ChemPubSoc Europe

DOI: 10.1002/ejoc.201901173

EurJOC European Journal of Organic Chemistry

Minireview

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SPECIAL ISSUE

VIP

Photochemical Strategies for Carbon–Heteroatom Bond Formation

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Abstract: Photochemistry enables new synthetic means to form carbon–heteroatom bonds. Photocatalysts can catalyze carbon–heteroatom cross-couplings by electron or energy transfer either alone or in combination with a second catalyst. Photocatalyst-free methods are possible using photolabile substrates or by generating photoactive electron donor-acceptor complexes. This review summarizes and discusses the strategies used in light-mediated carbon–heteroatom bond formations based on the proposed mechanisms.

1. Introduction

The backbone of organic molecules mainly consists of C–C bonds, but the function is often derived from the presence of heteroatoms. Almost all natural products, pharmaceuticals, agrochemicals, and polymeric materials contain carbon–heteroatom bonds that are often introduced by the synthetic chemist through nucleophilic substitutions and transition metal-catalyzed cross-coupling reactions.[1] The resurgence of photochemistry[2] has resulted in a series of C–heteroatom bond formations that are complementary to traditional transformations.

The most common way to harness visible light is photocatalysis. Upon irradiation, a photocatalyst (PC) can induce chemical reactions by two modes of action (Figure 1). In photoredox catalysis (PRC), an excited PC accepts or donates a single electron, enabling oxidative or reductive quenching cycles.[3] Depending on the reaction conditions, both events can occur with the same PC. An excited photocatalyst can also transfer its excited state energy to a substrate or reagent to induce chemical reactions.[4]

Photocatalysts can generally be divided into metal complexes, organic dyes and heterogeneous semiconductors (Figure 1). Ruthenium and iridium polypyridyl complexes are the

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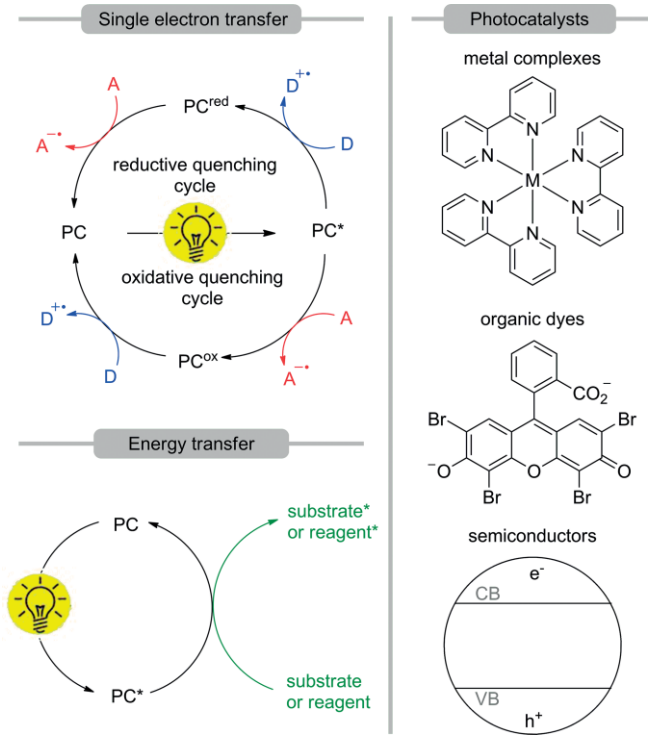


Figure 1. Modes of action in photocatalysis and classes of photocatalysts.

most common photocatalysts due to their strong absorption, stability, long excited state lifetime and the straightforward tunability by ligand modifications.[5] Photoactive complexes with earth-abundant metals,[6] and organic dyes are alternatives,[7] but suffer from limited photostability. Semiconductors, such as TiO_2, CdS, CdSe or carbon nitrides (CN), are attractive heterogeneous PCs due to their straightforward preparation, high stability, and recyclability.[8]

Photocatalysis can be used in synergy with other catalytic reactions in dual catalytic processes.[9] The combination with transition metal catalysis resulted in a series of novel approaches for carbon–carbon and carbon–heteroatom cross-coupling reactions.[9,10] Here, the key is either a direct single electron (SET) or energy transfer (EnT) between the photoredox and transition metal catalyst, or the interception of a photogenerated intermediate by the transition metal catalyst.

Reactions can be also triggered by light in the absence of a photocatalyst using photolabile starting materials, in case of photoactive intermediates.[11] In addition, electron-rich and electron-poor molecules can form electron donor-acceptor (EDA) complexes that absorb light in the visible region and induce SET events to trigger chemical transformations (Figure 2).[12]

Figure 2. Formation of an EDA complex and generation of a radical pair.

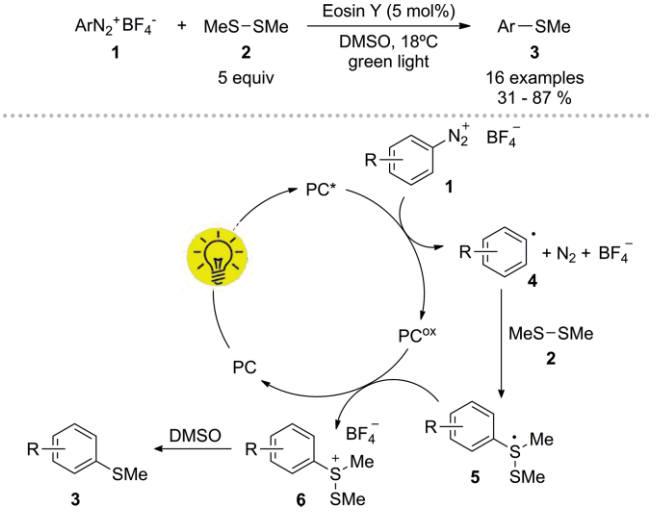
This review provides an overview of photochemical approaches for the formation of C–N, C–S, C–O, and C–P bonds. Selected examples are discussed on the basis of the underlying strategy and mechanistic proposal. A detailed discussion on the selection criteria for photocatalysts is beyond the scope of this survey and can be found elsewhere.[2–10] It is, however, important to note that photochemical transformations can be highly complex and various mechanisms might be plausible or even operating simultaneously in certain cases.[13]

2. Photocatalytic Carbon–Heteroatom Bond Formation

In this section, carbon–heteroatom couplings solely catalyzed by a PC are discussed. These reactions are triggered by the formation of highly reactive intermediates that are generated when starting materials or reagents quench the excited photocatalyst (PC*). The structures of the photocatalysts can be found at the end of this review.

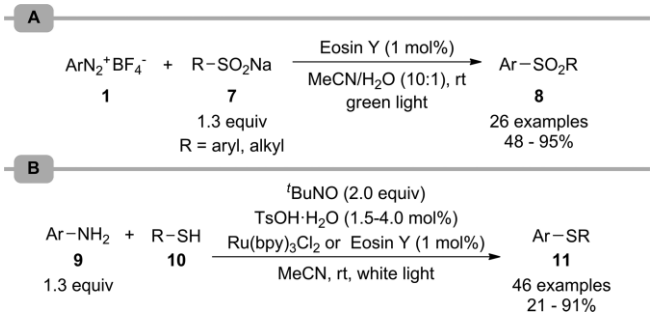
2.1. Oxidative Quenching of PC*

Aryl diazonium salts (**1**) have a rich history as precursors of aryl radicals (**4**).[14] In traditional photochemical protocols, irradiation with UV light results in photodecomposition of **1**, forming N_2 and an aryl radical (**4**) that can be converted into aryl fluorides (Balz–Schiemann reaction), but a competitive heterolytic cleavage limits this approach. More recently, aryl diazonium salts (**1**) became one of the most common oxidative quenchers in visible-light PRC and enable the selective generation of **4** from **1** which was used for a broad range of applications.[14,15] In the synthesis of thioanisoles (**3**), the aryl radical (**4**) was proposed to react with disulfides affording **5**, that donates an electron to the oxidized photocatalyst (PC^{Ox}, Scheme 1).[16]



Scheme 1. Synthesis of aryl sulfides by reduction of aryl diazonium salts by PRC.

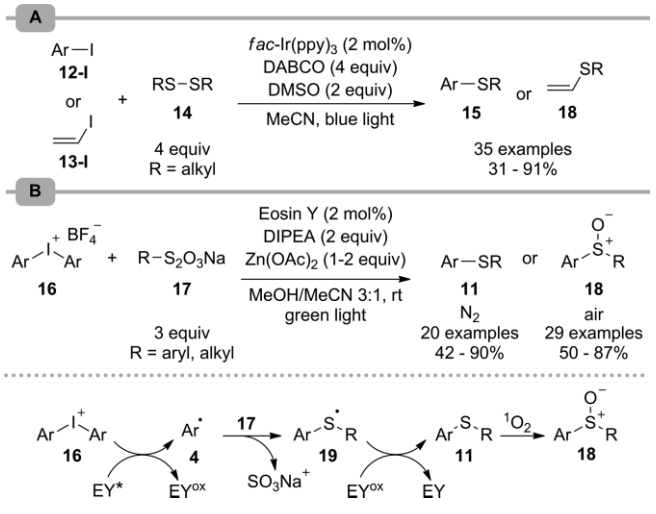
Similarly, the coupling of aryl diazonium salts (**1**) with sulfinate salts (**7**) provided the corresponding aryl sulfones (**8**, Scheme 2, A).[17]



Scheme 2. Synthesis of aryl sulfones (A) and aryl sulfides (B) by reduction of aryl diazonium salts by PRC.

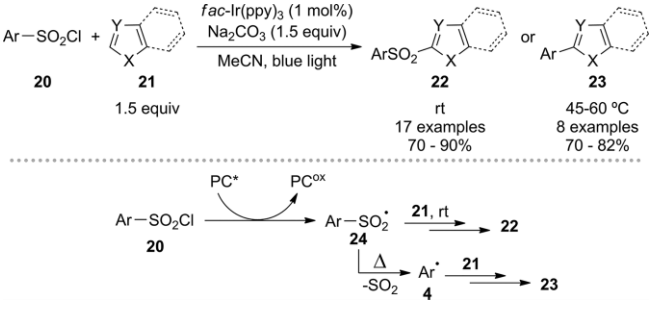
To avoid the isolation of potentially explosive diazonium compounds, Noël showed that aryl diazonium salts (**1**) can be generated in situ from the corresponding anilines (**9**) and subsequently undergo photocatalytic C–S cross-couplings with thiols (**10**, Scheme 2, B).[18] Mechanistic studies indicated that the oxidative quencher is likely a diazosulfide intermediate rather than **1**.

Aryl halides (**12**) are also potential radical precursors but have reduction potentials that are inaccessible to most photocatalysts.[15] Irradiation of $Ir(ppy)_3$ (ppy = 2-phenylpyridine) results in the strongly reducing $[Ir(ppy)_3]^*$ (Ir^{IV}/Ir^{III*} –1.76 V vs. SCE), which was demonstrated to reduce aryl iodides (**12-I**) and vinyl iodides (**13-I**) enabling C–S bond formations. (Scheme 3, A).[19] Luminescent quenching experiments and transient absorption spectroscopy showed that **12-I** is reduced by the excited photocatalyst, confirming an oxidative quenching cycle. Diaryl iodonium salts (**16**) can be used as alternative substrates with less reducing PCs such as Eosin Y (EY^{ox}/EY^* –1.11 V vs. SCE). This was demonstrated for the synthesis of aryl sulfides (**11**) from thiosulfates (**17**) under anaerobic conditions (Scheme 3, B).[20] In air, singlet oxygen ($^1O_2$) was generated, resulting in a subsequent oxidation to form the corresponding sulfoxides (**18**) in good to excellent yield.



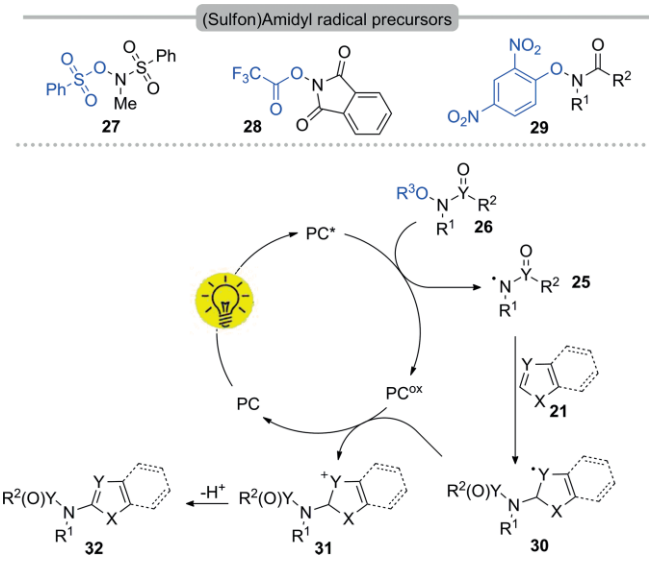
Scheme 3. Synthesis of aryl and vinyl sulfides by reduction of aryl iodides (A) or diaryl iodonium salts (B) by PRC.

Minisci type radical additions to heteroaromatic systems enable the direct functionalization of (hetero)aromatic compounds[21] and were extensively studied using photocatalysis.[22] Complementary to C–S bond formation via aryl radicals, the reduction of sulfonyl chlorides (**20**) by oxidative quenching of an excited iridium photocatalyst results in sulfonyl radicals (**24**) that were coupled with heterocycles affording the corresponding sulfonylation products (**22**, Scheme 4).[23] At elevated temperatures, extrusion of SO_2 resulted in the formation of aryl radicals, and the corresponding C–C coupling products were obtained (**23**).



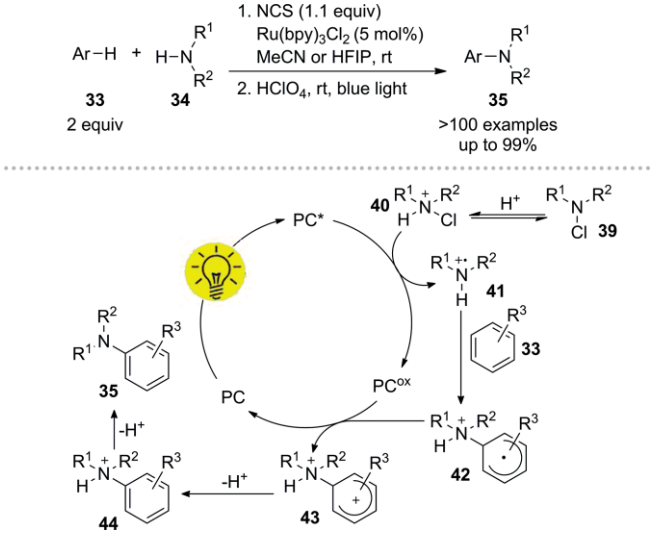
Scheme 4. Temperature controlled sulfonylation and arylation of heterocycles by PRC.

Aromatic and heteroaromatic amines are an important structural motif in pharmaceuticals and are usually prepared by using transition-metal catalyzed cross-couplings.[1e] The formation of *N*-centered radicals that react with unactivated (hetero)aromatic compounds is an appealing alternative. Amidyl and sulfonamidyl radicals (**25**) were accessed by reductive cleavage of suitable precursors (**26**) such as *N*-sulfonyloxysulfonamides (**27**),[24] *N*-acyloxyphthalimides (**28**),[25] and *N*-aryloxyamides (**29**)[26] using a sufficiently strong reducing PC (Scheme 5). The electrophilic radical species (**25**) was proposed to react with (hetero)aromatic compounds (**21**), to form a radical intermediate (**30**), that is subsequently oxidized by the photocatalyst, closing the catalytic cycle and affording the desired products (**32**) after deprotonation.



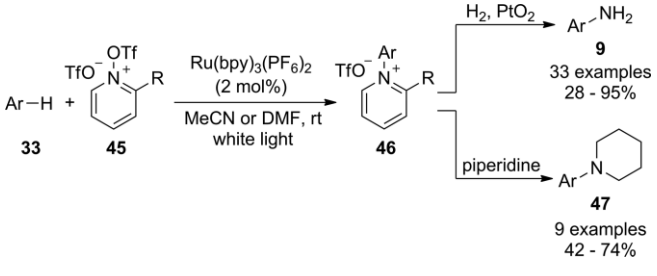
Scheme 5. Amidation of heterocycles via the formation of amidyl radicals using PRC.

Aminyl radicals, on the contrary, are nucleophilic and the repulsive interaction between their lone pair and the aromatic coupling partner makes them unsuitable for reactions with (hetero)aromatics.[27] Leonori and co-workers could overcome this synthetic hurdle by applying acidic conditions.[28] While their initial protocol required electron-poor *O*-aryl hydroxylamines as radical precursors,[28a] the authors developed a protocol which enabled the direct use of secondary and primary alkylamines (**34**, Scheme 6).[28b] Key to the success was the in situ generation of *N*-chloroammonium species (**40**) using *N*-chlorosuccinimide (NCS) under acidic conditions. **40** readily quenches the excited PC forming a highly electrophilic aminium radical (**41**) which undergoes regioselective radical addition with a broad range of arenes (**33**), forming the respective aniline derivatives (**35**) in good to excellent yield.



Scheme 6. Amination of arenes by PRC through reduction of *N*-chloroammonium cations.

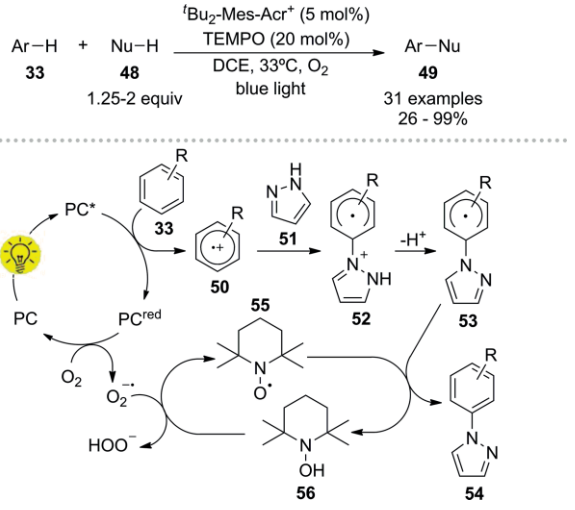
Ritter,[29] Togni and, Carreira[30] developed the amination of arenes (**33**) via the generation of *N*-pyridyl radical cations from triflyloxy pyridinium derivatives (**45**, Scheme 7). Oxidative quenching of excited $Ru(bpy)_3(PF_6)_2$ by **45** was confirmed with Stern-Volmer quenching studies. EPR experiments corroborated the existence of the *N*-pyridyl radical cation.[30] The method yielded *N*-aryl pyridinium triflates (**46**), which were subsequently converted into the corresponding aniline (**9**) or piperazine derivatives (**47**).



Scheme 7. Amination of arenes by PRC via formation of pyridyl radical cation.

2.2. Reductive Quenching of PC*

Single electron oxidation of arenes (**33**) to form arene radical cations (**50**) requires PCs with highly positive excited state reduction potentials such as acridinium dyes.[7] The electrophilic radical **50** was coupled with nucleophiles, such as azoles (**51**) to form carbon–heteroatom bonds (Scheme 8).[31] Molecular oxygen as terminal oxidant was problematic as the generated reactive oxygen radicals caused side reactions, as well as degradation of the organic photocatalyst. Addition of sub-stoichiometric amounts of TEMPO (**55**, 2,2,6,6-tetramethylpiperidine-1-oxyl) mitigated these problems, significantly improving the selectivity. It was proposed that **55** aromatizes radical intermediate **53** to yield the desired C–N coupling product (**54**) and **56** was regenerated by superoxide ($O_2^{\bullet-}$). Triplet oxygen without additional TEMPO was instead well tolerated in the sulfonamidation of pyrroles and the alkoxylation of imidazopyridines.[32]

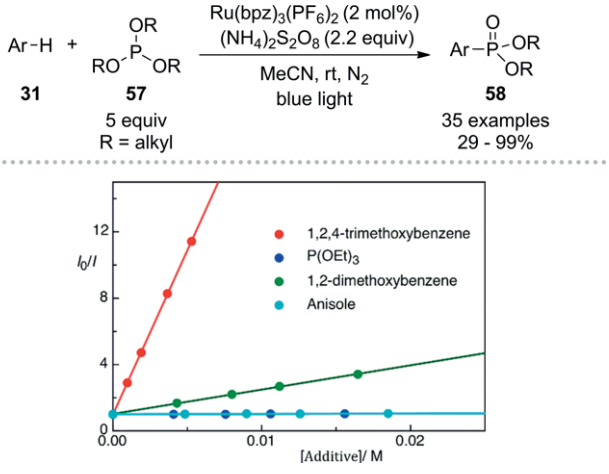


Scheme 8. Photoredox catalyzed direct C-H amination using an external oxidant and a radical mediator.

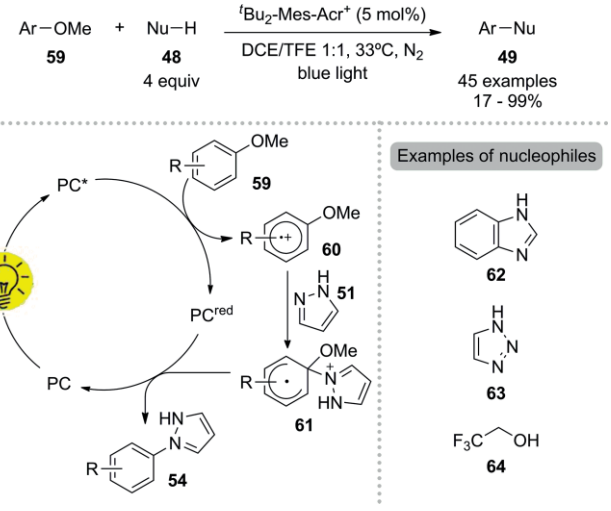
Ammonium persulfate was used as terminal oxidant in the phosphorylation of arenes (**33**) using $Ru(bpz)_3(PF_6)_2$ (bpz = 2,2′-bipyrazine) as PC (Scheme 9).[33] Stern–Volmer analysis confirmed reductive quenching of PC* (+1.45 V vs. SCE) by electron-rich arenes such as 1,2,4-trimethoxybenzene (+1.12 V vs. SCE) and 1,2-dimethoxybenzene (+1.45 V vs. SCE). Anisole was not suitable using this protocol as is does not quench PC* due to its high oxidation potential (+1.76 V vs. SCE).

An oxidant-free methodology was developed for cation radical-accelerated nucleophilic aromatic substitutions of anisole derivatives (**59**, Scheme 10).[34] The radical intermediate (**61**) formed from SET oxidation and addition of the nucleophile served as an electron acceptor to close the catalytic cycle. A similar strategy was used to activate aryl triflates using acetone as triplet sensitizer using UV light to realize several C–C, C–O, and C–N bond formations.[35]

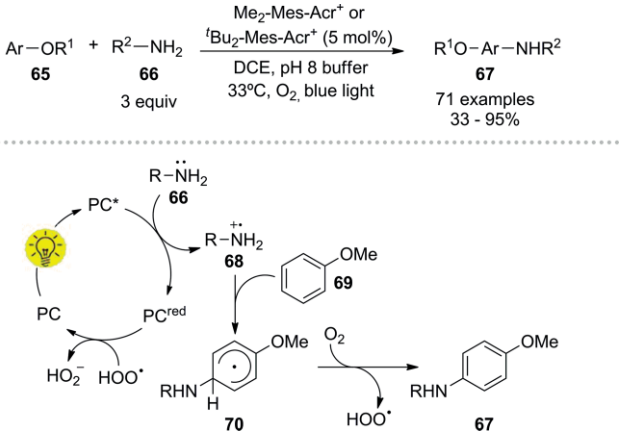
If the arene has a higher reduction potential than the PC* (e.g. anisoles, **65**), the coupling reaction can be initiated by oxidation of the heteroatom through reductive quenching of PC*.[36] Primary amines (**66**), for example, form an electrophilic *N*-centered radical cation (**68**, Scheme 11).[36a] Addition of **68**



Scheme 9. Aryl phosphonylation using photoredox catalysis. Stern-Volmer quenching plots for $Ru(bpz)_3(PF_6)_2$ in the presence of different starting materials. Reproduced with permission [ref 33].



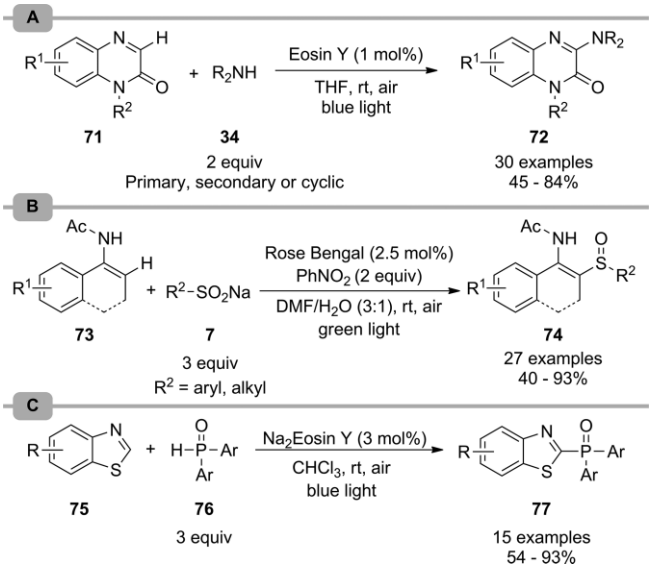
Scheme 10. Arylation of nucleophiles by activation of anisoles using PRC.



Scheme 11. Amination of anisoles via formation of aminyl radical cations using PRC.

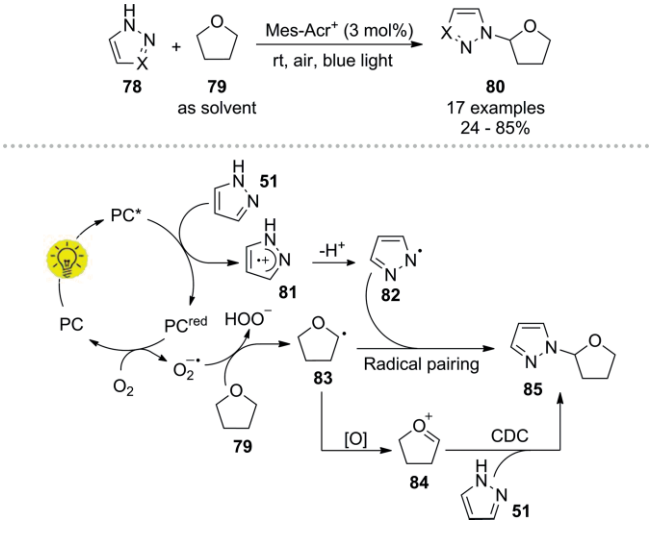
to **69** was reported to give a cyclohexadienyl radical intermediate **70** which is oxidized to the desired arylamine (**67**) by molecular oxygen. Notably, low *ortho*/*para* selectivity was observed, as the alkyloxy substituent activates both positions.

The same strategy was applied to the amination of quinoxalinones (**71**, Scheme 12, A).[36b] Oxidation of aryl sulfinate salts (**7**) was shown to induce C–S bond formation using Rose Bengal as PC (Scheme 12, B).[36c–36f] Moreover, the generation of phosphonyl radicals from aryl phosphonates was used for C–P bond formations in a similar approach (Scheme 12, C).[36g]



Scheme 12. Synthesis of arylamines (A), sulfones (B) and phosphonates (C) by oxidation of heteroatoms using PRC.

Radical combination rather than addition was proposed to operate in the coupling of azoles (**78**) and tetrahydrofuran (**79**) (Scheme 13).[37] A single electron oxidation of pyrazole (**51**) was proposed to generate radical **82**. Reduction of oxygen results in $O_2^{\bullet-}$, which abstracts a hydrogen atom from **79**. The resulting

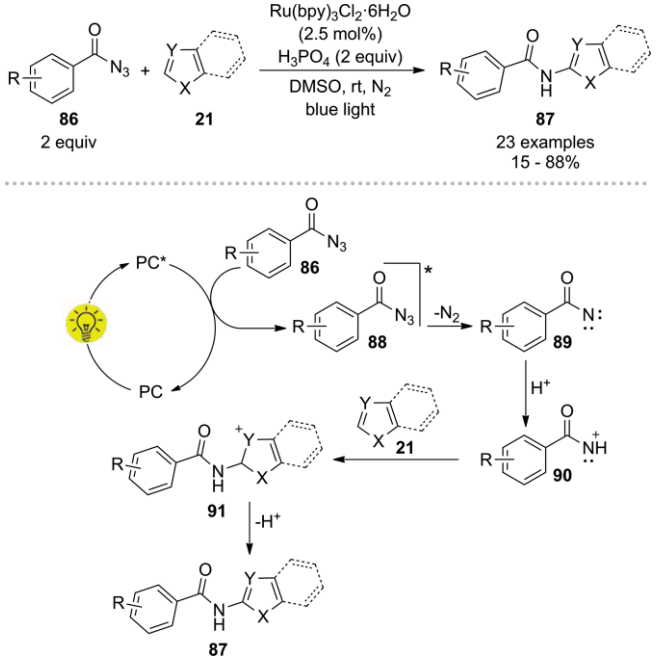


Scheme 13. Photoredox catalyzed C–N bond formation through radical pairing or cross-dehydrogenative coupling.

radical (**83**) either directly couples with **82**, or forms **84** after a SET event followed by cross-dehydrogenative coupling (CDC). A possibility that was not taken into account is a HAT process between **82** and **79** to form radical **83** and pyrazole (**51**), followed by the CDC coupling pathway.

2.3. Quenching of PC* through Energy Transfer

Quenching of PC* through energy transfer rather than single electron oxidation or reduction was reported to be responsible for the photocatalytic amidation of heteroarenes (**21**) using benzoyl azides (**86**, Scheme 14).[38]



Scheme 14. Amidation of heteroarenes through an energy transfer process.

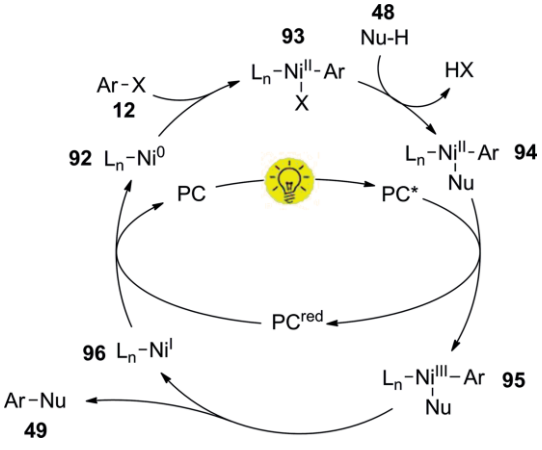
Energy transfer from PC* to the azide triggers N_2 extrusion. The resulting benzoyl nitrene (**89**) reacts with **21** to form the desired amide (**87**) after deprotonation. An electron transfer pathway was excluded, as benzoyl azides are not sufficiently electron-deficient to be reduced by PC*. Furthermore, the addition of TEMPO did not affect the transformation, indicating the absence of radical intermediates.

3. Carbon–Heteroatom Bond Formation by Combining Photo- and Transition-Metal Catalysis

Transition metal catalysis plays a key role in the formation of C–C and C–heteroatom bonds.[1a,1b] While palladium catalysis is well established, more sustainable alternatives using nickel or copper are less common. High temperatures, strong bases or reducing agents, as well as air-sensitive metal complexes are required to realize catalysis with abundant metals, thus hampering their application. Recently, the combination of transition metal- and photocatalysis (metallaphotoredox catalysis) was shown to overcome these drawbacks, enabling cross-couplings with abundant metals under mild conditions.[10a] Different modes of action are possible in metallaphotoredox catalysis. In most cases, modulation of the transition metals' oxidation state by the photocatalyst or addition of photocatalytically generated radicals are essential for product formation. Energy transfer from the excited photocatalyst can also activate intermediates in transition metal catalysis, inducing thermodynamically unfavorable processes.

3.1. Oxidation State Modulation in Metallaphotoredox Catalysis

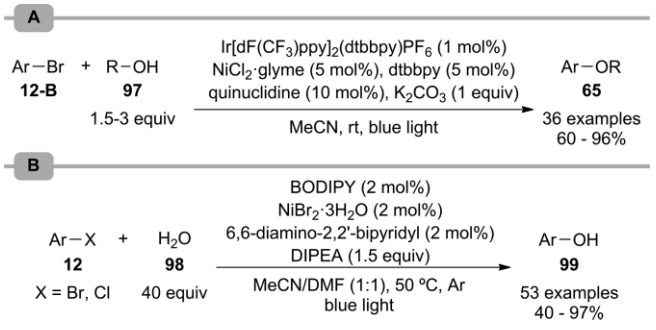
Palladium readily performs rigid two-electron processes in Pd^0/Pd^{II} systems that are responsible for carbon–heteroatom bond formations in Buchwald–Hartwig type reactions.[1a,1e] The low electronegativity of Ni enables facile oxidative addition into carbon–halide bonds, but reductive elimination is difficult.[39] While thermolysis of Ni^{II} oxametallacycles resulted in β-hydride elimination of undesired carbonyl compounds, oxidation to Ni^{III} complexes through single electron transfer (SET) with stoichiometric oxidants was shown to induce reductive elimination of C–O coupling products.[40] Combination of nickel's electronic versatility with photoredox catalysis rather than stoichiometric redox reagents afforded more efficient SET processes.[10] Oxidative addition of an aryl halide (**12**) to Ni^0 followed by ligand exchange with a suitable nucleophile (**48**) results in thermodynamically stable Ni^{II} complexes (**94**). Oxidation of **94** to a Ni^{III} intermediate (**95**) by reductive quenching of PC* was proposed to trigger reductive elimination of the desired product (**49**, Scheme 15). Single electron oxidation of PC^{red} restores PC and Ni^0 (**92**) for the next turnover.



Scheme 15. Nickel metallaphotoredox catalysis by oxidation state modulation.

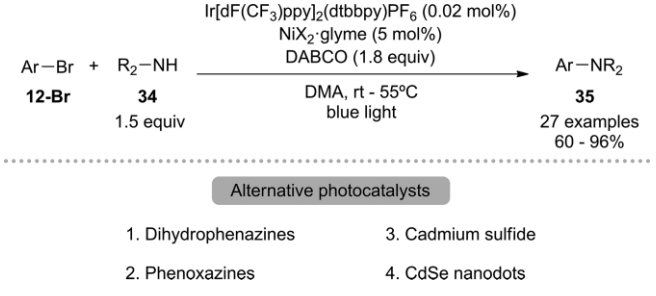
This concept was applied for the synthesis of ethers (**65**) by cross-coupling of aryl bromides (**12-Br**) with aliphatic alcohols (Scheme 16, A).[41] The addition of quinuclidine significantly enhanced the C–O bond formation, which was explained by a proton-coupled electron transfer process.[42] The protocol was adapted for the direct cross-coupling of aryl bromides (**12-Br**) and chlorides (**12-Cl**) with water to prepare phenols (**99**, Scheme 16, B).[43] More recently, this strategy was adapted to

the macrocyclization of peptides.[44] Replacement of the expensive iridium PCs by recyclable, heterogeneous semiconductors was feasible.[45]



Scheme 16. Synthesis of aryl alkyl ethers (A) and phenols (B) by nickel metallaphotoredox catalysis.

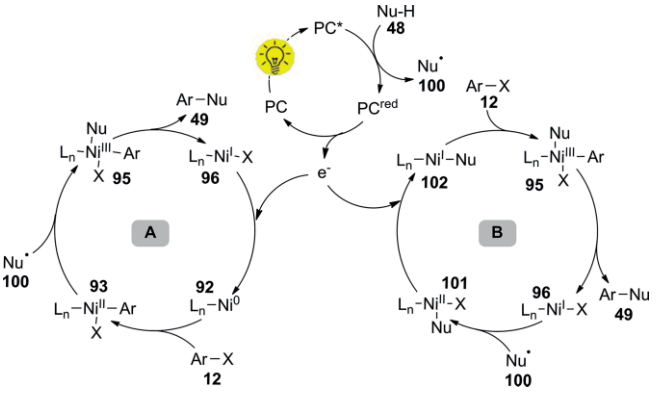
A similar mechanistic scenario is likely responsible for the coupling of **12-Br** with primary and secondary amines (**34**, Scheme 17).[45b,46] In contrast to the C–O bond formation discussed above, unligated Ni^{II} salts were used as common ligands, such as dtbbpy (4,4′-di-*tert*-butyl-2,2′-bipyridine), reduced the reaction rate significantly. Computational studies indicated that the amine substrate itself acts as a ligand for the photocatalytically generated, active Ni^0 species.[46a,47]



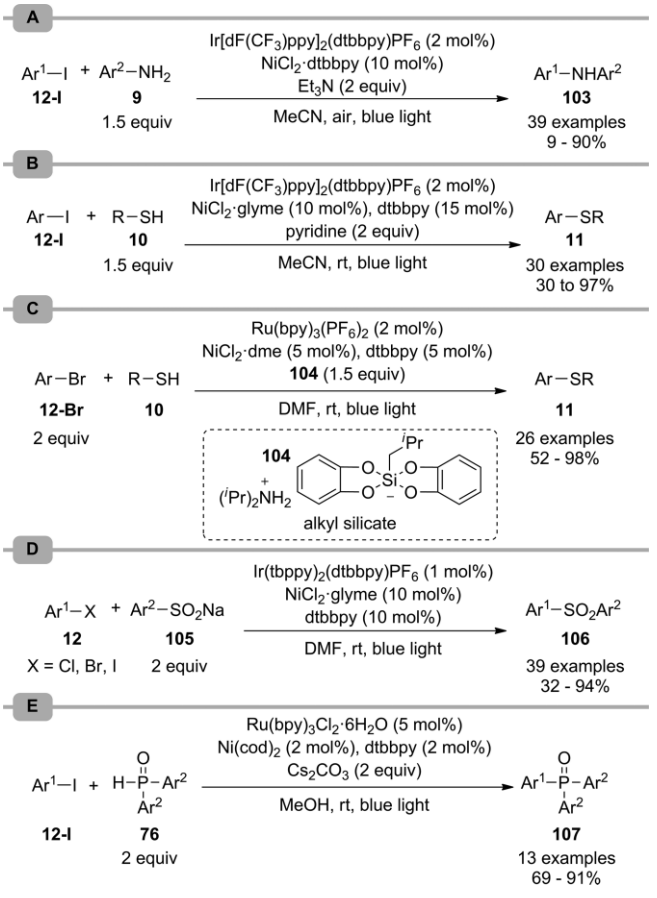
Scheme 17. Synthesis of arylamines by nickel metallaphotoredox catalysis.

Reductive elimination of carbon–heteroatom coupling products from nickel complexes was also proposed to proceed through addition of a photochemically generated radical (**100**) to Ni^{II} intermediates (**93**, Scheme 18, A).[48] Alternatively, radical addition to Ni^{I} (**96**) results in a Ni^{II} species that is re-reduced to Ni^{I} before oxidative addition of **12** (Scheme 18, B).[49] All three mechanistic scenarios for the amination of aryl halides (Scheme 15 and Scheme 18) are plausible and these pathways may even operate simultaneously. In fact, for the coupling of aryl iodides (**12-I**) with anilines (**9**) or aryl azides (Scheme 19, A),[48a,48b,49a] the formation of amine radicals was supported by fluorescence quenching studies.[48a,48b]

Thiyl radicals were generated from thiols (**10**), through reductive quenching of PC*, for C–S cross-couplings with aryl iodides[45a,49b] or bromoalkynes[49c] in presence of a nickel catalyst. The thioetherification of aryl iodides (**12-I**, Scheme 19, B) does likely not involve a Ni^0 species.[49b] In a related protocol, an alkyl silicate (**104**) was used as reductive quencher, forming a



Scheme 18. Nickel metallaphotoredox catalysis by oxidation state modulation and interception of radical intermediates.

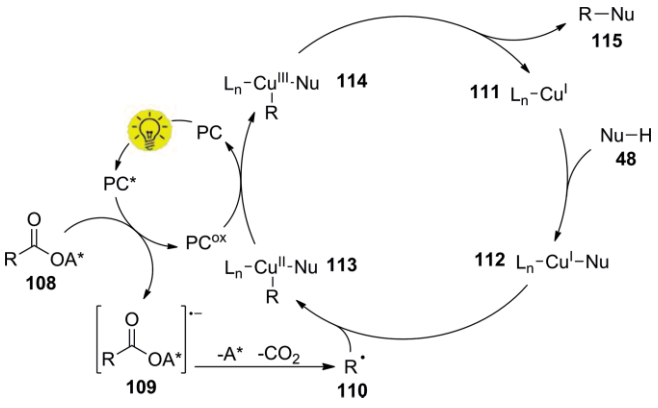


Scheme 19. Synthesis of arylamines (A), thioethers (B, C), diaryl sulfones (D) and aryl phosphane oxides (E) by nickel metallaphotoredox catalysis.

C-centered radical that generates thiyl radicals through intermolecular H-atom abstraction (Scheme 19, C)[48c,48d] In contrast to the direct thiyl radical formation,[45a,49b] this methodology works well with aryl bromides (**12-Br**). Similarly, sulfur- and phosphorus-centered radicals can be generated for the synthesis of sulfones (**106**)[48e–48g] and phosphine oxides respectively (Scheme 19, D & E).[48h,48i]

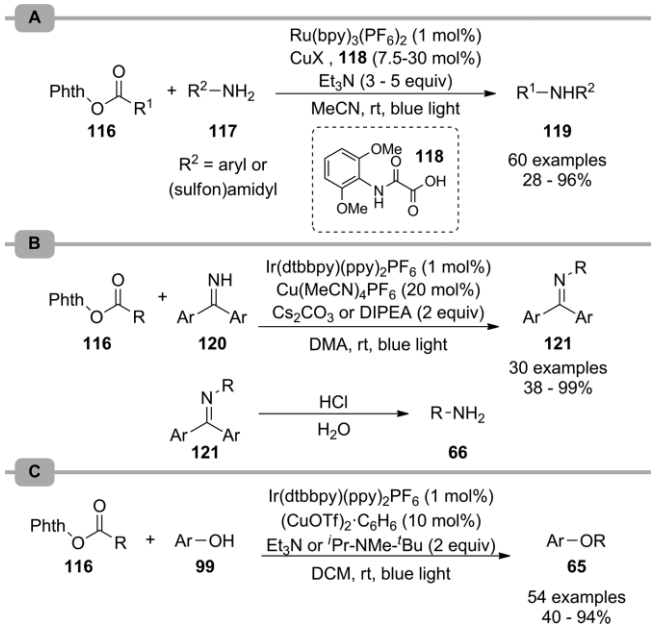
Combining photoredox and copper catalysis enabled carbon–heteroatom cross-coupling reactions by generating alkyl radicals from redox-active esters (**108**, Scheme 20).[50] Addition of

110 to a copper–amido complex and the following SET oxidation by PC^{ox} triggers reductive elimination of the desired product (**115**).



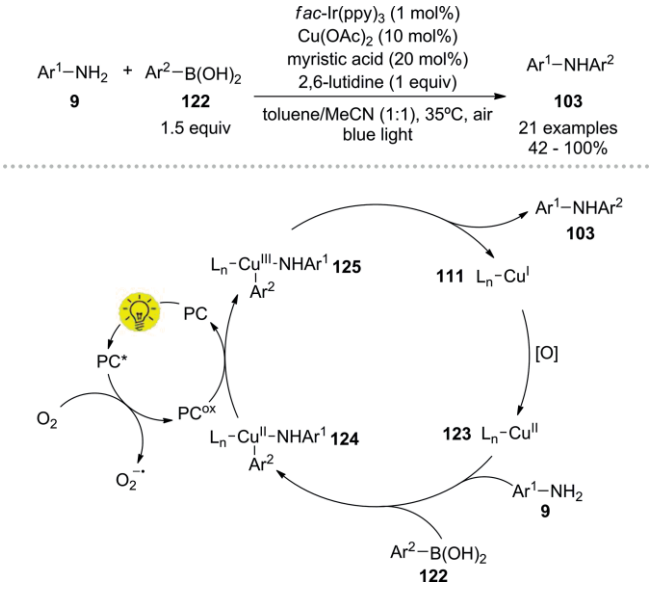
Scheme 20. Copper metallaphotoredox catalysis by oxidation state modulation.

Following this strategy, anilines, amides, and sulfonamides were coupled with alkyl radicals derived from the corresponding *N*-hydroxyphthalimide esters (**116**, Scheme 21, A),[50a] or dialkyl iodomesitylene dicarboxylates.[50c] The use of benzophenone imines (**120**) as nucleophiles resulted in **121** which was subsequently hydrolyzed, furnishing primary amines (**66**) in good to excellent yields (Scheme 21, B).[50b] A similar mechanistic concept was reported for the formation of aryl alkyl ethers by coupling phenols with alkyl radicals generated from **116** (Scheme 21, C).[51]



Scheme 21. Synthesis of amines (A), imines (B) and alkyl aryl ethers (C) by copper metallaphotoredox catalysis. CuX = CuBr (20 mol-%), Cu(MeCN)PF$_6$ (50 mol-%), or CuCl (20 mol-%); ester/nucleophile stoichiometry depends on the type of ester.

The copper catalyzed cross-coupling of aryl boronic acids and alcohols (Chan–Evans–Lam coupling) requires aerobic conditions to access the key Cu^{III} intermediate through oxidation with triplet oxygen.[52] Kobayashi and co-workers showed that efficiency problems resulting from the limited solubility of O_2 in organic solvents can be addressed by combing copper and photoredox catalysis (Scheme 22).[53] This strategy also enabled the use of electron-deficient aryl boronic acids, which are troublesome under traditional conditions.

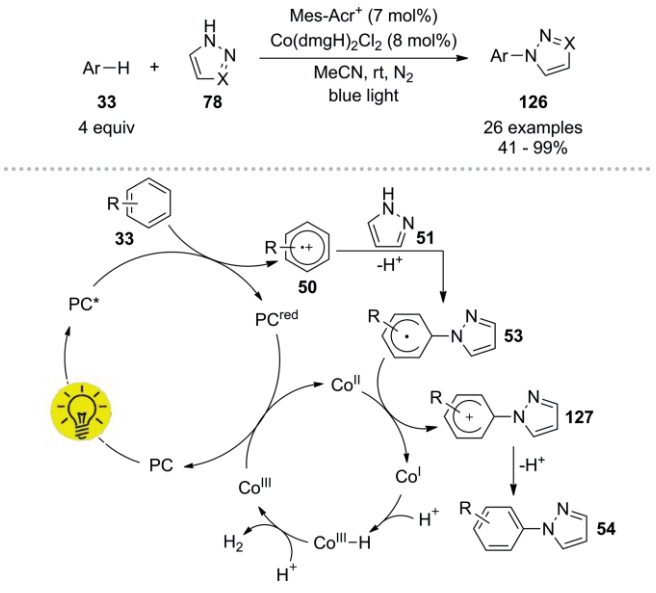


Scheme 22. Synthesis of diarylamines by copper metallaphotoredox catalysis.

3.2. Photoredox and Proton Reduction Catalysis

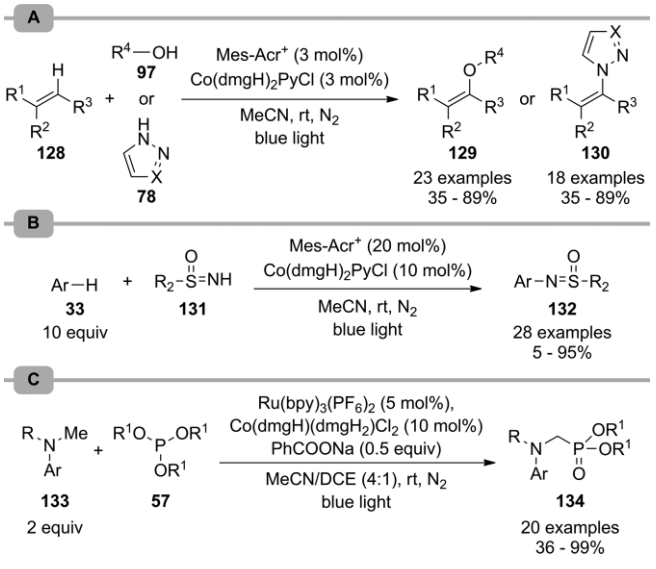
Most of the reactions involving single electron oxidation of arenes (**33**) to the corresponding radical cations (**50**) discussed in section 2.2 require a sacrificial single electron acceptor (O_2 or persulfates). These terminal oxidants can be omitted when photoredox catalysis is combined with cobalt catalysis.[54] In a seminal report, Lei showed that the *N*-arylation of azoles, which was originally carried out using O_2 in presence of TEMPO (Scheme 8),[31a] can be carried out with catalytic amounts of $Co(dmgH)_2Cl_2$ (dmg = dimethylglyoxime) to avoid not only the stoichiometric oxidant, but also formation of side products and catalyst degradation due to reactive oxygen species (Scheme 23).[54a] In the proposed catalytic cycle, reductive quenching of the acridinium photocatalyst affords the radical cation **50**, that reacts with the azole (**51**) to form **53**. The Co^{III} catalyst is reduced to Co^{I} by two consecutive single electron transfer events, one to regenerate the PC and one to afford cation **127** that, upon deprotonation, gives the desired amination product. The reduced cobalt catalyst is protonated to form a Co^{III}-H species, which subsequently reacts with another proton to release H_2 and regenerate the cobalt catalyst.

This dual catalytic CDC approach was subsequently applied to the coupling of azoles (**78**) and alcohols (**97**) with alkenes (**128**, Scheme 24, A)[54b] and for the etherification of arenes.[54c] The same catalytic system enables an oxidant-free arylation of NH-sulfoximines (**131**, Scheme 24, B).[54d] Stern–Volmer studies showed that both starting materials quench PC* and generation of both radical cations might be responsible for the C–N



Scheme 23. C-H amination by combined photoredox and proton reduction catalysis.

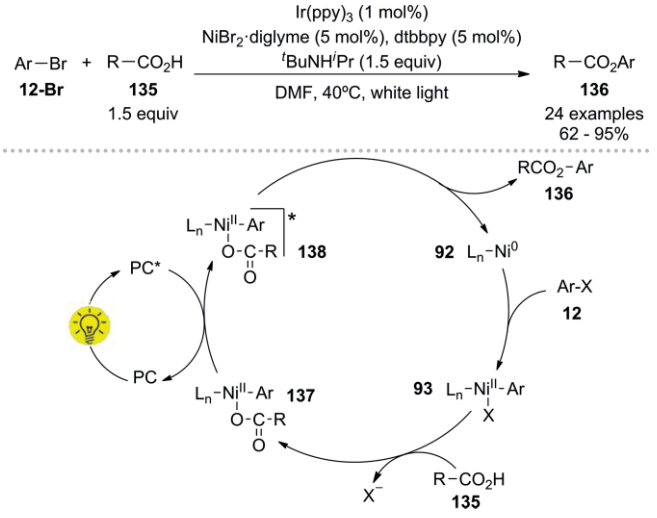
coupling. The scope of this catalytic strategy was further expanded to the phosphonylation of C(sp^2)–H[54f] bonds as well as *N*,*N*-dialkylanilines (**133**, Scheme 24, C).[54e]



Scheme 24. Synthesis of vinyl ethers and amines (A), aryl sulfoximines (B) and α-aminophosphonates (C) by combination of photoredox and proton reduction catalysis.

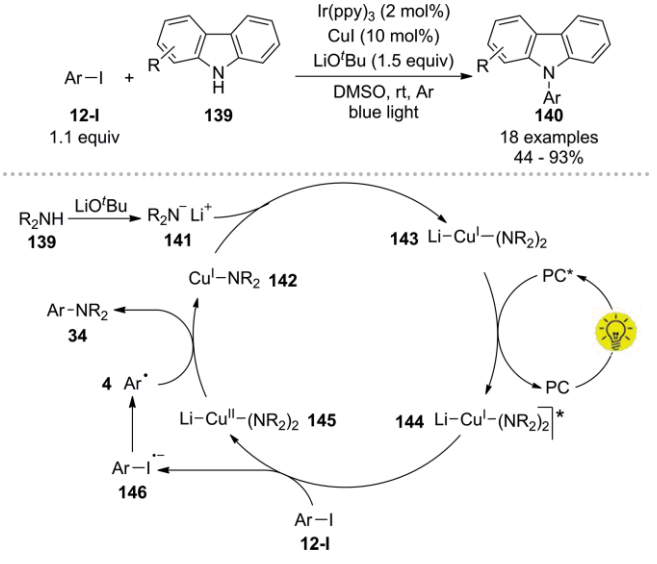
3.3. Energy Transfer to Metal Catalysts

Activation of Ni^{II} complexes to induce reductive elimination by energy transfer rather than SET oxidation was proposed for the coupling of aryl bromides and carboxylic acids yielding the respective esters (**136**, Scheme 25).[55] Key to the success was the use of $Ir(ppy)_3$ as PC which has high triplet energy in its excited state. Further, $Ir(ppy)_3$* is a weak SET oxidant, which avoids decarboxylative C–C cross-couplings.[56] More recently, the same transformation was realized using organic sensitizers[57] and heterogeneous photocatalysts, such as graphitic carbon nitrides[58] and lead halide perovskites.[59] A similar mechanistic scenario was proposed for the *N*-arylation of sulfonamides,[60] sulfoximines,[61] and carbamates.[62]



Scheme 25. Synthesis of aryl esters by energy transfer to a nickel intermediate.

Energy transfer to copper intermediates was reported to be responsible for the light-mediated coupling of carbazoles (**139**) with aryl iodides (**12-I**, Scheme 26).[63] Coordination of amide **141** results in a Cu complex (**143**) that is promoted to an excited state (**144**) by PC*. Electron transfer from **144** to **12-I** generates an aryl radical (**4**) that reacts with the Cu^{II} intermediate (**145**) to afford the desired arylamines (**34**).



Scheme 26. Synthesis of arylamines by energy transfer to a copper intermediate.

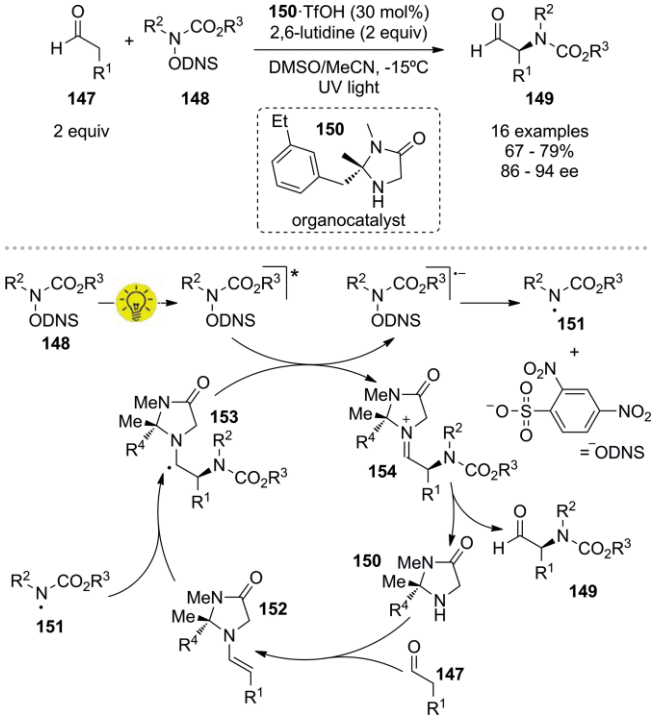
4. Photocatalyst-Free Carbon–Heteroatom Coupling Reactions

Photocatalysts are not always necessary for reactions involving visible light as an energy source. Photolabile starting materials,

the formation of electron donor-acceptor complexes (EDA), or intermediates that absorb visible light can also trigger photochemical carbon–heteroatom bond formations.

4.1. Photolabile Starting Materials

The direct enantioselective α-amination of aldehydes (**147**, Scheme 27) was realized by generating *N*-centered radicals (**151**) from dinitrophenylsulfonyloxy (ODNS) substituted amides (**148**) upon irradiation with UV light in presence of an imidazolidinone catalyst (**150**).[64] The carbamoyl radical (**151**) can react with an enamine intermediate (**152**) formed from the condensation of **150** and **147** which, after SET oxidation, eliminates the desired product. A variety of protected amines and aldehydes were successfully coupled with high enantiomeric excess.

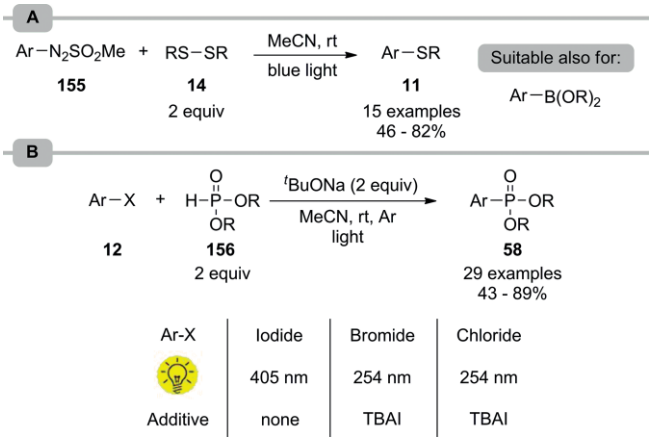


Scheme 27. Enantioselective α-amination by combining a photolabile starting material with organocatalysis.

Visible light was used to form aryl radicals (**4**) form azosulfones (**155**) for photocatalyst-free C-S and C-B bond formation (Scheme 28, A).[65] These protocols are variations of the reactions discussed in section 2.1 involving diazonium salts (**1**, Scheme 1 & Scheme 2). In fact, **155** were synthesized from the corresponding diazonium salts (**1**) using sodium methanesulfinate. Similarly, aryl radicals can also be accessed through photoinduced cleavage of aryl halides (**12**) for C-P bond formation (Scheme 28, B).[66] While visible light (405 nm) was suitable for the activation of aryl iodides, chlorides and bromides required photons with higher energy (254 nm) as well as tetrabutylammonium iodide (TBAI) as additive.

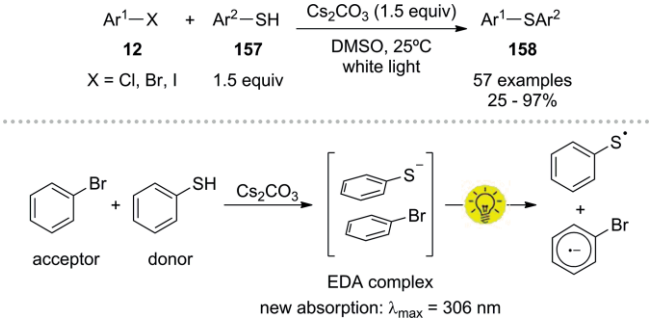
4.2. Electron Donor-Acceptor Complexes

Miyake and co-workers showed that aryl halides (**12**) and thiophenolates form an EDA complex with an absorption maximum



Scheme 28. Synthesis of aryl sulfides (A) and phosphonates (B) by photochemical generation of aryl radicals without photocatalysts.

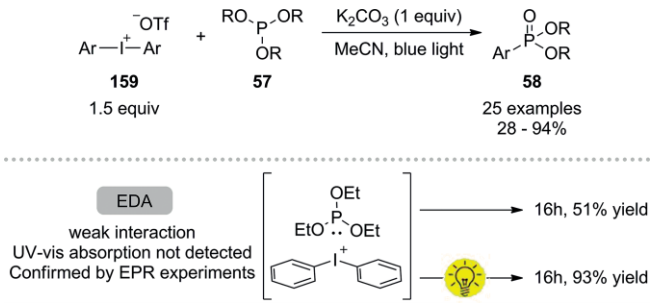
of 306 nm. If the concentration of this EDA complex is high, visible light absorption up to 515 nm was observed which enabled the synthesis of diaryl sulfides (**158**) using visible light (Scheme 29).[67] The choice of the base was crucial and the best results were obtained with Cs_2CO_3 and K_2CO_3, whereas Na_2CO_3 gave only low yields under otherwise identical conditions. The same catalytic system also works for the C–S coupling of aryl halides and sulfinate salts.[68]



Scheme 29. Thioetherification via EDA complex formation.

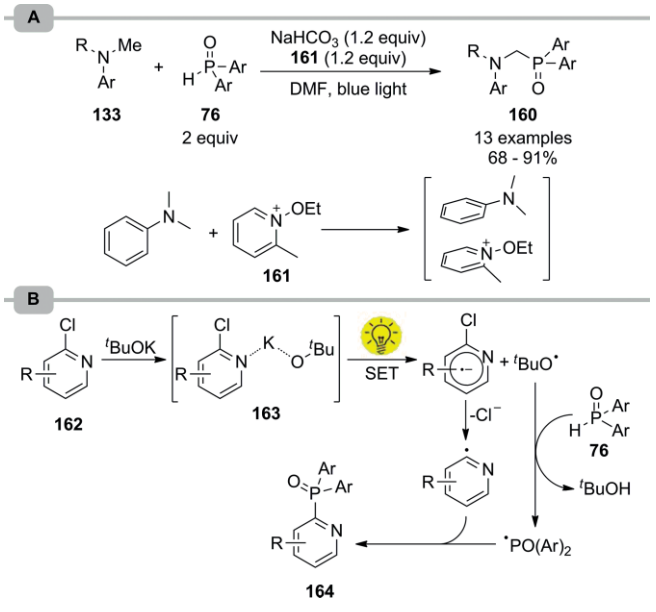
The arylation of phosphites (**57**) can be significantly accelerated using visible light, as an EDA complex is proposed to result from the combination of diaryliodonium triflates (**159**) and **57** (Scheme 30).[69] The EDA complex could, however, not be detected by UV/Vis or NMR spectroscopy as it is presumably labile and forms only in low concentration. EPR analysis in the presence of a spin trap and 405 nm irradiation showed two spin adducts which were assigned as the phenyl radical and the phosphorus radical anion, indirectly proving the existence of the EDA complex.

N-ethoxy-2-methylpyridinium (**161**) is a good electron acceptor and was shown to form EDA complexes that absorb above 400 nm with electron donors such as arylamines (**133**).[70] SET results in a nitrogen centered radical that reacts with diarylphosphanes to form **160** (Scheme 31, A).[70] Chloropyridines (**162**) were activated towards C–P couplings by formation of an EDA complex with potassium *tert*-butoxide (Scheme 31, B).[71] Blue light irradiation induced the formation of two radical species. The *tert*-butoxy radical activates phos-



Scheme 30. Arylation of phosphites via EDA complex formation.

phane oxide (**76**) to form a phosphinyl radical that pairs with the pyridyl radical to yield the desired C–P bond.

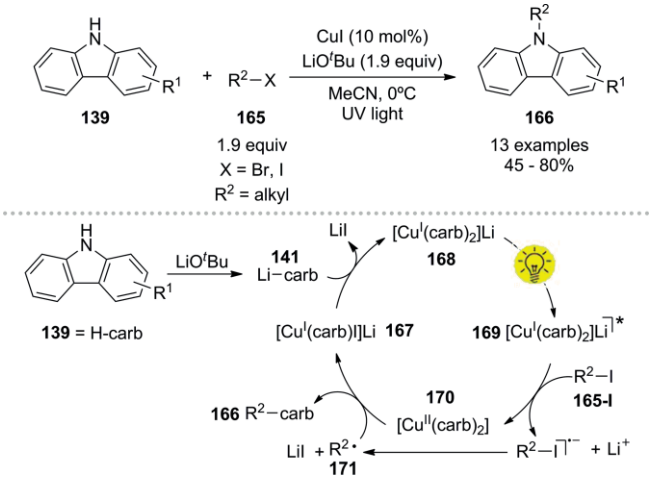


Scheme 31. α-Phosphorylation of arylamines (A) and phosphinylation of heteroaryl halides (B) via EDA complex formation.

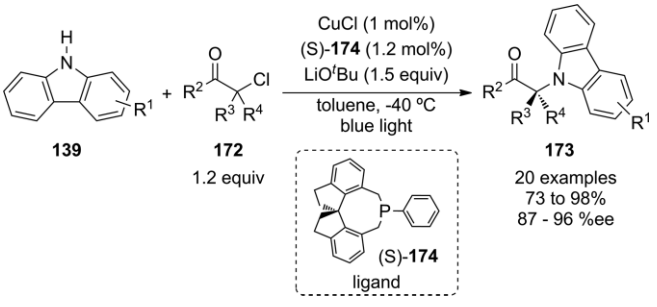
4.3. Photoinduced Metal Catalysis

Analysis of the mechanism of the copper-catalyzed Ullmann-type C–N bond formation unveiled a light-mediated coupling protocol between carbazoles (**139**) and aryl as well as alkyl halides (**165**, Scheme 32).[72] Lithiation of **139**, followed by transmetalation of **141** by the copper catalyst generates a Cu^{I}-carbazolide that absorbs UV-light. A photoinduced electron transfer from **169** to the iodide **165-I**, results in a Cu^{II} species and radical **171**. The reaction of the alkyl radical (**171**) with the Cu^{II} intermediate (**170**) affords the desired C-N bond. The scope of this reaction was extended with regard to both coupling partners.[73]

Using a chiral ligand, the enantioconvergent coupling of carbazoles (**139**) and racemic tertiary alkyl chlorides (**172**) was achieved (Scheme 33).[74] Remarkably, the chiral phosphane ligand (**174**) not only enabled asymmetric copper-catalyzed cross-couplings but also allowed the use of visible light instead of UV irradiation.

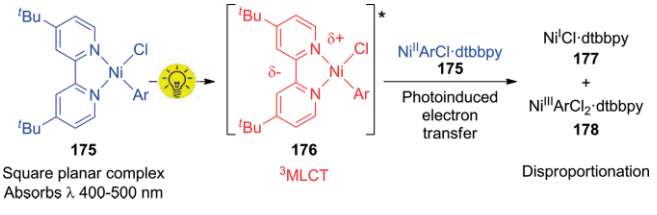


Scheme 32. Coupling of alkyl halides and carbazoles induced by photoexcitation of a copper complex.



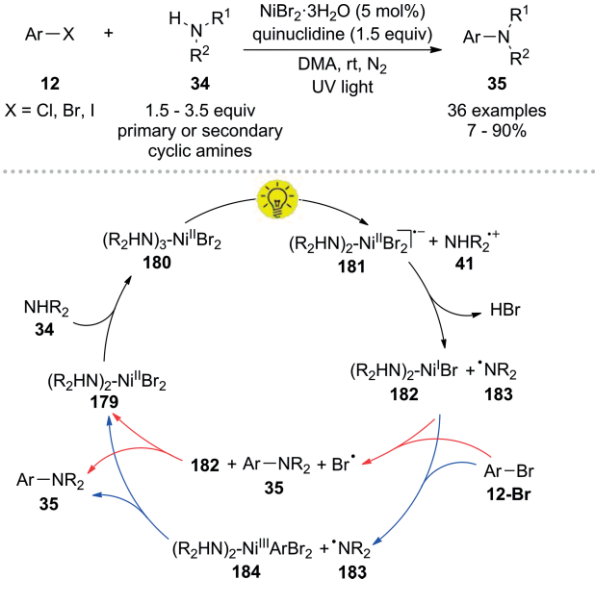
Scheme 33. Enantioselective coupling of tertiary alkyl chlorides and carbazoles by photoexcitation of copper complexes.

Doyle and co-workers carefully studied the photophysical properties of Ni^{II} aryl halide complexes, that are proposed intermediates in nickel metallaphotoredox catalyzed reactions.[75] The UV/Vis spectrum of **175** exhibits an absorption band in the visible region which is attributed to a metal-to-ligand charge transfer transition (MLCT). A photoinduced electron transfer (PET) between the excited ^{3}MLCT complex **176** and the ground state complex **175** results in disproportionation to Ni^{I} (**177**) and Ni^{III} (**178**, Scheme 34). Based on their findings, the authors showed that a combination of $Ni(COD)_2$ (COD = 1,5-cyclooctadiene) and dtbbpy is catalytically active towards the cross-coupling of alcohols and aryl halides using blue light and proposed that the photogenerated Ni^{I} complex (**177**) is the catalytically active species.



Scheme 34. Photoactivation and disproportionation of a nickel aryl halide complex.

A photocatalyst-free amination through direct sensitization of nickel complexes with UV-light was also reported (Scheme 35).[76] The coupling of aryl halides (**12**) with a series of primary and secondary amines (**34**) was proposed to start by coordination of two to three amine molecules to $NiBr_2 \cdot H_2O$. The resulting $Ni^{II}Br_2(NHR_2)_n$ complexes were found to absorb visible light (550 nm for n = 2, 430 nm for n = 3) enabling photoinduced amine-to-metal electron transfer that generates aminyl radical species (**183**, Scheme 35). The C–N coupling likely results from direct reaction of **183** with **12**, followed by addition of a bromine radical to **182**. Alternatively, oxidative addition of the aryl halide to $Ni^{I}Br \cdot (NHR_2)_2$ can generate a Ni^{III} complex (**184**). This intermediate can react with the aminyl radical to form the desired C–N coupling product.



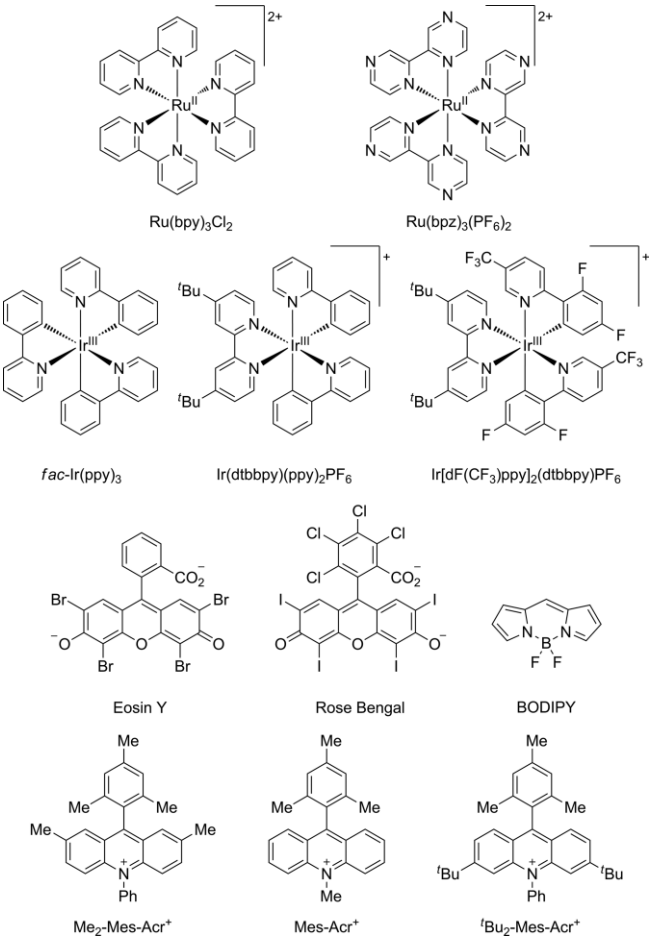
Scheme 35. Aryl amination by photoexcitation of nickel complexes.

5. Summary and Outlook

Light is a sustainable and traceless reagent for chemical transformations that can be used by various strategies. Visible light irradiation of a photocatalyst can trigger the plethora of carbon-heteroatom bond formations by generating reactive intermediate from otherwise unreactive starting materials or reagents. Thermodynamically prohibited processes in transition metal catalysis can be triggered by using the combination with photochemistry. The vast majority of visible light-mediated protocols is currently carried out in the presence of a suitable photocatalyst. The recent development of photocatalyst-free approaches, especially via EDA complexes and photoinduced metal catalysis is promising but is still in its infancy.

The examples listed in this review showcase how applying photochemistry to improve pre-existing techniques often resulted in discovering completely new reactivities. This partially explains why photochemistry has attracted large interest in the last decade and will certainly play a key role in the future of organic synthesis.

Structures of Photocatalysts



Acknowledgments

We gratefully acknowledge the Max–Planck Society for generous financial support. B. P. acknowledges financial support by a Liebig Fellowship of the German Chemical Industry Fund (Fonds der Chemischen Industrie, FCI).

Keywords: Cross-coupling · Photochemistry · Photocatalysis · Photoredox catalysis · Metal catalysis

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Received: August 8, 2019