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Pierre H. Dixneuf, Jean-François Soulé. Functionalization of C(sp2)–H Bonds of Arenes and Heteroarenes Assisted by Photoredox Catalysts for the C–C Bond Formation. Organometallics for Green Catalysis, pp.225-265, 2018, 10.1007/3418_2018_22 . hal-01988115

HAL Id: hal-01988115

https://univ-rennes.hal.science/hal-01988115

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Functionalization of C(sp^2)–H Bonds of Arenes and Heteroarenes Assisted by Photoredox-Catalysts for the C–C Bond Formation

Pierre H. Dixneuf and Jean-françois Soulé

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Abstract The formation of C–C bonds from arenes and heteroarenes through transition metal-catalyzed C–H bond functionalizations is one of the major achievements of these last decades. It is now possible to perform such transformations under mild reaction conditions with the help of visible-light photocatalysis leading to eco-friendly and safer-process to build organic molecules or materials. This chapter will focus on photoredox catalysis which involves a C(sp^2)–H bond functionalization step for the formation of C(sp^2)–C bonds [i.e., direct arylations and (perfluoro)alkylations] and will show how this hot topic contribute to the development of green chemistry.

Keywords Visible light; MLTC Photoredox catalysis; C(sp^2)–H bond; C–C Bond formation

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1. Introduction

During the last two decades catalytic C-H bond functionalizations, for cross-coupled C-C bond formation, have progressively replaced the useful metal-catalyzed cross-coupling reactions between a stoichiometric amount of an organometallic species and a (hetero)aromatic halide. The advantages involve the atom economy of the process as the C–H bond no longer needs to be transformed into a carbon-halide bond or in an organometallic reagent, and the reduction of steps to lead to useful complex molecules from medicinal compounds to polyfunctional ligands and molecular materials. [1-12]

The $C(sp^2)$–H bond functionalizations usually require previous activation by a transition metal catalyst, either via initial insertion of low-valent metal into the C-H bond such as Ru(0), Rh(I) or Ir(I) catalysts of via C–H bond deprotonation in the presence of Ru(II), Rh(III) or Ir(III) or Pd(II) catalysts. For both activation processes the regioselectivity control is the main problem and usually a tolerated directing group brings a suitable solution.[13-15] Whereas the metal C–H bond activation steps are relatively easily performed the functionalization of the (M–C) carbon of intermediate requires higher energy. In addition, for the regeneration of high valent metal catalysts a stoichiometric amount of oxidant is often required. These drawbacks motivate the search of better C–H bond functionalizations with high regioselectivity, absence of stoichiometric amount of oxidant and mild conditions.

Since the pioneer works by Gafney and Adamson, who showed that single-electron-transfer (SET) event can be initiated by the triplet charge-transfer excited state of $[Ru(bpy)_3]^{2+}$,[16] the application of polypyridine-metal complexes with metal-ligand charge transfer (MLCT) properties in catalysis has become a useful alternative approach to create new C–C bonds,[17-26] and more recently to functionalize C–H bonds.[27-30] The first photoredox functionalization of $C(sp^2)$–H bond was reported in 1984 by Deronzier with the $[Ru(bpy)_3]^{2+}$-assisted the cyclization of stilbenediazonium salts.[31]

Photoredox catalysts (PC^n), such as *tris*(2,2′-bipyridine)ruthenium(II) $[Ru(bpy)_3^{2+}]$ or *fac*-*tris*(2-phenypyridine)iridium(III) *fac*-$[Ir(ppy)_3]$ under simple irradiation by low energy visible light leads to their long lifetime photoexcited state ($*PC^n$), resulting from electron transfer from the dπ orbital of the metal center to the π* orbital of the 2,2′-bipyridine or 2-phenylpyridine ligand (MLCT) followed by intersystem crossing. Then, photo-excited state ($*PC^n$) undergoes SET in two different scenarios:

i) *in a reductive quenching cycle*, SET occurs from an electron donor **D** to $*PC^n$ associated with formation of reduced $PC^{(n-1)}$ followed by the reduction of an electron acceptor **A** associated with regeneration of the ground state of the catalyst photoredox (PC^n) (Figure 1a).

ii) *oxidative quenching cycle*, SET occurs from *PC^n to an electron acceptor **A** associated with formation of the high-oxidation-state $PC^{(n+1)}$ followed by the oxidation of an electron donor **D** associated with regeneration of the ground state of the photoredox catalyst (PC^n) (Figure 1b).

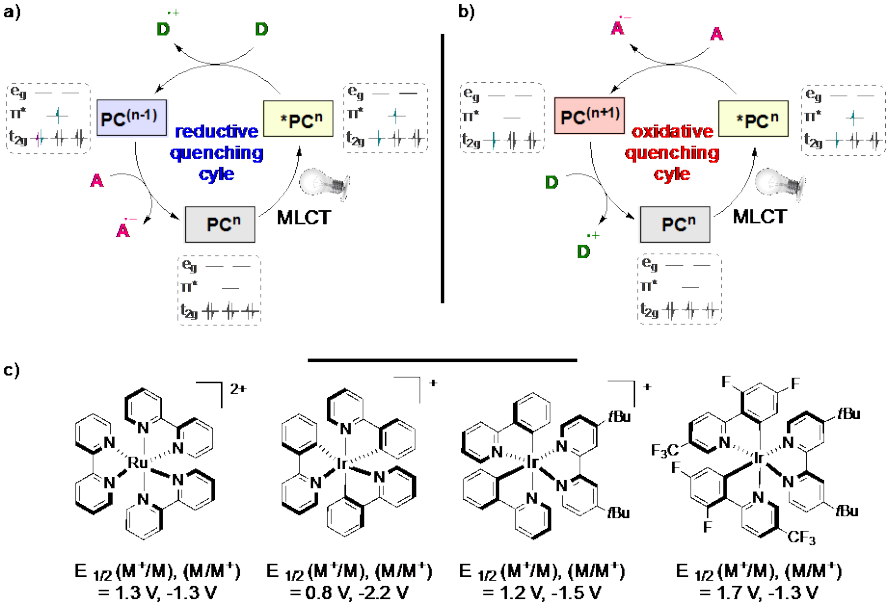


Figure 1. ^{3}MLCT excited state: diagram of energy and electron transfer processes a) reductive quenching cycle b) oxidative quenching cycle c) Chemical structures of some common photoredox-catalysts and their redox potentials in V *vs.* SCE. SCE: saturated calomel electrode.[32]

The above generated cations or anions radicals easily decompose into carbon-centered radicals, which add regioselectively to molecules such as arenes, heterocycles and even alkenes to form a new C(sp^2)-C bond from C(sp^2)-H bond at room temperature. These low-energy visible light photoinitiated processes offer a new life to radical generations and reactions but more importantly they offer new ways of regioselective functionalizations of C(sp^2)-H bonds with high atom economy under very mild conditions. *They constitute an excellent, fast developing contribution to green chemistry.*

This is why this chapter will present the contributions of metal complex photoredox catalysts to functionalize, by C(sp^2)–C bond formation, the C(sp^2)–H bonds of arenes and heterocycles.

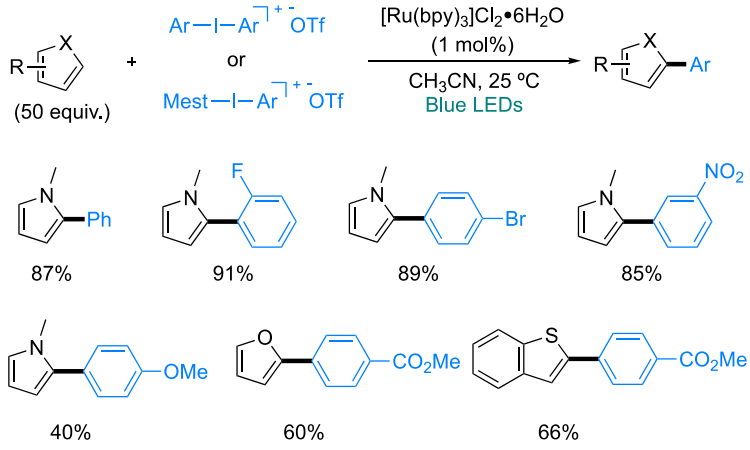
This chapter will present the different methods based on MLCT photoredox metal complexes to transform C(sp^2)–H bonds of 5-atom and 6-atom heterocycles

and of functional arenes into C(sp^2)–C bonds only. The reactions will be classified by the nature of substrates and by type of functionalization: arylation, perfluoroalkylation, and alkylation. The conditions of the photoredox catalyzed reactions will be pointed out to show the mild energy and conditions and that photoredox systems are current available keys to develop green catalysis processes.

2. Functionalizations of 5-atom ring heteroarene C(sp^2)–H bonds

2.1. Photoredox-assisted arylation of 5-atom heteroarene C(sp^2)–H bonds

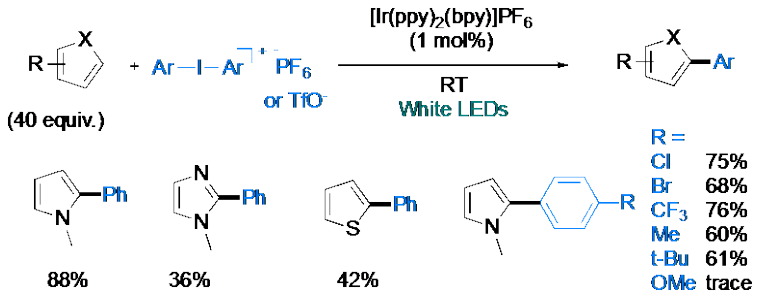
In 2013, Xue, Xiao and co-workers demonstrated that $[Ru(bpy)_3]^{2+}$ under blue LEDs promotes the arylation of pyrroles, furans, and benzothiophene using diaryl iodonium salts as aryl radical precursors (Scheme 1).[33] The regioselectivity of the arylation is similar to those observed with palladium catalysts in the presence of aryl halides,[13] namely at the α-positions. While the C–H arylation of heteroarenes can be performed at room temperature, a huge amount of heteroarenes (50 equivalents) is required, which make this protocol not really attractive from a synthetic point of view. The authors have proposed a mechanism based on oxidative quenching pathway.



Scheme 1. $Ru(bpy)_3^{2+}$-assisted arylation of heteroarenes with diaryliodonium salts

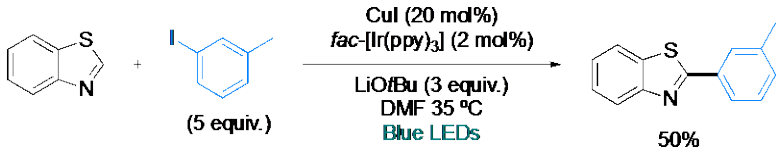
Tobisu, Chatani and co-workers also employed diaryliodonium salts as aryl radical precursors for the C(sp^2)–H bond arylation of heteroarenes such as pyrroles, imidazoles and thiophenes using $[Ir(ppy)_2(bpy)]PF_6$ as photoredox catalyst (Scheme 2).[34] In all cases the arylation takes place mainly at the C2-position. A wide range of substituents at the *para*-position of the diaryliodonium salts are

tolerated such as chloro, bromo, trifluoromethyl, methyl, *tert*-butyl, while *para*-methoxy substituted diaryliodonium salts failed to react under these reaction conditions.



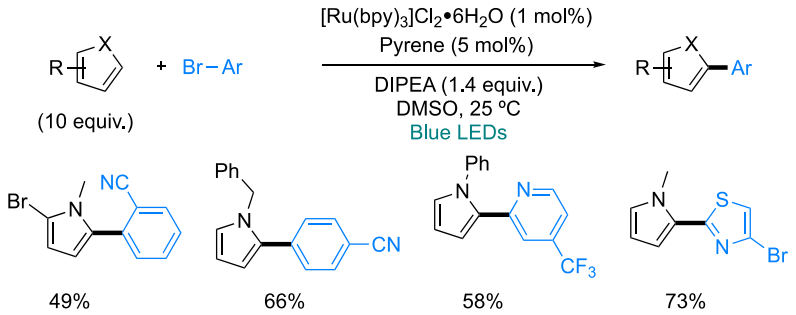
Scheme 2. $[Ir(ppy)_2(bpy)]PF_6$-promoted arylation of heteroarenes using diaryliodonium salts

The generation of aryl radicals from aryl halides and pseudohalides are very challenging due to do their high reduction potentials, which are beyond the reach of many typical photoredox catalysts including $Ru(bpy)_3$. In 2016, Ackermann and co-workers reported the merge of *fac*-$[Ir(ppy)_3]$ photoredox catalyst and CuI(I) to promote the C2 arylation of benzothiazole using 3-tolyl iodide (Scheme 3).[35]



Scheme 3. Merging of *fac*-$[Ir(ppy)_3]$ and Cu(I) for the C2-arylation of thiazole using aryl iodide

In 2017, König and co-workers employed visible-light photoredox catalyst $[Ru(bpy)_3]^{2+}$ to generate radical anions from pyrenes to promote the formation of aryl radical from aryl halides via SET event, also called sensitization-initiated electron transfer (Scheme 4).[36] Pyrroles and indoles were arylated at the α-position using only electron-poor aryl bromides (e.g., bromobenzonitriles, bromobenzoates and heteroaryl bromides). Again, a huge amount of heteroarenes (10 equiv.) is required. In addition, this catalytic system is also operative using aryl triflate instead of aryl halides.



Scheme 4. $Ru(bpy)_3^{2+}$-promoted arylation of (hetero)arenes using aryl bromides and chlorides.

Based on spectroscopic investigations, the authors proposed a catalytic cycle depicted in Figure 2. After visible-light photoexcitation of $Ru(bpy)_3^{2+}$, $*Ru(bpy)_3^{2+}$ transfers its energy to pyrene (Py). The excited Py* is then reductively quenched by *N*,*N*-diisopropylethylamine (DIPEA) to generate the radical anion $[Py]^{\bullet-}$ and the radical cation $[DIPEA]^{\bullet+}$. Then, $[Py]^{\bullet-}$ transfers one electron to the (hetero)aryl halide, yielding the (hetero)aryl radical precursor $[(Het)ArX]^{\bullet-}$ which generates the aryl radical ($Ar^{\bullet}$) and neutral Py to complete the catalytic cycle. Finally, the radical $Ar^{\bullet}$ reacts with (hetero)arenes to afford C–C coupling products. In a competing pathway, the radical $Ar^{\bullet}$ abstracts a hydrogen atom either from $[DIPEA]^{\bullet+}$ or from the solvent (in this case DMSO) to give undesired reduction products and diisopropylamine.

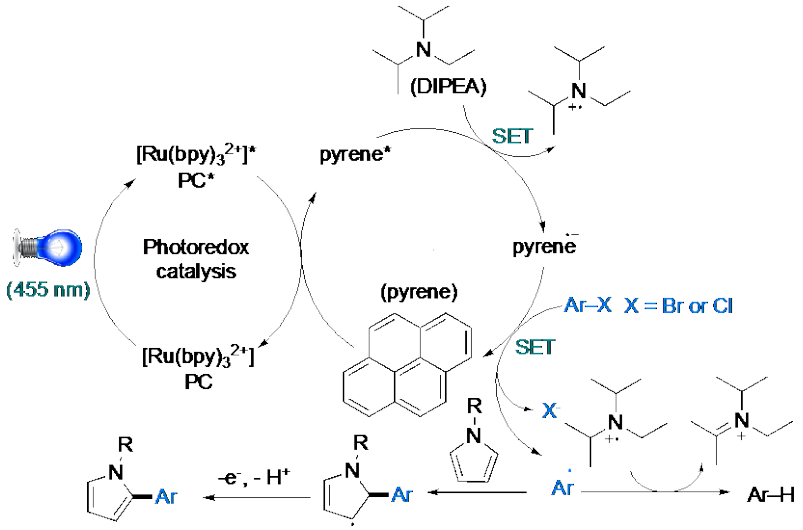
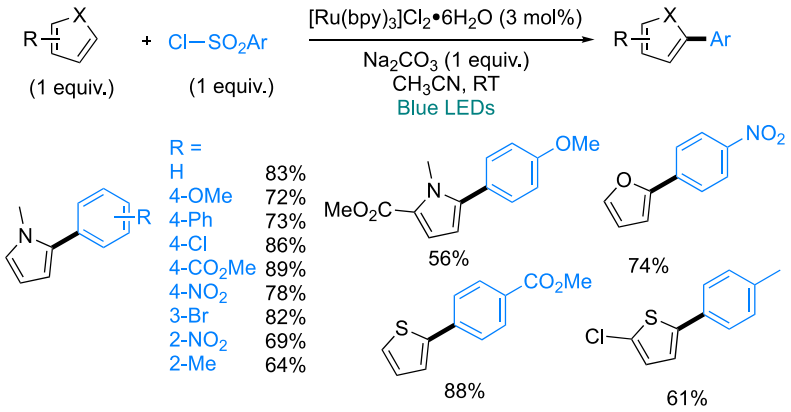


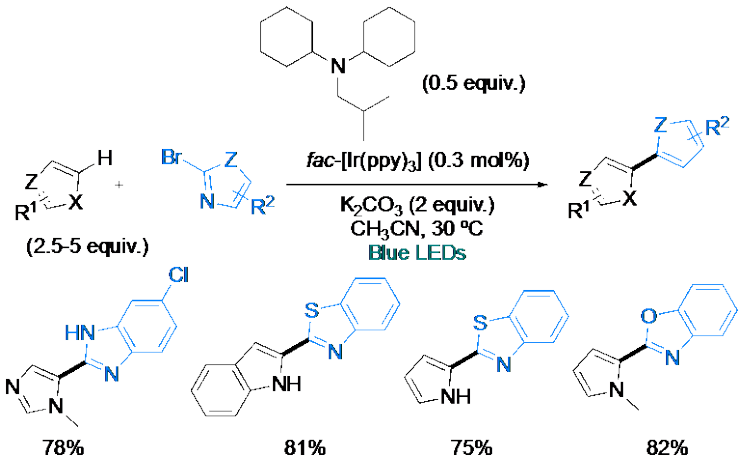
Figure 2. Proposed catalytic cycle for pyrene sensitization-initiated electron transfer catalytic C–H arylation reactions

In 2016, Natarajan *et al.* achieved the visible-light-mediated C(sp^2)–H bond arylations of 5-atom ring heteroarenes with benzenesulfonyl chlorides at room temperature using $[Ru(bpy)_3]Cl_2$ as photosensitizer and blue LEDs irradiation (Scheme 5).[37] The reaction occurred at the α-position and tolerated a broad range of functional groups. It is noteworthy that β-arylated thiophenes are synthetized by palladium-catalyzed C–H bond desulfitative arylation.[38-42] The authors proposed a radical pathway through an oxidative quenching cycle.



Scheme 5. $Ru(bpy)_3^{2+}$-promoted arylation of heteroarenes with arenesulfonyl chlorides

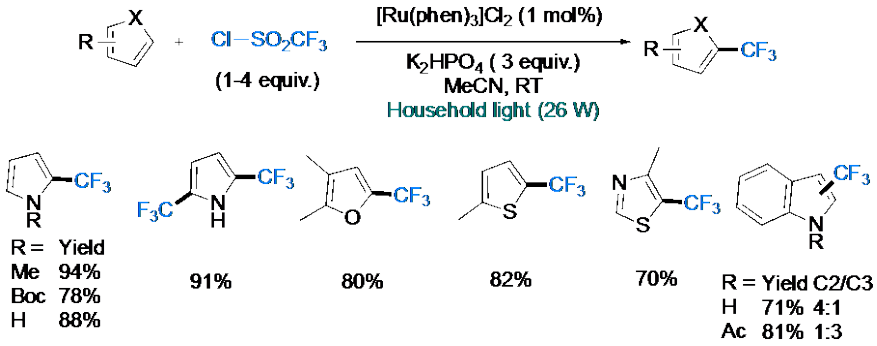
In 2016, Weaver and co-workers demonstrated that the formation of 2-azolyl radicals from 2-bromoazoles can be achied using *fac*-$[Ir(ppy)_3]$ photoredox catalysis (Scheme 6).[43] They employed *N*-cyclohexyl-*N*-*iso*butyl-*N*-cyclohexanamine as sacrificial oxidizing agent, and an oxidative quenching cycle allow the formation of aryl radical, which could be trapped by electron-rich arenes, pyrroles, indoles, imidazoles, pyridines, and thiophenes to allow the formation of heterobiaryls in good yields. A wide range of 2-bromoazaoles including the one bearing sensitive halo-bonds have been employed.



Scheme 6. Heteroarylation of (hetero)arenes with 2-bromoazoles using Ir-based photoredox catalyst

2.2. Photoredox-assisted perfluoroalkylation of 5-atom heteroarene C(sp^2)–H bonds

In 2011, MacMillan and co-workers succeeded to generate $CF_3^{\bullet}$ radical from trifluoromethanesulfonyl chloride using visible-light photoredox catalysis (Scheme 7).[44] Trifluoromethylation of C(sp^2)–H bonds of 5-atom ring heteroarenes such as pyrroles, furans, thiophenes and thiazoles at the C2 or C5 position were achieved under mild reaction conditions using 1 mol% $[Ru(phen)_3]Cl_2$ as photoredox catalyst. Notably, mixture of C2 and C3 trifluoromethylated indoles were obtained depending on the N-substituents.



Scheme 7. $Ru(phen)_3^{2+}$-catalyzed trifluoromethylation of heteroarenes using trifluoromethanesulfonyl chloride

Oxidative quenching cycle was proposed with the generation of $CF_3^{\bullet}$ radical *via* SET reduction promoted by photo-excited *PC (Figure 3)..[45,46]

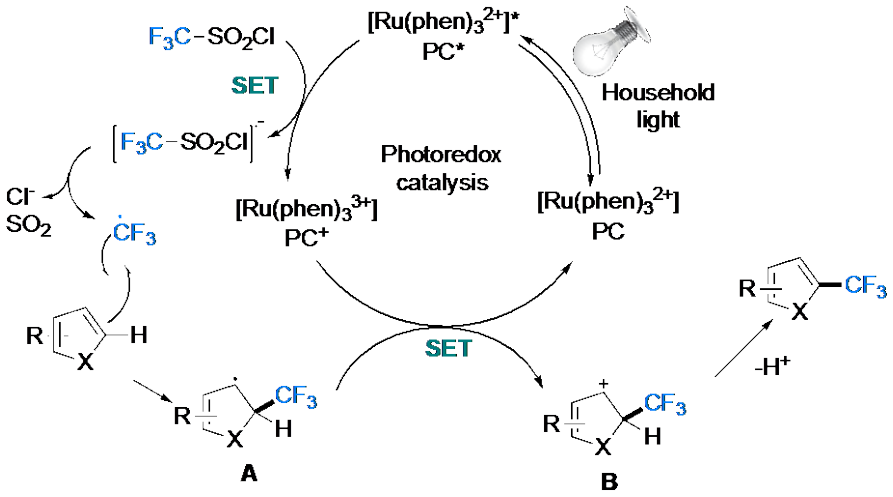
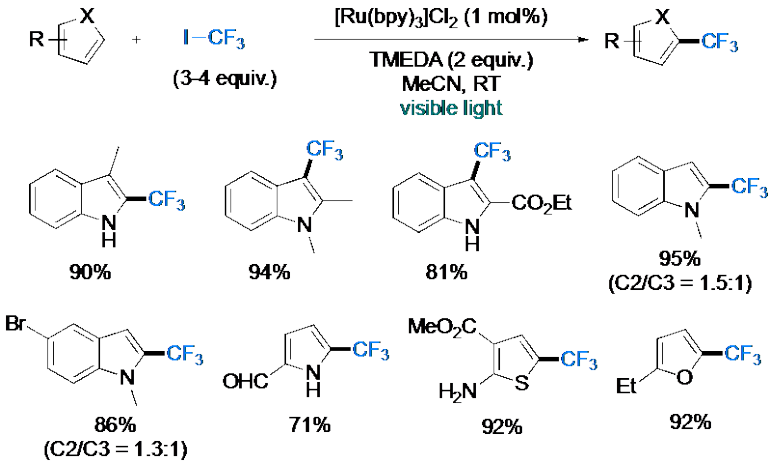


Figure 3. Proposed mechanism for visible light mediated trifluoromethylation of (hetero)arenes with CF_3SO_2Cl

Cho and co-workers disclosed that trifluoroiodomethane can also generate $CF_3^{\bullet}$ radical under visible-light photoredox conditions allowing the C(sp^2)–H bond trifluoromethylation of 5 atom ring heteroarenes (Scheme 8).[47] The reaction was carried out using 1 mol% $[Ru(bpy)_3]Cl_2$ in the presence of 2 equivalents of TMEDA (*N,N,N′,N′*-tetramethylethylenediamine) as base in acetonitrile under visible light. Indoles are successfully trifluoromethylated at C2 or C3 depending on the indolyl substituent, whereas pyrroles, thiophenes and furans are regioselectively functionalized at the C2 or C5 position. Notably, Noël and co-workers have developed a continuous flow version of this reaction to allow the trifluoromethylation of five-atom heteroaromatics in larger scale.[48,49]



Scheme 8. $Ru(bpy)_3^{2+}$-catalyzed trifluoromethylation of heterocycles with trifluoroiodomethane

Based on the mechanism study,[49] the authors proposed a reductive quenching pathway. Indeed, the generated Ru^{3+} species is reduced by SET from TMEDA which plays the role of an electron donor (Figure 4).

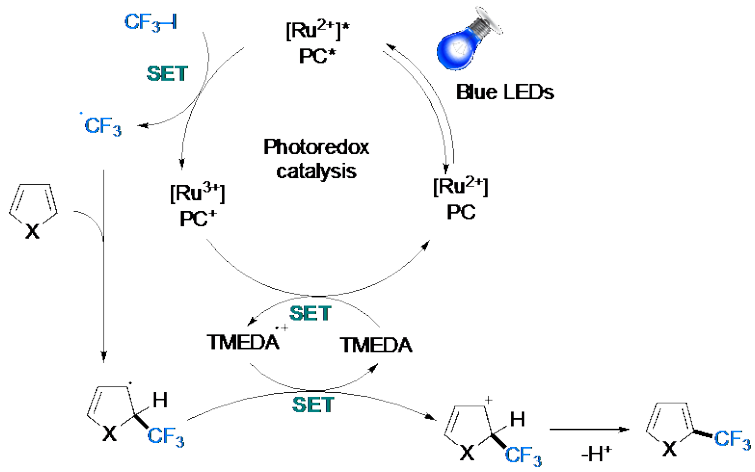
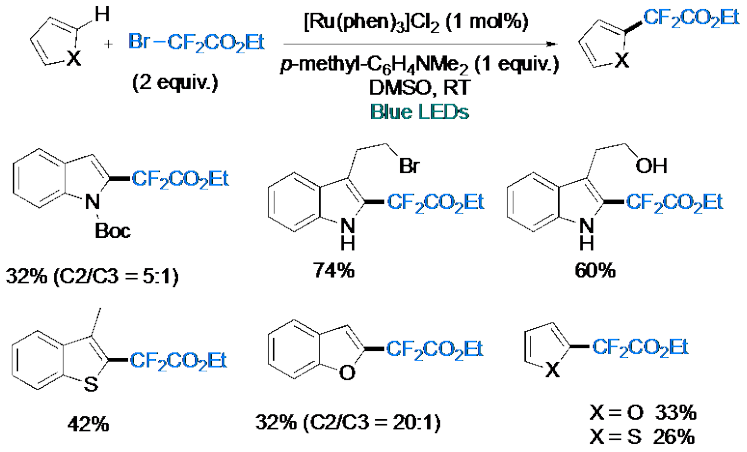


Figure 4. Proposed mechanism for visible light mediated trifluoromethylation of heteroarenes with CF_3I

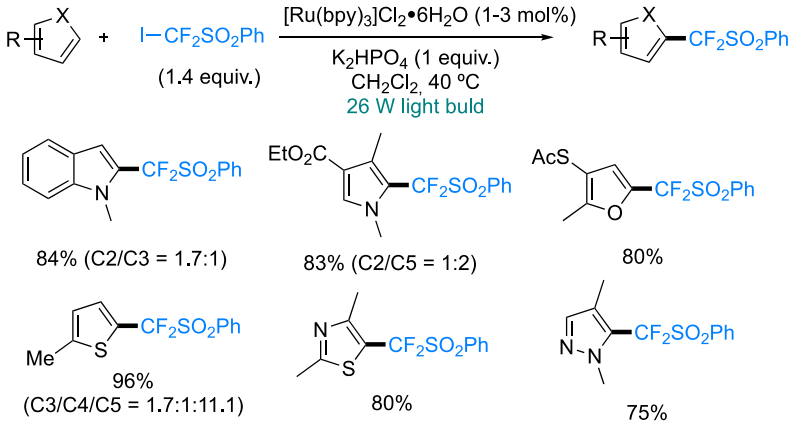
In 2013, Qing and co-workers succeeded the ethoxycarbonyldifluoromethylation of C(sp^2)–H bond heteroarenes by generating $^{\bullet}CF_2CO_2Et$ radical from ethyl difluorobromoacetate using visible-light photoredox system (Scheme 9).[50] In the presence of 1 mol% of $[Ru(phen)_3]Cl_2$ as photoredox catalyst and 4-*N*,*N*-trimethylaniline as sacrificial reductant, under blue LEDs irradiation, a set of 3-

substituted indoles are difluoromethylenated at C2 position in good to high yields. Indole led to mixture of C2 and C3 regioisomers in 5:1 ratio. Ethoxycarbonyldifluoromethylation of benzofuran give also mixture of C2 and C3 regioisomers. While *N*-methylpyrrole, furan and thiophene are regioselectively alkylated at the C2 position in moderate yields. The reaction tolerates reactive functional groups (e.g., alkyl and aromatic bromides, unprotected alcohols, carboxylic acids, amides, and nitriles). Oxidative quenching pathway enabled the generation of CF_2CO_2Et radical from ethyl difluorobromoacetate by SET has been proposed.



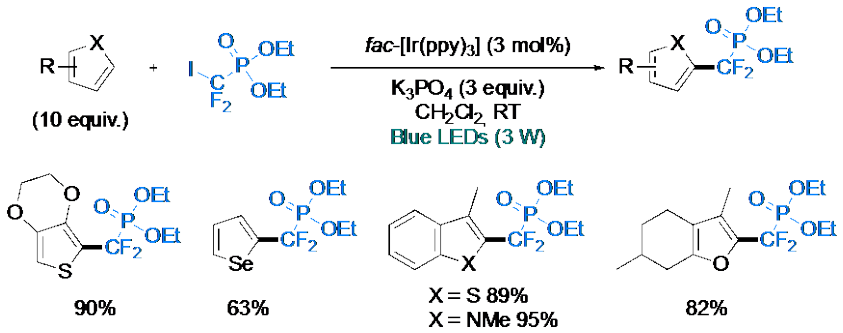
Scheme 9. $Ru(Phen)_3^{2+}$-catalyzed difluoromethylenation of heteroarenes with ethyl 2-bromo-2,2-difluoroacetate

In 2014, Wang and co-workers employed $PhSO_2CF_2I$ –a well-established difluoromethylation reagent developed by Prakash and Hu–[51] in visible-light photoredox-catalyzed difluoromethylation of electron-rich 5 atom ring N-, O-, and S-containing heteroarenes (Scheme 10).[52] Pyrroles, (benzo)furans, thiophenes and thiazoles are regioselectively difluoromethylated at α-position using 1-3 mol% of $[Ru(bpy)_3]Cl_2$ associated with K_2HPO_4 as a base in CH_2Cl_2 under visible light. Pyrazole reacts at the C5 position. Again, indole gives a mixture of C2 and C3 regioisomers, unless the C3 position is substituted.



Scheme 10. $Ru(bpy)_3^{2+}$-catalyzed difluoromethylation of heteroarenes with ((difluoroiodomethyl)sulfonyl)benzene

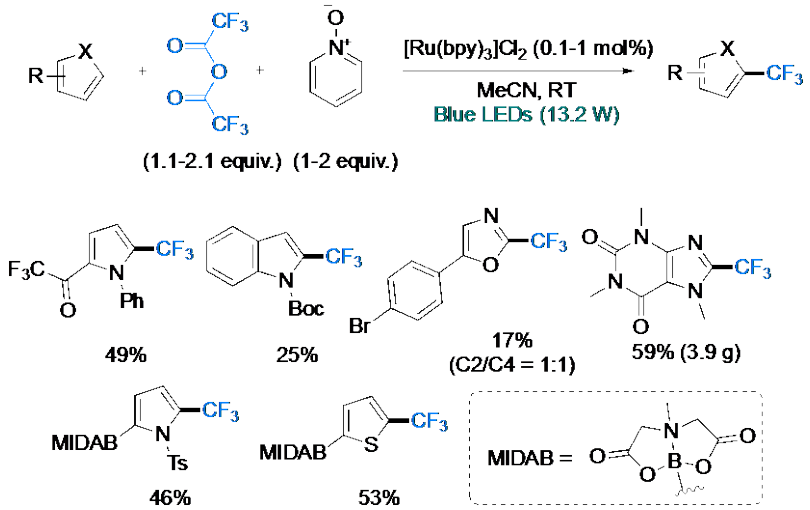
In 2014, Liu and co-workers employed commercially available diethyl bromodifluoromethyl phosphonate as difluoromethyl radical precursor using *fac*-[Ir(ppy)$_3$] as a photosensitizer and blue LEDs as a light source (Scheme 11).[53] A set of 5-atom heterocycles (e.g., thiophenes, selenophene, (benzo)furan, benzothiophene, indoles, …) are functionalized at the α-position in good yields.



Scheme 11. *fac*-[Ir(ppy)$_3$]-promoted difluoromethylenephosphonation of heteroarenes with bromodifluoromethylphosphonate

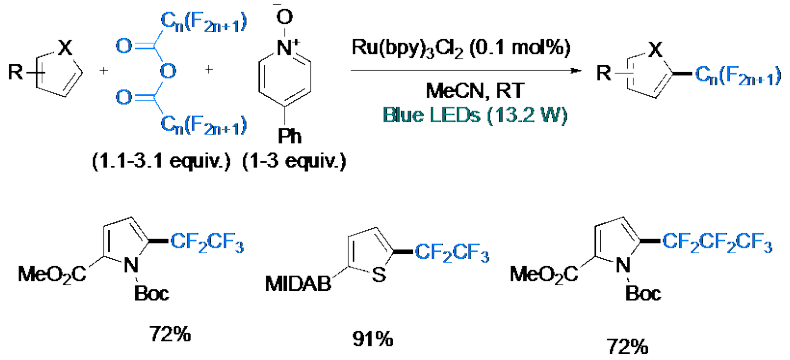
In 2015, Stephenson and co-workers succeeded to generate $CF_3^{\bullet}$ radical from cheap and abundant trifluoroacetic anhydride using visible-light photoredox catalysis in the presence of pyridine *N*-oxide allowing the trifluoromethylation of 5-atom ring heteroarenes (Scheme 12).[54] A set of heteroarenes such as pyrroles, indoles, isoxazoles, caffeine, and thiophenes were trifluoromethylated at α-position using 01-1 mol% $[Ru(bpy)_3]Cl_2$ as photosensitizer. Interestingly, the protected boronic MIDAB (*N*-methyliminodiacetic acid) functionality is tolerated by these radical conditions, allowing further cross-coupling reactions. The reaction

can be also conducted in large scale using both flow system (20 g) and batch (100 g).



Scheme 12. $Ru(bpy)_3^{2+}$-catalyzed trifluoromethylation of heteroarenes with trifluoroacetic acid anhydride associated to pyridine *N*-oxide

Later, they discovered that the use of 4-phenyl pyridine *N*-oxide instead of pyridine *N*-oxide led to better results, and they extended the reaction to $C(sp^2)$–H bond pentafluoroethylation and heptafluoropropylation of heteroarenes with pentafluoropropionic anhydride or heptafluorobutyryl acid anhydride (Scheme 13).[55]



Scheme 13. $Ru(bpy)_3^{2+}$-catalyzed perfluoroalkylation of heteroarenes with anhydride associated to 4-phenylpyridine *N*-oxide

The detailed mechanism is depicted in Figure 5.[55] In the presence of trifluoroacetic anhydride, 4-phenylpyridine *N*-oxide is acylated. This acylated spe-

cies (**A**) can readily quench the photoexcited catalyst $*Ru^{2+}$, and the reduced reagent (**B**) proceeds to fragment to a carboxyl radical along with 4-phenylpyridine (PhPy). The carboxyl radical readily extrudes CO_2 to form the $CF_3^{\bullet}$ radical and its addition to the electron-rich π-system results in selective formation of the product after re-aromatization.

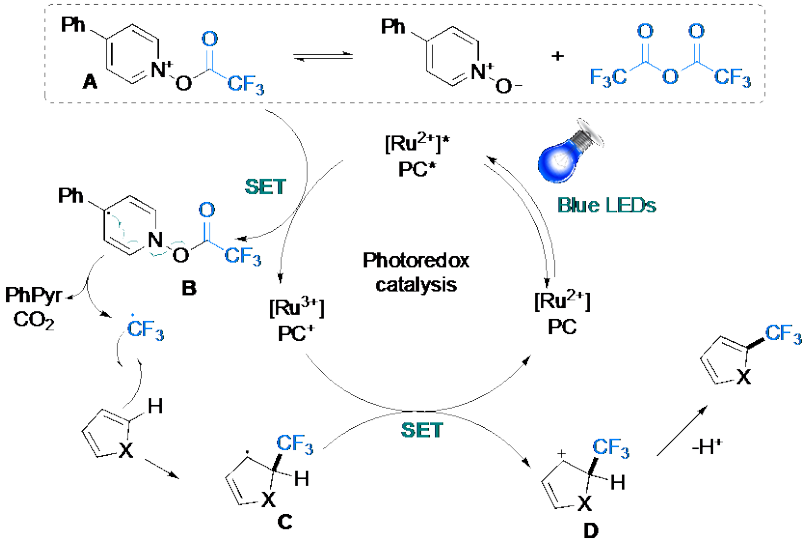


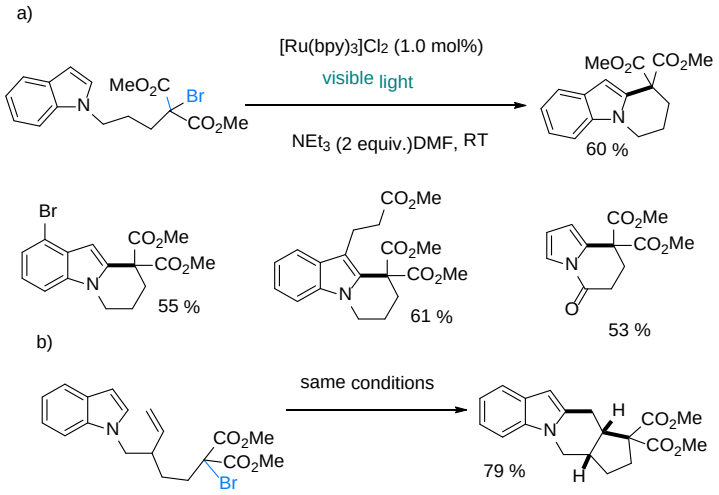
Figure 5. Proposed mechanism for perfluoroalkylation of heteroarenes with anhydride associated to 4-phenylpyridine *N*-oxide

2.3. Photoredox-assisted alkylation of 5-atom heteroarene C(sp^2)–H bonds

The photoredox assisted alkylation of heterocycle C(sp^2)–H bonds, to form new cross-coupled C(sp^2)–C bonds, was first initiated by the single electron transfer (SET) from the excited photoredox system under visible light to a derivative with C(sp^3)-Br bond which then generates a radical. Usually with heteroarenes this radical adds regioselectively to an unsaturated double bond and a C-C bond is formed. After oxidation and deprotonation, a heteroarene with new C(sp^2)–C(sp^3) bond is obtained.

Stephenson *et al.* reported in 2010 the utilization of the photoredox catalyst tris(2,2′-bipyridyl)ruthenium dichloride $[Ru(bpy)_3]^{2+}(Cl^-)_2$, under visible light for the intramolecular regioselective alkylation of indoles and pyrroles containing a N-alkyl chain bearing a terminal C(sp^3)–Br bond. The excited photoredox system, under visible light from a household light bulb, is then reduced in the presence of amine NEt_3 and then allows the single electron transfer (SET) to the C(sp^3)–Br group which generates a reactive radical. This radical adds at the heterocycle C2 with formation of a new 6-atom ring at room temperature. (Scheme 14a).[56]

The same photoredox system in the presence of amine has been used by Stephenson to promote cascade radical cyclizations with successive formation of two C-C bonds to produce polycyclic heterocycle at room temperature (Scheme 14b).[56]



Scheme 14. Intramolecular alkylation of indoles and pyrroles at C2 promoted by $[Ru(bpy)_3]^{2+}$photoredox and amine.

The reaction mechanism is presented on Figure 6.[56] It involves the excitation of the photoredox complex by visible light and the excited species $[*Ru(bpy)_3]^{2+}$ is reduced by triethylamine by one SET to produce the Ru(I) intermediate $[Ru(bpy)_3]^{+}$species. The Ru(I) complex is able to transfer one electron to the sp^3C–Br group which generates $[Ru(bpy)_3]^{2+}$ and an electrophilic radical **A**. The later adds regioselectively to the C2 carbon and the resulting radical **B** can be oxidized into cation **C** by $[Ru(bpy)_3]^{2+}$ or trialkylammonium radical cation. The cation **C** by loss of a proton leads to the functionalized indole **D** or pyrrole.

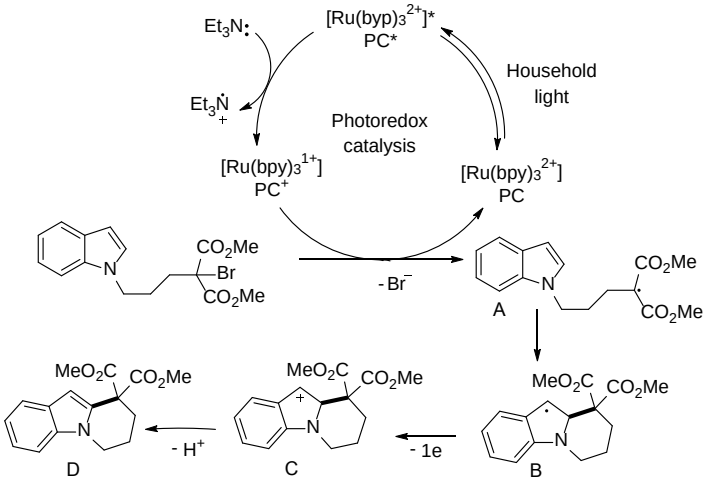
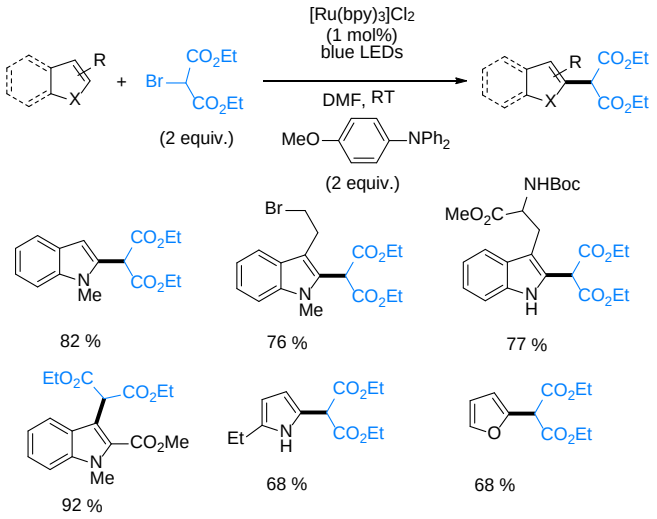


Figure 6. Stephenson's mechanism for intramolecular alkylation at C2 of 5-atom heterocycles C(sp^2)–Hbonds

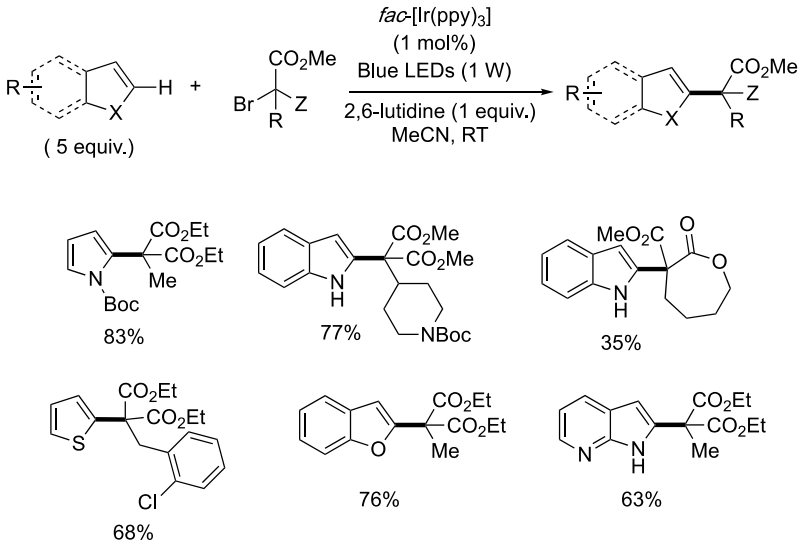
The same year the Stephenson group has shown that similar conditions could be applied to the intermolecular alkylation of 5-atom heterocycles, with the help of the photoredox system $[Ru(bpy)_3]Cl_2$ under blue LEDs (λ_{max} = 435 nm) irradiation. The reaction is performed with bromomalonates and indoles, with 2 equiv. of amine : NEt_3 or better *p*-$MeOC_6H_4NPh_2$, in DMF at room temperature. It leads to the regioselective alkylation at C2 carbon of indoles, or at C3 when C2 carbon is substituted (Scheme 15).[57] The reaction tolerates C(sp^2)–Br or even primary C(sp^3)–Br bonds.

The mechanism of this reaction is analogous to that described in Figure 6. The $Ru(bpy)^{1+}$ intermediate, arising from the visible light excitation of $Ru(bpy)_3^{2+}$ and one electron reduction by the amine, transfers 1 electron to bromomalonate to produce the $(MeO_2C)_2CH^{\bullet}$ radical which adds to the heterocycle C2 carbon bearing a C–H bond.



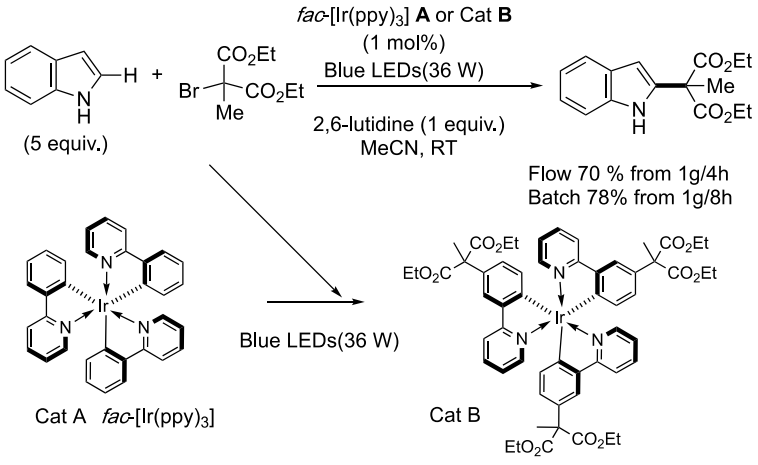
Scheme 15. Photoredox $[Ru(bpy)_3]^{2+}$ and amine for the intermolecular alkylation C2–H and C3-H bonds of 5-atom heterocycles.

Later in 2016, Stephenson used the photoredox *fac*-[$Ir(ppy)_3$] complex in the presence of 1 equivalent of 2,6-lutidine which promotes the regioselective functionalization with electron-deficient radicals, generated from functional bromomalonate derivatives, of C2–H bond of heteroarenes (Scheme 16).[58] Whereas the weakly reducing photo-excited $[*Ru(bpy)_3]^{2+}$ was almost inefficient for this reaction, the success was reached by the use of the strongly reducing complex when excited by visible light *fac*-[$*Ir(ppy)_3$], [$E_{1/2}{}^{IV/III}* = - 1.73$ V *vs* SCE]. This (heterocycle) C(2)–C(sp^3) bond formation of pyrroles, thiophenes, indoles and benzofurans tolerates chloro, allyl, *N*Boc and lactone groups.



Scheme 16. Photoredox *fac*-[Ir(ppy)$_3$]-promoted C2-H coupling of N, O, and S-heterocycles with bromomalonates

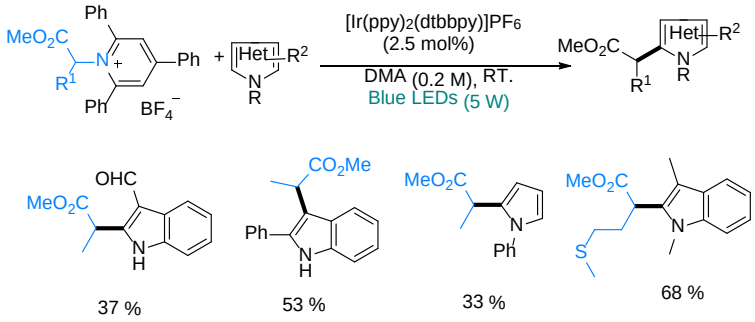
This reaction was carried out in a flow process with the photoredox *fac*-[Ir(ppy)$_3$] **A**, with a 36W blue LEDs. This reaction with **A** allows the transformation of 1 g of material in 4 hours at room temperature with 70% yield (Scheme 17).[58] Under the same conditions a batch reaction with 1g led after 8 h to 78 % yield. The recovered photoredox shows that the regioselective tris alkylation of *fac*-[Ir(ppy)$_3$] **A** by the bromomalonate took place at the *para*-position of the three Ir-C bonds to produce the photoredox catalyst **B** which is as efficient as its parent *fac*-[Ir(ppy)$_3$] **A** (Scheme 17).[58]



Scheme 17. Flow process promoted by *fac*-[Ir(ppy)$_3$] and modified photoredox system

Its is noteworthy that Barriault *et al.* showed that unactivated *primary*, *secondary*, and *tertiary* bromoalkanes could generate nucleophilic radicals for the regioselective C2 alkylation of heteroarenes with the help of gold photoredox system [Au$_2$(bis(diphenylphosphino)methane)$_2$]Cl$_2$ [Au$_2$(dppm)$_2$]Cl$_2$ irradiated with UVA LEDs (365 nm).[59] This efficient system does not operate via MLCT as the Ru, Ir-based photoredox catalysts.

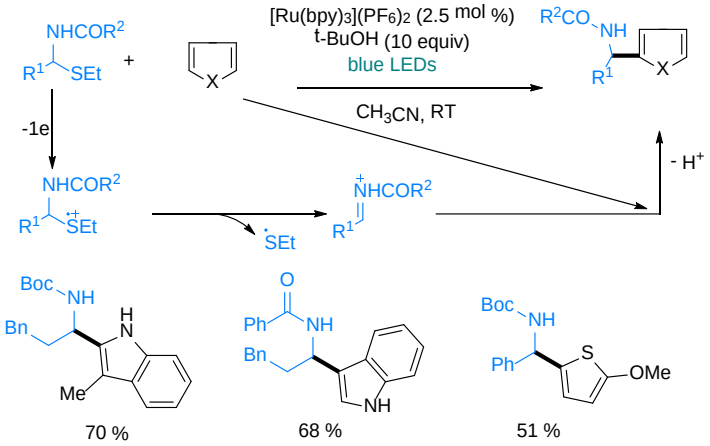
Glorius has shown in 2017 that alkylation of heteroarenes could be performed from a Katritzky salt, arising from the reaction of primary amine or aminoacid with a pyrylium salt, in the presence of the photoredox complex [Ir(ppy)$_2$(dtbbpy)]PF$_6$ under visible light irradiation (Scheme 18).[60] Thus the radical formally results from deamination of the initial amine and aminoacid. The regioselective alkylation of indoles and pyrroles has been performed successfully, from aminoacid derived radicals, at room temperature in DMA. A single electron is transferred to the Katritzky salt from the light excited [*Ir(ppy)$_2$(dtbbpy)]$^+$, the formed radical releases the deaminated radical which adds to the heteroarene at C2 position. The 2-alkylated heteroarene is generated by oxidation and deprotonation of the heterocyclic radical.



Scheme 18. Examples of alkylation of *N*-heteroarenes with radical from amino-acids *via* their Katritzky salts

Masson *et al.* in 2016 have shown that the photoredox [Ru(bpy)$_3$](PF$_6$)$_2$ under visible light irradiation could promote the capture of one electron from an α-Amidosulfide, with help of oxygen, to generate beside the RS• radical an *N*-acyliminium cation. The latter is then able to perform regioselective aza-Friedel-Crafts reaction with electron-rich heterocycles, thus their alkylation, such as indoles and thiophene (Scheme 19).[61] The reaction is performed with 10 equiv. of *t*-BuOH at room temperature as in the presence of *t*-BuOH there is decreasing of α-aminosulfide oxidation potential. Organic photoredox such as Eosin Y can perform the same alkylation of heterocycles with *N*-acyliminium cations. As the light excited species [*Ru(bpy)$_3$]$^{2+}$ cannot directly oxidize the α-amidosulfide, it is pro-

posed that $[*Ru(bpy)_3]^{2+}$ transfer one lectron to oxygen to give the radical anion O_2-• and the $Ru(bpy)_3^{3+}$ species which then captures one electron from RCH(NHZ)SEt to produce the EtS· radical and the *N*-acyliminium cation able to add to electron rich heteroarenes (Scheme 19).[61]

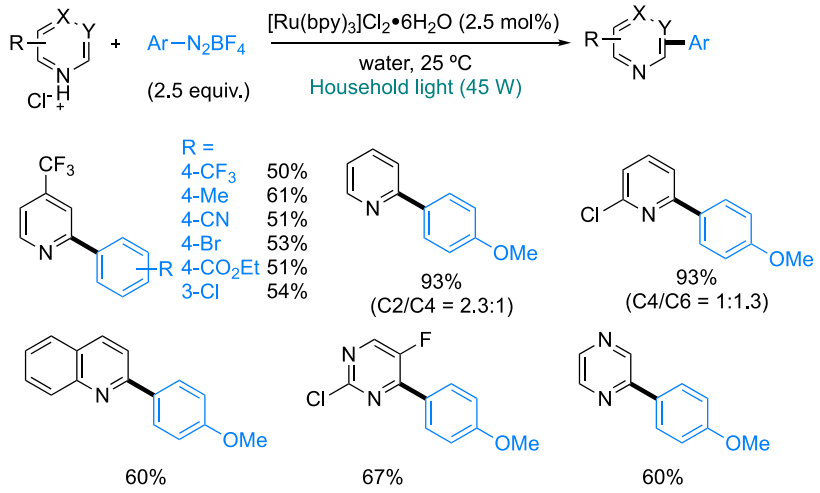


Scheme 19. Aza-Friedel-Crafts reaction of heterocycles with *N*-acyliminium cation generated from α-amidosulfides and photoredox

3. Functionalizations of 6-atom ring heteroarenes

3.1. Photoredox-assisted arylation of 6-atom heteroarene C(sp^2)–H bonds

In 2014, Xue and co-workers have employed aryldiazonium salts as aryl radical precurssors in photoredox-catalyzed C–H bond arylation of pyridine, quinolines and pyrazine derivatives (Scheme 20).[62] The reaction was carried out in water using $[Ru(bpy)_3]Cl_2 \cdot 6H_2O$ as a photosensitizer and household light. The arylation took place at C2 position when C4-substituted pyridines are employed, while unsubstituted, C2- or C3- substituted pyridines led to mixtures of regioisomers. The authors showed that using aqueous formic acid as solvent, pyrazine and pyridazine could be also arylated.



Scheme 20. $Ru(bpy)_3^{2+}$-catalyzed arylation of *N*-heteroarenes with aryldiazonium salts

Inspired by Deronzier for the intramolecular C–H bond arylation with diazonium stilbenes, [31,63] the authors suggested an oxidative quenching cycle as mechanism key step (Figure 7). They proposed two possible pathways for the last step of resulting radical oxidation into carbocation intermediate: *i)* a common oxidation by the strongly oxidizing $[Ru(bpy)_3]^{3+}$ or *ii)* an oxidation by the aryldiazonium salt leading to an autocatalytic reaction.

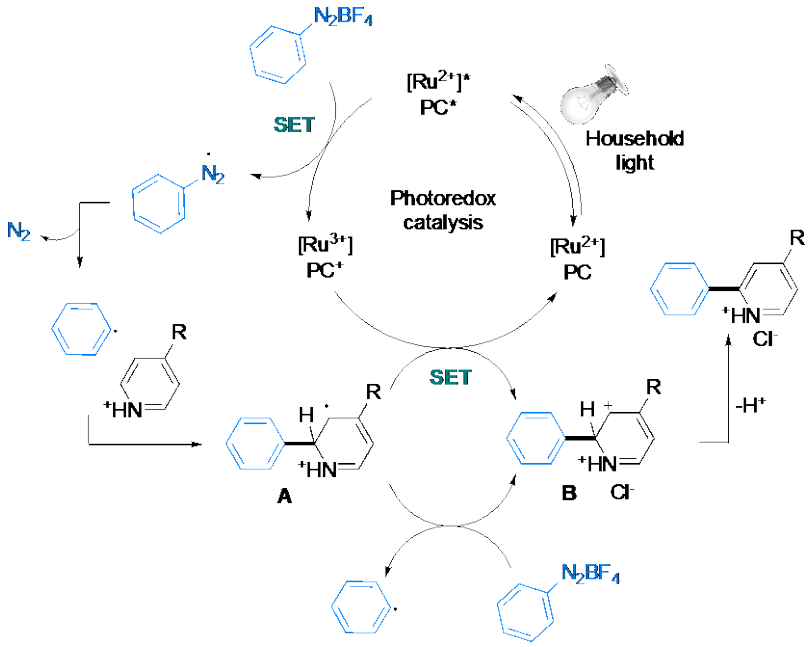
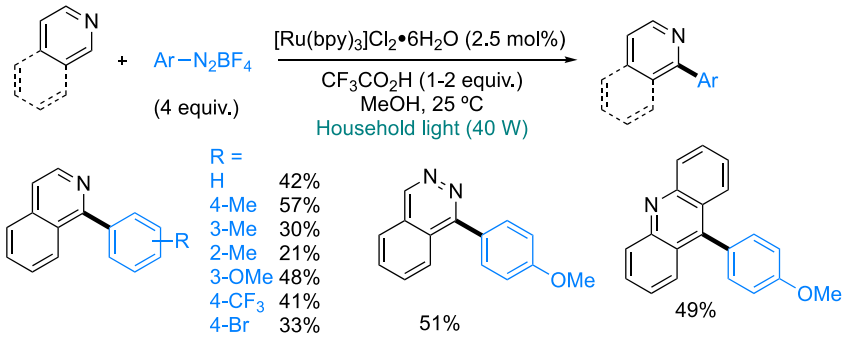


Figure 7. Proposed mechanism for arylation of *N*-heteroarenes with aryldiazonium salts

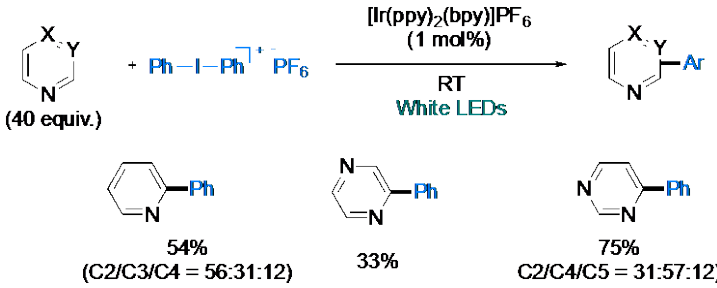
Meanwhile, Lei and co-workers achieved the regioselective C2-arylation of isoquinolines (Scheme 21).[64] Trifluoroacetic acid was used to *in-situ* generate the isoquinolinium salts.



Scheme 21. $Ru(bpy)_3^{2+}$-catalyzed isoquinoline with aryldiazonium salts

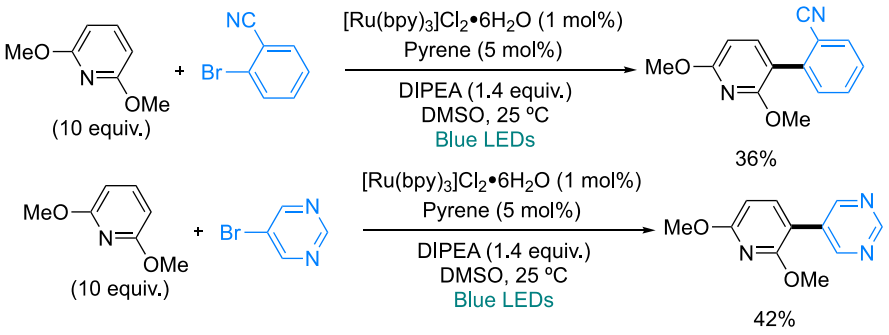
The conditions described by Tobisu, Chatani and co-workers for the C–H arylation of 5-atom ring heteroarenes with diaryliodonium salts and $[Ir(ppy)_2(bpy)]PF_6$ as photoredox catalyst (Scheme 2), were also operative for the phenylation of pyr-

idines, pyrazine derivatives, albeit low yields and poor regioselectivity were observed (Scheme 22).[34]



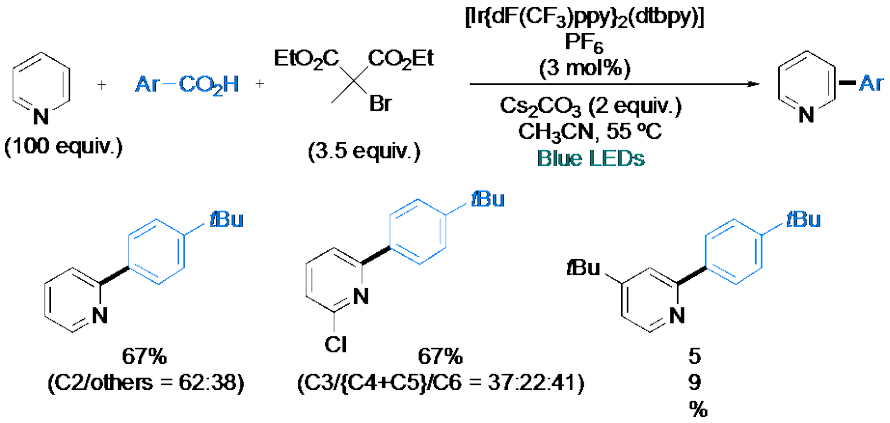
Scheme 22. $[Ir(ppy)_2(bpy)]PF_6$- catalyzed the phenylation of pyridine and pyrazine derivatives with diaryliodonium salts

König and co-workers applied their catalytic system based on pyrene sensitization-initiated electron transfer using $[Ru(bpy)_3]^{2+}$ to the arylation of 2,6-dimethoxypyridine with 2-bromobenzonitrile or 5-bromopyrimidine (Scheme 23).[36]



Scheme 23. $Ru(bpy)_3^{2+}$-catalyzed arylation of 2,6-dimethoxypyridine with aryl bromides

In 2017, Glorius and coworkers reported the $C(sp^2)$–H bond arylation of pyridines using carboxylic acids are suitable source of radicals *via* a visible light-mediated decarboxylation (Scheme 24).[65] The key step was the formation of benzoyl hypobromite, which is *in situ* prepared by reaction of carboxylic acid and diethyl 2-bromo-2-methylmalonate. In the presence of photoredox system, namely 3 mol% $[Ir\{dF(CF_3)ppy\}_2(dtbbpy)](PF_6)_2$ under blue LEDs irradiation, such benzoyl hypobromite easily decomposes into aryl radical which could be trapped by heteroarenes such as pyridines derivatives. The reaction was not regioselective and mixtures of regioisomers were obtained, except from 4-tertbutylpyridines. Although a huge amount of pyridine derivatives (100 equiv.) is required.



Scheme 24. [Ir{dF(CF_3)ppy}$_2$(dtbbpy)](PF_6)$_2$-catalyzed arylation of pyridinewith aryl carboxylic acids

The authors proposed a reductive quenching of PC (*Ir(III)/Ir(II)) by the benzoate anion providing aroyloxy radical (Figure 8). The authors denied the direct decarboxylation of carboxylic acid, which required high temperature. Therefore, they proposed pathway involving bromination of radical anion of carboxylic acid generated by SET of *PC to carboxylic acid to form the benzoylhypobromite **A**. The resulting hypobromite can be reduced by the Ir(II) ($E_{1/2}^{III/II}$ = -1.37 V vs SCE) leading to intermediate **B** and its decarboxylation to afford the key aryl radical ($Ar^{\bullet}$). Finally, the aryl radical is trapped by (hetero)arene to generate the cyclohexadienyl radical **C**, which, following oxidation to the aryl cation and deprotonation, affords the cross aryl-heteroaryl product.

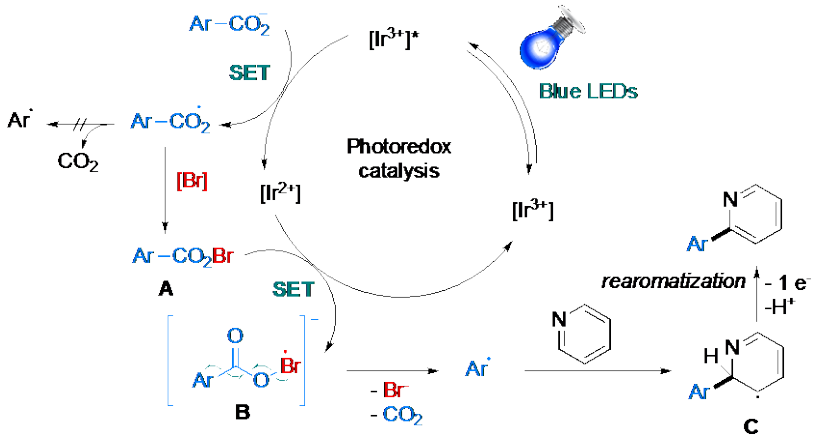
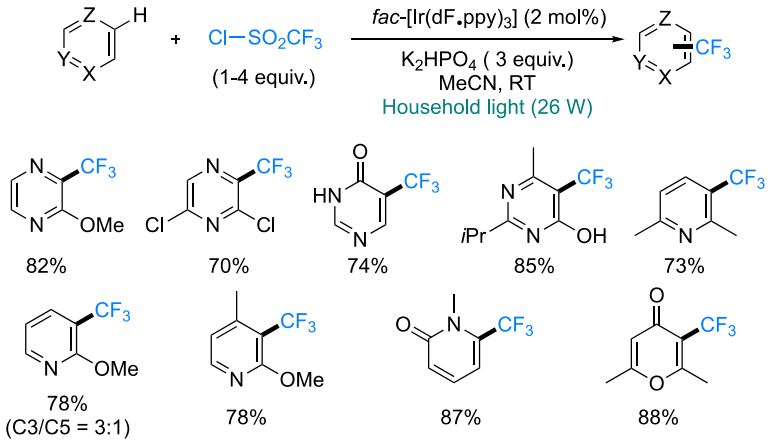


Figure 8. Proposed mechanism for arylation with carboxylic acids

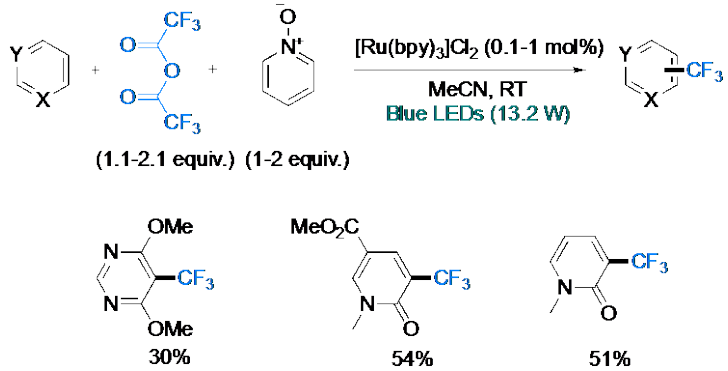
3.2. Photoredox-assisted perfluoroalkylation of 6-atom heteroarene C(sp^2)–H bonds

The trifluoromethylation of pyridines, pyrazines, pyrimidines, and pyrones using trifluoromethanesulfonyl chloride was accomplished by MacMillan and coworkers using *fac*-[Ir(dF.ppy)$_3$] as photoredox catalyst (Scheme 25).[44] The regioselectivity is substrate dependent and when multi-sites are available, a mixture of regioisomers is often obtained.



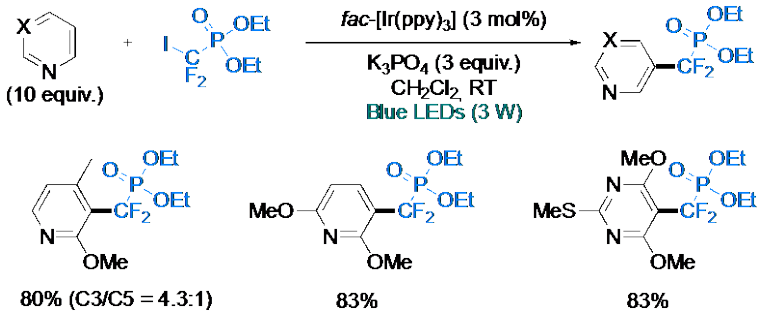
Scheme 25. *fac*-[Ir(dF.ppy)$_3$]-catalyzed trifluoromethylation of 6-atom heterocycles using trifluoromethanesulfonyl chloride

The generation of $CF_3^{\bullet}$ radical from trifluoroacetic anhydride and pyridine *N*-oxide under photoredox catalysis (Scheme 12) was also applied to the trifluoromethylation of 6-atom heterocycles (Scheme 26).[54] Pyrimidine where C2 and C5 position were blocked by methoxy substituent was successfully trifluoromethylated at C3 position. *N*-methyl pyridinones were also functionalized at the C3 position.



Scheme 26. $Ru(bpy)_3^{2+}$-catalyzed trifluoromethylation of 6-atom heterocycles with trifluoroacetic acid anhydride associated to pyridine *N*-oxide

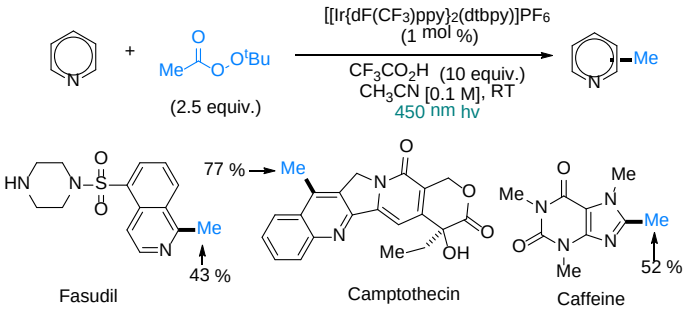
In 2014, during their investigations on C(sp^2)–H bond difluoromethylation of heteroarenes from diethyl bromodifluoromethyl phosphonate as radical source (Scheme 11), Liu and co-workers showed that the reaction can be also applicable to pyridines and pyridimidine (Scheme 27).[53] From 2-methoxy-4-methylpyridine a mixture of C3 and C5 trifluoromethylated was obtained, while from 2,6-dimethoxypyridine only C3-trifluoromethylate pyridine was obtained.



Scheme 27. *fac*-$[Ir(ppy)_3]$-catalyzed fifluoromethylenephosphonation of 6-atom heterocycles with bromodifluoromethylphosphonate

3.3. Photoredox-assisted alkylation of 6-atom heteroarene C(sp^2)–H bonds

DiRocco *et al.* have found in 2014 the way to formally alkylate with small methyl or ethyl groups the C-H bond of *N*-heterocycles. They used $[Ir\{dF(CF_3)ppy\}_2(dtbbpy)]PF_6$ as photoredox and *tert*-butylperacetate (*t*BPA) or *tert*-amylperacetate to generate methyl or ethyl radical respectively. These small radicals are useful to modify biologically active molecules with small alkyl groups. Thus Fasudil, Camphothecin or caffeine have been methylated that way (Scheme 28).[66]



Scheme 28. Methylation of *N*-heterocycles with *tert*-butylperacetate

The *t*-BuO• radical is known to produce the methyl radical and acetone. Thus on visible light the excited {*Ir(III)} species (E° = -0.89 V *vs* SCE) can transfer one electron to the protonated *t*BPA, *via* proton-coupled electron transfer (PCET) which thus provides, beside an Ir(IV) species, the *t*-BuO• radical and then methyl radical. (Figure 9).[66] The methyl radical adds to the protonated N-heterocycle regioselectively at C2. After deprotonation of the resulting cation one electron is captured by the Ir(IV) system to regenate the Ir(III) photoredox PC and the methylated heteroarene.

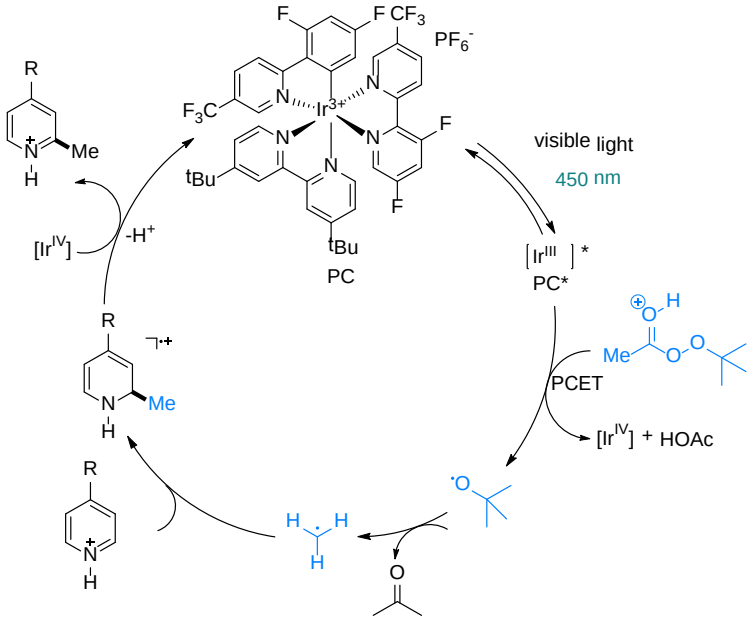
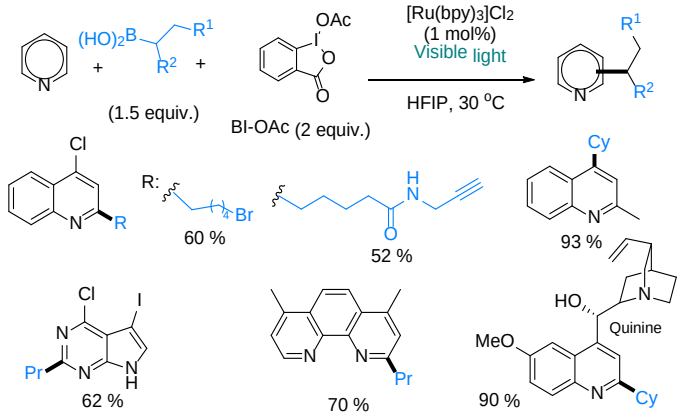


Figure 9. Catalytic cycle for the photocatalyzed methylation of N-heterocycles

Peng Liu and Gong Chen have discovered an intermolecular alkylation of 6-atom *N*-heteroarenes with alkylboronic acids with 2 equivalents of acetoxybenziodoxole (BI-OAc). The reaction is mediated by the photoredox system $[Ru(bpy)_3]Cl_2$ in hexafluoroisopropanol (HFIP) (Scheme 29).[67] Arylhalide, ester, carbamate, alkyne groups can be tolerated on the boronic alkyl group. The C2 alkylation of 4-chloroquinoline, pyridines, phenanthroline and quinine was selectively obtained, or at C4 when a substituent was present at C2 position.



Scheme 29. Alkylation of 6-atom *N*-heteroarenes using alkyl boronic acid and hypervalent iodine

The reaction can be explained as shown on (Figure 10).[67] The light excited $[*Ru(bpy)_3]^{2+}$ species transfers one electron (SET) to BI-OAc to generate acetate and a radical adding to the boronic acid to give intermediate **A**. The later gives the radical R° , beside species **B**, which adds to the protonated N-heterocycle at C2 to produce **C**, which releases the protonated alkylated heterocycle**.**

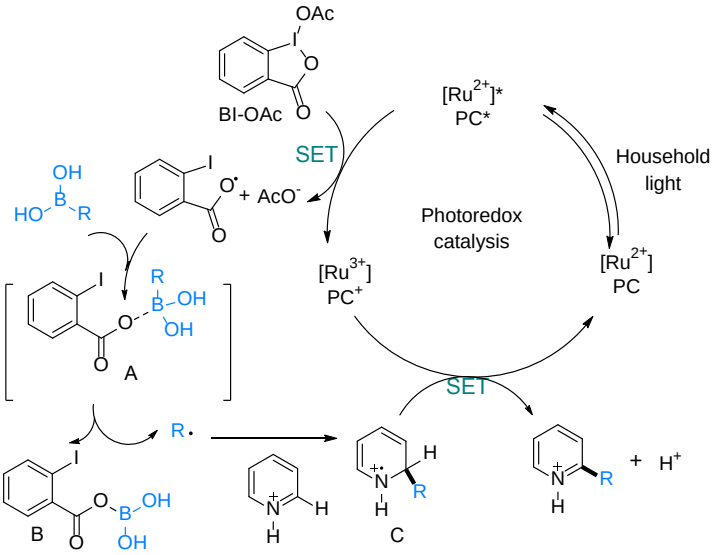
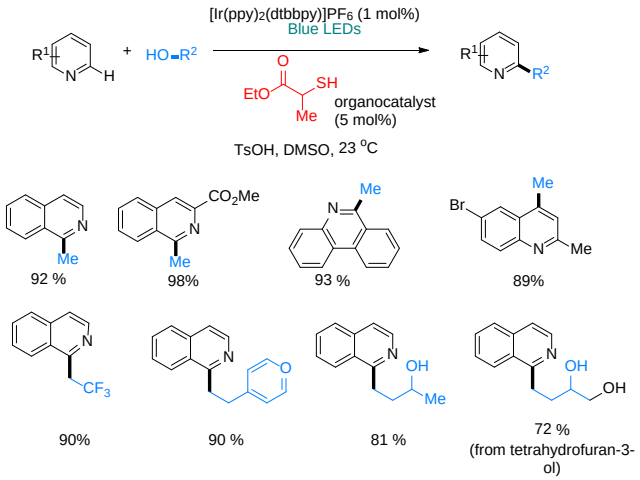


Figure 10. Mechanism for photocatalyzed C–H bond alkylation of heteroarenes

MacMillan in 2015 combined the action of a metal-containing Ir(III) photoredox $[Ir(ppy)_2(dtbbpy)]PF_6$ and of a thiol ester as organocatalyst to activate alco-

hols and generate a radical to directly alkylate C(sp^2)–H bonds of heteroarenes (Scheme 30).[68] This dual photoredox-organocatalysis method is expected to generate $HOCH_2^{\bullet}$ radical from methanol which adds to the protonated heterocycle at C2 position when it is non substituted. Thus, a variety of *N*-heterocycles have been methylated. Using a variety of primary alcohols R-CH_2OH the $RCH^{\bullet}$-OH radicals could be generated to alkylate heteroarenes. This reaction can be performed also with diols, primary ether and even tetrahydrofuran. The method was also applied to the alkylation of natural product derivatives such as Fasudil and Milrinone..



Scheme 30. Alkylation of heteroaromatic C–H bonds directly with primary alcohols via the dual photoredox and organocatalyst actions.

The mechanism is depicted on Figure 11 for the methylation of pyridine with methanol. On light excitation the photoredox {*Ir(III)} complex by SET to the heteroarene leads to a strong oxidant {Ir^{4+}} species which allows the oxidation of the deprotonated thiol organocatalyst to produce the thiyl radical **A•**. **A•** is able to capture a H atom of methanol to produce the radical $HOCH_2$• (**B**), which adds to the carbon C2 of the protonated pyridine. The generated hydroxymethyl-pyridine cation (**C**) is deprotonated and eliminates water via a spin-centre shift SCS process and generates the radical (**D**). **D** is deprotonated and reduced by SET from excited {Ir(III)} to give the methylated product **E** and the {Ir^{4+}} oxidant.

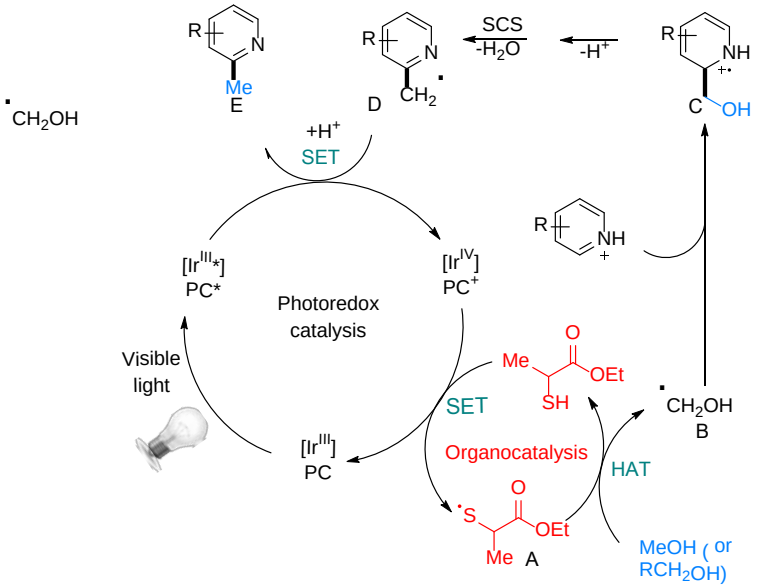
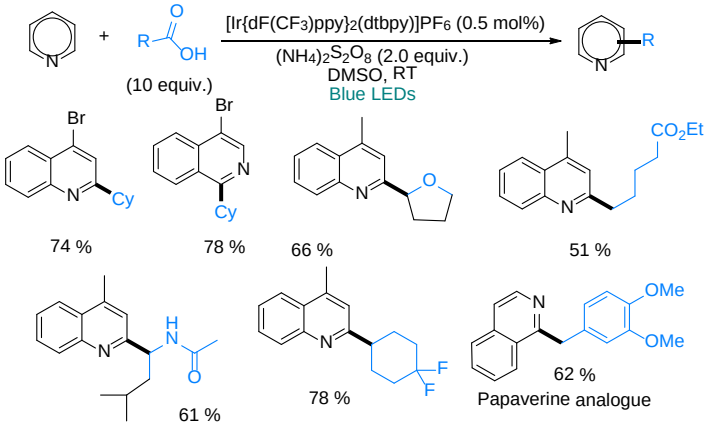


Figure 11. Proposed mechanism for the direct methylation of pyridine at C2–H bond

Glorius et al. in 2017 have found the way to generate radicals by decarboxylation of simple carboxylic acids RCO_2H, with the help of the photoredox system $[Ir\{dF(CF_3)ppy\}_2(dtbbpy)]PF_6$, and these radicals $R^{\bullet}$ add regioselectivity to 6-atom heterocycles, preferentially at C2 (Scheme 31).[69] This method which requires the presence of ammonium persulfate $(NH_4)_2S_2O_8$ offers the way to introduce a large variety of alkyl groups at C2 of heterocycles such as benzoimidazole and benzothiazole, isoquinoline and quinoxaline or fasudil derivatives. A large variety of primary, secondary, tertiary alkyl groups of carboxylic acids can be used but a large amount (10 equivalents) of carboxylic acid leads to reach high yields. Importantly aminoacid derivatives allow the introduction of a functional alkyl group containing an amino goup.



Scheme 31. Alkylation of *N*-heteroarenes with radical generated from carboxylic acids

The authors proposed the mechanism depicted with cyclohexylcarboxylic acid in Figure 12. Proposed catalytic cycle for alkylation of *N*-heteroarenes with carboxylic acid and $S_2O_8^{2-}$.[69] LED irradiation (λ max = 455 nm) produces a long-lived excited state {*Ir(III)} species ($E_{1/2}$ IV/*III = −0.88 V vs SCE in CH_3CN/H_2O), which can transfer one electron to $(NH_4)_2S_2O_8$ to give SO_4^{2-} and $SO_4^{\bullet}$ anions, beside the {Ir^{4+}}complex. The radical anion $SO_4^{\bullet}$ captures the hydrogen atom from any acid RCO_2H, then the radical $RCO_2^{\bullet}$ affords the radial R• (**A**) on decarboxylation. The R• radical adds to the *N*- heteroarenes at C2 position. The resulting radical (**B**) allows the reduction of the {Ir^{4+}} species to regenerate the photoredox system {Ir(III)} and leads the 2-alkylated heteroarene **C**.

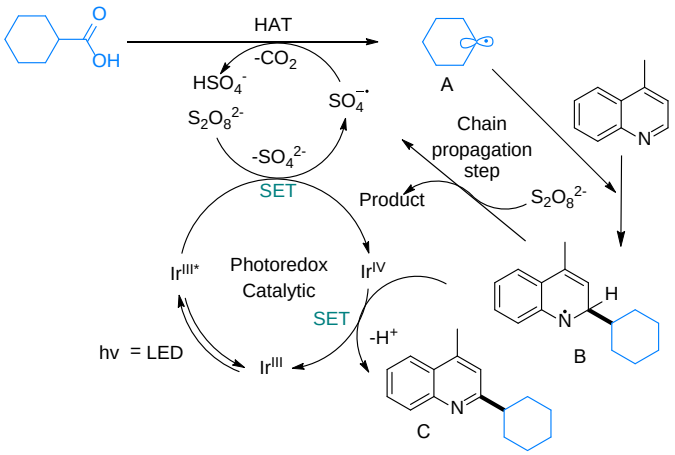
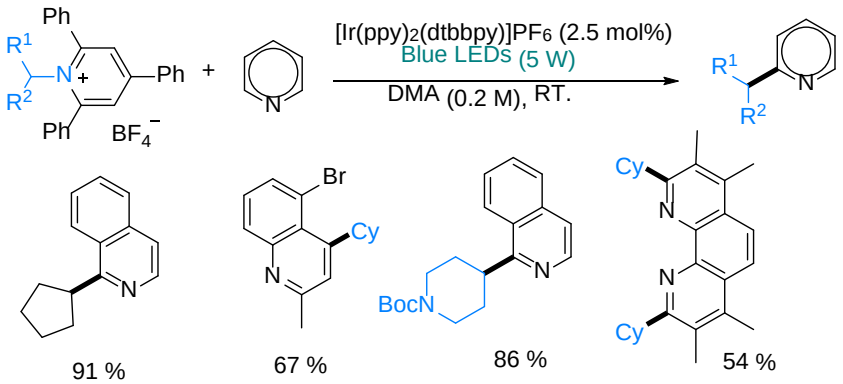


Figure 12. Proposed catalytic cycle for alkylation of *N*-heteroarenes with carboxylic acid and $S_2O_8^{2-}$.

The 2017 Glorius's method for alkylation of 5-atom heterocycles using a Katritzky salt, simply made form primary amine and pyrylium salt (see Scheme 18) was also applicable to 6-atom heterocycles and took place selectively at non substituted C2. The radical generation from amine salt is promoted by the photoredox system [Ir(ppy)$_2$(dtbbpy)]PF$_6$ under visible light irradiation (λ max 455 nm) (Scheme 32). [60] The reaction is efficient with a variety of alkyl groups and it tolerates halides on the aromatic ring. The generation of the radical is initiated by SET from the excited species {*Ir(III)} to the Katritzky salt. Isoquinoline, quinoline or phenanthroline have been selectively alkylated in good yields.[60]

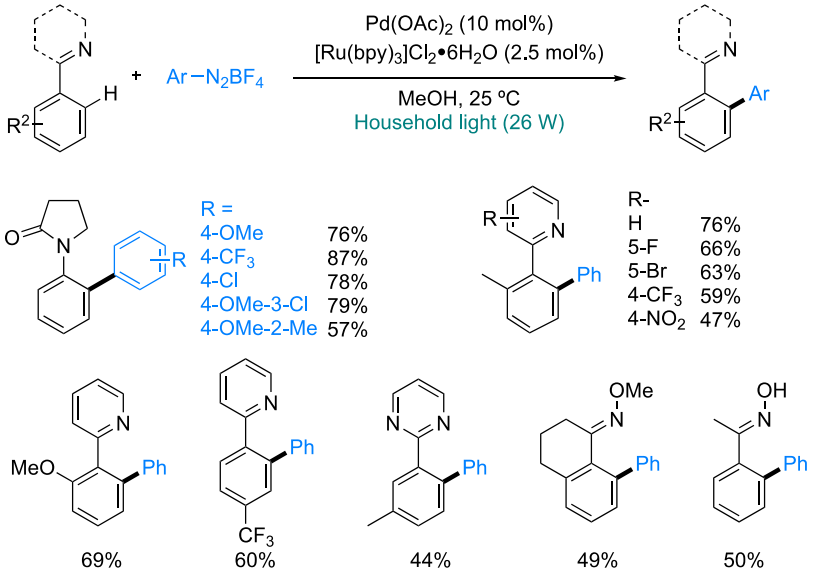


Scheme 32. Alkylation of 6-atom *N*-heteroarenes with radical from primary amines related Katritzky salts

4. Functionalizations of arenes

4.1. Photoredox-assisted arylation of arene C(sp^2)–H bonds

Based on the pioneer Deronzier's works on the photoredox C(sp^2)–H bond cyclization of diazonium stilbenes using Ru(bpy)$_3^{2+}$,[31,63] Sanford and co-workers developed a dual catalysis composed by palladium and photoredox catalysis for the *ortho*-directed C(sp^2)–H bond arylation of 2-arylpyridine derivatives with aryl diazonium (Scheme 33).[70] The major advantage is that the reaction occurred at room temperature, while palladium-catalyzed direct arylation using aryl halides required 150 ºC. A broad range of substituted aryl diazonium salts were efficiently coupled with *N*-phenylpyrrolidone. Moreover, 2-phenylpyridines bearing halogen, trifluoromethyl, methoxy or nitro group on the pyridine unit could be employed. Other directing groups such as amides, pyrazoles, pyrimidines, and oxime ethers also reacted under these reaction conditions.



Scheme 33. Merging Pd-catalyzed C–H functionalization and visible-light photocatalysis

The authors proposed two separate catalytic cycles including photoredox catalytic cycle and palladium catalytic cycle (Figure 13).[70] The photoreduction of the aryldiazonium salt gives aryl radical species (**A**), concomitantly affording oxidated-state photosensitizer (Ru^{3+}). Pd(II)-mediated directed C–H activation gives palladacycle, which could be oxidated by an aryl radical to give Pd(III) intermediate (**B**). Single electron oxidation of this Pd(III) by Ru^{3+} affords Pd(IV) intermediate (**C**) and regenerates the (Ru^{2+}). Finally, reductive elimination of Pd(IV) intermediate (**C**) produces the desired C–H bond arylated product and regenerates Pd(II) catalyst.

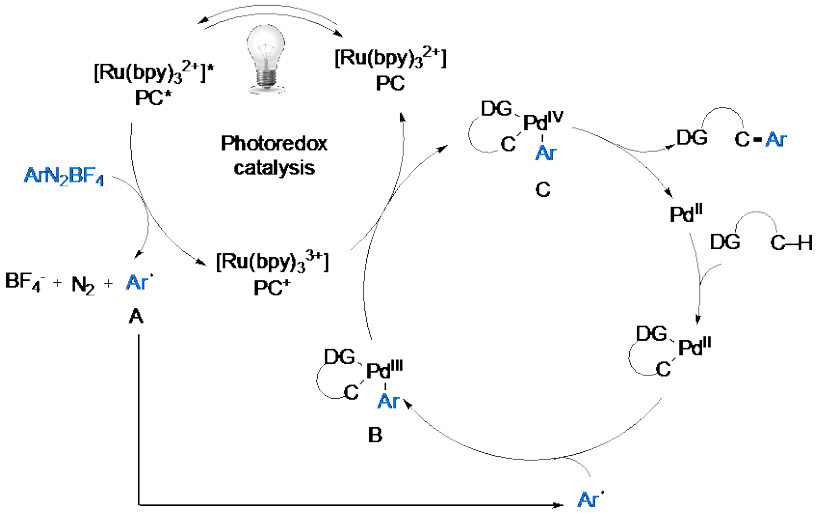
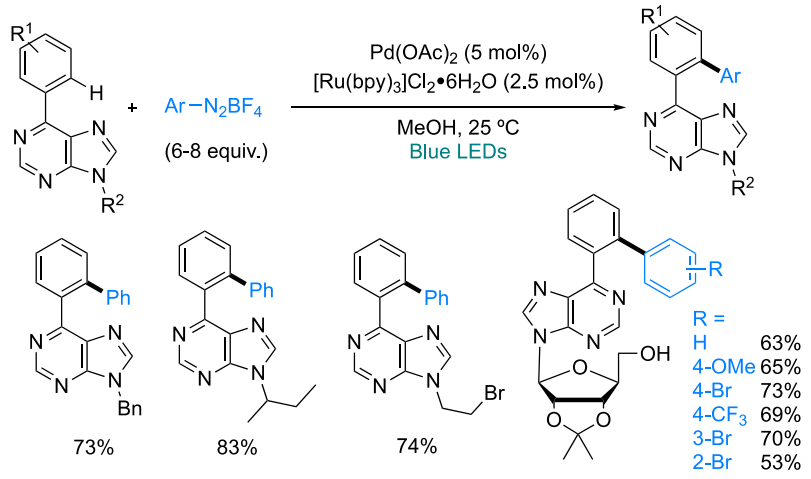


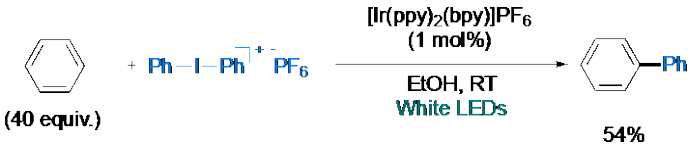
Figure 13. Proposed catalytic cycle of C–H bond arylation *via* dual catalysis

Later, Guo and co-workers extended this protocol to the *ortho*-arylation of purine nucleosides, in which the purine unit plays the role of directing group (Scheme 34).[71]



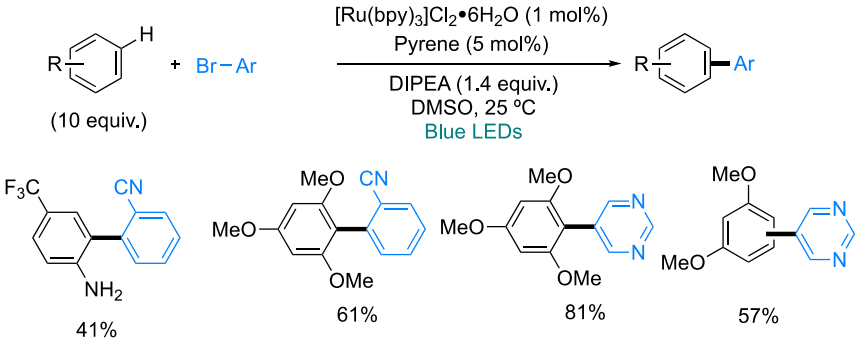
Scheme 34. Dual catalysis $Pd(OAc)_2/Ru(bpy)_3^{2+}$ for arylation of purine nucleosides using aryldiazonium salts

Tobisu, Chatani and co-workers have reported one example of non-directed arylation using photoredox conditions (Scheme 35).[34] From benzene –used as reagent and solvent– and diphenyliodonium hexaphosphate, biphenyl was obtained in 54% yield using $[Ir(ppy)_2(bpy)]PF_6$ as photoredox catalyst.



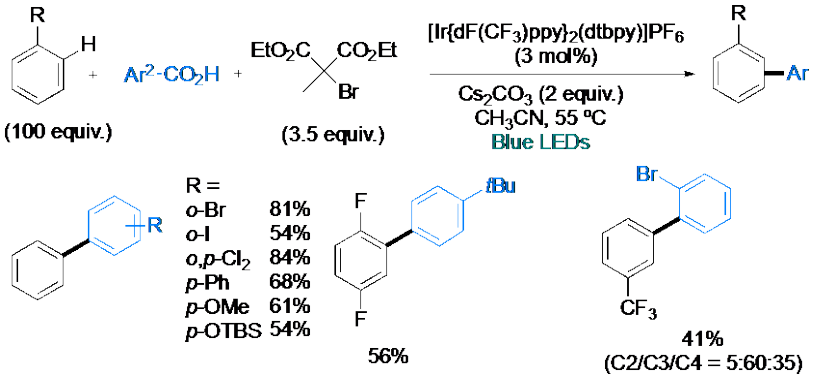
Scheme 35. $[Ir(ppy)_2(bpy)]PF_6$- catalyzed phenylation of benzene with diaryliodonium salts

Aryl radicals, generated from electron-poor aryl bromides using pyrene sensitization-initiated electron transfer strategy, can be trapped by electron-rich arenes such as anilines, 1,3,5-trimethoxybenzene or 1,3-dimethoxybenzene as demonstrated by König and co-workers (Scheme 36).[36] Notably, 4-trifluoromethylaniline is regioselectively arylated at C2-position, albeit only one example is demonstrated.



Scheme 36. $Ru(bpy)_3^{2+}$-promoted arylation of arene using aryl bromide.

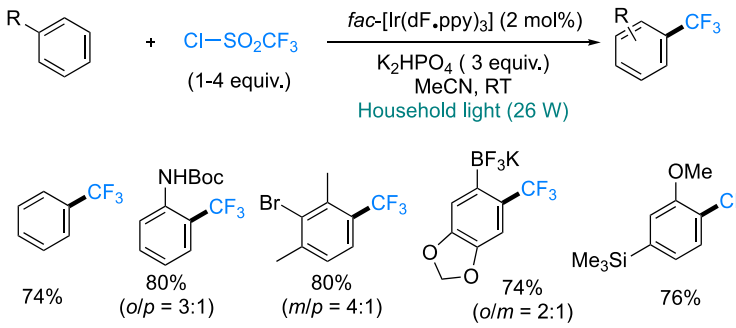
Glorius and co-workers reported photoredox-catalyzed $C(sp^2)$–H arylation of simple arenes using of aryl radical generated from decarboxylation of aryl carboxylic acids in the presence of diethyl 2-bromo-2-methylmalonate (Scheme 37).[65] Interestingly, the reaction is not limited to the classical electron rich arenes, but electron-deficient arenes such as 1,4-difluorobenzene and trifluorotoluene led to biaryl products in good yields, albeit 100 equivalents of arene are required.



Scheme 37. [Ir{dF(CF_3)ppy}$_2$(dtbbpy)](PF_6)-catalyzed Arylation of arenes with aryl carboxylic acids

4.2. Photoredox-assisted perfluoroalkylation of arene C(sp^2)–H bonds

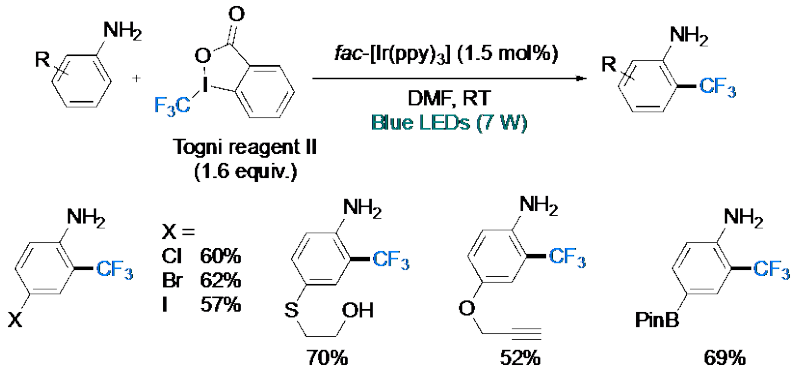
MacMillan and co-workers have reported the first example of photoredox-assisted trifluoromethylation of arene C(sp^2)–H bonds using trifluoromethanesulfonyl chloride as CF_3 radical source (Scheme 38).[44] Using [Ir(dF.ppy)$_3$] as photoredox catalyst, benzene was trifluoromethylated in good yield. N-Boc aniline was regioselectively functionalized at *ortho*-position. Notably, the reaction tolerate reaction functions such as C–Br, C–B and C–Si bonds.



Scheme 38. *fac*-[Ir(dF.ppy)$_3$]-catalyzed trifluoromethylation of arenes using trifluoromethanesulfonyl chloride

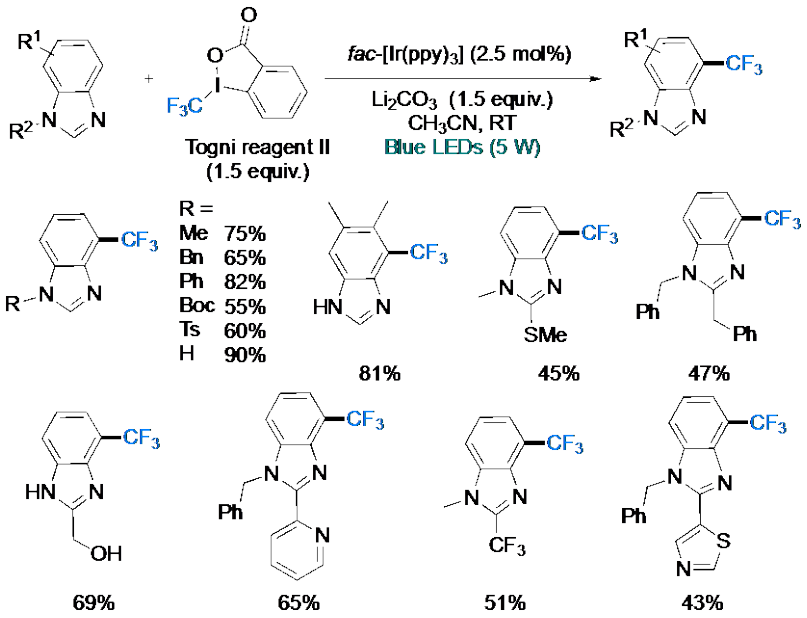
In 2014, Ma, Zhu and co-workers succeeded to trifluoromethylated *N*H_2-aniline derivatives using visible-light-promoted radical C(sp^2)−H bonds functionalizations (Scheme 39).[72] They found that the Togni Reagent II was the best candidate to generate CF_3 radical –using 1.5 mol% of *fac*-[Ir(ppy)$_3$] as photocatalyst under blue LEDs irradiation– which is then trapped by anilines to afford C2-trifluoromethylated anilines. Anilines bearing electron-donating and -withdrawing groups are both trifluoromethylated. The reaction tolerates sensitive groups such

as C–halo, C–OH, C–Bpin bonds. The reaction involves an oxidative quenching pathway.



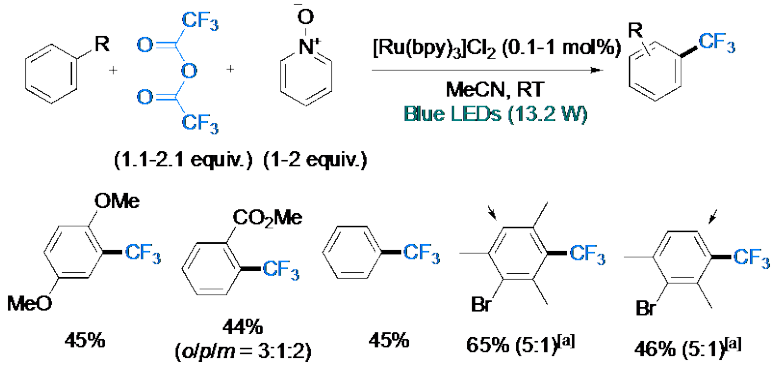
Scheme 39. *fac*-[Ir(ppy)$_3$]-catalyzed trifluoromethylation of anilines with Togni reagent

In 2017, Yang, Xia and co-workers discovered that if benzoimidazole derivatives is employed instead of anilines, the reaction led to C4-trifluoromethylated benzimidazoles (Scheme 40).[73] A broad range of *N*-substituents (e.g., *NH*, *N*-methyl, *N*-benzyl, *N*-phenyl, *N*-tosyl and *N*- Boc) are tolerated. The presence of substituents on the benzene ring did not affect both yield and regioselectivity. Moreover, the reaction is not sensitive to ether, thioether, ester, chloro, heteroaryl, CF_3 and free hydroxyl groups.



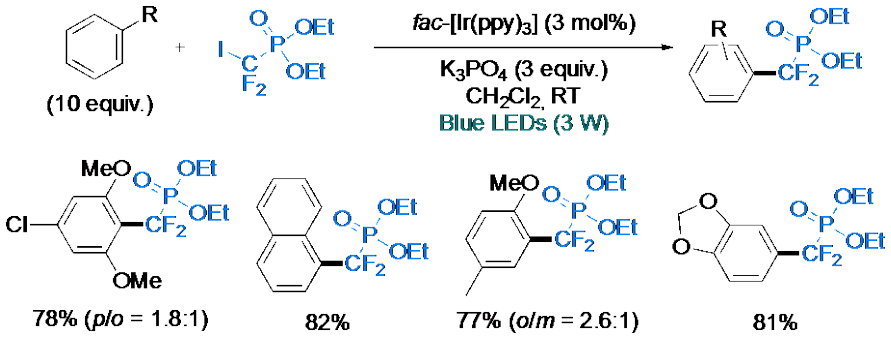
Scheme 40. *fac*-[Ir(ppy)$_3$]-catalyzed C4-trifluoromethylation of benzimidazoles with Togni reagent

Photoredox-assisted C(sp^2)–H bond trifluoromethylation of arenes was also achieved by the Stephenson's method, which generated the $CF_3^{\bullet}$ radical from irradiation under blue LEDs of the adduct composed by trifluoroacetic anhydride and pyridine *N*-oxide in the presence of [Ru(bpy)$_3$]Cl$_2$ (Scheme 41).[54] When the substrates have multi-reactive sites, a mixture of mono-and di-trifluoromethylated arenes are often obtained.



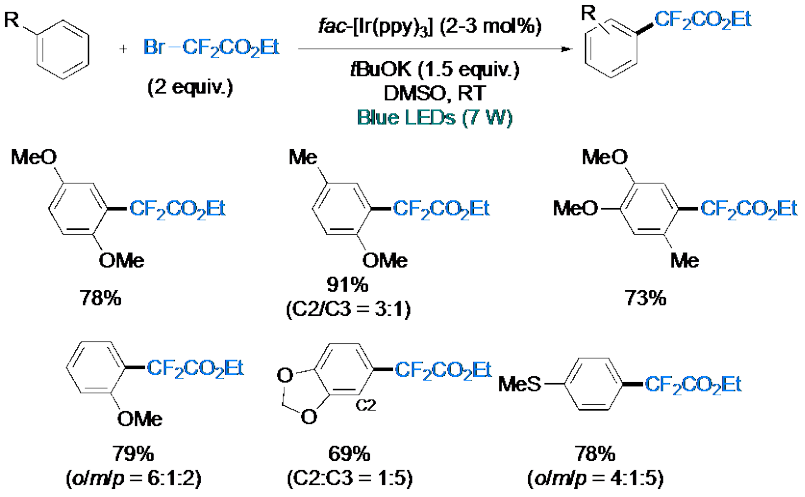
Scheme 41. Trifluoromethylation of (hetero)arenes with trifluoroacetic acid anhydride associated to pyridine *N*-oxide [a] minor doubly functionalized product, 4 equiv. of pyridine N-oxide and 8 equiv. of TFAA, 24 h

In 2014, Liu and co-workers achieved the difluoromethylene phosphonation of arene C(sp^2)–H bonds (Scheme 42).[53] Simple arenes such as benzene or naphthalene undergo trifluoromethylation in moderate to good yields, but the reaction is more efficient with electron-rich arenes such as trimethoxybenzene. In the presence of the arenes bearing different substituents, the trifluoromethylated arenes are formed as a mixture of regioisomers.



Scheme 42. *fac*-[Ir(ppy)$_3$]-promoted difluoromethylenephosphonation of arenes with bromodifluoromethylphosphonate

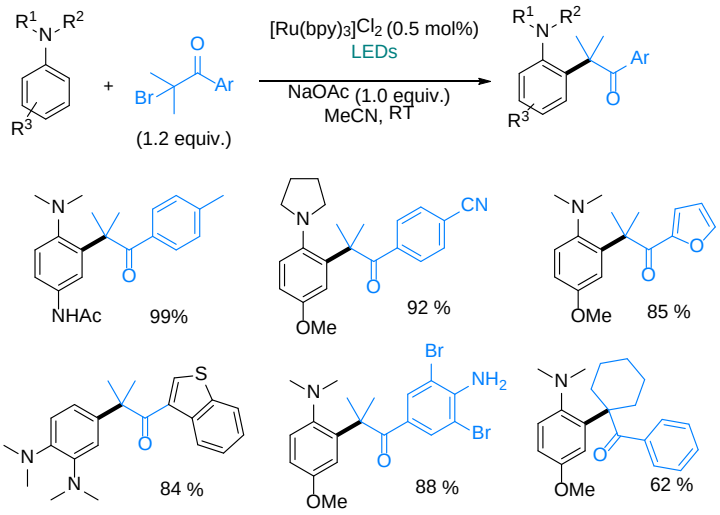
In 2014, You, Cho *et al.* succeeded in the difluoromethylation of C(sp^2)–H bond of arenes with ethyl 2-bromo-2,2-difluoroacetate (Scheme 43).[74] They employed *fac*-[Ir(ppy)$_3$] as photocatalyst and *t*BuOK as base in DMSO under blue LEDs irradiation to produce the desired difluoromethylated benzenes in good yields. The reaction is mainly limited to electron-rich benzenes and products were often obtain as mixture of regioisomers when multi-sites are present on the arene.



Scheme 43. *fac*-[Ir(ppy)$_3$]-catalyzed difluoroalkylation of electron-rich benzene derivatives with ethyl 2-bromo-2,2-difluoroacetate

4.3. Photoredox-assisted alkylation arene C(sp^2)–H bonds

In 2016 Xu Cheng *et al.* have shown that alpha-bromoketones could be used as radical precursors via SET from the visible light irradiated photoredox system [*Ru(bpy)$_3$]$^{2+}$ and that the resulting radical add regioselectively at C2 of *N*,*N*-dialkylanilines (Scheme 44).[75] This method allow the transformation of arene C(sp^2)–H bond into C(sp^2)–C(sp^3) bond. The reaction yields increase in the presence of the base NaOAc, and the simple [Ru(bpy)$_3$]Cl$_2$ photoredox system is more efficient than *fac*-[Ir(ppy)$_3$] or organic photoredox. The reaction is efficient for various alpha-bromoketones bearing halide or nitrile on the arene group and for alpha -bromoketones containing a heterocycle group such as furan or thiophene. Sunlight is also effective for this reaction and shows the robustness of the reaction intermediates.



Scheme 44. Regioselective alkylation at C2 of anilines with alpha-bromoketones containing (hetero)aryl groups

The proposed mechanism involves the formation of the strong reducing Ru(I) species which thus allows a SET to the ArCO(Me)$_2$C-Br generating [Ru(bpy)$_3^{2+}$]. And the radical ArCO(Me)$_2$C• (**A**).The later adds regioselectively to C2 of aniline giving radical **B** . This radical **B** is able to transfer one electron to the excited photoredox [*Ru(bpy)$_3^{2+}$] to give the Ru(I) species and the cation **C**, which is easily deprotonated by NaOAc (Figure 14). [75]

It is noteworthy that this mechanism is different from the Stephenson mechanism for alkylation of heteroarenes from alkylbromides with the same

$[Ru(bpy)_3]Cl_2$ photoredox complex (see Figure 6),[56] for which the reaction was performed in the presence of NEt_3, which is known to reduce $[*Ru(bpy)_3^{2+}]$ into a Ru(I) species.

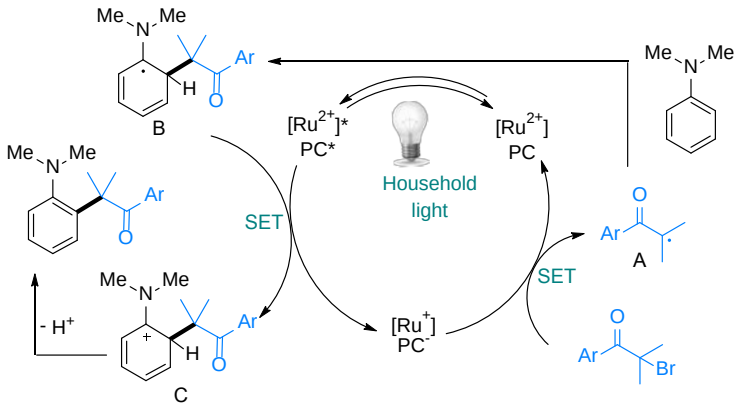
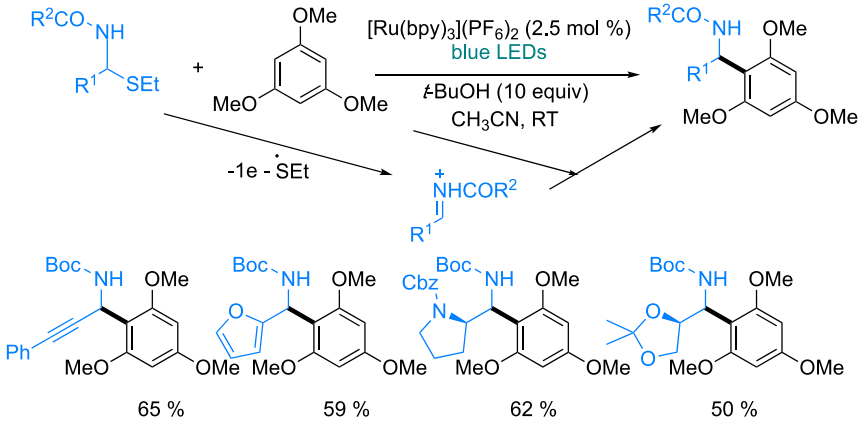


Figure 14.Proposed mechanism for quaternary alkylation of anilines with α-bromoketones with $[Ru(bpy)_3^{2+}]$ photoredox

Masson et al, reported that α-amidosulfides can release one electron with the help of a photoredox partner and then generate, beside a RS• radical, a *N*-acyliminium cation allowing the alkylation of 5-atom heteroarenes (Scheme 19).[61] They also show that the same conditions can perform the photocatalyzed aza-Friedel-Crafts reaction of electron rich arenes such as trimethoxybenzene with $Ru(bpy)_3](PF_6)_2$ and thus formally the regioselective alkylation. The reaction is applicable to α-amidosulfides and α-carbamoylsulfides. Importantly chiral **α**-amidosulfides allow the selective formation of one diastereoisomer without racemization.



Scheme 45. Photocatalyzed aza- Friedel-Crafts reaction of trimethoxybenzene from α-amidosulfide derivatives

5. Conclusion

The above examples of visible light-promoted photoredox catalysis for the selective transformations of C(sp^2)–H bonds into C(sp^2)–C bonds, mostly at room temperature, show that this methodology offers one of most efficient ways for C(sp^2)–H bond arylation and (perfluoro)alkylation of 5- and 6-atom heterocycles and functional arenes. They require low energy and mild conditions for radical production from simple substrates and generate low by-product quantity which then offer green contribution to the catalytic processes. This methodology is a useful alternative to the metal-catalyzed C–H bond activation/functionalization. This review shows also that photoredox catalysts offer one of the best way to produce radicals under mild conditions through SET events with the valorization of light as a green and abundant energy source.

Although a lot of efforts have been dedicated to the design of radical precursors, one of major challenge remains to control the regioselectivity of the radical additions with some substrate such as arenes in order to achieve regioselective C(sp^2)–H bond functionalizations. It is likely that in a close future more photoredox systems, based on MLCT metal complexes but also on functional polydentate ligands, will be designed to produce new useful radicals for C–C bond formations with higher regioselectivity, but also for C-O and C-N bond formations, from C(sp^2)–H bonds.

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