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Review

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Radical Fluoroalkylation Reactions

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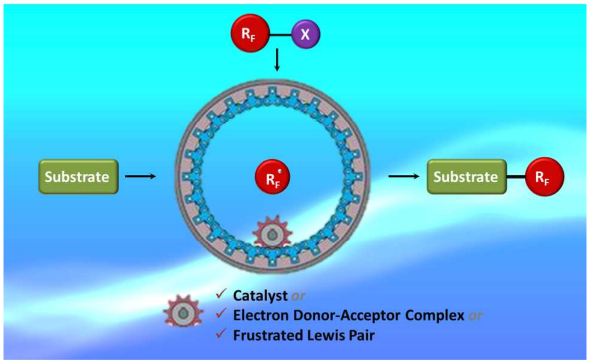
Abstract

Recent protocols and reactions for catalytic radical perfluoroalkylations (R_F = C_nF_{2n+1}, n ≥ 2) will be described. The production of R_F radicals that effect both addition and substitution reactions on organic substrates can be realized through a range of diverse methods such as the well-established visible light transition metal-mediated photocatalysis, organic dye-photocatalyzed reactions, by Electron Donor Acceptor (EDA) complexes or more recently through Frustrated Lewis Pairs (FLP). Thus, perfluoroalkylation reactions of carbon-carbon multiple bonds, isocyanides, nitrones, hydrazones, β-ketoesters, α-cyano arylacetates, sulfides, and (hetero)arenes will be described. Specially emphasis will be made on examples published after 2015 where higher fluorinated series of fluoroalkylating reagents are studied.



Keywords: perfluoroalkylation; organophotocatalysis; transition metal-photocatalysis; EDA complex; FLP perfluoroalkylation; catalytic perfluoroalkylations

1.-INTRODUCTION

The prevalence and advantages of fluoro(alkyl)-substituted organic compounds span a range of different fields such as medicinal chemistry, agrochemistry, materials science,[1] etc., and has motivated a revived interest in synthetic methods which follow more benign and environmentally-concerned protocols. In this regard, radical fluoroalkylation methods have come to the forefront as compared to polar strategies. This is due to the poor stabilization of the perfluoroalkyl cation or anion species, as compared to the radical intermediates.[2] However, designs of new electrophilic perfluoroalkylating reagents (i.e.: perfluoroalkyl-derived Togni´s reagent) and their use have been recently proposed.[3]

As a matter of fact, catalytic methods have prevailed over stoichiometric protocols. The realm of synthetic catalytic perfluoroalkylation methods extend from thermal, photocatalyzed or transition metal- / organic dye-mediated ones, and more recently, to visible light photoactivation of electron-donor-acceptor (EDA) complexes or frustrated Lewis pairs (FLP). All these methods are able to produce R_F radicals.

Perfluoroalkyl halides R_F-X (X = Br, I) can be a source of perfluoroalkyl radicals R_F. These R_F radicals can be produced either through direct homolysis of R_F-X bond,[4] through electron transfer[5] (ET) processes from either excited organometallic photocatalyst[6] or non-metal photoactive complexes,[7] or through (transition)metal-mediated thermal ET events. This is so on account of the accessible reduction potentials of most R_F-X as compared to their alkyl halide analogs.

Other sources of perfluoroalkyl radicals R_F can be fluorinated sulfones and sulfonyl chlorides that have been amply used as CF_2X (X = H / R / F) radical precursors by the groups of Hu [8] and Dolbier, [9] and recently discussed in review articles dealing with these strategies.[10,11,12,13]

Perfluorobutyl sulfanyl chloride ($C_4F_9SO_2Cl$) has recently been employed by the group of Liu [14,15] to effect catalytic asymmetric radical aminoperfluorobutylations of alkenes triggered by CuBr and a chiral phosphoric acid catalyst.

The bromodifluoromethylphosphonium bromide and triflate salts have also been exploited as sources of CF_2H and CF_2R radicals and have been developed by the groups of Qing [16] and Dilman [17,18] . These methods have been revisited in difluoromethylation reviews.[13 11] The use of Hantzsch esters for fluoroalkylation (difluoromethylation) reactions also have been proposed by the groups of Ryu [19] and Dilman.[17,18]

Photocatalysts combining a transition metal and organo-ligands have been the standard choice for effecting fluoro(alkylation) reactions and many other types of C-C bond formation reactions. [20] The reason for the prevalence of these methods rely on the favorable redox properties of such catalysts acting in reductive and oxidative quenching cycles, with readily accessible triplet manifolds where metal-to-ligand charge transfer complexes ease the redox exchange of single electrons.[20] Thus ruthenium and iridium salts with pyridine-derived ligands (e.g.: $Ru(bpy)_3Cl_2$, ruthenium-tris(2,2'-bipyridyl) dichloride;

$[Ir(dtbbpy)(ppy)_2]PF_6$, 4,4'-Di-tert-butyl-2,2'-bipyridine)bis[(2-pyridinyl)phenyl]iridium(III) hexafluorophosphate and others) are among the most popular metal-organo photocatalysts to achieve an array of synthetic organic transformations.[21,22]

Organic dyes with their high extinction coefficients, [23,24] being inexpensive, nontoxic, readily available, and easy to separate or extract from reaction mixtures render them excellent alternatives to metal complexes. As a matter of fact, organic dyes[25] such as Rose Bengal,[26] Eosin Y, Red Nile,[27] anthraquinone-2-carboxylic, anthraquinone-2-sulfonic acids[28] and others[29] have successfully been used in the production of perfluoroalkyl R_F or other carbon-centered radicals triggered by visible light irradiation. Moreover, photocatalysts absorbing in the red region of the electromagnetic spectrum have allowed even lower energy irradiation sources to be used capable of effecting reductive quenching cycles.[30]

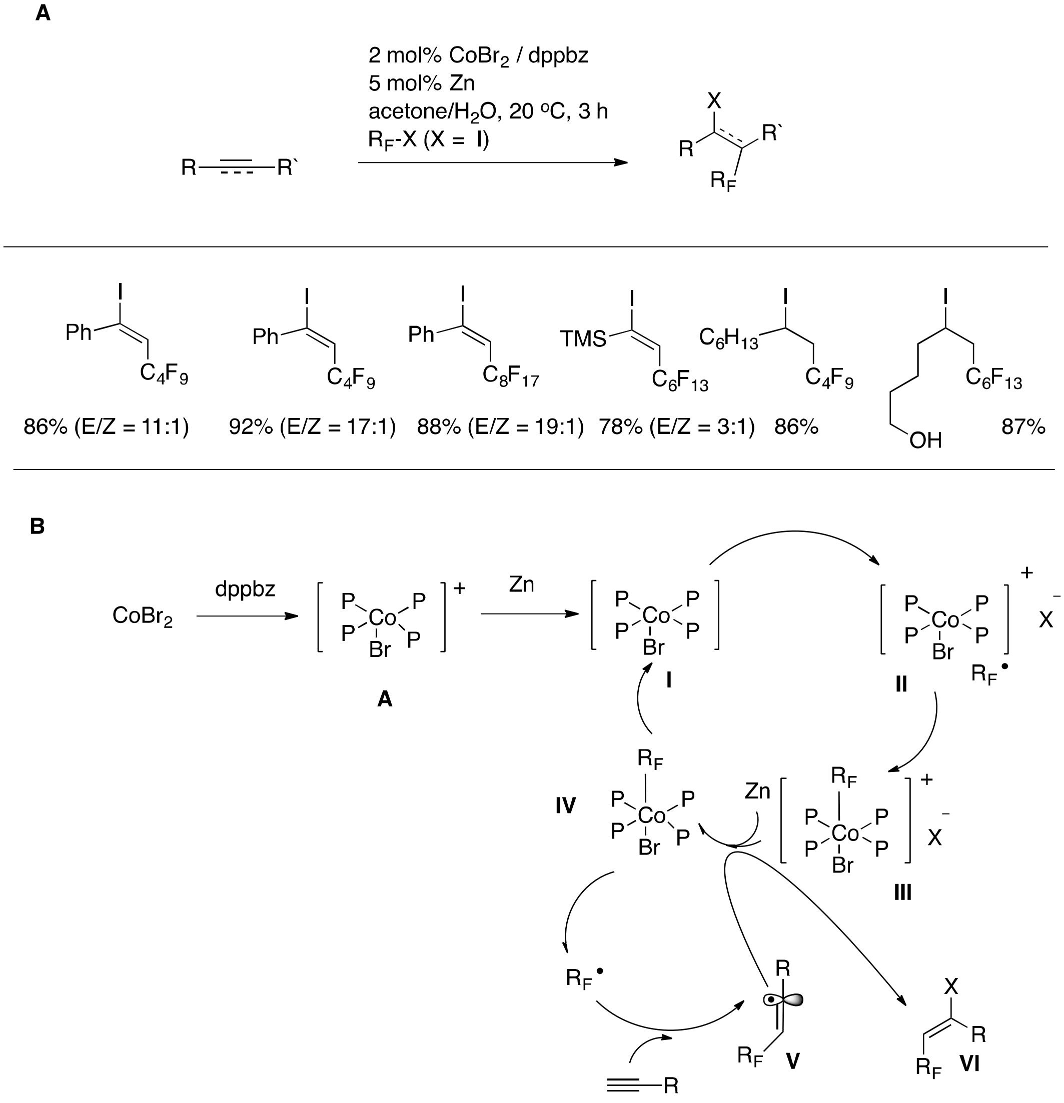
This review manuscript will not include catalytic radical trifluoromethylation,[31] difluoromethylation (CHF_2 / CF_2) [11], or fluorination [32] reactions or the radical incorporation of fluorinated groups such as XCF_3 / XCF_2H / XR_F (X = O,[32b] S, [33] Se), as introduction of these groups have been reviewed and discussed elsewhere. Some radical perfluoroalkylation reactions [34] have been reviewed[34e], however, the scope of the present approach is to introduce new catalytic fluoroalkylation ($R_F = C_nF_{2n+1}$, $n \geq 2$) reactions developed in the literature since 2015, which have exerted a great impact on radical fluoroalkylation strategies. On doing so, the perfluoroalkylation of carbon-carbon multiple bonds, sulfides, isocyanides, nitrones, hydrazones, α-cyano arylacetates, β-ketoesters, and (hetero)aromatic rings will be described according to three main strategies: *i*.-(photo)catalysis by transition metals; *ii*.-photocatalysis by organic dyes; *iii*.- by EDA complexes or FLP.

2.- RADICAL PERFLUOROALKYLATION REACTIONS BY TRANSITION METAL-MEDIATED (PHOTO)CATALYSIS

Visible light transition metal-photocatalyzed [35] perfluoroalkylation [36] reactions of organic substrates have been discussed and reviewed in the literature up to 2015. [34e,37] However, new and interesting contributions on catalytic metal-mediated radical perfluoroalkylation reactions have been introduced since then, either activated by light or by thermal processes.

2.1.-Perfluoroalkylation of carbon-carbon multiple bonds: olefins and alkynes

In a very recent report [38] von Wangelin and colleagues have disclosed the highly regioselective cobalt-catalyzed halofluoroalkylation of alkynes towards the synthesis of highly regioselective halofluoroalkenes under mild conditions. The procedure utilizes a three-component catalyst comprising of $CoBr_2$, dppbz (1,2-bis(diphenylphosphino)benzene) and zinc in acetone/water. The substrate scope is illustrated in Scheme 1(A).

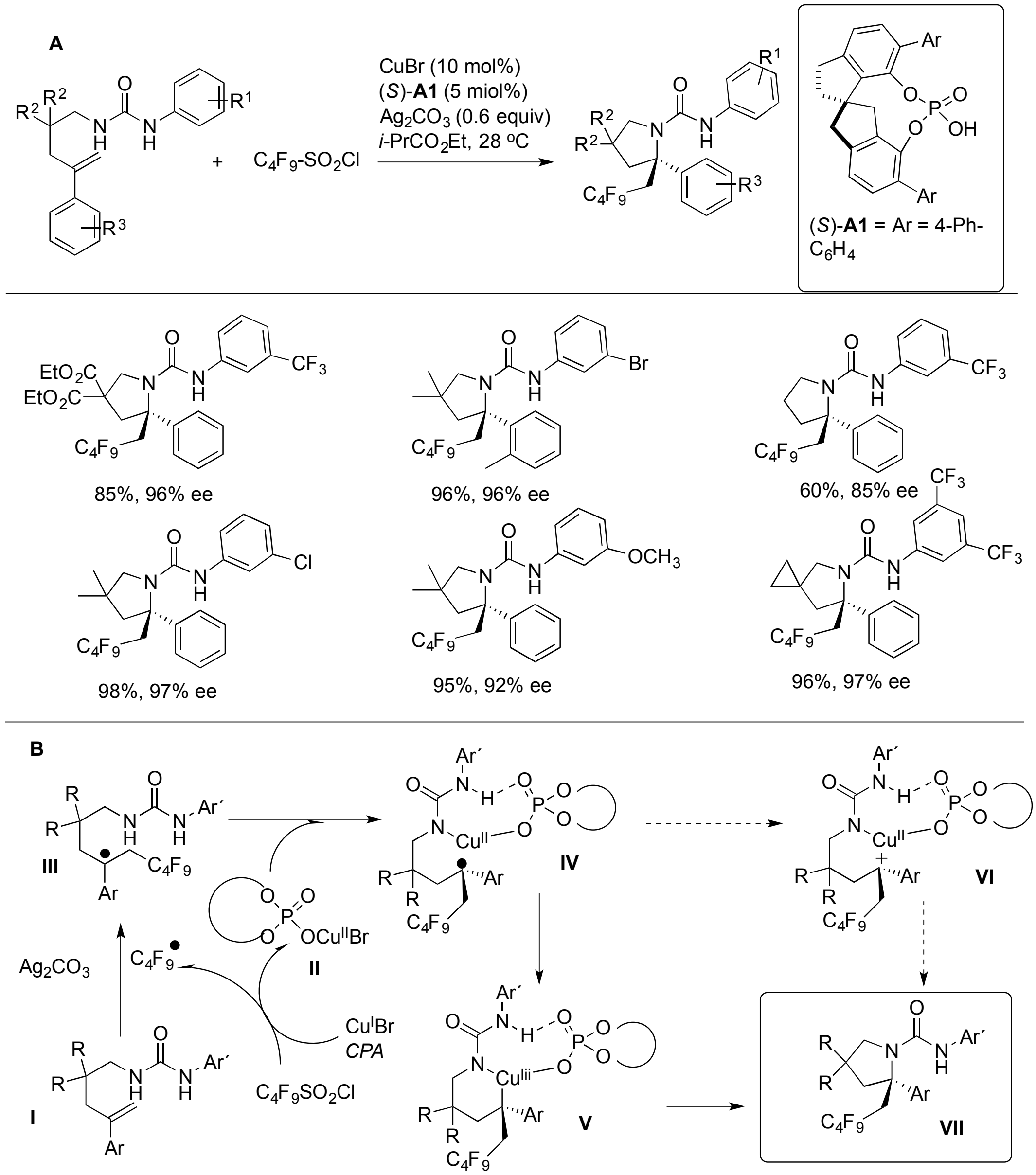


Scheme 1. (A) Scope of the $CoBr_2$-catalyzed perfluoroalkylation of olefins and alkynes. (B) Proposed reaction mechanism

The authors [38] carried out several mechanistic probe experiments. The reaction in the presence of TEMPO did not provide the desired product, instead, a TEMPO-R_F adduct was encountered. They also found that the initial Co(I) species formed cannot catalyze the reaction but requires the presence of zinc (employed only in catalytic amount). The authors [38] observed that the halogen atom X in the product does not originate from R_F-X via an atom transfer radical addition (ATRA [39]) reaction, but instead is transferred from the cobalt catalyst. This is an important difference between this reaction and an ATRA [40,39] process. Besides, the addition of water did not result in a hydroxyl-perfluoroalkylated product, which could be indicative that the transfer occurs to a radical intermediate rather than a carbocation. Intermediate **I** and **II** (Scheme 1B) have been characterized by ^{31}P NMR spectroscopy and MS, respectively.

The mechanistic proposal entails coordinating $CoBr_2$ with dppbz (1,2-bis(diphenylphosphino)benzene), generating cation **A** (Scheme 1(B)). Through reduction by Zn metal, coordination compound **I** is formed which further hexacoordinates with R_F-X to generate **III** which is reduced to species **IV** capable of releasing R_F radicals that add to the alkyne to afford radical adduct **V.** Radical adduct **V** renders final product **VI**.

Liu and collaborators [15,41] have recently accomplished the enantioselective aminoperfluorobutylation of olefins employing perfluorobutyl sulfanyl chloride as source of C_4F_9 radicals, a chiral phosphoric acid catalyst ((**S)-A1**, Scheme 2 (**A**)), and CuBr



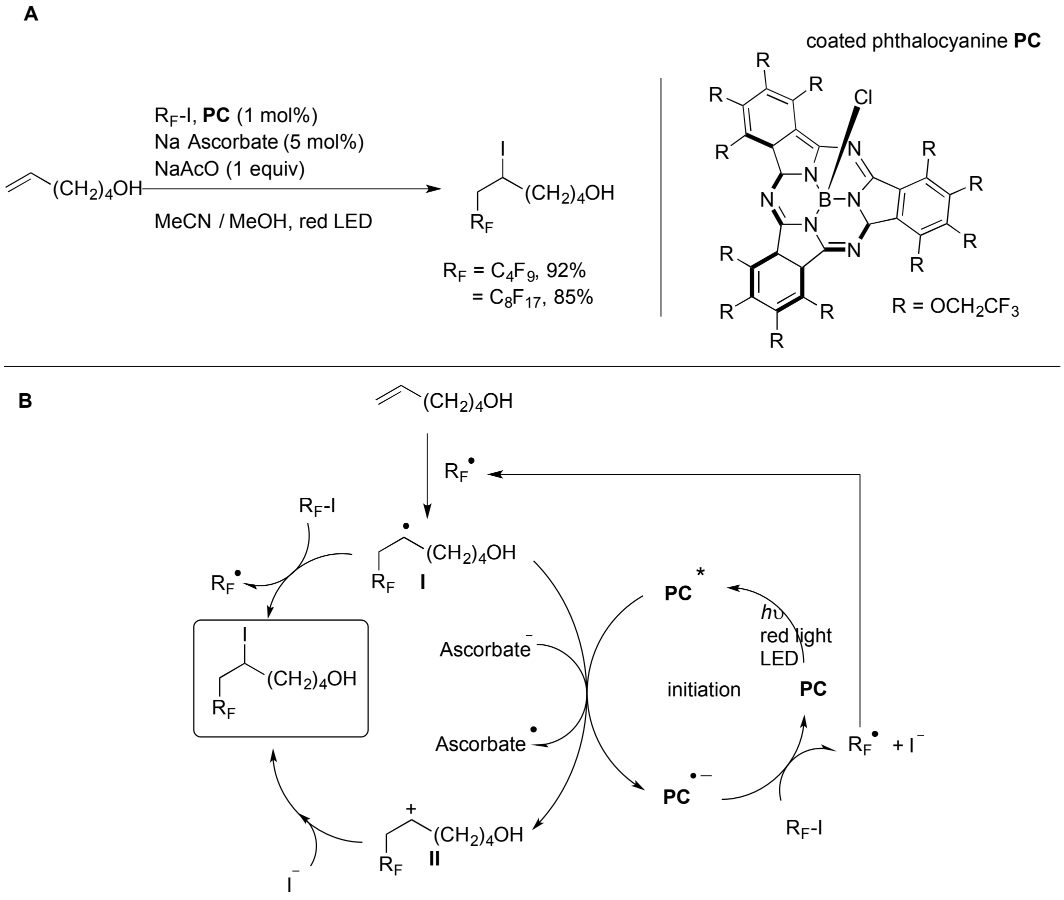
Scheme 2. (**A**). Scope of the enantioselective aminoperfluorobutylation of olefins with chiral phosphoric acid CPA (*S*)-**A1** and CuBr. (**B**). Proposed reaction mechanism

The reaction (Scheme 2 (**A**)) affords high yields of enantioselective aminoperfluoroalkylated olefins with excellent enantiomeric excess. The authors[15,41], probed the reaction mechanism through a series of mechanistic experiments. The presence of TEMPO, a radical scavenger, afforded trace of products. A radical clock substrate (i.e.: 1-(2,2-dimethyl-4-(2-phenylcyclopropyl)pent-4-en-1-yl)-3-(3-(trifluoromethyl)phenyl)urea) afforded a mixture of rearranged and unrearranged products, purporting the presence of radicals. Absence of CPA catalyst affords a racemic mixture of C_4F_9-substituted isomers.

The authors[15,41] proposed a reaction mechanism as depicted in Scheme 2 (**B**). C_4F_9 radicals are generated from the electron transfer reaction of the corresponding $C_4F_9SO_2Cl$ with CuBr and the phosphoric acid. Subsequent addition of C_4F_9 radical to alkene **I** gives the alkyl radical **III**, which could be trapped by Cu(II) phosphate **II** to form a Cu(II) species **IV**, in which alkyl radical intermediate could be trapped by Cu(II) phosphate to generate a Cu(III) species **V** (Scheme 2 (**B**)). During this process, the chiral phosphate could control the facial selectivity of such reaction via both hydrogen-bonding interactions with the N–H bond adjacent to the aryl group and ion-pairing interactions in a concerted transition state. Then, reductive elimination of the resulting Cu(III) species **V** would afford the final product **VII** along with the regeneration of the copper Cu(I) and the phosphoric acid. However, the authors [15,41] suggested another pathway (path b) via single-electron oxidization of intermediate **IV** to the corresponding carbocation intermediate **VI**, which undergoes C–N bond formation to give final product **VII**.

Employing lower energy light (irradiation wavelengths longer than 500 nm) for chemical reactions remains a challenge to achieve non-toxic, environmentally-friendly, mild, and selective transformations. In this regard, red light has gained attention for its application in “greener” visible-light photoredox reactions.[42] Red light has the benefits of low power (600–700 nm), no risk of light hazard, and inexpensive lamps. More interestingly, it penetrates even the turbid media.

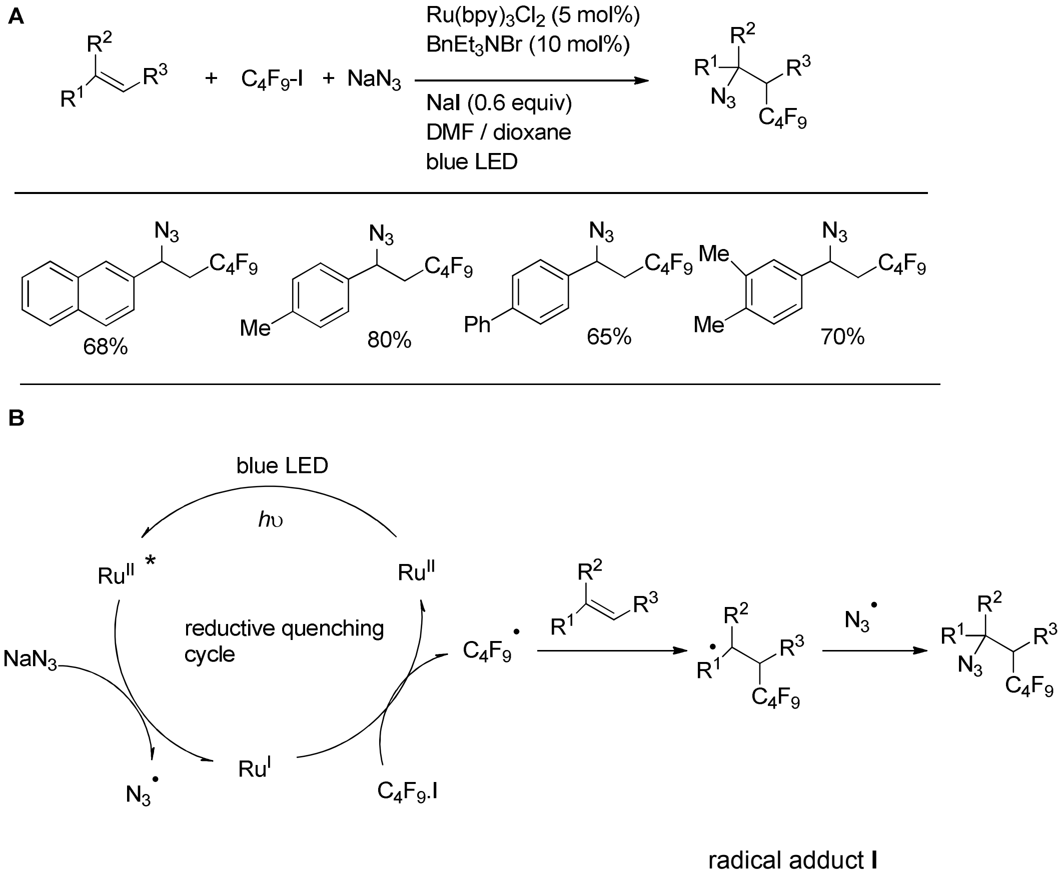
Shibata and colleagues [30] have accomplished the perfluoroalkylation of olefins and alkynes employing trifluoroethoxy-coated subphthalocyanine and red-light irradiation. The scope of the reaction is depicted in Scheme 3(A).



Scheme 3. (**A**) Red-light photocatalytic perfluoroalkylation of olefins. (**B**) Proposed reaction mechanism

The authors [30] proposed a reaction mechanism such as that illustrated in Scheme 3(B). They found that the reaction requires both photocatalyst and light (from a red LED) to proceed. In an initiation event, photo-excited trifluoroethoxy subphthalocyanine **PC** (Scheme 3A) accepts one electron from sodium ascorbate to form an anion radical of **PC**.[43] The anion radical of **PC** [$E^{o}_{\mathbf{PC/PC^{\cdot-}}}$= -0.69 V vs. SCE) could reduce R_F-I (E^{o}= -1.26 V vs. SCE for C_4F_9I) to generate the R_F radical (although this reduction process (from the reduced photocatalyst to R_F-I) is a thermodynamically unfavorable electron transfer by about 0.6 V, sodium ascorbate and/or sodium acetate probably acts as a Lewis acid to support this step through the activation of the carbon-iodine bond to bypass this energy barrier. Next, the R_F radical attacks the double bond to furnish a radical intermediate **I**. The radical species **I** has enough oxidative power ($E^{o\,\prime}$= +0.47 V vs. SCE for secondary alkyl radical)[44] to regenerate an active radical anion species of the catalyst **PC** and cation **II**, which can suffer nucleophilic attack by iodide anion to render the final product. The authors[30] also considered that the mechanism may proceed through a self-propagating radical chain step, in which the alkyl radical **I** abstracts the iodine atom of R_F-I to generate the product and a R_F radical as the chain carrier (the classical ATRA[39] reaction). However, light irradiation is required not only for the initiation of the reaction but also to maintain the propagation.

Jiao and co-workers[45] have accomplished the radical azidoperfluoroalkylation of olefins employing $Ru(bpy)_3Cl_2$ as photocatalyst, and R_F-I as perfluoroalkyl radical source in the presence of NaN_3. The scope of the transformation is depicted in Scheme 4(A).

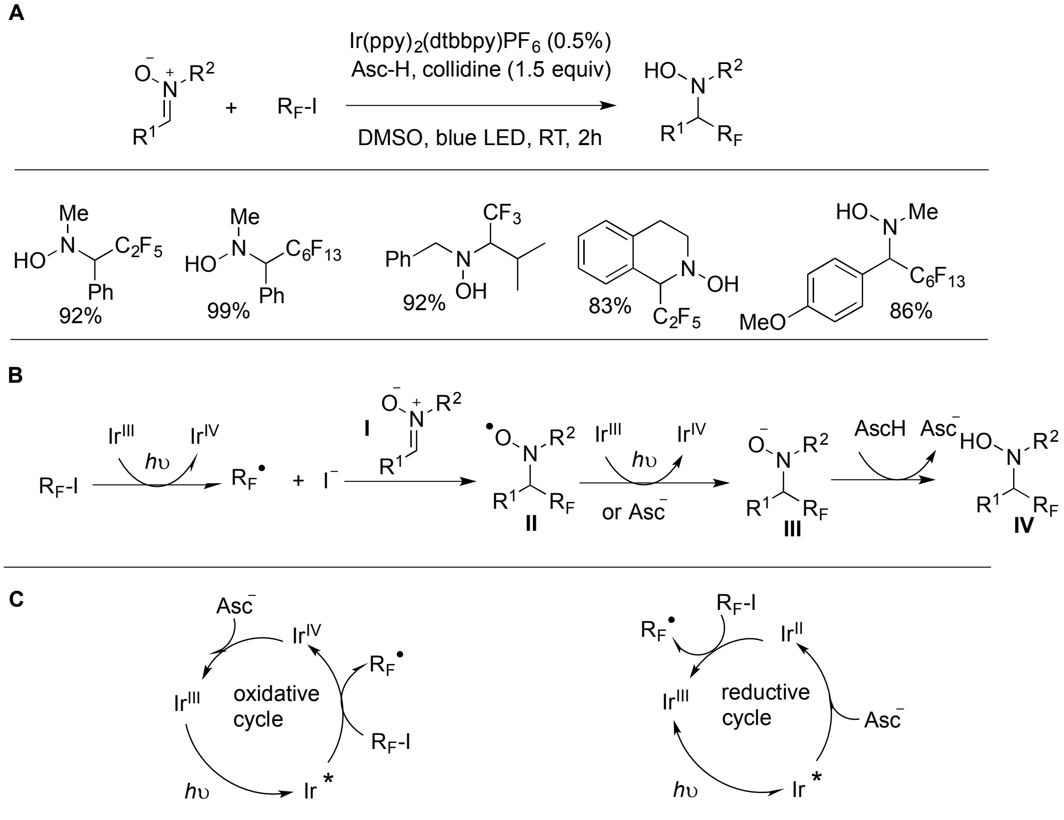


Scheme 4. (A) Scope of the azidoperfluoroalkylation of olefins (B) Proposed photocatalyzed mechanism

The authors[45] probed that the azidofluoroalkylation product is not formed by the relay of iodofluoroalkylation product and subsequent substitution with the azido N_3 anion. Another important observation that threw light into the mechanism is that the addition of either NaN_3 or NaI to the excited Ru-catalyst resulted in a strongly enhanced quenching effect. These results indicated that a reductive quenching of $Ru^{II}*$ by either NaN_3 (or NaI) was involved in the mechanism, as shown in Scheme 4(B). The proposed mechanism (Scheme 4(B)) starts by excitation of the Ru^{II} photocatalyst by irradiation with a blue LED, generating a Ru^{II} excited catalyst (triplet state), capable of oxidizing the azide anion to the azide radical and producing Ru^{I} in the process. This reduced state of the Ru catalyst is an excellent reductant to C_4F_9-I, generating C_4F_9 radicals in the process and re-establishing the catalysts into its original oxidation state (i.e. II). These C_4F_9 radicals add to the olefin to generate radical adduct **I**. Adduct **I** is trapped by azide radical to form the product.

2.2.-Perfluoroalkylation of carbon-nitrogen double bonds: nitrones and hydrazones

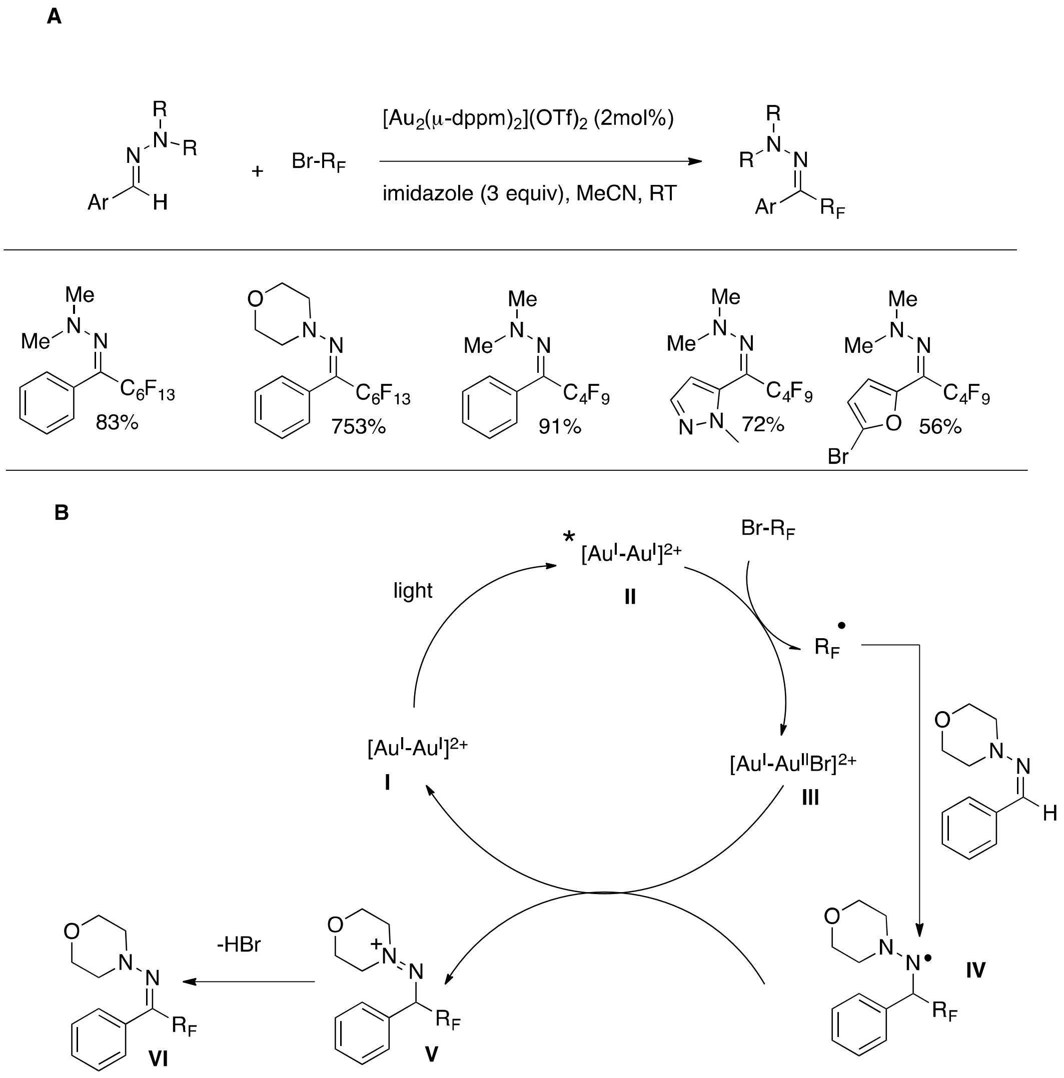
Dilman and collaborators[46] have recently reported the perfluoroalkylation of nitrones employing an iridium photocatalyst and ascorbic acid as reducing agent. Some examples are illustrated in Scheme 5(A).



Scheme 5. (A) Examples of perfluoroalkylation of nitrones. (B) Generation of R_F radicals and ulterior addition to nitrones. (C) Oxidative and reductive quenching cycles of the photocatalyst

The authors [46] postulate a reaction mechanism such as that shown in Scheme 5(B) & (C). There exist two possibilities for the production of R_F radicals. In the oxidative quenching cycle (Scheme 5(C), left), the excited Ir^{III*} photocatalyst reduces R_F-I to R_F radicals (and iodide anion) rendering the catalyst in a high oxidation state (Ir^{IV}), which is re-generated by ascorbate anion. In the reductive quenching cycle of the photocatalyst (Scheme 5(C), right), the excited Ir^{III*} photocatalyst is reduced by ascorbate anion to an Ir^{II} species, which is an excellent reductant to R_F-.I yielding R_F radicals. Once R_F radicals are generated, addition to nitrone **I** (Scheme 5(B)) renders nitroxyl radical **II**, which is further reduced by ascorbate or the Ir^{III} catalyst to anion **III**. Anion **III** is protonated by ascorbic acid to give final perfluoroalkylated hydroxylamine **IV**. Reactions of nitrones with partially fluorinated iodides require the use of morpholine instead of collidine (2,4,6-trimethylpyridine) as base.

Hashmi and colleagues[47] have accomplished the Au-catalyzed photoredox perfluoroalkylation of hydrazones.[12] The scope of the transformation is represented in Scheme 6(A).

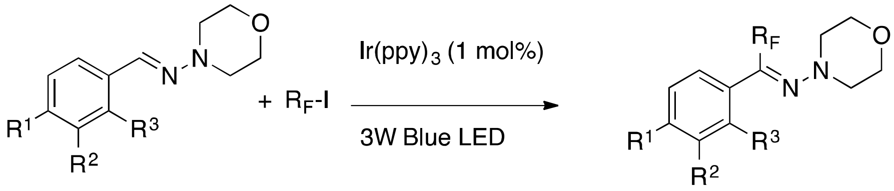


Scheme 6. (A) Substrate scope for the Au-catalyzed perfluoroalkylation of hydrazones.(B) proposed reaction mechanism

Probe experiments such as the addition of radical trap TEMPO or electron-scavenger 1,4-dinitrobenzene significantly inhibited the product formation. The key radical intermediate ($R_F = CF_2PO(OEt)_2$) was observed by EPR spectroscopy. The mechanism involves irradiation of **I**, which generates the long-lived excited species **II**, which in turn is a strong reductant ($E^o([Au_2]^{3+}/{}^*[Au_2]^{2+}) = -1.5 – 1.7$ V). Following ET from **II** to Br-R$_F$ affords radical

R_F and intermediate **III**. Radical R_F attacks hydrazone to produce the three-electron π-bonding intermediate **IV**. Oxidation of radical **IV** by gold species **III** (to give **V**), followed by deprotonation affords the perfluoroalkylated product **VI**.

In a more recent report, Shi and Shen [48] have informed the visible light-mediated perfluoroalkylation of hydrazones [49] through the use of $Ir(ppy)_3$ photocatalyst in DMF as a solvent. The scope of the transformation is illustrated in Scheme 7.



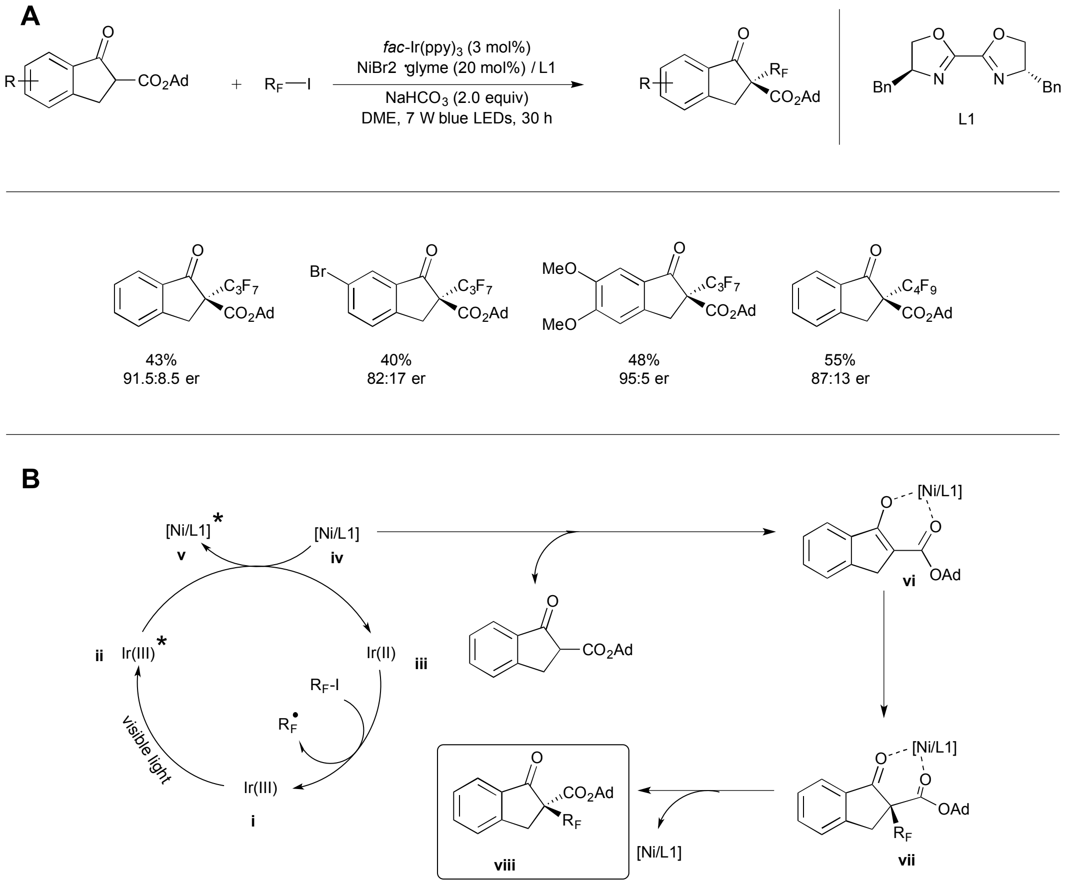
R = H, $R_F = C_4F_9$	88%
R^1 = Me, R^2,R^3 = H, $R_F = C_4F_9$	69%
R^1 = Cl, R^2,R^3 = H, $R_F = C_4F_9$	92%
R^1 = CN, R^2,R^3 = H, $R_F = C_4F_9$	90%

Scheme 7. Scope of the perfluoroalkylation of hydrazones with $Ir(ppy)_3$ catalyst

The proposed mechanism is similar to that shown in Scheme 5(C) (oxidative cycle) except that the Ir(III) photocatalyst is regenerated from the oxidized Ir(IV) species through the oxidation of the aminyl radical (like adduct **IV**, Scheme 6(B)) to the hydrazonium ion (**V** , Scheme 6(B)).

2.3.-Perfluoroalkylation of the α-position of carbonyl compounds: β-ketoesters and 2-acyl imidazoles

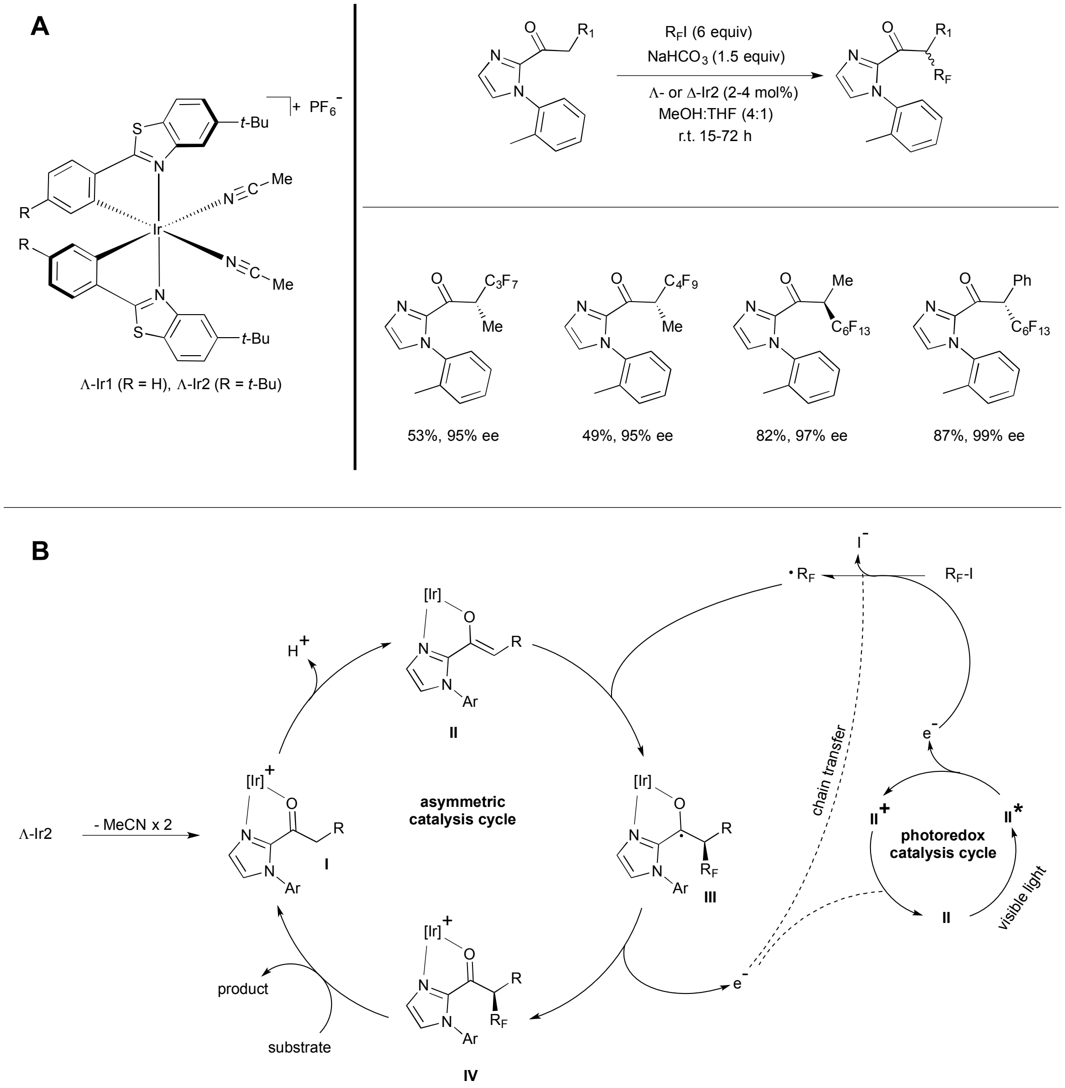
Xiao and colleagues [50] have recently informed the enantioselective radical perfluoroalkylation of β-ketoesters through an asymmetric photoredox[36] and nickel catalysis. The scope of the transformation is illustrated in Scheme 8(A).



Scheme 8. (A) Scope of the enantioselective radical perfluoroalkylation of β-ketoesters through an asymmetric photoredox and nickel catalysis. (B) Proposed reaction mechanism

The authors [50] suggested a radical pathway based on probe experiments. The reaction was completely inhibited by radical scavenger TEMPO. In the presence of 1,1-diphenylethylene (a radical trap), a perfluoroalkyl-substituted product (i.e.:2-perfluoroalkyl-1,1-diphenylethylene) was isolated. The authors noticed that continuous irradiation is necessary, indicating little or no radical propagation. Also, an oxidative quenching cycle of the photocatalyst was considered by the authors. However, on the basis of redox potentials (E* Ir(III)/Ir(IV) = -0.89 V vs SCE higher than the E $C_4F_9I/C_4F_9^{\bullet}$ = -1.24 V), an oxidative quenching cycle (that in which Ir(III) is oxidized to Ir(IV)) has to be ruled out. Therefore, a reductive quenching cycle of the photocatalyst should be operational (see Scheme 8(B)) where the Ir(II) photocatalyst reduces R_F-I to R_F radicals and, in turn, Ir(III) species is re-formed. Therefore, ET from the [Ni/L1] to the photocatalyst (E Ir(III)*/Ir(II) = +1.21 V vs SCE) is thermodynamically favorable. It has also been demonstrated by the authors [50] that the emission of the excited photocatalyst is quenched by [Ni/L1], purporting that an ET within the pair takes place. On the basis of these and other experiments,[50a] the proposed mechanism (Scheme 8(B)) entails photoexcitation of the photocatalyst **I** by visible light, affording species excited **II** which can suffer reductive quenching by complex **IV** to yield complex **V** and Ir(II) (species **III**). This Ir(II) species is a strong reductant of R_F-I , affording R_F radicals and regenerating the ground state of the photocatalyst (Ir(III)). The substrate is activated by the chiral Lewis acid to afford intermediate **VI**, which is trapped by radical R_F to give intermediate **VII**, whereupon the final product ensues. To end the cycle, oxidation of [Ni/L1] by Ir(III)* regenerates the Ni/L1 species.

The visible-light-activated enantioselective perfluoroalkylation of 2-acyl imidazoles using a chiral iridium complex has been reported by Meggers *et al.* [50b] where the Ir complex presents a dual functionality: as photoredox sensitizer and as chiral director. By increasing the steric congestion of the substrate, the enantioselectivity of the reaction was improved (i.e.: a methyl in the *ortho* position of the aryl group linked to the *N* atom of the imidazole moiety). On the other hand, the reaction yield correlated with the bulk of the ligands, where *t*-Bu groups at the phenyl moieties increase the HOMO energy and turns Ir^{2+} into a better electron donor. The scope of the reaction has been probed with respect to the substrate and the perfluoroalkyl groups (Scheme 9(A)).

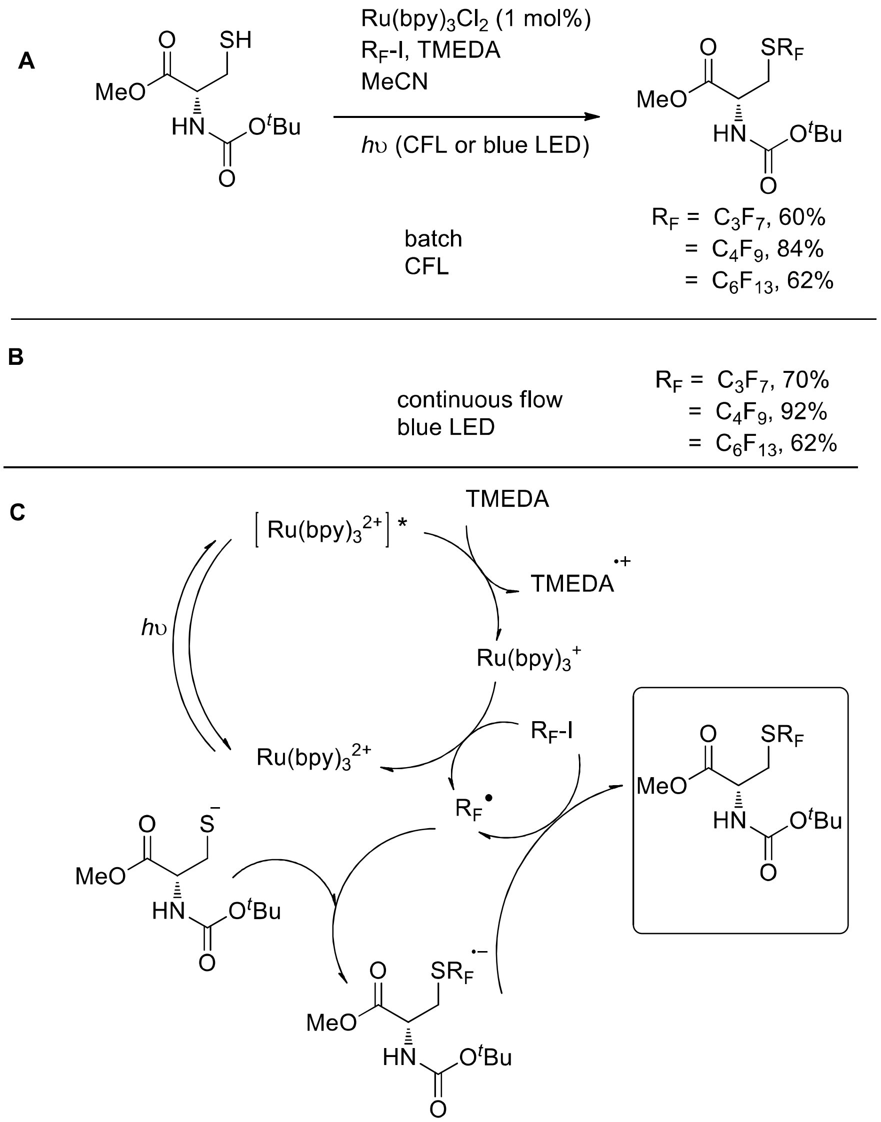


Scheme 9. (A) Substrate scope with respect to 2-acyl imidazoles and to perfluoroalkyl iodides and perfluorobenzyl iodide. (B) Proposed mechanism for the photoactivated asymmetric perfluoroalkylation of 2-acyl imidazoles

The authors propose a mechanism (Scheme 9(B)) involving coordination of the substrate with the Ir complex comprising the release of two acetonitrile ligands, which generates coordinated intermediate **I**, followed by deprotonation forming the enolate complex **II**. This enolate complex makes possible the catalytic photoredox cycle, forming perfluoroalkyl radicals via a single electron transfer reduction. Perfluoroalkyl radical addition to give the ketyl intermediate **III** is a highly stereoselective process. Ulterior oxidation to intermediate **IV** takes place releasing the final product and coordinating to a new substrate molecule. The electron released in the oxidation of **III** will either reduce R_FI to R_F radicals or reduce species **II**$^+$ (see photoredox catalysis cycle).

2.4.-Perfluoroalkylation of sulfides

Noël and collaborators [51,52] have accomplished the visible light-induced perfluoroalkylation of cysteine derivatives employing $Ru(bpy)_3{}^{2+}$ as photocatalyst and inexpensive R_FI as perfluoroalkyl radical source. The process can be accelerated in a photomicroreactor with notable increased yields. Some examples are illustrated in Scheme 10(A).

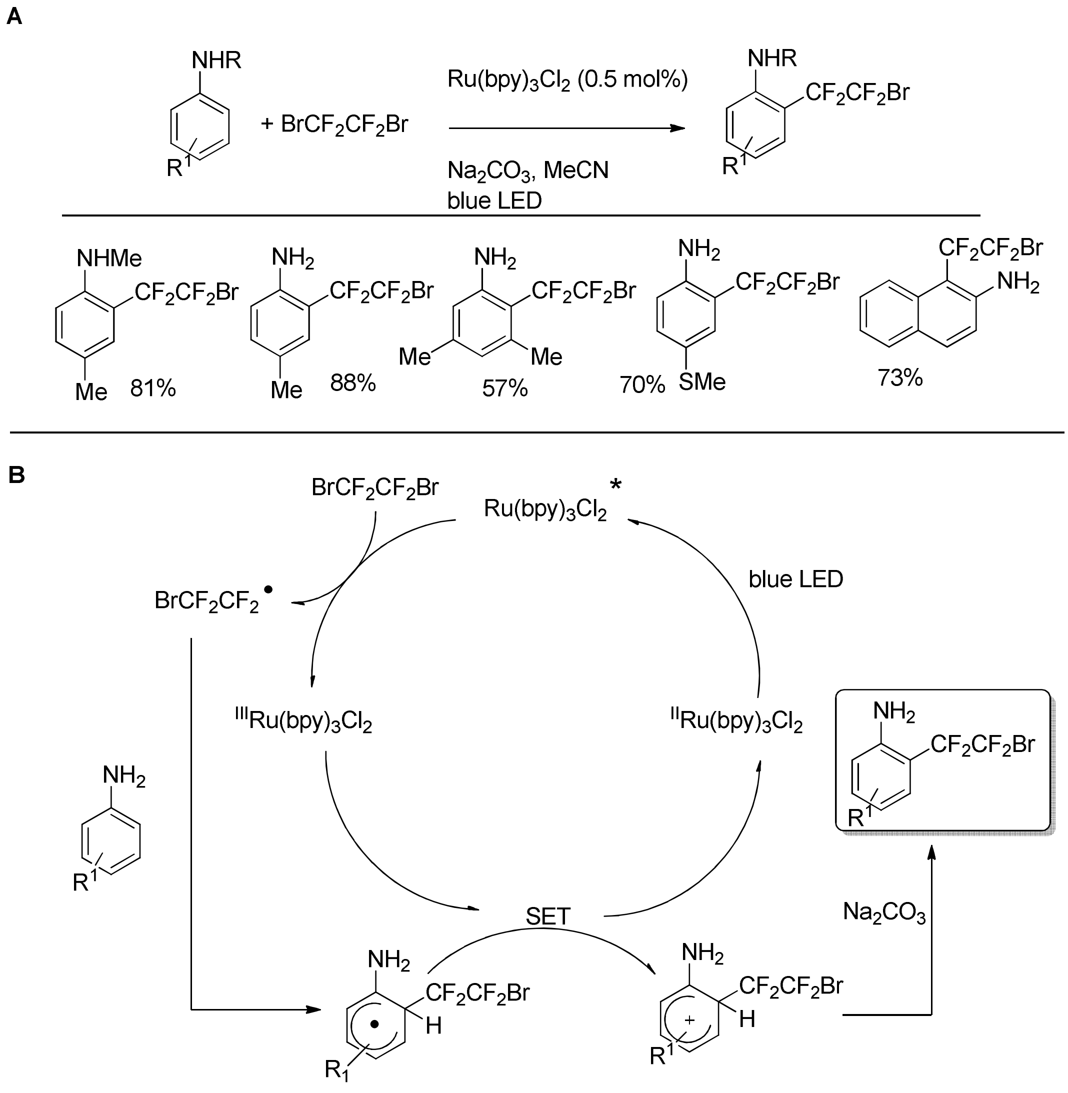


Scheme 10. (A) Examples of perfluoroalkylation of cysteine in batch through $Ru(bpy)_3^{2+}$ photocatalysis. (B) Idem to (A) in continuous flow. (C) Proposed reaction mechanism

Thus, the authors [51] extended the perfluoroalkylation protocol to a continuous flow microreactor and obtained excellent yields for the perfluoroalkylation of cysteine (Scheme 10(B)). A significant acceleration of the reaction rate was observed for perfluoroalkylation, thus affording the formation of the desired products within only 5 min residence time. The authors[51] proposed a mechanism such as that depicted in Scheme 10(C). Excitation of the photocatalyst $[Ru(bpy)_3]^{2+}$ either by the CFL or a blue LED source triggers a metal-to-ligand charge transfer state that is reduced by TMEDA. Following, $[Ru(bpy)_3]^{+}$ reduces R_F-I to R_F radicals (and iodide anion) and regenerates the catalyst into the starting oxidation state (i.e.: $[Ru(bpy)_3]^{2+}$). This radical (i.e. R_F) can subsequently react with cysteine to form the S−R_F linkage. The radical anion of the substitution product undergoes another single electron transfer step (SET) either to R_FI (chain-propagating SET) or to $[TMEDA]^{\bullet+}$ (chain-terminating SET). The authors measured the quantum yield of this transformation against the oxidation of 1,9-diphenylanthracene with singlet oxygen and found a value of Φ = 126, which demonstrates that a chain propagating single electron transfer (SET) step is indeed present in the light-induced perfluoroalkylation of cysteine.

2.5.-Perfluoroalkylation of (hetero)arenes[53]

Li, He and co-workers[54] have recently reported a visible-light-promoted direct fluoroalkylation of anilines with $BrCF_2CF_2Br$ through the use of $Ru(bpy)_2Cl_2$ photocatalyst. A brief scope of the reaction is depicted in Scheme 11(A).



Scheme 11. (A) Some examples for perfluoroalkylation of anilines. (B) Proposed reaction mechanism

The authors[54] have proposed a reaction mechanism such as that illustrated n Scheme 4(B). Photocatalyst Ru(bpy)$_3^{2+}$ [55] is excited through irradiation with a blue LED. The resulting triplet excited state of the photocatalyst acts as a good electron reductant to $BrCF_2CF_2Br$, producing bromotetrafluorethyl radicals, which add to the aniline derivative, to afford a cyclohexadienyl-type radical intermediate which can be oxidized by the Ru^{III}

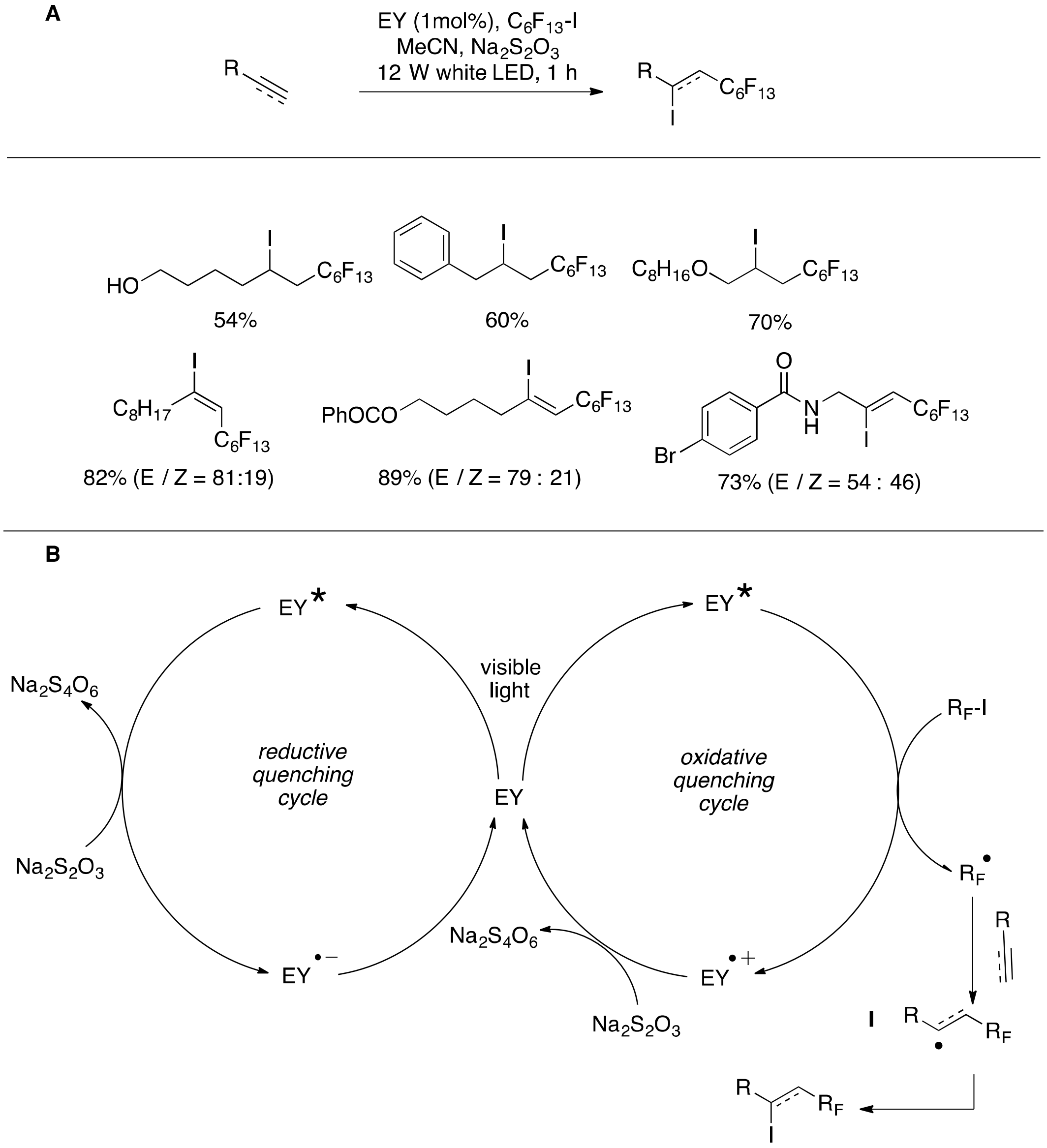
state of the catalyst to a Wheland intermediate, which suffers proton transfer to sodium carbonate.

3.- TRANSITION METAL-FREE PERFLUOROALKYLATION REACTIONS OF ORGANIC SUBSTRATES CATALYZED BY ORGANIC DYES

Organic-dye- photocatalyzed perfluoroalkylation reactions of organic substrates have been discussed and reviewed in the literature up to 2015. [34e] However, new and interesting contributions on catalytic dye-mediated radical perfluoroalkylation reactions[36] have been introduced ever since. Other non-metal-catalyzed perfluoroalkylation reactions have also been reviewed and reported by 2015.[56,37]

3.1.-Organo-catalyzed radical perfluoroalkylation of carbon-carbon multiple bonds: olefins and alkynes

Ikegami and colleagues [57] have reported the visible light iodoperfluoroalkylation of olefins and alkynes catalyzed by Eosin Y. [58] The scope of the transformation is illustrated in Scheme 12(A).

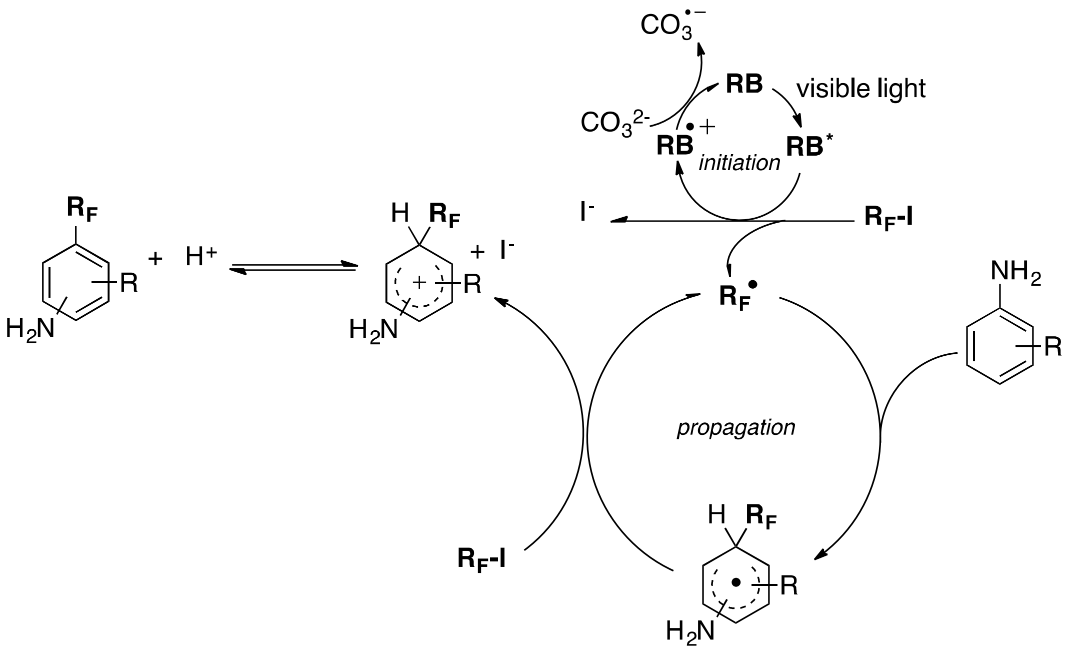


Scheme 12 (A) Scope of the Eosin Y-photocatalyzed perfluoroalkylation of alkenes and alkynes (B) Proposed reaction mechanism

The authors [57] proposed a reaction mechanism where photoexcitation of Eosin Y[58] (EY, Scheme 12(B)) could suffer either a reductive or oxidative quenching cycle (left and right, Scheme 12(B), respectively). Based on luminescence quenching experiments of EY by R_F-I, excited EY* reduces R_F-I to R_F radicals (oxidative quenching cycle) rendering EY radical cation in the process. EY is regenerated by reaction with $Na_2S_2O_3$ (or from iodide ion). R_F radical adds to the alkene (or alkyne) to render a radical intermediate **I** which can proceed to the iodoperfluoroalkylated product either through the following three routes: i) a radical chain reaction (propagation) with R_F-I; ii) oxidation of the radical adduct and nucleophilic iodide attack or iii) coupling of the carbon radical adduct with iodine radical. Probe experiments, and absence of light indicated that there is no or little chain reaction, ruling out route i). In the presence of alcohol or water, a hydroxyl or ether perfluoroalkylated product was not obtained, indicating that pathway ii) is also unlikely. Thus, the authors [57] concluded that the most probable route to product formation was iii), which is a radical-radical termination step.

3.2.- Organo-catalyzed radical perfluoroalkylation of (hetero)aromatic substrates

Barata-Vallejo [59] and colleagues have accomplished the radical perfluoroalkylation of aniline derivatives employing Rose Bengal (RB) as a photocatalyst, and Cs_2CO_3 as the base, in MeCN as solvent under visible light irradiation. In this work, a range of aniline derivatives with either electron donating or withdrawing groups could be perfluoroalkylated in yields ranging from 30% to quantitative. To account for the product formation, the authors[59] postulate a reaction mechanism such as that illustrated in Scheme 13.



Scheme 13. Proposed reaction mechanism for the Rose Bengal-photocatalyzed perfluoroalkylation of aniline derivatives

The authors[59] found that the reaction is accelerated with anilines bearing electron-donating groups. In the presence of TEMPO, a known radical scavenger, the reaction does not afford product. In the presence of 1,4-dinitrobenzene (a known radical anion scavenger), there is no reduction in product yield. Absence of light, interrupts product formation. Consequently, based on probe experiments a mechanism as illustrated in Scheme 13 is proposed.[59] Photocatalyst Rose Bengal **RB** is excited by means of visible light (compact fluorescent light, CFL) to an excited triplet state which is an excellent reductant to R_F-I (oxidative quenching cycle) to produce R_F radicals and the radical cation of **RB**. In turn, the photocatalyst is regenerated by CO_3^{2-} (initiation). R_F radicals combine with aniline derivative to afford the cyclohexadienyl-type radical intermediate **I**, which in a propagation step is oxidized by R_F-I to Wheland intermediate **II** and more R_F radicals, prolonging the radical chain. Intermediate **II** is deprotonated by the base, in a proton transfer (PT) step. This advantageous metal-free protocol should be confronted with the recently-published transition metal-mediated photocatalytic[60] perfluoroalkyation of anilines.

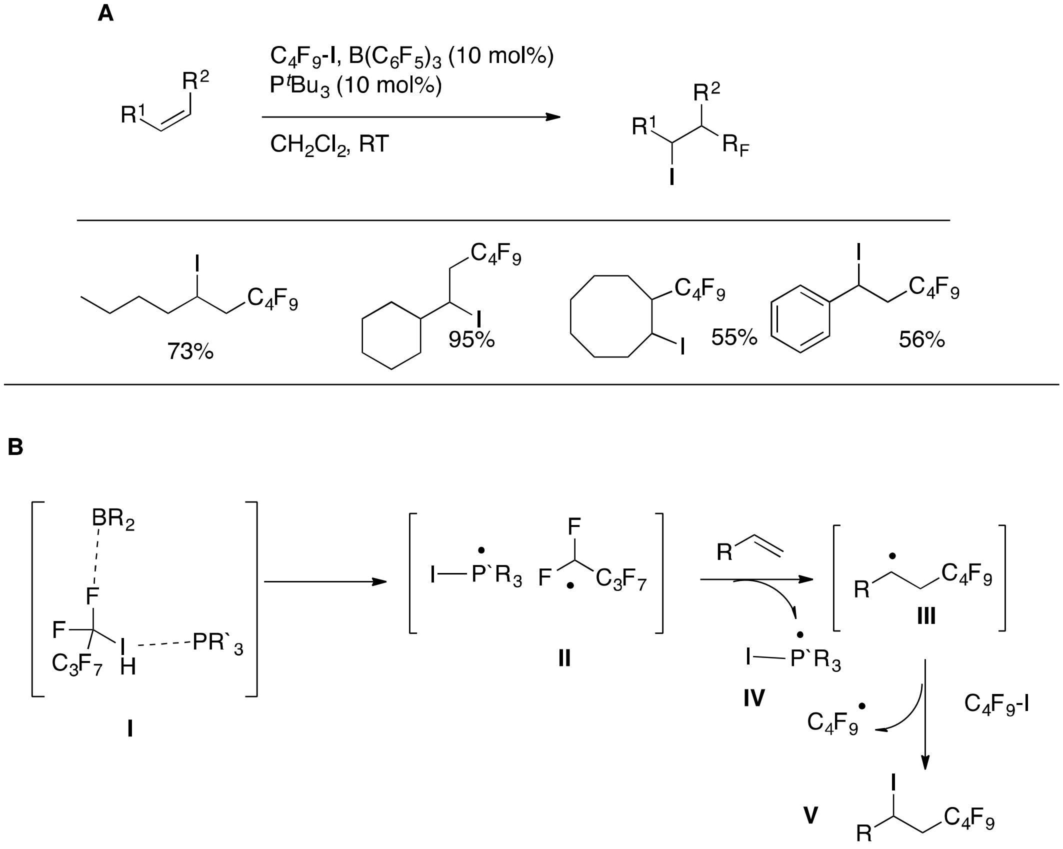
4.-PERFLUOROALKYLATION REACTIONS IN THE ABSENCE OF PHOTOCATALYSTS

4.1.-Perfluoroalkylation reactions by Frustrated Lewis Pairs (FLP)

4.1.1.-Perfluoroalkylation of carbon-carbon multiple bonds

Pairs of Lewis acids and Leis bases which are sterically demanding to form adducts are called frustrated Lewis pairs (FLP). [61]

Czekelius and colleagues[62] have utilized the concept of FLP to access perfluoroalkylation reactions of olefins. The reactions require only catalytic amounts of borane $B(C_6F_5)_3$ as Lewis acid, $P^t(Bu)_3$ as Lewis base, the perfluoroalkyl iodide R_F-I, an olefin in CH_2Cl_2 as solvent. The scope of the transformation is represented in Scheme 14(A).



Scheme 14 (A) Scope of the FLP formation of R_F radicals for the perfluoroalkylation of olefins. (B) Proposed reaction mechanism

The authors [62] found that when equal amounts of R_F-I and electron-rich phosphine $P^t(Bu)_3$ were dissolved in CD_2Cl_2, the ^{31}P NMR spectrum showed a significant upfield shift of the ^{31}P resonance, as well as the ^{19}F NMR spectrum of I-CF_2-C_3F_7, which indicated and I-P interaction. The electron-rich phosphine $P^t(Bu)_3$ forms a halogen bond to the R_F-I, supported by coordination of the borane $B(C_6F_5)_3$ to the fluorine substituent (structure intermediate **I**, Scheme 14(B)). This electron-rich phosphine $P^t(Bu)_3$ can reductively suffer an ET to R_F-I producing R_F radicals through an intermediate **II** (Scheme 14(B)). R_F radicals add to the olefin to form adduct **III**, which abstracts an iodine atom from R_F-I to further produce more R_F radicals and product **V**. The authors gained further proof of the radical pathway by reacting 1,6-heptadiene under the same protocol. Besides obtaining a double addition product, they found the cyclopentane derivative in a mixture of cis/trans isomers, which is consistent with a radical pathway. This cyclopentane derivative arises from *5-exo*-cyclization of 1-perfluorobutyl-6-hepten-2-yl radical. This protocol represents an advantage over the reported ATRA[39] reaction of olefins and alkynes with R_F-I mediated by $Ru(bpy)_3Cl_2$ and $[Ir\{dF(CF_3)ppy\}_2(dtbbpy)]PF_6$ photocatalysts[63b,c], since in the present case, no transition metal is used, neither photoactivation is necessary.

4.2.-Perfluoroalkylation reactions by Electron Donor Acceptor (EDA) complexes

Recently, the employment of electron donor-acceptor complexes (EDA complexes)[64,15] has superseded the use of organic photocatalysts in the visible light-induced production of R_F radicals and other types of carbon-centered radicals. These EDA complexes can be realized either through interaction of organic anions or heteroatomic lone electron pairs (oxygen-, nitrogen-, or sulfur-centered atoms) and R_F-I through well-established halogen bonding interactions. [65] Halogen-bonding has some advantages when compared with other intermolecular non-covalent interactions such as hydrogen bonding: i) greater directionality, ii) the atoms involved are more polarizable, iii) offers the possibility of different solubility profiles when taking into account R_F-I compounds. These non-covalent interactions can be profited to initiate single electron transfer (SET) events. These so called non-covalent interactions (i.e.:

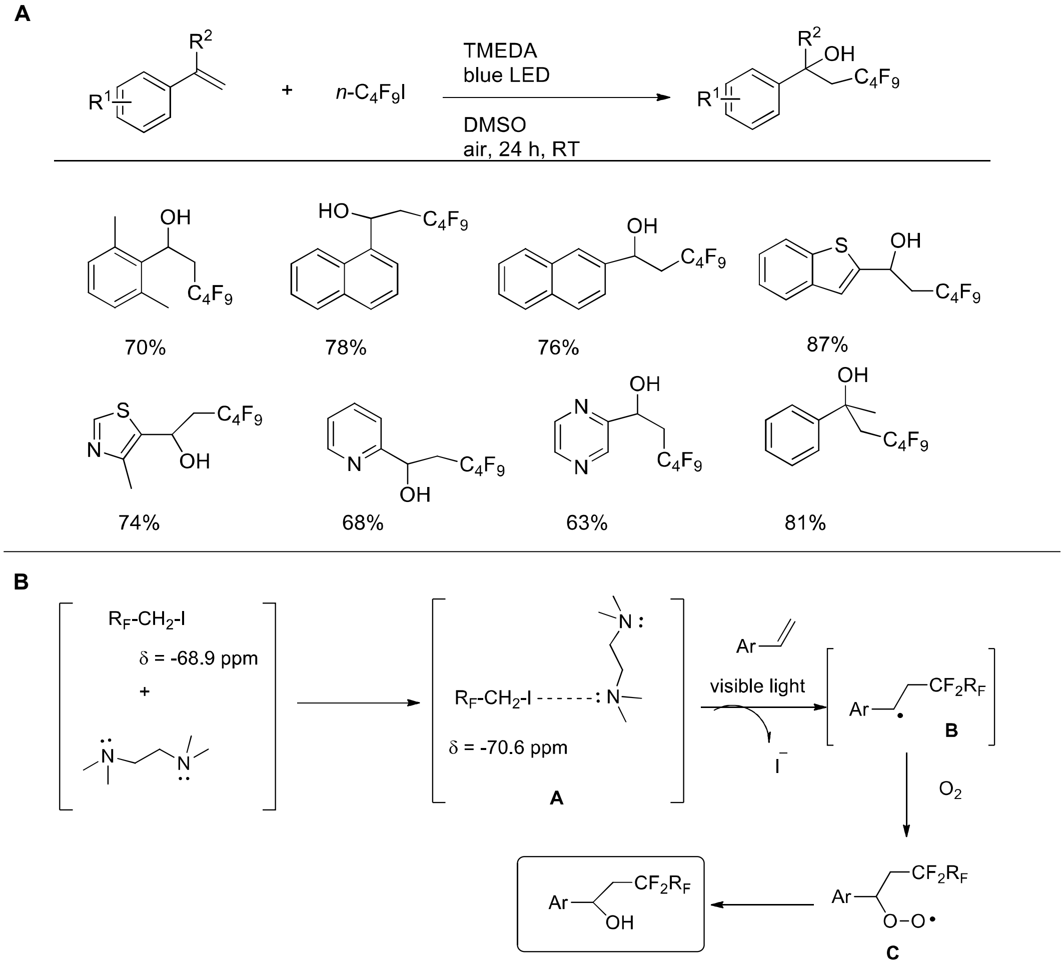
EDA complexes) can be excited by absorbing visible light, or in some cases spontaneously. [66]

Upon light excitation (or thermally induced) [45], these EDA complexes promote an intramolecular electron transfer ET between the lone electron pairs of the heteroatoms or the heteroatom-centered anion and the C-I σ^* antibonding orbital from the R_F-I, generating C-centered radicals. Thus, the production of R_F radicals induced by visible light (or by spontaneous ET) [66] and absence of photocatalysts (either organic or organometallic) has emerged as an even more environmentally respectful alternative and protocols that make use of these EDA complexes can be regarded as a further stage of development, simplifying reaction conditions and minimizing the use of chemicals, thus doing without the photocatalyst component.

Up to now the reported visible-light photoactive EDA complexes focus on i) employing R-I as electron acceptors and amines, enamines, or enolates as electron donors; ii) interaction of the lone electron pair from the N atom of amines (or O-/ N-centered anions) and electron poor substrates; iii) other interactions of electron deficient and electron rich organic cores. Visible-light photoactivation of these EDA complexes trigger fragmentation, substitution, and multiple-component reactions, facilitating formation of new intramolecular or intermolecular C-C bonds.[27] This has a parallel and reminiscence between the well-studied high energy photoinduced electron transfer (PET) between donor-acceptor (DA) complexes used in the past (i.e.: cyanoarenes and amines).[66] As a matter of fact, several years ago, MacMillan coined the phrase “No catalyst is better” as a new paradigm in catalyzed reactions. [67]

4.2.1-Perfluoroalkylation of carbon-carbon multiple bonds: olefins, and β,γ-unsaturated hydrazones

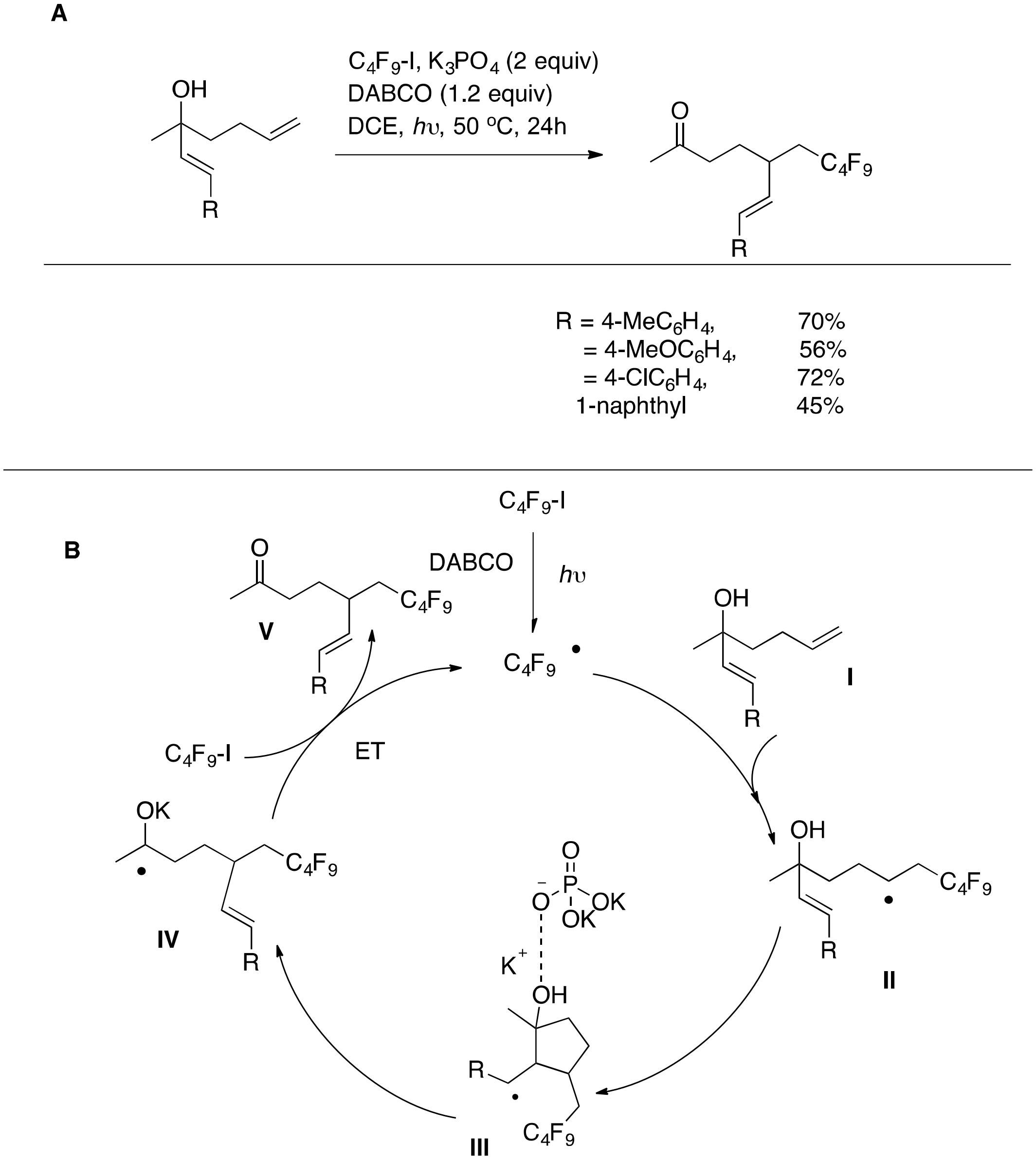
Chen and colleagues[68] have very recently reported a visible-light photoinduced hydroxyperfluoroalkylation of styrenes by means of an Electron Donor Acceptor (EDA) complexes. When styrenes are made to react in the presence of TMEDA / air, DMSO as solvent, a blue light diode as irradiation source and C_4F_9-I, a radical addition reaction ensues. The scope of the transformation is illustrated in Scheme 15(A).



Scheme 15 (A) Scope of the hydroxyperfluoroalkylation of styrenes through EDA complexes. (B) Proposed reaction mechanism for the hydroxyperfluoroalkylation of styrenes through EDA complexes

Conducting [64] the above reaction in the presence of a photocatalysts such as Ir(ppy)$_3$ had a detrimental effect when attempts were made to drive the reaction on a large scale (> 1 mmol scale). Support for the EDA complex between R$_F$-I and TMEDA was provided by ^{19}F NMR experiments. The use of hydroquinone and 1,4-dinitrobenzene partially or completely suppresses the reaction. The authors propose a reaction mechanism such as that shown in Scheme 15(B). An EDA complex between TMEDA and R$_F$-CH$_2$-I is formed (**A**, Scheme 15(B)), through halogen bonding interaction of R$_F$-I and TMEDA. Under visible light irradiation, complex **A** is photoactivated affording R$_F$ radicals which add to the styrene derivative to form perfluoroalkylated benzyl radical **B**. Radical **B** captures O$_2$ from air to afford peroxyl radical **C**, which renders the final product.[68]

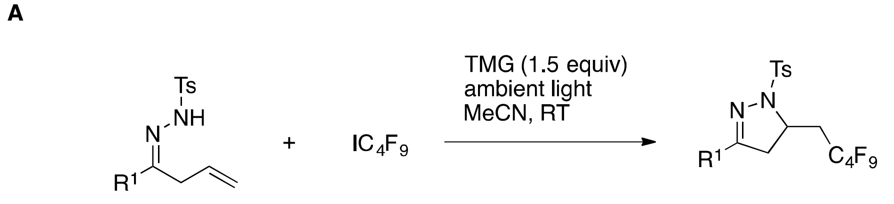
In a very recent report Studer[69] and colleagues have informed a perfluoroalkylation of olefins followed by radical alkenyl migration. The scope of the transformation is illustrated in Scheme 16(A).



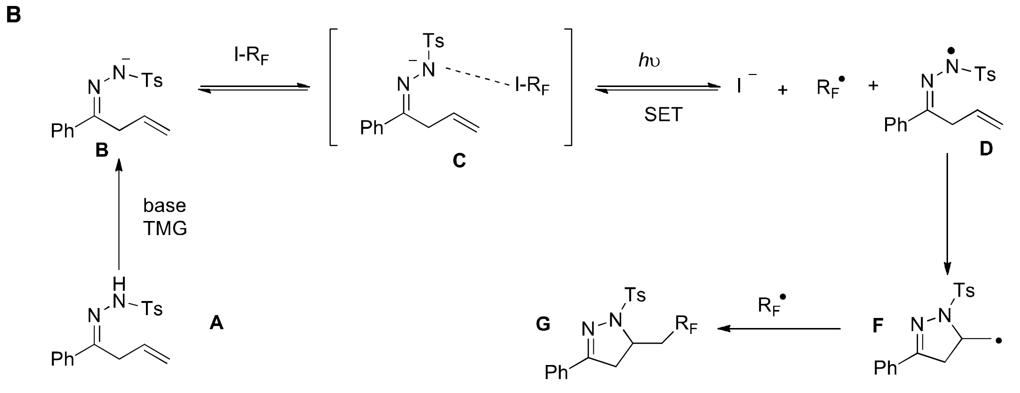
Scheme 16 (A) Substrate scope. (B) Proposed reaction mechanism

The initiation takes place by visible light irradiation of the halogen bond complex formed between the R_F-I and DABCO to afford R_F radicals (as in complex **A**, Scheme 15(B)). This radical R_F adds to the terminal carbon position of olefin **I**, to give adduct **II.** The other internal double bond is supposed to be protected or shielded by the quaternary carbon and remains unreactive at this stage. 5-exo cyclization leads to radical adduct **III**. In this case, the phosphate anion suffers hydrogen bonding with the tertiary alcohol (see structure **III**) leading to the activation of the C-C bond towards cleavage, affording the ketyl radical (ion) **IV**, which by an ET to R_F-I propagates the cycle and affords the final product **V**. This methodology has also been proposed by the same authors [54] [70] for the perfluoroalkylation of olefins followed by β-alkynylation.[71]

On the other hand, Cai and colleagues[72] have accomplished the ambient-light-promoted radical perfluoroalkylation / cyclization of β,γ-unsaturated hydrazones[49] towards the synthesis of perfluoroalkyl-substituted pyrazolines through EDA complexes and absence of photocatalysts in the presence of 1,1,3,3-tetramethylguanidine (TMG). The scope of the transformation is illustrated in Scheme 17(A).



R^1 = Ph	89%
= 4-Me-C_6H_4	82%
= 4-MeO-C_6H_4	80%
= 4-F-C_6H_4	92%
= 4-Cl-C_6H_4	93%
= 4-Br-C_6H_4	96%
= 4-CF_3-C_6H_4	87%
= 4-CN-C_6H_4	84%



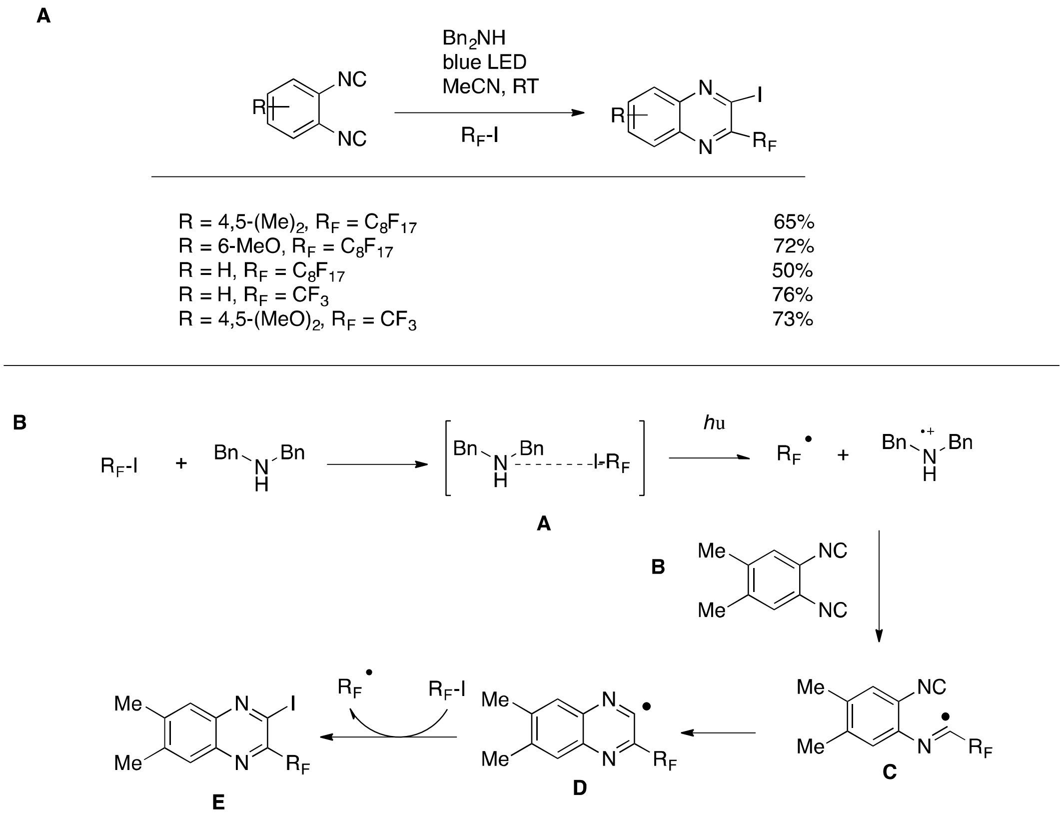
Scheme 17. (A) Scope of the perfluoroalkylation of β,γ-unsaturated hydrazones through visible light-excitation of EDA complexes formed from TMG[73] and R_F-I. (B) Proposed EDA mechanism for the perfluoroalkylation of β,γ-unsaturated hydrazones through visible light-excitation

The authors [72] postulate a mechanism such as that shown in Scheme 17(B). The reaction proceeds through the formation of an EDA complex (between TMG[73] and R_F-I, **C** Scheme 17(B)). Deprotonation of β,γ-unsaturated hydrazone **A** affords anionic intermediate **B** under basic conditions. Halogen bond adduct **C** is produced from a non-covalent weak interaction between **B** and R_F-I. This adduct **C** can initiate a visible-light-triggered ET to produce R_F radicals (and iodide anion) and a *N*-centered radical **D**. TMG acts not only as a base, but also as a halogen bond acceptor to speed the formation of R_F radicals. The resultant radical **F** reacts with R_F radical to produce perfluoroalkylated pyrazoline **G**.

4.2.2.-Perfluoroalkylation of carbon-nitrogen double bonds: hydrazones, and isocyanides

In another very recent report, Studer and colleagues[71c] have informed perfluoroalkylation of hydrazones employing a perfluoroalkyl derivative of the Togni reagent, which is reduced by tetrabutyl ammonium iodide (TBAI) which acts as one electron donor to produce R_F radicals. Although this initiation is not through an EDA complex, its utility should be confronted with previously reported methods[48] by Shi and Shen (*vide supra*) to obtain perfluoroalkyl-substituted hydrazones.

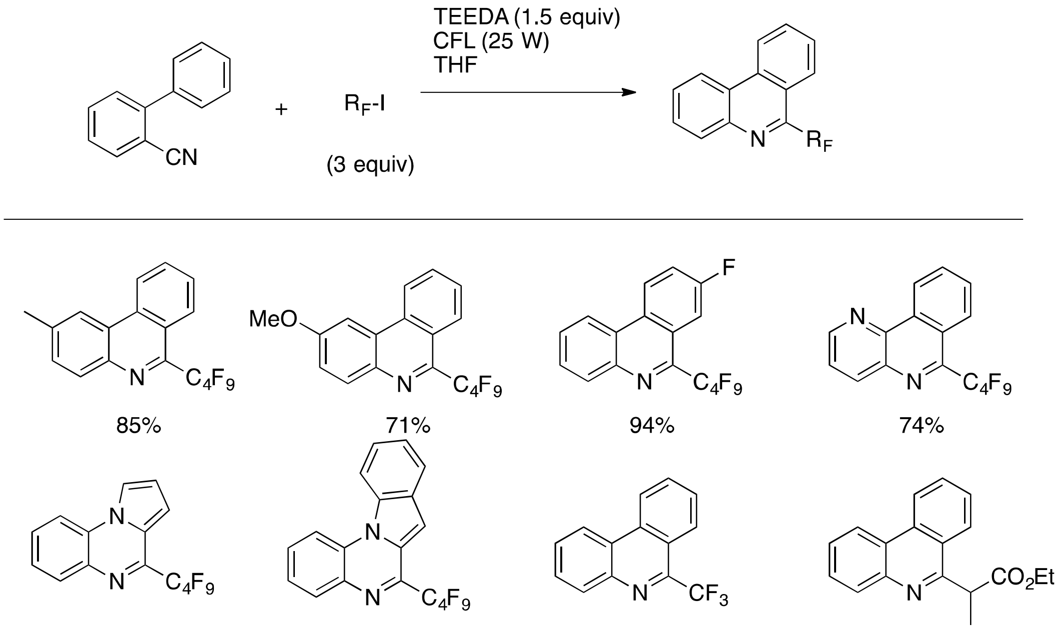
Ma, Yu and colleagues[74] have informed a halogen-bond-promoted double radical isocyanide insertion with R_F-I in the presence of organic bases (Bn_2NH). The scope of the transformation is depicted in Scheme 18(A).



Scheme 18. (A) Synthesis of 2-fluoroalkylated quinoxalines by hydrogen-bonded adducts. (B) Proposed reaction mechanism for the double radical isocyanide insertion

The authors[74] proposed a reaction mechanism based on a halogen-bonded adduct between an amine and R_F-I. When Bn_2NH is present, an encounter complex **A** through the halogen bonding adduct with R_F-I is formed. ET is initiated by visible light irradiation, affording perfluoroalkyl radical $R_F\bullet$, the radical cation of $Bn_2NH^{+\bullet}$, and iodide anion. Perfluoroalkyl radical $R_F\bullet$ adds to the diisocyanide **B**, generating radical adduct **C,** wherefrom radical cyclization ensues, affording intermediate **D**, which abstracts an iodine atom from R_F-I to afford the final product **E**. The process is illustrated in Scheme 18(B).

Chen and colleagues[75a] have also accomplished the synthesis of perfluoroalkyl-substituted phenanthridines through the use of excited EDA complexes. They employed *N,N,N´,N´*-tetraethylethylene diamine (TEEDA) as base, visible light (CFL), R_F-I, in the presence of 2-isocyano-1,1´-biphenyl. The scope of the transformation is illustrated in Scheme 19. This result represents a notorious advantage over[75b,c] the reported *fac*-Ir(ppy)$_3$-photocatalyzed method of isocyanides[75c], since no transition-metal photocatalyst is employed when the EDA complex methodology is utilized. However, the reaction proceeds with excess TEEDA, and no reagent is employed in catalytic or sub-catalytic quantities.

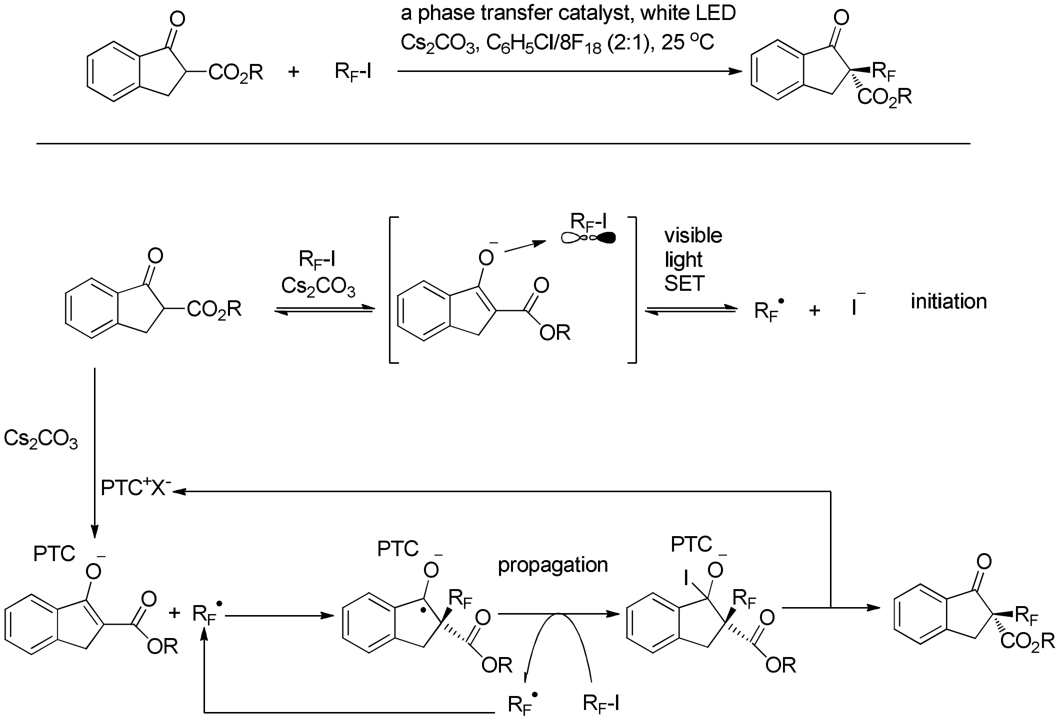


Scheme 19. Scope of the phenanthridine synthesis through EDA complexes

The authors[75a] proposed a reaction mechanism based on a halogen-bonded adduct between TEEDA and R_F-I. When TEEDA is present, an encounter complex is formed through halogen bonding with R_F-I. ET is initiated by visible light irradiation, affording perfluoroalkyl radical $R_F\bullet$, the radical cation of $TEEDA^{+\bullet}$, and iodide anion. Perfluoroalkyl radical $R_F\bullet$ adds to the isocyanide (as in Scheme 18), generating a radical adduct**,** wherefrom homolytic radical cyclization ensues, affording a radical intermediate which can be oxidized by RF-I to a Wheland intermediate that suffers ulterior proton transfer (PT) to yield the final phenanthridine-R_F-substituted product.

4.2.3.-Perfluoroalkylation of the α-position of carbonyl compounds: β-ketoesters

In 2014, Melchiorre and colleagues [76] have disclosed the metal-free photoinduced aromatic perfluoroalkylation of α-cyano arylacetates. Later on, in 2015 the same authors[77] have reported a strategy for the enantioselective[78] perfluoroalkylation of β-ketoesters through EDA complexes. The scope of the transformation is represented in Scheme 20.



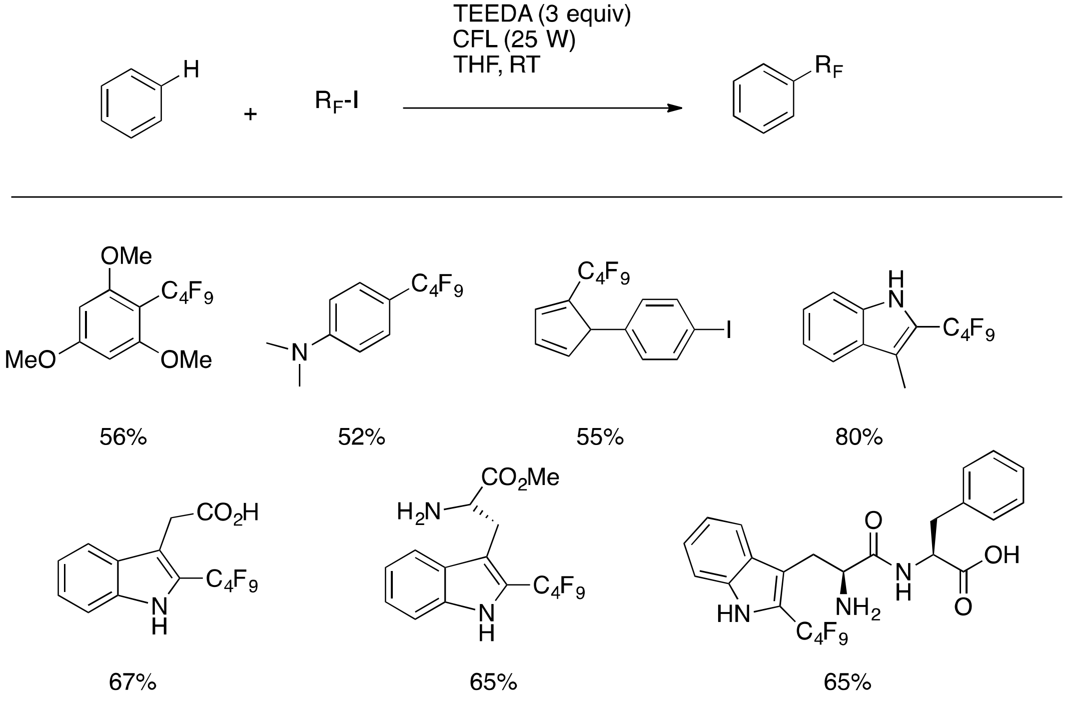
Scheme 20. Photoinduced enantioselective perfluoroalkylation of β-ketoesters

The phase transfer catalysts (PTC) is a cinchona-derived PTC catalyst (i.e.: *N*-3,4,5-trifluorobenzylcinchonium ion). Cheng and colleagues [79] have very recently undertaken a computational analysis to study the origin of the enantioselectivity of the above reaction employing density functional theory. By means of TD-DFT calculations (at the M06-2X/6.31G(d)+Lanl2dz level) EDA complexes through a C-I bond paralleled the plane of the enolate instead of a halogen bonding interaction between the R_F-I and the enolate which are responsible for visible light absorption. Also, from transition state structures, electrostatic interactions between the enolate and the PTC catalyst are observed.

A series of experiments were performed to gain insight into the mechanism of the reaction. The authors [76,77] propose a mechanism which is initiated by the photochemical activity of the EDA complex as shown in brackets (Scheme 20), formed upon aggregation of the enolate-type compound and R_F-I. A visible-light-driven electron transfer leads to the formation of R_F radicals, which then react with the enolate to form the new C-C bond. The adduct abstracts an iodine atom from RF-I, affording an organic iodide which upon ulterior iodide elimination results in the perfluoroalkylated β-ketoester.

4.2.4.-Perfluoroalkylation reactions of arenes

Chen and colleagues[75] have also accomplished homolytic aromatic substitution (HAS) by perfluoroalkyl radicals profiting from the visible light irradiation of EDA complexes formed between a base (TEEDA) and R_F-I. The scope of the transformation is illustrated in Scheme 21. These reactions do not necessitate the use of photocatalysts. [80]

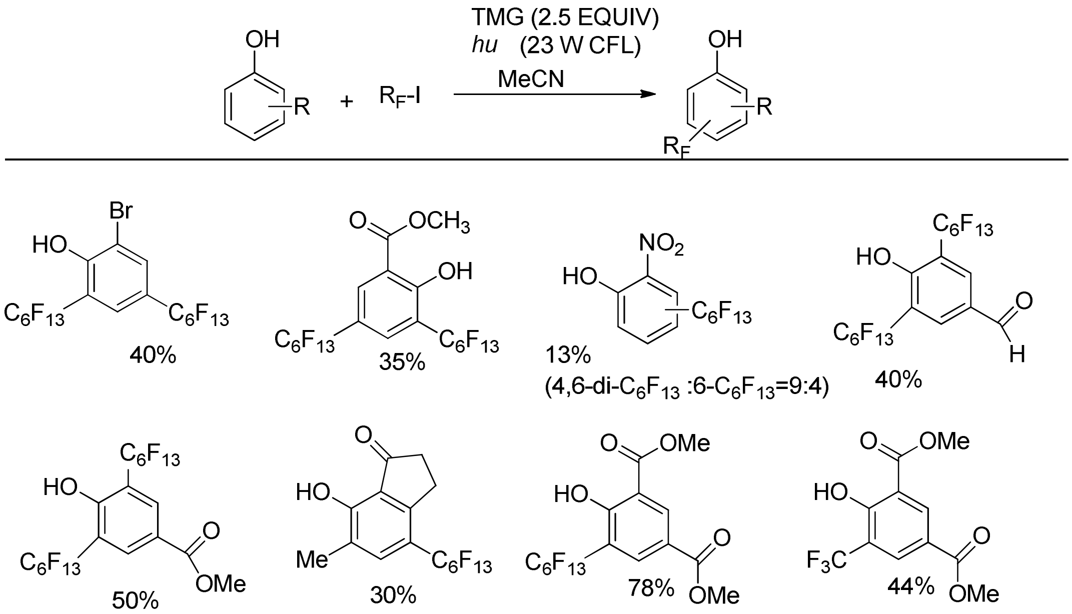


Scheme 21. Scope of the HAS employing visible light-irradiated halogen bond complex between TEEDA and R_F-I

The authors [75] found that the equilibrium constant between TEEDA and $C_{10}F_{21}$-I is 1.1 M^{-1}, forming a 1 : 1 complex. The authors concluded that the low intensity irradiation in the UV region of a CFL source is responsible for promoting excitation of the halogen bond complex that produces R_F radicals.

The formation of R_F radicals is postulated to be similar to that shown in Scheme 15(B). These R_F radicals effect HAS to the arene ring forming a cyclohexadienyl- R_F-substituted radical intermediate which is further oxidized to a sigma complex which suffers deprotonation rendering the final R_F-substituted arene product.

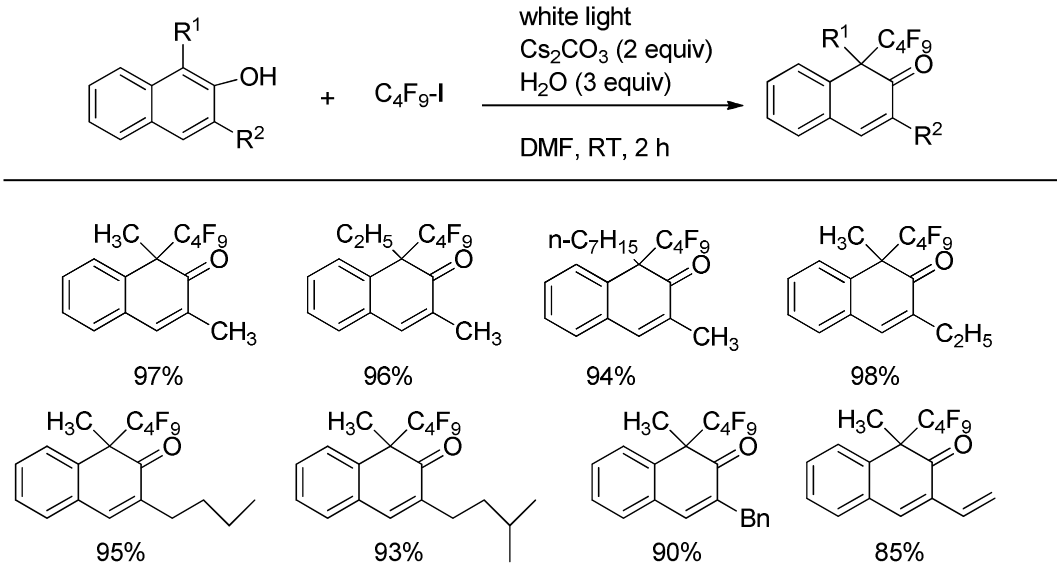
Melchiorre and colleagues [81] effected the perfluoroalkylation of phenols by accessing an EDA complex of the phenolate and R_F-I, which upon visible light irradiation produced R_F radicals. The scope of the reaction is represented in Scheme 22.



Scheme 22. Scope of the perfluoroalkylation of phenol derivatives

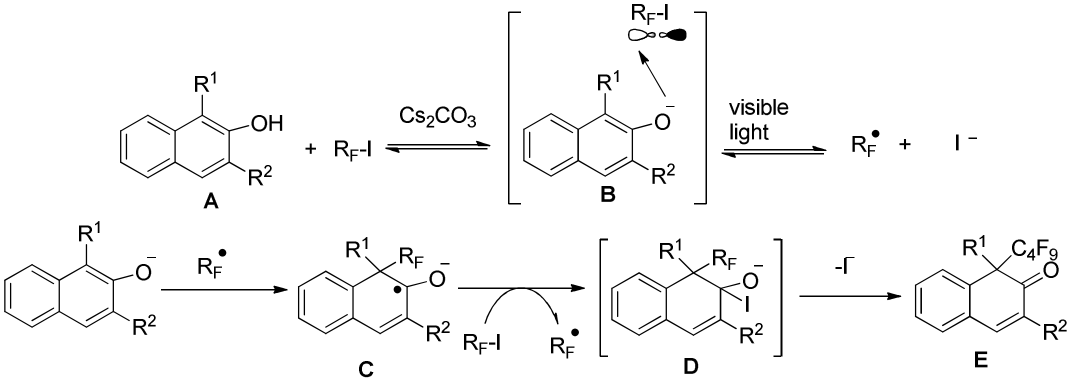
The authors[81] postulate a reaction mechanism in which the phenolate formed upon initial addition of TMG to the starting phenol MeCN solution activates a ground state EDA complex with R_F-I. Upon visible light absorption, this EDA complex affords R_F radicals. The substitution mechanism follows a classical HAS pathway, in which R_F radicals substitute the phenolate and the radical anion of the substitution intermediate propagates the chain. In the case of salicylaldehyde, this complex has a particular absorption and emission spectra (λ_{em} = 490 nm). A series of Stern Volmer plots show that R_F-I suppresses the excited state of the afore-mentioned EDA complex.

Xu and colleagues[82a] have accomplished the visible light-promoted dearomatizative fluoroalkylation of β-naphthols in the absence of photocatalysts. The protocol represents an advantageous synthesis, as the known perfluoroalkylation strategies of naphthols always led to *O*-fluoroalkylation. The scope of the transformation is represented in Scheme 23.



Scheme 23. Naphthols used in perfluoroalkylation reactions

This strategy of intermolecular charge transfer within EDA complex is effective for the introduction of R_F groups into naphthols. The authors propose a reaction mechanism such as that depicted in Scheme 24.



Scheme 24. Proposed mechanism for the EDA complex and perfluoroalkylation of naphthols

To commence with, in the presence of Cs_2CO_3, β-naphthol **A** (Scheme 24) is deprotonated to afford the β-naphtholate **B**. Visible light irradiation of the EDA complex between **B** and R_F-I promotes an ET leading to the formation of electron-deficient R_F radical through the reductive cleavage of the R_F-I bond. R_F radical is trapped by **A**, resulting in the ketyl radical intermediate **C**. **C** abstracts an iodine atom from R_F-I, providing R_F radical (propagation) and intermediate **D**. Unstable **D** collapses with loss of iodide anion to afford final product **E**. Probe experiments show that the reaction is suppressed in the presence of TEMPO. Alternatively, ketyl intermediate **C** can reduce R_F-I to afford product **E** directly in an ET step.

The perfluoroalkylation of sulfides has also been reported to proceed in the absence of photocatalysts and presence of organic base TMEDA.[7]

CONCLUSIONS

Relevant progress has been made in the last few years with regards to catalytic radical perfluoroalkylation reactions. Besides the well-established transition metal-mediated visible light-photocatalysis to generate R_F radicals, organic dye-visible light-photocatalyzed processes have also been reported to afford R_F radicals in comparable yields. With visible light-photoactivated organic dyes, radical perfluoroalkylation reactions have been accomplished both in substitution and addition processes on numerous organic families of compounds. As for employing red light to generate R_F radicals by catalysis, this has great benefits which include: i) lower power employed (600–700 nm), ii) no risk of light hazard, iii) the use of inexpensive lamps, and iv) more interestingly, it can penetrate even the turbid media. Employing lower power light (i.e.: red light) for chemical reactions still remains a challenge associated with choosing the right chromophoric photocatalyst. In this regard, red light has gained attention for its application in “greener” visible-light photoredox reactions. Although research in this area is in its infancy (only applied to the perfluoroalkylation of carbon-carbon multiple bonds), red-light-photocatalytic perfluoroalkylation reactions remained to be applied to substitutions on aromatic rings, and many other functional groups such as isocyanides, nitrones, sulfides, etc.

More recently, the no-catalyst-is better paradigm involving the use of visible-light photoactive Electron Donor Acceptor (EDA) complexes has superseded the employment of visible light activated photocatalyst, being able to produce R_F radicals for effecting either substitution or addition perfluoroalkylation reactions. Thus, the production of R_F radicals induced by visible light and absence of photocatalysts (either organic or organometallic) has emerged as an even more environmentally respectful alternative and protocols that make use of these EDA complexes can be regarded as a further stage of development, simplifying reaction conditions and minimizing the use of chemicals, thus doing without the photocatalyst component. In this manner, perfluoroalkylation reactions of carbon-carbon multiple bonds, isocyanides, α-cyano arylacetates, β-ketoesters, and aromatic rings have been reported. The radical perfluoroalkylation of a few other families of organic compounds, such as heteroaromatics, nitrones and hydrazones remain to be studied by visible light-photoactivation of EDA complexes. Interesting, the use of Frustrated Lewis Pairs (FLP) is a newly developed strategy reported to generate R_F radicals. The use of FLP for perfluoroalkylation reactions has only been studied for substituting olefins with R_F groups (in ATRA [21] reactions) and remains a field for exploration. The use of FLP is expected to be an active area for producing R_F radicals to effect substitution and addition reactions of several families of organic compounds.

REFERENCES

(1) Barata-Vallejo, S.; Bonesi, S. M.; Postigo, A. Perfluoroalkylation Reactions of (Hetero)arenes. *RSC Advances* **2015**, *5*, 62498-62518.

(2) (a) Petrov, V. A.; Davidson, F. Polyfluorinated Carbocations Stabilized by Oxygen and Sulfur. *J. Fluorine Chem*. **1999**, *95,* 5-13. (b) Tsuzuki, S.; Umecky, T.; Matsumoto, H.; Shinoda, W.; Mikami, M. Interactions of

Perfluoroalkyltrifluoroborate Anions with Li Ion and Imidazolium Cation: Effects of Perfluoroalkyl Chain on Motion of Ions in Ionic Liquids. *J. Phys. Chem. B* **2010**, *114*, 11390-11396.

(3) Janhsen, B.; Studer, A. Perfluoroalkylation of Aryl-*N*,*N*-dimethyl Hydrazones Using Hypervalent Iodine(III) Reagents or Perfluoroalkyl Iodides. *J. Org. Chem*. **2017**, *82*, 11703-11710.

(4) Wang, Y.; Wang, J.; Li, G.-X.; He, G.; Chen, G. Halogen-Bond-Promoted Photoactivation of Perfluoroalkyl Iodides: A Photochemical Protocol for Perfluoroalkylation Reactions. *Org. Lett.* **2017**, *19*, 1442–1445.

(5) (a) Wakselman, C. Single Electron-transfer Processes in Perfluoroalkyl Halides Reactions. *J. Fluorine Chemistry*, **1992**, *59*, 367-378. (b) Furin, G. G. Some New Aspects in the Application of Perfluoroalkyl Halides in the Synthesis of Fluorine-containing Organic Compound. *Russ. Chem. Rev.* **2000**, *69*, 491-522. c) Handbook on Fluorous Chemistry. Ed. J. A. Gladysz, D. P. Curran, I. T. Horvath, Wiley VCH, **2004**.

(6) Visible Light Photocatalysis in Organic Chemistry, Ed. C. R. J. Stephenson, T. P. Yoon, D. W. C. MacMillan, Wiley-VCH **2018**.

(7) Yerien, D. E.; Barata-Vallejo, S.; Camps, B.; Cristófalo, A. E.; Cano, M. E.; Uhrig, M. L.; Postigo, A. Electron-Catalyzed Radical Perfluoroalkylation of Organic Sulfides: the Serendipitous Use of the TMEDA/I_2 Complex as a Radical Initiator. *Catal. Sci. Technol.* **2017**, *7*, 2274-2282.

(8) (a) Xing, B.; Ni, C.; Hu, J. Copper-Mediated Di- and Monofluoromethanesulfonylation of Arenediazonium Tetrafluoroborates: Probing the Fluorine Effect. *Chinese J. Chem*., **2018**, *36*, 206 - 212. (b) Miao, W.; Zhao, Y.; Ni, C.; Gao, B.; Zhang, W.; Hu, J. Iron-Catalyzed

Difluoromethylation of Arylzincs with Difluoromethyl 2-Pyridyl Sulfone. *J. Am. Chem. Soc.*, **2018**, *140*, 880 - 883. (c) Jiang, F.; Ni, C.; Hu, J. Efficient Nucleophilic Difluoromethylation of Aldehydes with (Phenylsulfonyl)difluoromethylzinc and (Phenylsulfonyl)difluoromethylcadmium Reagents. *J. Fluorine Chem*., **2017**, *198*, 67 - 75. (d) Liu, Q.; Xiao, X.; Ni, C.; Hu, J. Stereoselective Carbonyl Olefination with Fluorosulfoximines: Facile Access to *Z* or *E* Terminal Monofluoroalkenes. *Angew. Chem., Int. Ed*. **2017**, *56*, 619 - 623. (e) Miao, W.; Ni, C.; Zhao, Y.; Hu, J. Nucleophilic Iododifluoromethylation of Carbonyl Compounds Using Difluoromethyl 2-Pyridyl Sulfone. *Org. Lett.* **2016**, *18*, 2766–2769. (f) Li, X.; Zhao, J.-W.; Hu, M.; Chen, D.; Ni, C.; Wang, L.; Hu, J. Copper-mediated Aerobic (Phenylsulfonyl)difluoromethylation of Arylboronic Acids with Difluoromethyl Phenyl Sulfone. *Chem. Comm*. **2016**, *52*, 3657 - 3660. (g) Rong, J.; Deng, L.; Tan, P.; Ni, C.; Gu, Y.; Hu, J. Radical Fluoroalkylation of Isocyanides with Fluorinated Sulfones by Visible-Light Photoredox Catalysis. *Angew. Chemie, Int. Ed.* **2016**, *55*, 2743 - 2747. (h) He, Z.; Tan, P.; Ni, C.; Hu, J. Fluoroalkylative Aryl Migration of Conjugated *N*-Arylsulfonylated Amides Using Easily Accessible Sodium Di- and Monofluoroalkanesulfinates. *Org. Lett*. **2015**, *17*, 1838 – 1841. (i) Li, X.; Zhao, J.; Zhang, L.; Hu, M.; Wang, L.; Hu, J., Copper-Mediated Trifluoromethylation Using Phenyl Trifluoromethyl Sulfoxide. *Org. Lett.* **2015**, *17*, 298 - 301. (j) Gao, B.; Zhao, Y.; Hu, J.; J. Hu, Difluoromethyl 2-Pyridyl Sulfone: A Versatile Carbonyl *Gem*-difluoroolefination Reagent. *Org. Chem. Frontiers* **2015**, *2*, 163 - 168. (k) Miao, W.; Ni, C.; Zhao, Y.; Hu, J. Radical (2-Pyridylsulfonyl)difluoromethylation of Terminal Alkenes with Iododifluoromethyl 2-Pyridyl Sulfone. *J. Fluorine Chem*. **2014**, *167*, 231 – 236. (l) Shen, X.; Zhou, M.; Ni, C.; Zhang, W.; Hu, J. Direct Monofluoromethylation of *O*-, *S*-, *N*-, and *P*-Nucleophiles with PhSO(NTs)CH_2F: The Accelerating Effect of α-Fluorine Substitution. *Chem. Sci.* **2014**, *5*, 117-122. (m) Zhang, W.; Zhao, Y.; Ni, C.; Mathew, T.; Hu, J. Palladium-catalyzed Allylation of 2,2,2-Trifluoroethyl Phenyl Sulfone, a Potential 2,2,2-Trifluoroethyl Pronucleophile. *Tetrahedron Lett*. **2012**, *53*, 6565-6568. (n) Huang, W.; Ni, C.; Zhao, Y.; Zhang, W.; Dilman, A.D.; Hu, J. Nucleophilic Difluoromethylation of CN Bonds in Heterocycles with Difluoromethyl Silane Reagents. *Tetrahedron*, **2012**, *68*, 5137-5144 (o) Huang, W.; Ni, C.; Zhao, Y.; Gao, B.; Hu, J. Nucleophilic Difluoromethylation of *N,N*-Acetals with TMSCF2SO2Ph Reagent Promoted by Trifluoroacetic Acid: A Facile Access to α-Difluoromethylated Tertiary Amines. *J. Fluorine Chem*. **2012**, *143*, 161-166. (p) Wang, F.; Zhang, L.; Zheng, J. ; Hu J. Chlorodifluoromethyl Aryl Ketones and Sulfones as Difluorocarbene Reagents: The Substituent Effect. *J. Fluorine Chem*. **2011**, *132*, 521-528. (q) Zhu, L.; Li, Y; Zhao, Y.; Hu, J. Nucleophilic (Phenylsulfonyl)difluoromethylation of Alkyl Halides Using PhSO2CF2SiMe3: Preparation of Gem-Difluoroalkenes and Trifluoromethyl Compounds. *Tetrahedron Lett*. **2010**, *51*, 6150-6152.

(9) (a) Lopez, S.E.; Gallagher, R..; Gilliland, R.J.; Ghiviriga, I.; Dolbier Jr., W. R. Synthesis of 3-Phenylsulfonyl-2-trifluoromethyl-1H-indoles: A Copper Catalyzed Cyclization Approach. *J. Fluorine Chem.* **2017**, *193*, 118-125. (b) Zhang, Z.; Martinez, H.; Dolbier, W. R. Photoredox Catalyzed Intramolecular Fluoroalkylarylation of Unactivated Alkenes. *J. Org. Chem*. **2017**, *82*, 2589-2598. (c) Zhang, Z.; X. Tang, J.; Dolbier, W. R. Jr. Photoredox-Catalyzed Intramolecular Difluoromethylation of *N*-Benzylacrylamides Coupled with a Dearomatizing Spirocyclization: Access to CF_2H-Containing 2-

Azaspiro[4.5]deca-6,9-diene-3,8-diones. *Org.Lett.* **2016** *18*, 1048-1051. (d) Thompson, C.S.; Dolbier Jr , W. R. Carbomethoxydifluoromethylation of Enol Acetates with Methyl (Chlorosulfonyl)difluoroacetate Using Visible-light Photoredox Catalysis. Synthesis of 2,2-Difluoro-γ-ketoesters. *J. Fluorine Chem.* **2015**, *178*, 327-331. (e) Zhang, Z.; Tang, X. Dolbier Jr., W. R. Photoredox-Catalyzed Tandem Insertion/Cyclization Reactions of Difluoromethyl and 1,1-Difluoroalkyl Radicals with Biphenyl Isocyanides. *Org. Lett*. **2015,** *17*, 4401-4403. (f) Zhang, Z.; Tang, X.; Thompson, C.S.; Dolbier Jr., W. R. Photoredox-Catalyzed Intramolecular Aminodifluoromethylation of Unactivated Alkenes. *Org. Lett*. **2015**, *17*, 3528-3531. (g) Lopez, S. E.; Mitani, A.; Pena, P.; Ghiviriga, I.; Dolbier Jr., W.R. Use of 1-Pentafluorosulfanyl-Phenylacetylenes for the Preparation of SF5-Substituted Five-membered Ring Heterocycles Through 1,3-Dipolar Cycloadditions. Isoxazoles and Isoxazolines. *J. Fluorine Chem*. **2014**, *176*, 121-126.

(10) Barata-Vallejo, S.; Lantano, B.; Postigo, A. Recent Advances in Trifluoromethylation Reactions with Electrophilic Trifluoromethylating Reagents. *Chem. Eur. J*. **2014**, *20*, 16806-6829.

(11) Yerien, D. E.; Barata-Vallejo, S.; Postigo, A. Difluoromethylation Reactions of Organic Compounds. *Chem. Eur. J*. **2017**, *23*, 14676-14701.

(12) Barata-Vallejo, S.; Postigo, A. Metal-Mediated Radical Perfluoroalkylation of Organic Compounds. *Coord. Chem. Rev*. **2013***, 257*, 3051-3069.

(13) Lantaño, B.; Torviso, M. R.; Bonesi, S. M.; Barata-Vallejo, S.; Postigo, A. Advances in Metal-Assisted non-Electrophilic Fluoroalkylation Reactions of Organic Compounds. *Coord. Chem. Rev.* **2015**, *285*, 76-108.

(14) Lin, J.-S., Wang, F.-L.; Dong, X.-Y.; He, W.-W.; Yuan, Y.; Chen, S.; Liu, X.-Y. Catalytic Asymmetric Radical Aminoperfluoroalkylation and Aminodifluoromethylation of Alkenes to Versatile Enantioenriched-fluoroalkyl Amines, *Nat. Commun*. **2017**, *8*, 14841.

(15) (a) Li, X.-F; Lin, J.-S.; Liu, X.-Y. Catalytic Radical Intramolecular Aminoperfluoroalkylation and Aminodifluoromethylation of Unactivated Alkenes with Fluoroalkylsulfonyl Chlorides. *Synthesis* **2017**, *49*, 4213-4220. (b) Li, L.; Li, Z.-L.; Gu, Q.-S.; Wang, N.; Liu, X.-Y. A Remote C–C Bond Cleavage–enabled Skeletal Reorganization: Access to Medium-/Large-sized Cyclic Alkenes, *Sci. Adv*. **2017**; 3: e1701487.

(16) *a)* Hu, W.-Q.; Xu, X.-H.; Qing, F.-L. Visible Light Induced Hydrodifluoromethylation of Alkenes Derived from Oxindoles with (Difluoromethyl)triphenylphosphonium Bromide. *J. Fluorine Chem.* **2018**, *208*, 73–79**.** (*b)* Ran, Y.; Lin, Q.-Y.; Xu, X.-H.; Qing, F.-L. Radical Difluororomethylation of Thiols with Difluoromethylphosphonium Triflate under Photoredox Catalysis. *J. Org. Chem*. **2017**, *82*, 7373−7378. (*c)* Ran, Y.; Lin, Q.-Y.; Xu, X.-H.; Qing F.-L. Visible Light Induced Oxydifluoromethylation of Styrenes with Difluoromethyltriphenylphosphonium Bromide. *J. Org. Chem*. **2016**. *81*, 7001-7007. (d) Lin, Q.-Y.; Ran, Y.; Xu, X.-H.; Qing, F.-L. Photoredox-Catalyzed Bromodifluoromethylation of Alkenes with (Difluoromethyl)triphenylphosphonium Bromide. *Org. Lett.* **2016**, *18*, 2419–2422.

(17) Panferova, L. I.; Tsymbal, A. V.; Levin, V. V.; Struchkova, M. I.; Dilman, A. D. Radical Silyldifluoromethylation of Electron-Deficient Alkenes. *Org. Lett.* **2016**, *18*, 996-999.

(18) a) Dilman, A. D.; Levin, V. V. Difluorocarbene as a Building Block for Consecutive Bond-Forming Reactions. *Acc. Chem. Res.* **2018**, *51*, 1272–1280. (b) Tsymbal, A. V.; Levin, V. V.; Struchkova, M. I.; Kokorekin, V. A.; Korlyukov, A. A.; Dilman, A. D. Reductive Silylation of Gem-difluorinated Phosphonium Salts. *J. Fluorine Chem*. **2018**, *205*, 58-61.

(19) Sumino, S.; Uno, M.; Fukuyama, T.; Ryu, I.; Matsuura, M.; Yamamoto, A.; Kishikawa, Y. Photoredox-Catalyzed Hydrodifluoroalkylation of Alkenes Using Difluorohaloalkyl Compounds and a Hantzsch Ester. *J. Org. Chem*. **2017**, 82, 5469 – 5474.

(20) Romero, N. A.; Nicewicz, D. A. Organic Photoredox Catalysis. *Chem. Rev.* **2016**, *116*, 10075-10166.

(21) Shaw, M. H.; Twilton, J.; MacMillan, D. W. C. Photoredox Catalysys in Organic Synthesis. *J. Org. Chem*. **2016**, *81*, 6898-6926.

(22) Sun, J.; He, Y.; An, X. -D.; Zhang, X.; Yu, L.; Yu, S. Visible-Light-Induced Iminyl Radical Formation via Electron-Donor-Acceptor Complexes: a Photocatalyst-Free Approach to Phenanthridines and Quinolines. *Org. Chem. Front*. **2018**, *5*, 977-981.

(23) Ghosh, I.; König, B. Chromoselective Photocatalysis: Controlled Bond Activation through Light-Color Regulation of Redox Potentials. *Angew. Chem. Int. Ed*. **2016**, *55*, 7676-7679.

(24) Marzo, L.; Pagire, S. K.; Reiser, O.; König, B. Visible-Light Photocatalysis: Does it make a difference in Organic Synthesis? *Angew. Chem. Int. Ed*. **2018**. https://doi.org/10.1002/anie.201709766

(25) Li, Y.; Miao, T.; Li, P.; Wang, L. Photo-Driven Synthesis of C6-Polyfunctionalized Phenanthridines from Three-Component Reactions of

Isocyanides, Alkynes, and Sulfinic Acids by Electron Donor-Acceptor Complex. *Org. Lett*. **2018**, *20*, 1735-1739.

(26) Barata-Vallejo, S.; Yerien, D. E.; Postigo, A. Benign Perfluoroalkylation of Aniline Derivatives through Photoredox Organocatalysis under Visible-Light Irradiation. *Eur. J. Org. Chem*. **2015**, 7869-7875.

(27) Xu, J.; Shanmugam, S.; Duong, H. T.; Boyer, C. Organo-Photocatalysts for Photoinduced Electron Transfer-Reversible Addition-Fragmentation Chain Transfer (PET-RAFT) Polymerization. *Polym. Chem.* **2015**, *6*, 5615-5624.

(28) Torviso, M. R.; Mansilla, D.; Garcia, S.; Lantaño, B.; Barata-Vallejo, S.; Postigo, A. Late-Stage Electron-Catalyzed Perfluoroalkylation of Coumarin Derivatives—Thermal Fluoroalkyl Radical Production from Sodium Perfluoroalkyl Sulfinate Salts. *J. Fluorine Chem*. **2017**, *197*, 42-48.

(29) (a) Bardagi, J. I.; Ghosh, I.; Schmalzbauer, M.; Ghosh, T.; König, B. Anthraquinones as Photoredox Catalysts for the Reductive Activation of Aryl Halides. *Eur. J. Org. Chem*. **2018**, 34-40. (b) Pitre, S. P.; McTiernan, C. D.; Scaiano, J. C. Library of Cationic Organic Dyes for Visible-Light-Driven Photoredox Transformations. *ACS Omega* **2016**, *1*, 66-76.

(30) (a) Matsuzaki, K.; Hiromura, T.; Tokunaga, E.; Shibata, N. Trifluoroethoxy-Coated Subphthalocyanine affects Trifluoromethylation of Alkenes and Alkynes Even under Low-Energy Red-Light Irradiation. *ChemistryOpen* **2017**, *6***,** 226-230. (b) Matsuzaki, K.; Hiromura, T.; Amii, H.; Shibata, N. Trifluoroethoxy-Coated Phthalocyanine Catalyzes Perfluoroalkylation of Alkenes under Visible-Light Irradiation. *Molecules* **2017**, *22,* 1130-1142.

(31) (a) Ma, J.-A.; Cahard, D. Strategies for Nucleophilic, Electrophilic, and Radical Trifluoromethylations. *J. Fluorine Chem.* **2007**, *128*, 975-996. (b) Natte, K.; Jagadeesh, R. V.; He, L.; Rabeah, J.; Chen, J.; Taeschler, C.; Ellinger, S.; Zaragoza, F.; Neumann, H.; Brückner, A.; Beller, M. Palladium-Catalyzed Trifluoromethylation of (Hetero)Arenes with CF_3Br. *Angew. Chem. Int. Ed*. **2016**, *55*, 2782-2786.

(32) (a) Lantaño, B.; Postigo, A. Radical Fluorination Reactions by Thermal and Photoinduced Methods. *Org. Biomol. Chem*. **2017**, *15*, 9954-9973. (b) Lee, J. W.; Spiegowski, D. N.; Ngai, M.-Y. Selective C–O Bond Formation via a Photocatalytic Radical Coupling Strategy: Access to Perfluoroalkoxylated (OR_F) Arenes and Heteroarenes. *Chem. Sci.* **2017**, *8*, 6066-6070.

(33) Barata-Vallejo, S.; Bonesi, S. M.; Postigo, A. Late Stage Trifluoromethylthiolation Strategies for Organic Compounds. *Org. Biomol. Chem*. **2016**, *14*, 7150-7182.

(34) (a) Ma, J.-N.; Cahard, D. Asymmetric Fluorination, Trifluoromethylation, and Perfluoroalkylation Reactions. *Chem. Rev.* **2004**, *104*, 6119-6146. (b) Barata-Vallejo, S.; Bonesi, S. M.; Postigo, A. Photocatalytic Fluoroalkylation Reactions of Organic Compounds. *Org. Biomol. Chem*. **2015**, *13*, 11153-11183. (c) Ma, J.-A.; Cahard, D. Update 1 of: Asymmetric Fluorination, Trifluoromethylation, and Perfluoroalkylation Reactions. *Chem. Rev.* **2008**, *108*, PR1-PR43.

(35) Stephenson, C. R. J.; Yoon, T. P.; MacMillan, D. W. C. in *Visible Light Photocatalysis in Organic Chemistry*; Wiley-VCH; **2018**; 389-410. ISBN: 978-3-527-33560-2.

(36) Dagousset, G.; Carboni, A.; Masson, G.; Magnier, E. In *Modern Synthesis Processes and Reactivity of Fluorinated Compounds.* 1st Ed.; Groult, H.; Leroux, F.; Tressaud, A.; Elsevier; **2017**; 389-426. ISBN: 978-0-128-03790-4. http://dx.doi.org/10.1016/B978-0-12-803740-9.00014-7.

(37) Song, H.-X.; Han, Q.-Y.; Zhao, C.-L.; Zhang, C.-P. Fluoroalkylation Reactions in Aqueous Media: A Review. *Green Chem.* **2018**, 20, 1662-1731.

(38) Wu, G.; von Wangelin, A. J. Stereoselective Cobalt-Catalyzed Halofluoroalkylation of Alkynes. *Chem. Sci.* **2018**, *9*, 1795-1802.

(39) Rawner, T.; Lutsker, E.; Kaiser, C. A.; Reiser, O. The Different Faces of Photoredox Catalysts: Visible-Light-Mediated Atom Transfer Radical Addition (ATRA) Reactions of Perfluoroalkyl Iodides with Styrenes and Phenylacetylenes. *ACS Catal.* **2018**, *8*, 3950-3956.

(40) Beniazza, R.; Atkinson, R.; Absalon, C.; Castet, F.; Denisov, S. A.; McClenaghan, N. D.; Lastecoueres, D.; Vincent, J.-M. Benzophenone vs. Copper/Benzophenone in Light-Promoted Atom Transfer Radical Additions (ATRAs): Highly Effective Iodoperfluoroalkylation of Alkenes/Alkynes and Mechanistic Studies. *Adv. Synth. Catal*. **2016**, *358*, 2949-2961.

(41) Liu, Y.-Y.; Yu, X.-Y.; Chen, J.-R.; Qiao, M.-M., Qi, X.; Shi, D.-Q; Xiao, W. J. Visible-Light-Driven Aza-ortho-quinone Methide Generation for the Synthesis of Indoles in a Multicomponent Reaction. *Angew. Chem. Int. Ed*. **2017**, *56*, 9527 –9531.

(42) (a) Rousset, E.; Chartrand, D.; Ciofini, I.; Marvaud, V.; Hanan, G. S. Red-Light-Driven Photocatalytic Hydrogen Evolution using a Ruthenium Quaterpyridine Complex. *Chem.Comm*. **2015**, *51*, 9261-9264. (b) Carling, C.-J.; Olejniczak, J.; Foucault-Collet, A.; Collet, G.; Viger, M. L.; Nguyen Huu, V. A.; Duggan, B. M.; Almutairi, A. Efficient Red Light Photo-Uncaging of Active Molecules in Water upon Assembly into Nanoparticles. *Chem. Sci*. **2016**, *7*, 2392-2398. (c) Zhang, H.; Trout, W. S.; Liu, S.; Andrade, G. A.; Hudson, D. A.; Scinto, S. L.; Dicker, K. T.; Li, Y.; Lazouski, N.; Rosenthal, J.; Thorpe, C.; Jia, X.; Fox, J. M. Rapid Bioorthogonal Chemistry Turn-on through Enzymatic or Long Wavelength Photocatalytic Activation of Tetrazine Ligation. *J. Am. Chem. Soc*. **2016**, *138*, 5978-5983.

(43) Wallentin, C.-J.; Nguyen, J. D.; Finkbeiner, P.; Stephenson, C. R. J. Visible Light-Mediated Atom Transfer Radical Addition via Oxidative and Reductive Quenching of Photocatalysts. *J. Am. Chem. Soc*. **2012**, *134*, 8875-8884.

(44) Wayner, D. D. M.; Houmam, A. Redox Properties of Free Radicals. *Acta. Chem. Scand.* **1998**, *52*, 377-384.

(45) Geng, X.; Lin, F.; Wang, X.; Jiao, N. Azidofluoroalkylation of Alkenes with Simple Fluoroalkyl Iodides Enabled by Photoredox Catalysis. *Org. Lett*. **2017**, *19*, 4738-4741.

(46) Supranovich, V. I.; Levin, V. V.; Struchkova, M. I.; Dilman, A. D. Photocatalytic Reductive Fluoroalkylation of Nitrones. *Org. Lett*. **2018**, *20*, 840-843.

(47) Xie, J.; Zhang, T.; Chen, F.; Mehrkens, N.; Rominger, F.; Rudolph, M.; Hashmi, A. S. K. Gold-Catalyzed Highly Selective Photoredox C(sp(2))-H

Difluoroalkylation and Perfluoroalkylation of Hydrazones. *Angew. Chem. Int. Ed*. **2016**, *55*, 2934-2938.

(48) Ji, H.; Ni, H.-Q.; Zhi, P.; Xi, Z.-W.; Wang, W.; Shi, J.-J.; Shen, Y.-M. Visible-Light Mediated Directed Perfluoroalkylation of Hydrazones. *Org. Biomol. Chem*. **2017**, *15*, 6014-6023.

(49) (a) Xu, P.; Li, W.; Xie, J.; Zhu, C. Exploration of C–H Transformations of Aldehyde Hydrazones: Radical Strategies and Beyond. *Acc. Chem. Res*. **2018**, *51*, 484−495. (b) Xu, X.; Zhang, J.; Xia, H.; Wu, J. C(sp^2)–H Functionalization of Aldehyde-Derived Hydrazones via a Radical Process. *Org. Biomol. Chem*. **2018**, *16*, 1227-1241.

(50) (a) Liu, J.; Ding, W.; Zhou, Q.-Q.; Liu, D.; Lu, L.-Q.; Xiao, W.-J. Enantioselective Di-/Perfluoroalkylation of β−Ketoesters Enabled by Cooperative Photoredox/Nickel Catalysis. *Org. Lett.* **2018**, *20*, 461-464. (b) Huo, H.; Huang, X.; Shen, X.; Harns, K.; Meggers, E. Visible-Light-Activated Enantioselective Perfluoroalkylation with a Chiral Iridium Photoredox Catalyst. *Synlett* **2016**, *27*, 749-753.

(51) Botecchia, C.; Wei, X.-J.; Kuijpers, K. P. L.; Hessel, V.; Noel, T. Visible Light-Induced Trifluoromethylation and Perfluoroalkylation of Cysteine Residues in Batch and Continuous Flow. *J. Org. Chem*. **2016**, *81*, 7301-7307.

(52) Straathof, N. J. W.; Noël, T. in *Visible Light Photocatalysis in Organic Chemistry*. Stephenson, C. R. J.; Yoon, T. P.; MacMillan, D. W. C.; Wiley-VCH, **2018**, Chapter 13: Accelerating Visible Light Photoredox Catalysis in Continuous Flow Microreactor, 389-410. ISBN: 978-3-527-33560-2.

(53) Bao, X.; Liu, L.; Li, J.; Fan, S. Copper-Catalyzed Oxidative Perfluoroalkylation of Aryl Boronic Acids Using Perfluoroalkylzinc Reagents. *J. Org. Chem.* **2018**, *83*, 463-468.

(54) Kong, J.; Jiang, J.; Huang, Y.; Lou, Y.-G.; Li, X.-F.; He, C.-Y. Ru(bpy)$_3$Cl$_2$ as a Photocatalyst for Visible-Light-Induced Fluoroalkylation of Anilines with BrCF$_2$CF$_2$Br: A Facile Route to 2-Bromo-1,1,2,2-tetrafluoroethyl Arenes. *Asian J. Org. Chem*. **2017**, *6*, 1737-1740.

(55) Zhang, X.; Li, Y.; Hao, X.; Jin, K.; Zhang, R.; Duan, C. Recyclable Alkylated Ru(bpy)$_3^{2+}$ Complex as a Visible-Light Photoredox Catalyst for Perfluoroalkylation. *Tetrahedron* **2018**, *74*, 1742-1748.

(56) Zhong, S.; Hafner, A.; Hussal, C.; Nieger, M. A.; Bräse, S. Metal-Free Radical Perfluoroalkylation of (Hetero)Arenes. *RSC Adv.* **2015**, *5*, 6255-6258.

(57) Yajima, T.; Ikegami, M. Metal-Free Visible-Light Radical Iodoperfluoroalkylation of Terminal Alkenes and Alkynes. *Eur. J. Org. Chem*. **2017**, 2126-2129.

(58) Tiwari, D. P.; Dabral, S.; Wen, J.; Wiesenthal, J.; Terhorst, S.; Bolm, C. Organic Dye-Catalyzed Atom Transfer Radical Addition-Elimination (ATRE) Reaction for the Synthesis of Perfluoroalkylated Alkenes. *Org. Lett.* **2017**, *19*, 4295-4298.

(59) Barata-Vallejo, S.; Yerien, D. E.; Postigo, A. Benign Perfluoroalkylation of Aniline Derivatives through Photoredox Organocatalysis under Visible-Light Irradiation. *Eur. J. Org. Chem*. **2015**, 7869-7875.

(60) He, C.-Y.; Gu, J.-W.; Zhang, X. Visible-Light-Mediated Direct Perfluoroalkylation and Trifluoromethylation of Free Anilines. *Tetrahedron Lett.* **2017**, *58*, 3939-3941.

(61) (a) Stephan, D. W. “Frustrated Lewis Pairs”: A Concept for New Reactivity and Catalysis. *Org. Biomol. Chem*. **2008**, *6*, 1535-1539. (b) Stephan, D. W.; Erker, G. Frustrated Lewis pairs: Metal-Free Hydrogen Activation and More. *Angew. Chem. Int. Ed*. **2010**, *49*, 46-76. (c) Hamilton, H. B.; Wass, D. F. How Important Are Radical Mechanisms in Frustrated Lewis Pair Chemistry? *Chem*. **2017**, *3*, 198-199. (d) Liu, L.; Cao, L. L.; Shao, Y.; Ménard, G.; Stephan, D. W. A Radical Mechanism for Frustrated Lewis Pair Reactivity. *Chem.* **2017**, *3*, 259-267. (e) Stephan, D. W.; Erker, C. Frustrated Lewis Pair Chemistry: Development and Perspectives. *Angew. Chem. Int. Ed*. **2015**, *54*, 6400-6441.

(62) Behrends, I.; Bahr, S.; Czekelius, C. Perfluoroalkylation of Alkenes by Frustrated Lewis Pairs. *Chem. Eur. J*. **2016**, *22*, 17177-17181.

(63) (a) Park, G.-R.; Choi, Y.; Choi, M. G.; Chang, S.-K.; Cho, E. J. Metal-Free Visible-Light-Induced Trifluoromethylation Reactions. *Asian J. Org. Chem*. **2017**, *6*, 436-440. (b) Nguyen, J. D.; Tucker, J. W.; Konieczynska, M. D.; Stephenson, C. R. J. Intermolecular Atom Transfer Radical Addition to Olefins Mediated by Oxidative Quenching of Photoredox Catalysts. *J. Am. Chem. Soc.* **2011**, *133*, 4160-4163.

(64) Arceo, E.; Jurberg, I. D.; Alvarez-Fernandez, A.; Melchiorre, P. Photochemical Activity of a Key Donor-Acceptor Complex can drive Stereoselective Catalytic α-Alkylation of Aldehydes. *Nat. Chem*. **2013**, *5*, 750-756.

(65) Lo, R.; Ganguly, B. Revealing Halogen Bonding Interactions with Anomeric Systems: An Ab Initio Quantum Chemical Studies. *J. Mol. Graphics & Modelling* **2015**, *55*, 123-133.

(66) Guengerich, F. P.; Macdonald, T. L. In *Advances in Electron Transfer Chemistry*; Mariano, P. Ed.; JAI Press Inc.; Greenwhich, Connecticut; **1994**; Vol. 4; 191-241. ISBN: 978-1-4831-0093-7.

(67) Pham, P. V.; Nagib, D. A.; MacMillan, D. W. C. Photoredox Catalysis: A Mild, Operationally Simple Approach to the Synthesis of α-Trifluoromethyl Carbonyl Compounds. *Angew. Chem. Int. Ed*. **2011**, *50*, 6119-6122.

(68) Chen, T.; Guo, Y.; Sun, K.; Wu, L.-Z.; Liu, W.-Q.; Liu, C.; Huang, Y.; Chen, Q.-Y. Photoinduced Hydroxylperfluoroalkylation of Styrenes. *Org. Chem. Front.* **2018,** *5***,** 1045-1048**.**

(69) Tang, X.; Studer, A. Alkene 1,2-Difunctionalization by Radical Alkenyl Migration. *Angew. Chem. Int. Ed*. **2018**, *57*, 814-817.

(70) Tang, X.; Studer, A. α-Perfluoroalkyl-β-Alkynylation of Alkenes via Radical Alkynyl Migration. *Chem. Science* **2017**, *8*, 6888-6892.

(71) (a) Qi, X.; Ai, H.-J.; Cai, C. -X.; Peng, J. -B.; Zheng, F.; Wu, X. -F. Palladium-Catalyzed Selective Synthesis of Perfluoroalkylated Enynes from Perfluoroalkyl Iodides and Alkynes. *Eur. J. Org. Chem*. **2017**, 2940-2943. (b) Xia, X.-F.; Yu, J.; Wang, D. Copper/Iron-Cocatalyzed Cascade Perfluoroalkylation/Cyclization of 1,6-Enynes with Iodoperfluoroalkanes. *Adv. Synth. Catal.* **2018**, *360*, 562-567. (c) Janhsen, B.; Studer, A. Perfluoroalkylation of Aryl-*N,N*-dimethyl Hydrazones Using Hypervalent Iodine(III) Reagents or Perfluoroalkyl Iodides. *J. Org. Chem*. **2017**, *82*, 11703-11710.

(72) Yu, J.-M.; Cai, C. Ambient-Light-Promoted Perfluoroalkylative Cyclization of β,γ-Unsaturated Hydrazones: Synthesis of Perfluoroalkylated Pyrazolines. *Eur. J. Org. Chem*. **2017**, 6008-6012.

(73) Sladojevich, F.; McNeill, E.; Borgel, J.; Zheng, S.-L.; Ritter, T. Condensed-Phase, Halogen-Bonded CF_3I and C_2F_5I Adducts for Perfluoroalkylation Reactions. *Angew. Chem. Int. Ed*. **2015**, *56*, 3712-3716.

(74) Sun, X.; Wang, W.: Li, Y.; Ma, J.; Yu, S. Halogen-Bond-Promoted Double Radical Isocyanide Insertion under Visible-Light Irradiation: Synthesis of 2-Fluoroalkylated Quinoxalines *Org. Lett.* **2016**, *18*, 4638-4641.

(75) Cheng, Y.; Jiang, H.; Zhang, Y.; Yu, S. Isocyanide Insertion: De Novo Synthesis of Trifluoromethylated Phenanthridine Derivatives. *Org. Lett*. **2013**, *15*, 5520 – 5523.

(76) Nappi, M.; Bergonzini, G.; Melchiorre, P. Metal-Free Photochemical Aromatic Perfluoroalkylation of α-Cyano Arylacetates. *Ang. Chem. Int. Ed*. **2014**, *53*, 4921-4925.

(77) Woźniak, Ł.; Murphy, J. J.; Melchiorre, P. Photo-organocatalytic Enantioselective Perfluoroalkylation of β-Ketoesters. *J. Am. Chem. Soc*. **2015**, *137*, 5678-5681.

(78) Thornbury, R.; Schäfer, G.; Toste, F. D. In *Modern Synthesis Processes and Reactivity of Fluorinated Compounds. Progress in Fluorine Science*,1st Ed.; Groult, H., Leroux, F., Tressaud, A., Eds.; Elsevier; **2017**; Chapter 9, Catalytic Enantioselective Fluorination, 223-263. IBSN: 978-0-128-03740-9.

(79) Yang, C.; Zhang, W.; Li, Y.-H.; Xue, X.-S.; Li, X.; Cheng, J.-P. Origin of Stereoselectivity of the Photoinduced Asymmetric Phase-Transfer-Catalyzed Perfluoroalkylation of β-Ketoesters. *J. Org. Chem*. **2017**, *82*, 9321-9327.

(80) Yerien, D. E.; Conde, R.; Barata-Vallejo, S.; Camps, B.; Lantaño, B.; Postigo, A. Transition Metal- and Organophotocatalyst-Free Perfluoroalkylation Reaction of

Amino(Hetero)Aromatics Initiated by the Complex [(TMEDA)I·I_3] and Visible Light. *RSC Adv.* **2017**, *7*, 266-274.

(81) Filippini, G.; Nappi, M.; Melchiorre, P. Photochemical Direct Perfluoroalkylation of Phenols. *Tetrahedron* **2015**, *71*, 4535-4542.

(82) (a) Guo, Q.; Wang, M.; Liu, H. L.; Wang, R.; Xu, Z. Visible-Light-Promoted Dearomatizative Fluoroalkylation of β-Naphthols via Intermolecular Charge Transfer. *Ang. Chem. Int. Ed*. **2018**, *57*, 4747-4751. (b) Kandukuri, S. R.; Bahamonde, A.; Chatterjee, I.; Jurberg, I. D.; Escudero-Adn, E. C.; Melchiorre, P. X-Ray Characterization of an Electron Donor–Acceptor Complex that Drives the Photochemical Alkylation of Indoles. *Angew. Chem.* **2015**, *127*, 1505-1509.