-iodosuccinimide (NIS) was found to be the optimal choice after screening of a series of halogen promoters such as *N*-bromosuccinimide (NBS), *N*-bromophthalimide (NBP) and so forth.[49] The reaction could be run just using 2 equivalents of NIS under visible light at room temperature. Four equivalents of NaI and PhI(OAc)$_2$ were employed in the method developed by the Nagib group (Scheme 36c).[50] The formation of triiodide between I_2 and a large excess iodide can solve the unproductive oxidations mediated by I_2. The strategy of the integration of I_2 and photoredox catalyst was also applied in this transformation (Scheme 36d).[51] The crucial factors of this methodology were the ratio of iodine and photoredox catalyst, air and a trace amount of water. The light irradiation functioned both in the excitation of photoredox catalyst and in the activation of the N–I bond formed in situ. An iodine-free protocol was also developed when ^{n}Bu$_4$NBr was used as catalyst and *m*-chloroperoxybenzoic acid (*m*CPBA) acted as terminal oxidant (Scheme 36e).[52] The reaction still worked when the catalytic amount of ^{n}Bu$_4$NBr was replaced with I_2 (Scheme 36f).[53] Very recently, this transformation was also achieved through direct electrolysis with the liberation of dihydrogen concomitantly (Scheme 36g).[54] Similar electrolysis conditions were also developed by the Lei group at nearly the same time (Scheme 36h).[55] Compared with the photochemical methods, much higher atomic economy was realized in the electrochemical method because no halogen or external oxidant was needed. In contrast to the above visible light mediated protocols, which were speculated to proceed through 1,5-hydrogen atom transfer, the benzylic carbon radical was proposed by Muñiz and coworkers to be involved in the reaction pathway rather than the N-centered radical. Although many reported reactions occurred at benzylic sites, the substrate scope of this chemistry could also extend to those without benzylic C–H.

The synthesis of piperidine derivatives has also been achieved by the Muñiz group through both photochemical[56] and electrochemical[54] methods (Scheme 37). The combination of a catalytic amount of iodine and a stoichiometric amount of NBS was used in the photochemical transformation. Direct constant-current electrolysis could also be employed to do the same reaction.

The triiodide protocol developed by the Nagib group was also tactfully applied in the synthesis of β-amino alco-

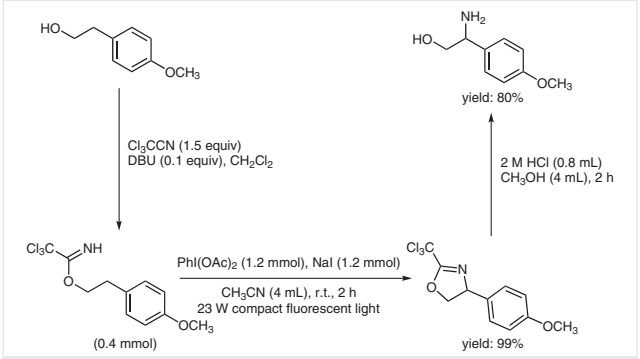


Scheme 36 Photochemical and electrochemical modified Hofmann–Löffler–Freytag reaction



Scheme 37 Preparation of a piperidine from intramolecular photochemical and electrochemical amination

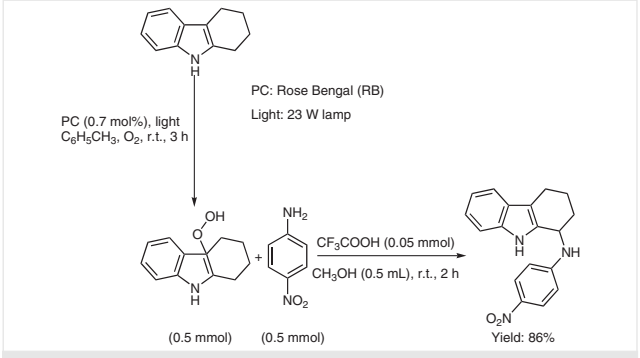
hol (Scheme 38).[57] Three steps were involved in the whole process, in which the intramolecular photochemical cyclization of the imidate was pivotal. The desired product could be obtained conveniently just by hydrolysis of the formed dihydrooxazole derivatives without further purification.



Scheme 38 Indirect β-amination of alcohol through photochemical cyclization of an imidate intermediate

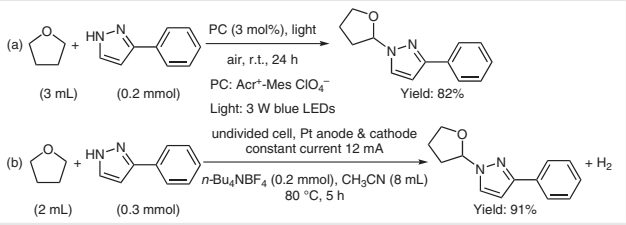
3.2 α C(sp^3)–H as C Nucleophiles

The strategy of C–H functionalization via intermediate peroxides was used in the amination of tetrahydrocarbazole derivatives by Klussmann et al. (Scheme 39).[58] In essence, this was a two-step process. The first step was the generation of the corresponding hydroperoxide in the presence of photosensitizer (Rose Bengal) and dioxygen mediated by visible light. The second step was Brønsted acid catalyzed nucleophilic substitution. Given that no oxidative conditions were involved in the amination step, aniline could be used as N nucleophile directly. The reactions could be run in three modes without obvious yield change: two step with isolation of hydroperoxide, one pot with solvent exchange and one pot without solvent exchange. Later, a detailed experimental and theoretical study was carried out on this reaction.[59]



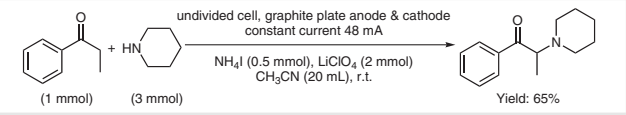
Scheme 39 Photochemical amination of tetrahydrocarbazole

The cross coupling between tetrahydrofuran and azoles has been achieved by the Lei group through both photoredox catalysis[60] and direct electrolysis[61] (Scheme 40). Compared with the photochemical method, the reaction time was sharply reduced in the electrochemical method. Both studies proposed that the N-centered radical, originating from oxidation, was the key intermediate.



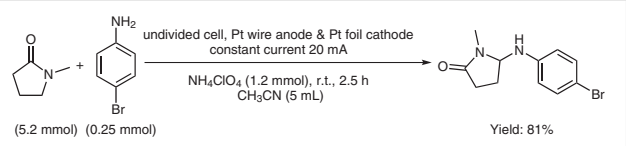
Scheme 40 Photochemical and electrochemical amination between tetrahydrofuran and azole

Zeng, Sun and co-workers reported the electrochemical synthesis of α-amino ketones mediated by iodide (Scheme 41).[62] After optimization of the reaction conditions, NH_4I was found to be a good choice of redox catalyst. The substrate scope of N nucleophiles was restricted to secondary amines; no desired product could be obtained in the presence of primary amines. The radical pathway was precluded because α-cyclopropyl substituted acetophenone could be tolerated in this protocol without ring opening. The proposed mechanism suggested that α-iodo ketone was the key reactive intermediate, which could be generated by the reaction between ketone and I_2 formed in situ. Subsequent nucleophilic substitution by the amine resulted in the target coupling product.



Scheme 41 Electrochemical synthesis of α-amino ketones mediated by iodide

Huang and co-workers reported the direct electrochemical coupling between *N*-methyl pyrrolidone and anilines (Scheme 42).[63] Besides electron-deficient anilines, anilines installed with electron-donating groups could still be compatible, albeit with lower yields. It was interesting to note that the efficiency of this transformation was very sensitive to the geometric dimensions of the Pt wire anode. As a shono-type oxidation, the reaction was initiated by the anodic oxidation of *N*-methyl pyrrolidone to its iminum cation. Subsequent trapping of the iminum cation by aniline could generate the target coupling product.



Scheme 42 Electrochemical oxidative cross coupling between γ-lactam and aniline

4 Conclusions and Outlook

Although no general mechanism can be drawn from the reactions discussed above, radical intermediates are proposed to be involved in most transformations. The reactions can be initiated from oxidation of either 'C–H' or 'N–H'. Photoredox catalysis and anodic oxidation provide a mild way to generate radicals because most reactions can be run at room temperature. Quite a lot of reported reactions can be realized through both photochemical and electrochemical approaches. Due to the essence of oxidative cross coupling, oxidant should be an indispensable component. However, external oxidant can be removed if the photoredox catalyst is accompanied by a cobaloxime catalyst. Moreover, no external oxidant is needed in electrolysis because the surplus hydrogens are evolved as dihydrogen. In general, less time is consumed in electrochemical process than photochemical methods to transform an identical amount of substrate. This may be rationalized by two considerations: (a) the low quantum yield of photochemical reactions, and (2) the productivity of electrochemical reactions is determined by the Faraday's laws of electrolysis. From the inspection of the substrate scope of both C–H and N–H nucleophiles, it can be seen that the success of many protocols are based on the delicate match of limited starting material. Broadening of the substrate scope may become an urgent need in the near future. Many intermolecular reactions are run on 1 versus n (n>1) molar ratio to attain better yields, which count against the principle of atomic economy and post treatment. Enabling the reactions to run on a 1:1 molar ratio is another target for future efforts.

For the photochemical aminations, the development of novel photocatalysts may be the most efficient way to improve the reactions. The involvement of redox mediator or electrocatalyst and modification of the electrode can supply more opportunities for the electrochemical aminations. The idea of combining photochemical and electrochemical process in the same reaction is challenging but may provide another avenue for the amination reactions.

Compared with the transition-metal catalyzed C–N bond-forming reactions, electrochemical or photochemical oxidative cross coupling between C–H and N–H have good potential for further application in industry. The reactions can be easily controlled to start and stop. When running on continuous flow mode, the productivity can be scaled up conveniently. Considerations such as current efficiency, energy efficiency, and quantum yield, which are not important in the laboratory, may be crucial factors for industrial manufacture.

Funding Information

This work was supported by the National Natural Science Foundation of China (21390402, 21520102003, 21272180) and the Natural Science Foundation of Hubei Province (2017CFA010, 2016CFB571). The Program of Introducing Talents of Discipline to Universities of China (111 Program) is also appreciated.

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