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PHOTOCATALYTIC FLUOROALKYLATION REACTIONS OF ORGANIC COMPOUNDS

Sebastián Barata-Vallejo[a], Sergio M. Bonesi[b],*, Al Postigo[a],*

[a].-Departamento de Química Orgánica, Facultad de Farmacia y Bioquímica, Universidad de Buenos Aires-Junín 954 CP 1113-Buenos Aires-Argentina

[b].-Departamento de Química Orgánica, CIHIDECAR-CONICET, Pabellón II, 3er piso, Ciudad Universitaria, Facultad de Ciencias Exactas y Naturales, Universidad de Buenos Aires, 1428, Buenos Aires, Argentina

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ABSTRACT

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Photocatalytic methods for fluoroalkyl-radical generation provide more convenient alternatives to the classical perfluoroalkyl-radical (R_f) production through chemical initiators, such as azo or peroxide compounds or the employment of transition metals through thermal electron transfer (ET) initiation process. The mild photocatalytic reaction conditions tolerate a variety of functional groups and, thus, are handy to the late-stage modification of bioactive molecules. Transition metal-photocatalytic reactions for R_f radical generation profit from the redox properties of coordinatively saturated Ru or Ir organocomplexes to act as both electron donor and reductive species, thus allowing for the utilization of electron accepting and donating fluoroalkylating agents for R_f radical production. On the other hand, laboratory-available and inexpensive photoorgano catalysts (POC), in the absence of transition metals, can also act as electron exchange species upon excitation, resulting in ET reactions that produce R_f radicals. In this work, a critical account of transition metal, and transition metal-free R_f radical production will be described with photoorgano catalysts, studying classical examples and the most recent investigations in the field.

INTRODUCTION

The recent advances of visible light-promoted photoredox catalysis have attracted renewed interest in radical-mediated organic syntheses.[1-21]

Photocatalysis PC, employs an electronically excited species PC* which functions as the catalyst. This methodology has been playing a relevant role in carbon-carbon bond formation reactions.[9] In this way photoredox catalysis can accomplish radical transformations which are not accessible employing conventional azo or peroxide initiators. Fluoroalkylation is a notable example where photoredox catalysis can be applied.

Trifluoromethylation has, in the past, relied on the use of transition metal catalysts, such as those containing Pd[22-32] and Cu [33-46]. Photoredox catalytic trifluoromethylation, fluoroalkylation and fluorination reactions provide a promising alternative to these existing methods, as it utilizes the environmentally benign protocols that rely on visible light or even sunlight irradiation. [47]

The mild reaction conditions tolerate a variety of functional groups and, thus, are handy to the ulterior modification of bioactive molecules. [48-50]

Photoredox-catalyzed fluoroalkylation reactions can either involve the employment of transition metals or else are transition metal-free photoreactions employing an organic photocatalyst, such as a dye. Among the transition metal photoredox-catalyzed reactions, they typically make use of coordinatively *4d* or *5d* transition metal complexes, among them Ru(II) polypyridine complexes [48-61] and cyclometalated Ir(III) complexes, [62-65] as the catalysts.

*Tri*s-chelated complexes of Ru(II) with 2,2′-bipyridyl and 1,10- phenanthroline ligands, have been intensively employed due to their outstanding chemical and

photophysical properties. In these types of catalysts, Ru^{2+} has a d^6 orbital arrangement and the σ donor orbitals of the bipyridine ligands localized on the nitrogen atoms interact with the π donor and π* acceptor orbitals delocalized on the aromatic rings. The light absorption by these catalysts promotes a single-electron transfer from a metal d orbital to the π* L ligand orbitals, giving rise to metal-to-ligand charge transfer (MLCT) excited states, and therefore, the following processes are involved: light absorption; MLCT excited states and quenching process.

After light excitation of these complexes, formation of a long-lived triplet ^{3}MLCT ensues, where the one-electron oxidized metal core acts as the oxidant, and the one-electron reduced ligand takes the role of the reductant, respectively. A variety of reagents, such as CF_3I,[50,55-57,59,62,66,67] silver trifluoroacetate, triflyl chloride (CF_3SO_2Cl),[49,64] the Langlois reagent, the Togni reagent, [51,53,54,60,65] the Umemoto reagent, [48,52,58,63,65] and the Shibata reagent, [61] can act as trifluoromethyl radical (•CF_3) sources, and the key step involves the reductive cleavage of these reagents under photoirradiation of the catalyst. Also perfluoroalkyl iodides and bromides have been employed with these catalysts. Two possible routes to the reductive generation of •CF_3 are available (Schemes 1 & 2).
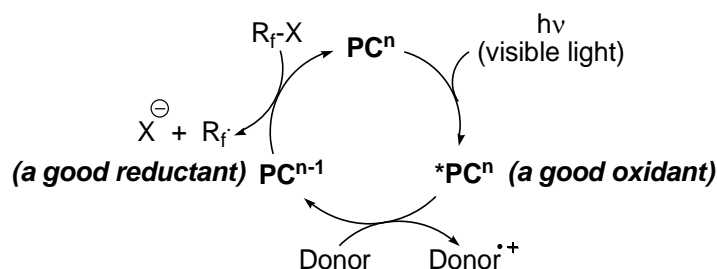
Scheme 1. Reductive quenching pathway for the generation of R_f radicals
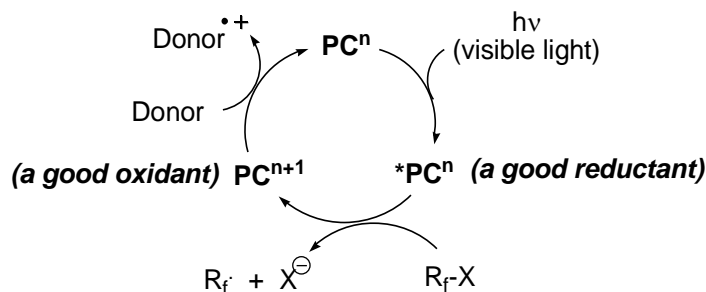
Scheme 2. Oxidative quenching pathway for the generation of R_f radicals

The excited catalyst can reduce the R_fX source (oxidative quenching pathway),

regeneration of the catalyst follows by means of an electron donor or else, the photoexcited

catalyst could be reduced by an electron donor to a one-electron reduced species that

transfers an extra electron to the R_fX source (reductive quenching pathway).

As shown in Schemes 1 & 2, the oxidative and reductive quenching cycles involve

the photoexcited catalyst and the one-electron reduced catalyst, acting as the reductant.

It has frequently been observed that photoredox catalysts (i.e.: $[Ru(bpy)_3]^{2+}$ and *fac*-

Ir(ppy)$_3$ (bpy = 2,2´-bipyridine and ppy = 2-phenylpyridinate), can induce both

oxidative[48,49,51,54,58,60,63-65] and reductive [50,55-57,59,62] quenching cycles, owed to the positive

driving forces for electron transfer to typical perfluoroalkyl halides.[7] The competition of the

two pathways precludes the elucidation of the molecular parameters of the catalysis. More

work should be devoted to identifying photoredox catalysts that operate by a single

quenching process.

As regards to metal-free photoorganocatalysis, these procedures mainly employ

organic dyes or large organic molecules of diverse chemical structures, such as 9-

fluorenone, xanthone, methylene blue, Rose Bengal etc. capable of absorbing the light in

the visible or near visible light regions. The excited photoorganocatalyst **POC*** (in the

singlet excited manifold) suffers rapid intersystem crossing to the triplet manifold (which is

a low energy triplet excited sate) and can accept an electron from an organic base additive

(i.e.: TMEDA, sacrificial donor), generating the radical anion of the photoorganocatalyst

($POC^{\bullet-}$). In turn, $POC^{\bullet-}$ transfers the electron to the R_fX, to generate radicals $R_f^{\bullet}$, which

enter the catalytic cycle (Figure 1, A = R_fX, S = sacrificial donor, *i.e.*: TMEDA).

Alternatively, the excited POC* can accept an electron from a perfluoroalkylsulfinate salt

($NaSO_2R_f$), generating $POC^{\bullet-}$ and $R_f^{\bullet}$ radicals (Figure 1, S = $NaSO_2R_f$, A = SO_2). More

infrequently, the excited organophotocatalyst **POC*** can directly donate an electron to the

R_fX or R_fSO_2Cl, to generate R_f radicals and produce the radical cation of the

photoorganocatalyst $POC^{\bullet+}$ that commence the catalytic cycle (Figure 2).
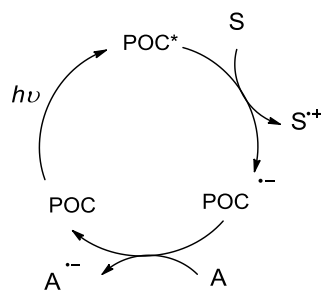
if S = sacrificial donor, then A = R_fX; $A^{\bullet-}$ = $R_f^{\bullet}$ + X^-
if S = R_fSO_2Na, then $S^{\bullet+}$ = $R_f^{\bullet}$ + SO_2 + Na^+, A = acceptor
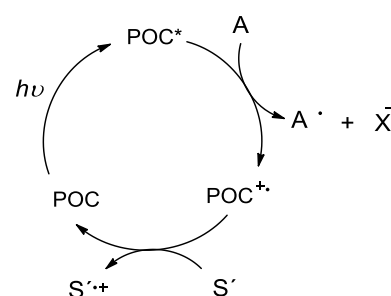
S ´= radical intermediate or electron donor
A = R_fX or R_fSO_2Cl

Figure 1. POC as an electron acceptor   Figure 2. POC as an electron donor

Examples of all these scenarios will be presented in this review. This account excludes

thermal transition metal-organocatalyzed fluoroalkylation reactions. Finally, in Section 4.-

summary Tables will be provided illustrating the photocatalysts employed this far for

achieving fluoroalkylation reactions of organic compounds.

1.-TRANSITION METAL PHOTOORGANOCATALYSIS

The relevance of transition metal photocatalysis PC, where the excited PC* acts as the catalyst, is manifested by the array of organic transformations that have been reported recently, in most cases involving C–C bond formation (via activation of C–H bonds) or oxidations.[68] Ru and Ir transition metal complexes are paramount examples of visible light photocatalysts.[5,10,69]

Photoredox catalysts can easily generate electrophilic radicals.[70-72] Polypyridyl organometallic complexes, such as [Ru(bpy)$_3$Cl$_2$], or those from Ir, can be activated by visible light and have proven to be mild and more sustainable alternatives for traditional photochemistry utilizing UV energy.[73-76]

1.1.-PERFLUOROALKYLATION OF ALIPHATIC COMPOUNDS
1.1.1.-FLUOROALKYLATION OF SP^3 CARBON ATOMS

MacMillan and collaborators [62] have performed a series of experiments designed to obtain the enantioselective perfluoroalkylation of aldehydes by means of photoredox catalysis through the use of photocatalyst Ir(ppy)$_2$(dtb-bpy)$^+$PF$_6^-$ ([(4,4′-*Bis*(1,1-dimethylethyl)-2,2′-bipyridine-*N*1,*N*1′]*bis*[2-(2-pyridinyl-*N*)phenyl-C]iridium(III) hexafluorophosphate]). The photoredox conditions are compatible with a variety of functional groups including ethers, esters, amines, carbamates and aromatic rings, as observed in Scheme 3, yielding 93-98% ee. Furthermore, a variation in the steric demand of the aldehyde substituent is feasible without loss in enantiocontrol.

R	Yield (%)	ee (%)
(CH$_2$)$_5$CH$_3$	79	99
(CH$_2$)$_3$OBn	72	95
(CH$_2$)$_3$COOEt	86	97
(CH$_2$)$_3$C$_{10}$H$_8$	78	98
CH$_2$Ph	75	97

61 % (93 % ee)

68 % (>20:1 dr; 99 % ee)

X	Yield (%)	ee (%)
CH$_2$	70	99
NBoc	70	98

62 % (>20:1 dr; 99 % ee)
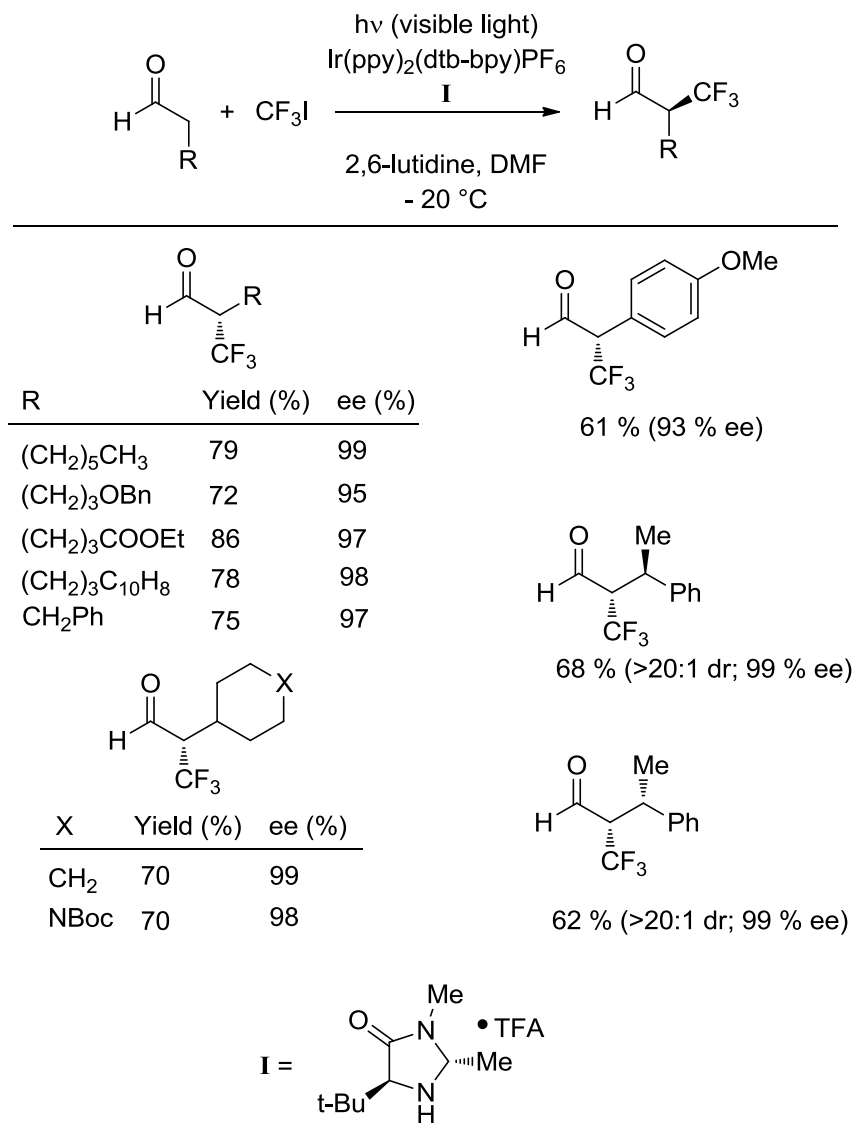
Scheme 3. Photoredox catalysis through the use of photocatalyst Ir(ppy)$_2$(dtb-bpy)$^+$

Also the protocol can be applied to other perfluoroalkyl sources as depicted in Scheme 4.

R	Yield (%)	ee (%)
CF_2CF_3	73	96
$(CF_2)_2CF_3$	69	99
$(CF_2)_3CF_3$	67	96
$CF(CF_3)_2$	72	98
$CF_2C_6F_5$	85	98
CF_2OCF_3	71	99
CF_2Br	68	99
CF_2COOEt	89	99
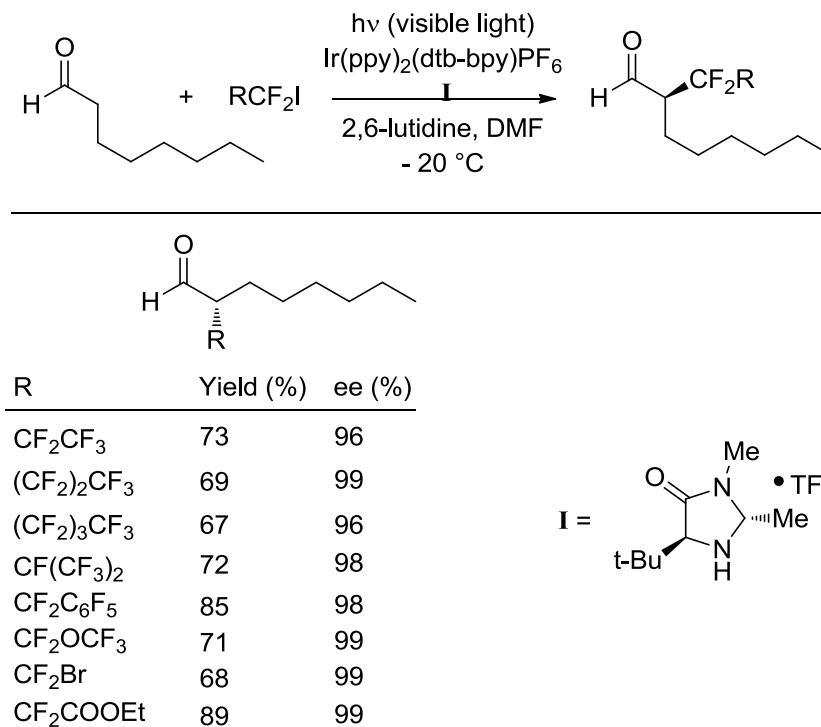
Scheme 4. Difluoromethylation of aldehydes by photoredox catalysis through the use of photocatalyst $Ir(ppy)_2(dtb-bpy)^+$

The reaction mechanism of the enantioselective perfluoroalkylation of aldehydes is described in Scheme 5.[62] The photocatalyst $Ir(ppy)_2(dtb-bpy)^+$ **A** (Scheme 5), is excited to *$Ir(ppy)_2(dtb-bpy)^+$ (**B**) excited state. **B** would then accept a single electron from a sacrificial quantity of enamine **G** (0.5 mol %) to form reductant **C** (Scheme 5) $(Ir(ppy)_2(dtbbpy); E = -1.51$ V *vs* SCE in $CH_3CN)^{[77]}$. At this stage this electron-rich iridium system **C** would suffer a single electron transfer (SET) with trifluoromethyl iodide ($E = -1.22$ V *vs* SCE in DMF) to give the electrophilic radical $CF_3^{\cdot}$, while regenerating the photoredox catalyst **A** (Scheme 5). The catalytic cycle would commence by condensation of the imidazolidinone catalyst **F** with an aldehyde to form the enamine **G** (Scheme 5).[62] Rapid addition of the trifluoromethyl radical to the π-rich olefin **G** would form the *R*-amino

radical **D**. It is expected that radical **D** should have a low barrier to oxidation, suitable for

an ulterior electron transfer event with the *Ir(ppy)$_2$(dtb-bpy)$^+$ **B** excited state, which would

close the catalytic cycle and form the iminium ion **E** (Scheme 5). Hydrolysis of iminium **E**

would then regenerate the organocatalyst **F** while yielding the optically enriched *R*-CF$_3$

aldehyde.
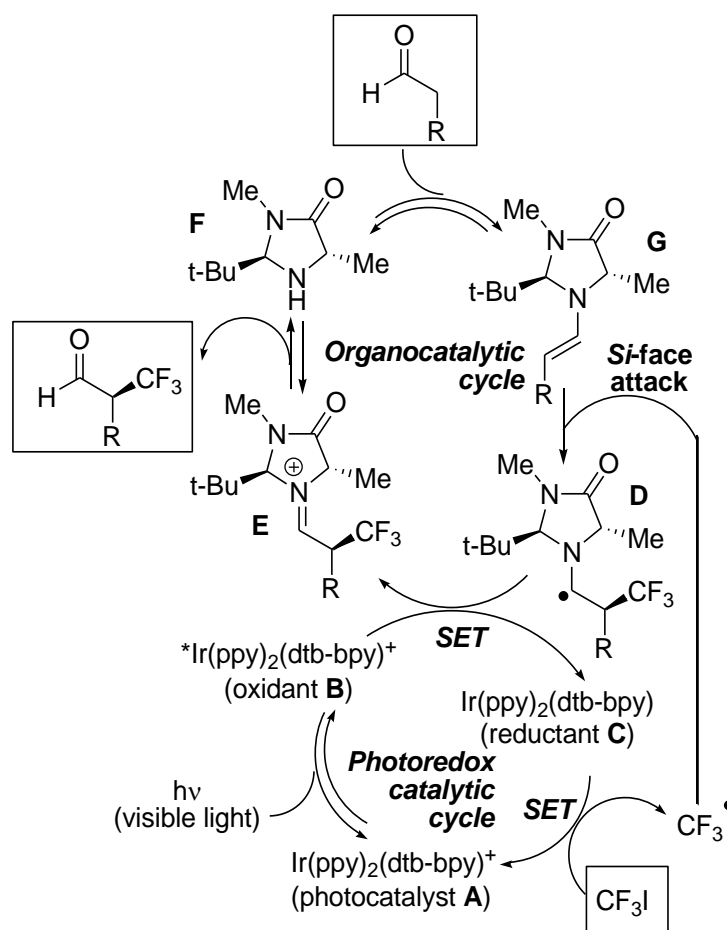
Scheme 5. Mechanism of the enantioselective perfluoroalkylation of aldehydes by
photocatalyst Ir(ppy)$_2$(dtb-bpy)$^+$

In a subsequent report, MacMillan and collaborators[78] have introduced the trifluoromethylation of arenes and heteroarenes by means of photoredox catalyst Ru(phen)$_3^{2+}$(PF$_6$)$_2$ (tris(1,10-Phenanthroline)ruthenium(II) hexafluorophosphate) and CF$_3$SO$_2$Cl rendering trifluoromethylated compounds in optimal yields (*vide infra* section 1.2.-).

1.1.2.-FLUOROALKYLATION OF *SP²* and *SP* CARBON ATOMS

Fukuzumi, Cho, You and co-workers have, for the first time, reported and developed the application of cyclometalated Pt^{II} complexes in photoredox catalytic trifluoromethylation of terminal alkenes.[79] The Pt^{II} photocatalyst bears a 2-phenylpyridinate and non-photoactive acetylacetonate, i.e.: Ptppy(acac) (Pt(acac)$_2$) ancillary ligands and is used in 1.0 mol%. The oxidative quenching photoredox catalysis has been investigated over a range of terminal alkenes in MeCN and at room temperature to provide the trifluoromethylated alkenes in excellent yields (Scheme 6).[79] A sacrificial electron-donor, such as DBU, is required and the photocatalytic reaction is completed within 6 h. The catalytic activity of the Pt(II) complex can be compared to the well-known photoredox catalyst, such as Ru(bpy)$_3$Cl$_2$ and Ir(ppy)$_2$(dtbbpy)PF$_6$.
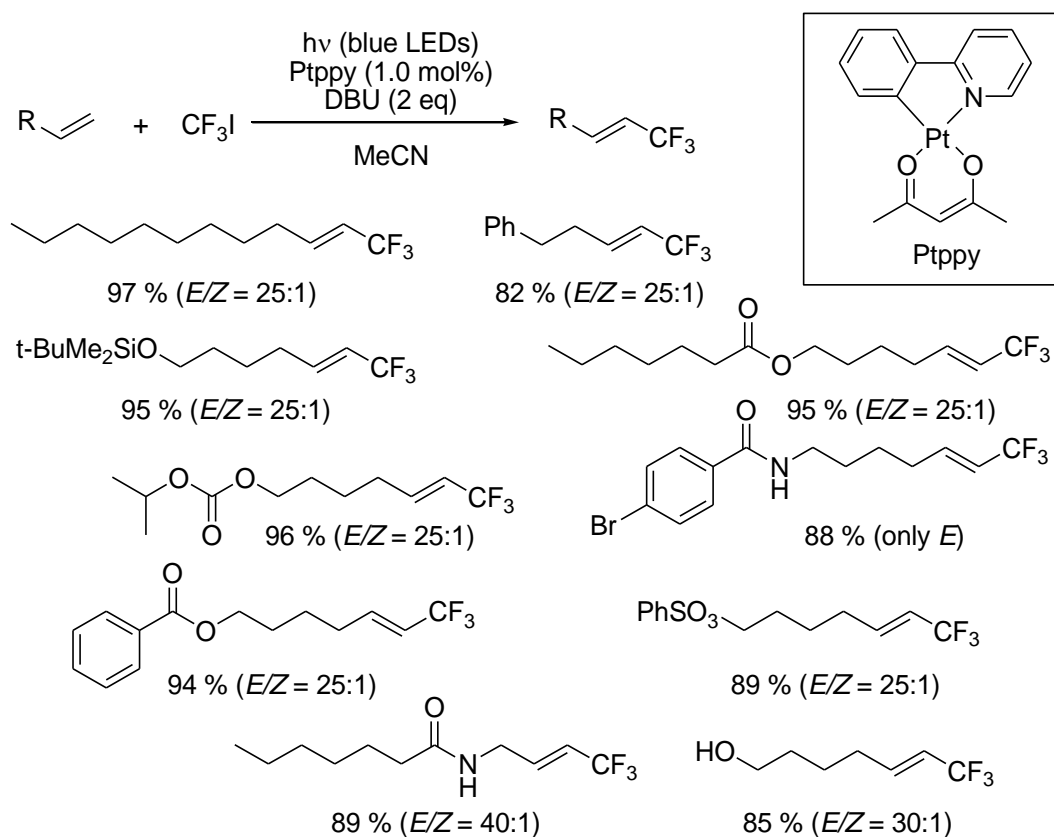
Scheme 6. Cyclometalated Pt^{II} complexes in photoredox catalytic trifluoromethylation of terminal alkenes

The reaction mechanism of the photocatalytic trifluoromethylation of alkenes is depicted in Scheme 7.[79] The photocatalyst Pt complex (Pt^{II}ppy hereafter) promotes an electronic transition to singlet state ^{1}MLCT, which undergoes ultrafast intersystem crossing to a ^{3}MLCT state (i.e., Pt^{III}ppy$^{-\cdot}$*). Oxidative electron transfer from Pt^{III}ppy$^{-\cdot}$* to CF_3I provides Pt^{III}ppy$^+$, iodide and trifluoromethyl radical. Addition of the radical to the terminal alkene provides intermediate **A** (Scheme 7). The photocatalytic cycle is completed by the reductive regeneration of Pt^{II}ppy with DBU, a sacrificial electron donor. Alternatively, Pt^{II}ppy is recovered through the radical-polar mechanism, which involves oxidation of intermediate **A** to give carbocation **B** (path a, Scheme 7). In these cases, the resulting

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cationic species is trapped by the strong nucleophile, I⁻, rendering the β-iodide intermediate

C (Scheme 7). This intermediate can be obtained through a propagation-chain reaction

(path b) that furnishes the intermediate **C** (Scheme 7). In either *paths a* or *b*, DBU-assisted

E_2 elimination provides the desired product, with the generation of ammonium iodide salts.
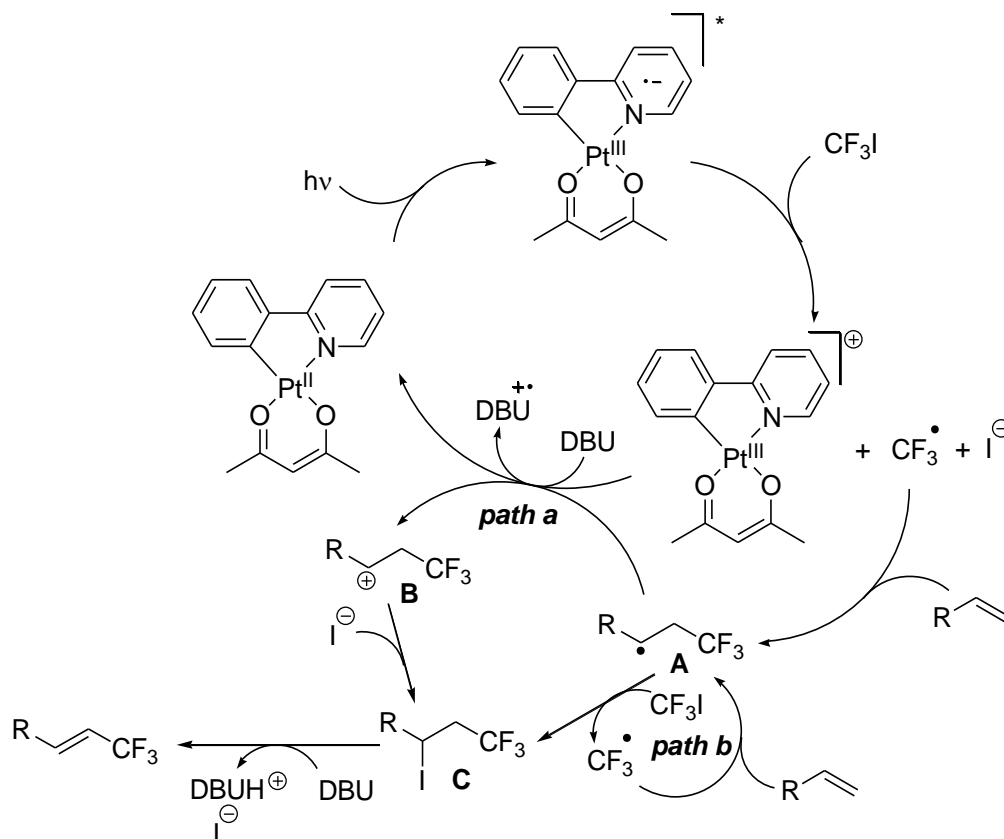
Scheme 7. Reaction mechanism of the photocatalytic trifluoromethylation of alkenes

Gouverneur and coworkers have developed the regioselective photocatalytic

hydrotrifluoromethylation of unactivated alkenes.[58] This photoreaction is effective with

$Ru(bpy)_3^{2+}(PF_6)_2$ as the photoredox catalyst under visible light excitation in the presence of

Umemoto's reagent as the trifluoromethyl radical source in MeOH as solvent at room

temperature. In this case, MeOH is the reaction solvent and the hydrogen donor.

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Furthermore, the photocatalytic reaction proceeds easily with terminal alkynes. The hydrotrifluoromethylated products from terminal and geminal unactivated alkenes and terminal alkynes are produced in moderate to good yields and with a noticeable regioselectivity as is depicted in Scheme 8.

(a) Hydrotrifluoromethylartion of terminal and geminal unactivated alkenes.
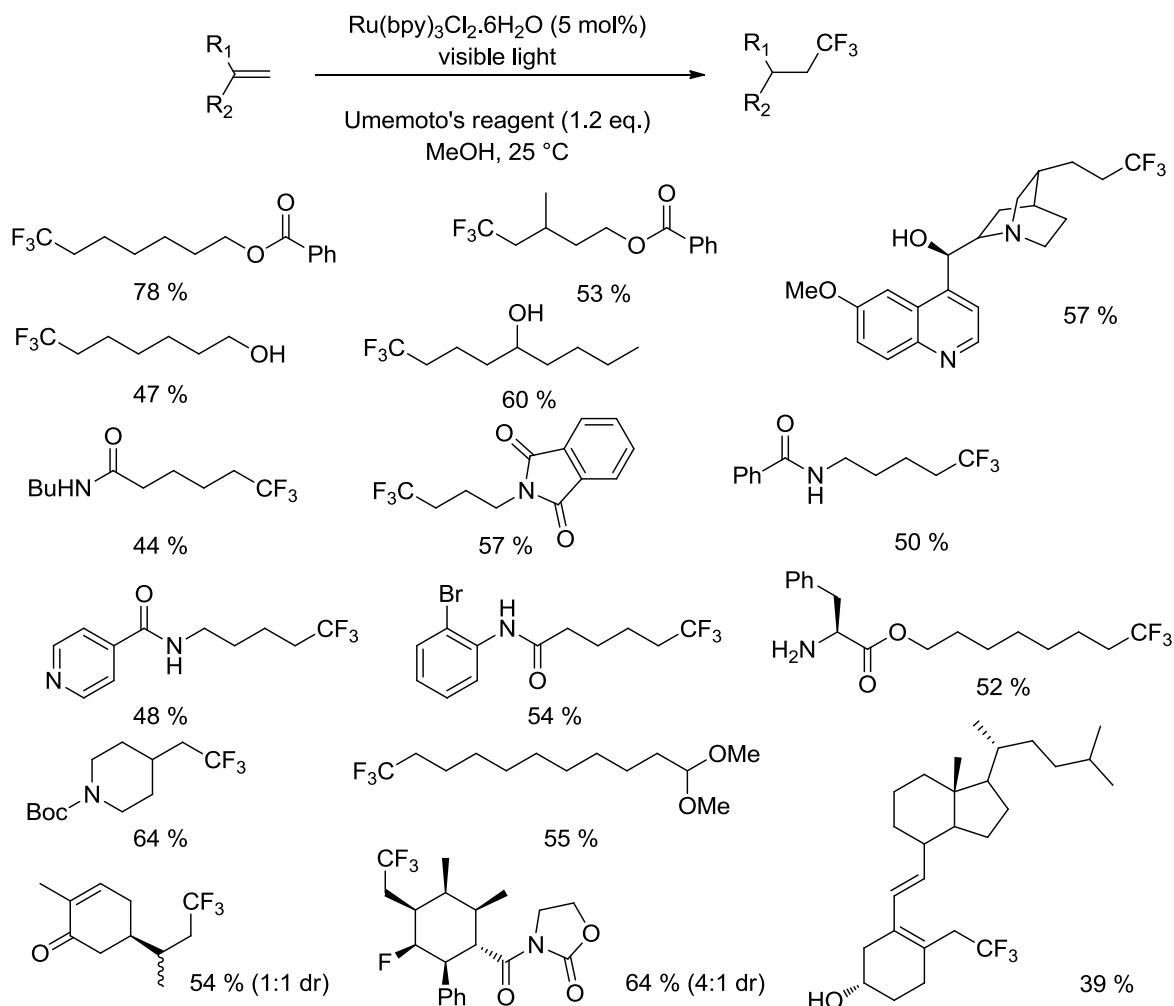
(b) Hydrotrifluoromethylation of terminal unactivated alkynes.
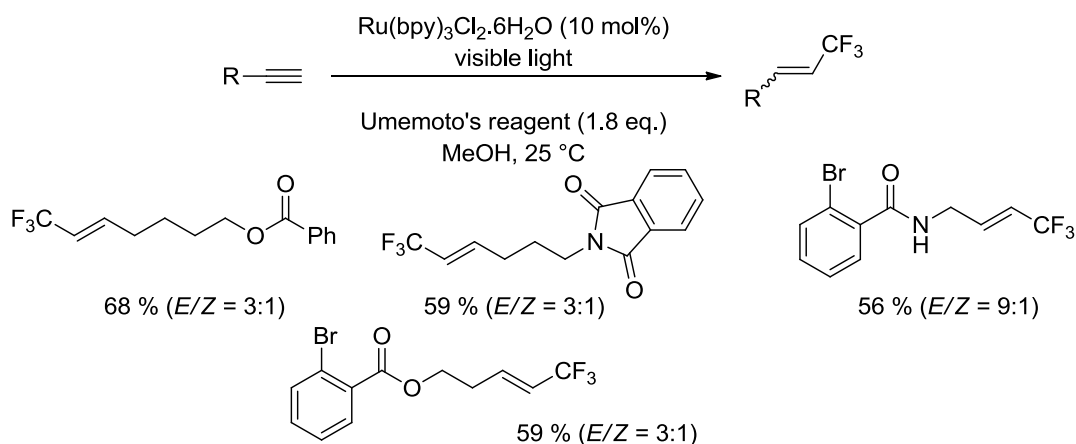
Scheme 8. Photocatalytic hydrotrifluoromethylation of unactivated alkenes

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Experimental evidence showing that methanol is the H-donor source has been supplied when the photoreaction is carried out in a 1:1 mixture of MeOH and CD_3OD and a normal kinetic isotope effect of 1.5 was observed.[58] Also, performing the reaction in CD_3OH as well as in CD_3OD the formation of hydrotrifluoromethyl deuterated products in both reactions unambiguously confirms that the α-C-H bond of methanol serves as the hydrogen atom source.

The preparation of a set of valuable CF_3-containing molecules, i.e.: trifluoromethylated alkenyl iodides, alkenes, and alkynes, synthesised from unactivated alkynes and CF_3I by efficient visible-light photoredox catalysis has been informed by Cho and co-workers.[80] Control of catalyst, base, and solvent enables the tuning of reactivity and selectivity for the reaction between an alkyne and CF_3I as is shown in Scheme 9.
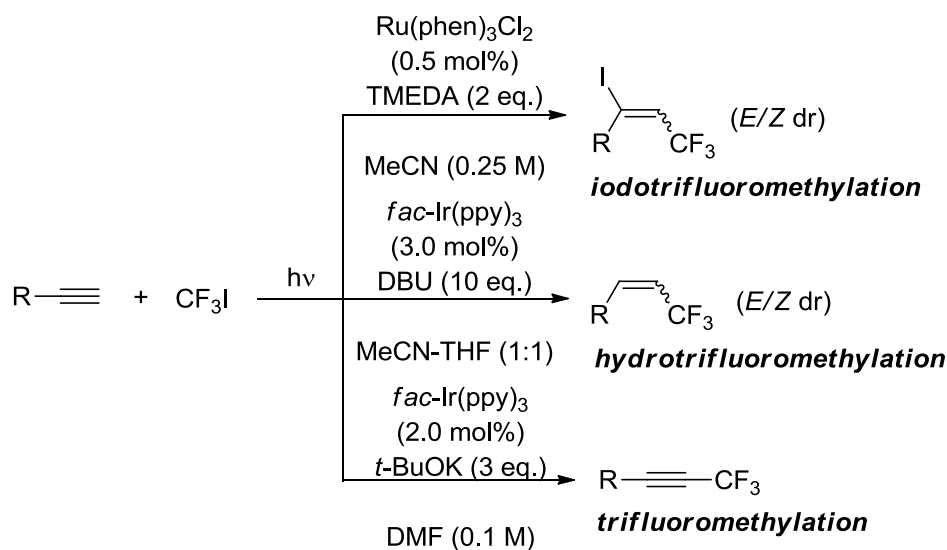
Scheme 9. Trifluoromethylation of terminal alkynes

The iodotrifluoromethylation of a variety of aromatic and aliphatic alkenes have been studied and the photocatalytic reaction occurs efficiently with a range of functional

groups (ATRA, atom transfer radical reactions).[80] The products are obtained in good yields with an excellent *E/Z* stereoselectivity favoring the formation of the *E* isomer. Alkynes with directing groups at the propargylic position, however, undergo selective iodotrifluoromethylation to exclusively afford the *Z* isomer. Some representative examples are shown in Scheme 10a. The substrate scope of the hydrotrifluoromethylation of alkynes has also been investigated[80] providing a mixture of the *E* and *Z*-alkenyl-CF$_3$ compounds in good to excellent yields (see Scheme 10b). In these experiments the iridium catalyst is found to be more effective than Ru catalyst and the adequate base turns out to be DBU, which functions not only as the reductive quencher of the photocatalyst, but also as a hydrogen atom donor. The last trifluoromethylation photocatalytic reaction of electron-donor and electron-withdrawing phenyl acetylene derivatives takes place with iridium photocatalyst in moderate yields (Scheme 10c). Unfortunately, aliphatic alkynes are not suitable substrates for this reaction.

(a) Scope of the iodotrifluoromethylation of alkynes.

R	Yield (%)	E/Z
H	92	18:1
Me	93	18:1
MeO	88	18:1
F	92	18:1

80 % (E/Z = 18:1)

95 % (Z only)

83 % (E only)

87 % (E/Z = 2.6:1)

(b) Scope of the hydrotrifluoromethylation of alkynes.

R	Yield (%)	E/Z
H	74	1:1.5
Me	78	1:1.6
MeO	65	1:1.2
F	95	1:1.4

60 % (E/Z = 1:1.4)

98 % (E only)

67 % (E/Z = 2:1)

73 % (E/Z = 3.1:1)
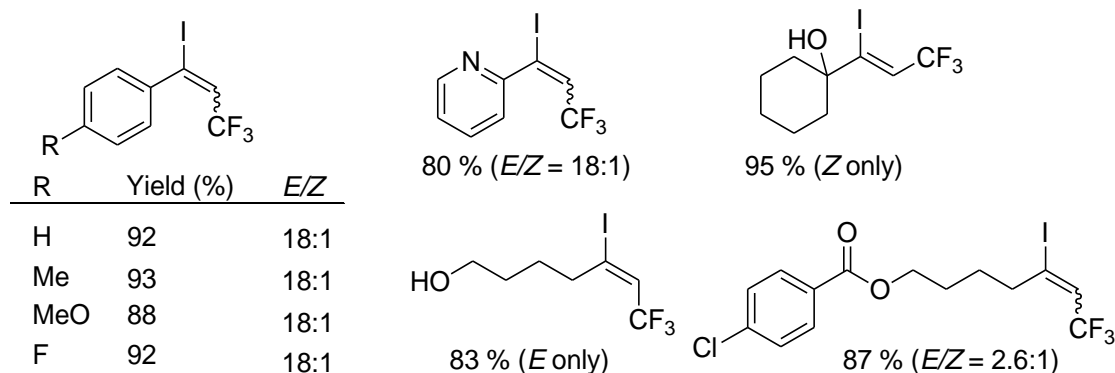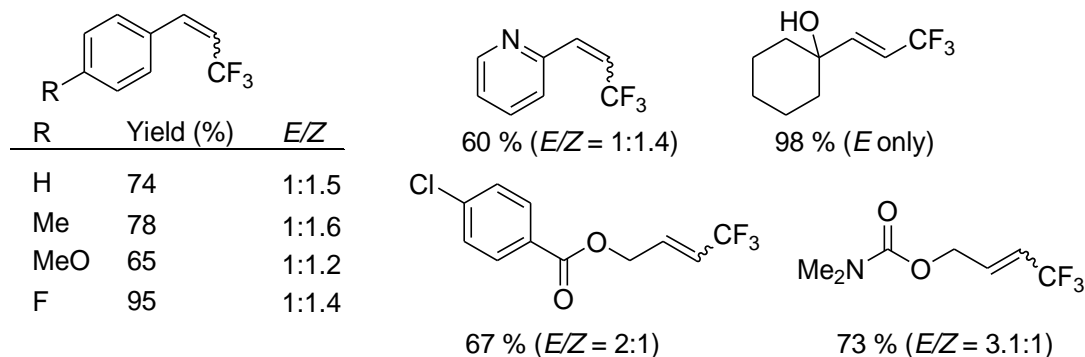
(c) Scope of the trifluoromethylation of alkynes.

R	Yield (%)
H	64
Me	65
MeO	68
F	62
NH_2	60
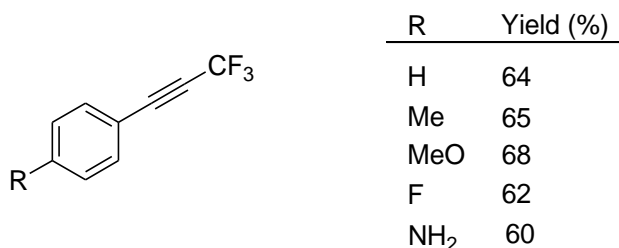
Scheme 10. Iodotrifluoromethylation of a variety of aromatic and aliphatic alkenes studied by photocatalytic reactions

Visible light-mediated atom transfer radical reaction (ATRA) of perfluoroalkyl iodides onto alkenes and alkynes employing both the reductive and oxidative quenching of [Ir{dF(CF$_3$)ppy}$_2$(dtbbpy)]PF$_6$ (*photocatalyst 1*, i.e.: [4,4′-Bis(1,1-dimethylethyl)-2,2′-bipyridine-*N*1,*N*1′]bis[3,5-difluoro-2-[5-(trifluoromethyl)-2-pyridinyl-*N*]phenyl-C]Iridium(III) hexafluorophosphate) and [Ru(bpy)$_3$]Cl$_2$ (*photocatalyst 2*) has been

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informed by Stephenson and coworkers[81]. These set of reactions provide the corresponding ATRA products in good to excellent yields. The oxidative photocatalytic cycle proceeds smoothly with both photocatalysts in 1.0 mol% under visible light in the presence of 2.0 equiv. of LiBr in DMF:H$_2$O (1:4) as well as in DMSO during 12 – 48 h. Some results are shown in Scheme 11.

Photocatalyst 1   *Photocatalyst 2*
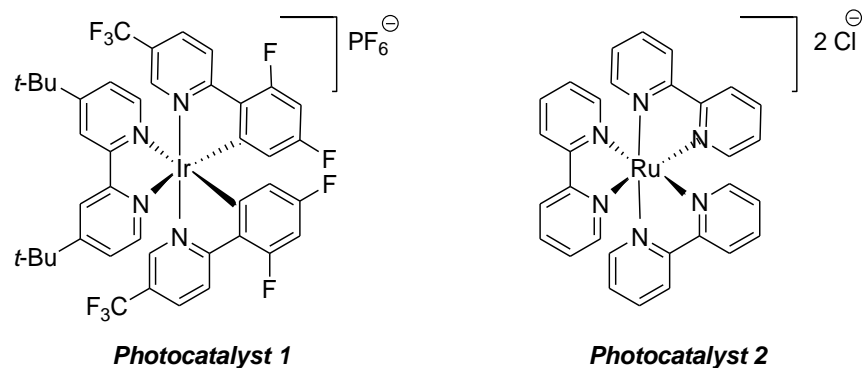
Substrate	*R$_f$-I*	*Product*	*Photocatalyst*	*Yield (%)*
(cyclohexene)	Br-CF$_2$-CO$_2$Me	(bromocyclohexyl CF$_2$CO$_2$Me)	1	75
			2	88
(pent-4-en-1-ol) OH	CF$_3$I	F$_3$C—(chain)—OH	1	90
	Br-CHF-CO$_2$Et	EtOOC—(chain)—OH	1	99
			2	99
(ester alkene) OEt	CF$_3$I	F$_3$C—(chain)—OEt	1	81
			2	90
(norbornene)	CF$_2$Br$_2$	(norbornane CF$_2$Br/Br)	1	88 (dr 5:1)
(β-pinene type)	CF$_2$Br$_2$	(product CF$_2$Br/Br)	1	92

Scheme 11. Visible light-mediated atom transfer radical reaction (ATRA) of perfluoroalkyl iodides onto alkenes and alkynes using the reductive and oxidative quenching cycles of [Ir{dF(CF$_3$)ppy}$_2$(dtbbpy)]PF$_6$ (*photocatalyst 1*) and [Ru(bpy)$_3$]Cl$_2$ (*photocatalyst 2*)

On the other hand, the reductive photocatalytic cycle proceeds in just 0.5 h with both photocatalysts (1.0 mol%) under visible light in the presence of 0.35 equiv. of sodium ascorbate as a sacrificial electron donor in MeCN:MeOH (4:3) giving the ATRA products in excellent yields which are illustrated in Scheme 12.[81] This ATRA reaction has a broad functional group tolerance and is competent with structurally diverse perfluorinated alkyl iodides.

(a) Perfluoroalkyl iodide scope.

R$_f$	Yield (%)
CF$_3$	90
C$_6$F$_{13}$	81
C$_8$F$_{17}$	99
C$_{10}$F$_{21}$	97
(CF$_3$)$_2$CF	81
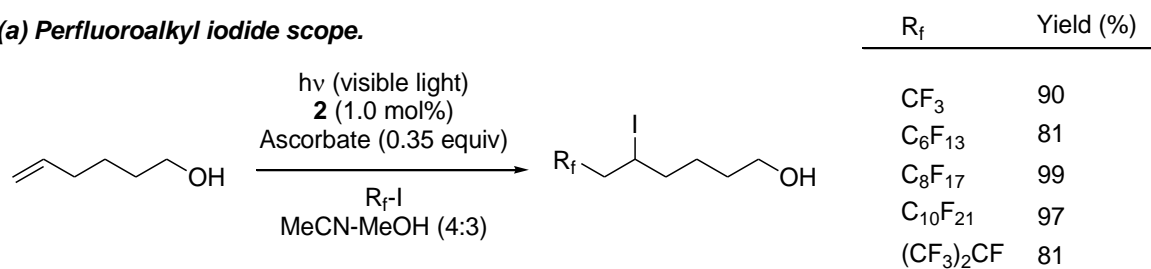
(b) Alkenes and alkynes scope.   R$_f$ -I = C$_8$F$_{17}$I   Photocatalyst: **2**

X	Yield (%)
Br	93
I	94
CN	90

99 %

88 %

94 % (dr 2:1)

94 %

96 %
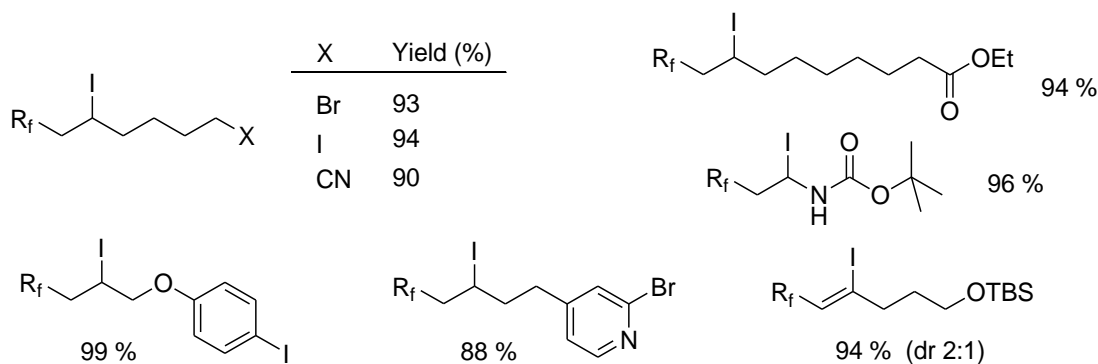
Scheme 12. ATRA photocatalyzed reaction with *photocatalyst 2*

The reaction mechanisms associated with the photocatalytic cycles are depicted in Scheme 13.[81] In the proposed mechanisms, the reductive and oxidative quenching cycles are initiated by visible-light excitation of the photocatalyst to produce the ^{3}MLCT. In the oxidative quenc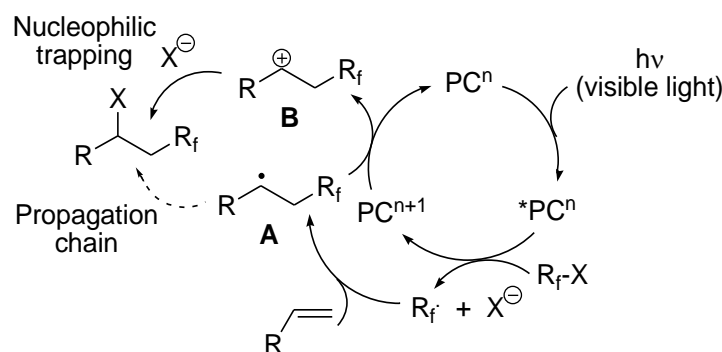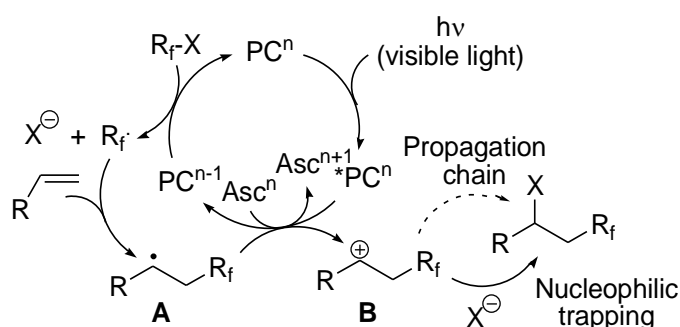hing cycle (Scheme 13a), the photocatalyst excited state ($*PC^n$) reduces the perfluoroalkyl iodides efficiently to afford the perfluoroalkyl radicals ($R_f^{\cdot}$). These radicals add to the alkene (or alkyne) to give the radical intermediate **A** which is oxidized to the carbocation intermediate **B** and finally trapped by the nucleophile rendering the corresponding ATRA products.

Besides, in the reductive quenching cycle (Scheme 13b) the photocatalyst excited state ($*PC^n$) is reduced by sodium ascorbate, a sacrificial electron donor, to provide the reduced catalyst (PC^{n-1}).[81] The reduced complex has a sufficiently strong reduction potential to effectively convert perfluoroalkyl iodides to electrophilic free radicals ($R_f^{\cdot}$). The radicals then undergo addition to the alkene or alkyne to provide the corresponding radical intermediate **A** (Scheme 13). Finally, these radicals are oxidized to the corresponding carbocation **B** followed by nucleophilic trapping with iodide, possibly preassociated as a counterion to the catalyst, providing the ATRA product (Scheme 13).

Noteworthy, participation of the radical intermediates **A** (Scheme 13) in a propagation chain reaction could be involved in the formation of the ATRA products and cannot be ruled out. However, the authors[81] state that the experimental evidence neither definitively confirms a radical-polar crossover mechanism nor rules out a radical chain propagation mechanism. Furthermore, if propagation is an active mechanistic component it is evident that the propagation chain reactions are short-lived.

(a) Oxidative quenching cycle.

(b) Reductive quenching cycle.

Scheme 13. Proposed reaction mechanisms for the photocatalyzed oxidative and reductive quenching cycles

An interesting report on the intermolecular trifluoromethylation of alkenes catalyzed by $[Ru(bpy)_3]^{2+}$ under visible light irradiation has been explored by Akita and co-workers.[48] The photocatalytic protocol achieves highly efficient and regioselective difunctionalization of terminal and internal alkenes, leading to a variety of β-trifluoromethylamines. This protocol involves the use of the photocatalyst, Umemoto's reagent and blue LEDs (425 nm) in acetonitrile – water as solvent mixture at room temperature. It is noteworthy to mention that acetonitrile, as the solvent, acts also as the *N*-nucleophile reagent which is known as an aminative carbocation trap agent involved in a Ritter-type reaction. Some selected examples are illustrated in Scheme 14.[48] Furthermore, Togni's reagents, i.e.: 1-

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trifluoromethyl-1,2-benziodoxol-3-(1*H*)-one) as well as 1-trifluoromethyl-1,3-dihydro-3,3-dimethyl-1,2-benziodoxole, do not afford any aminotrifluoromethylated product under the photocatalytic condition.

(a) Scope of terminal alkenes.

R	Yield (%)	R	Yield (%)
2-CH$_3$	91	2-Br	81
3-CH$_3$	91	4-CH$_2$CN	89
4-CH$_3$	91	3-CHO	78
4-F	83	3-COOMe	79
4-Cl	87	3-BocNH	75
4-Br	85	2-Br	84
4-CF$_3$	91		
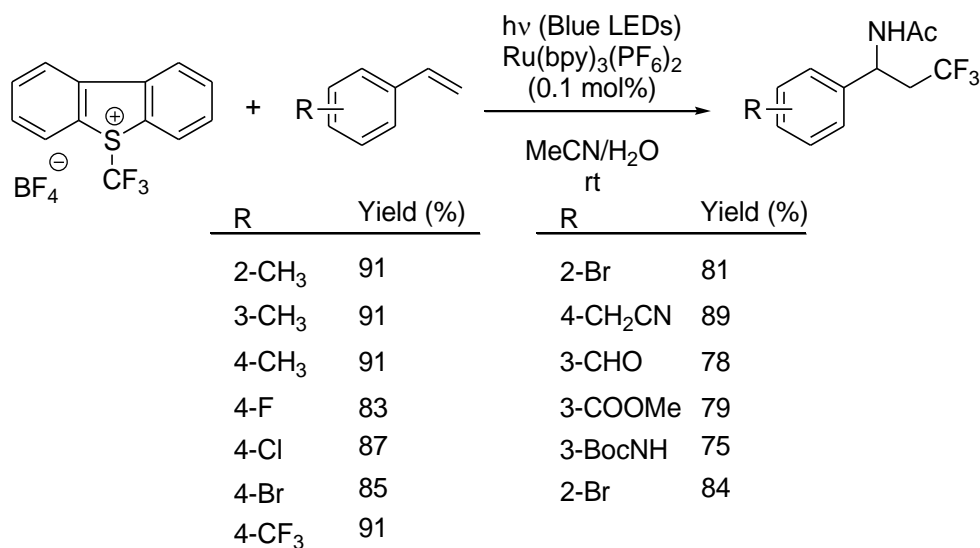
(b) Scope of internal alkenes.

R = CH$_3$ 87 % (65:35 dr)
R = Ph   77 % (89:11 dr)

R = CH$_3$ 80 % (79:21 dr)
R = Bn   77 % (73:27 dr)

71 % (71:29 dr)

82 % (71:29 dr)
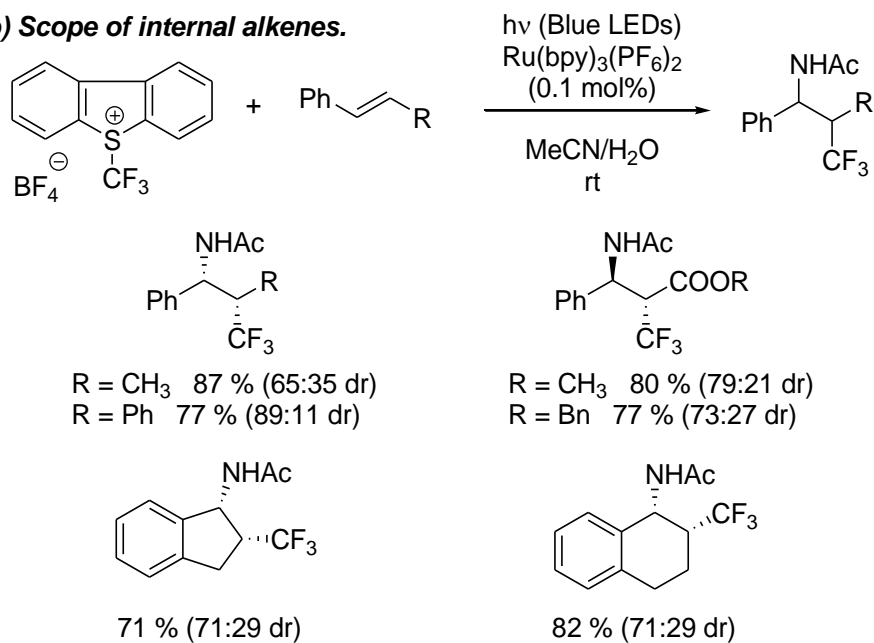
Scheme 14. Ru(bpy)$_3$$^{2+}$-photocatalyzed trifluoromethylation of heterocycles

An important feature of the above mentioned reactions is the possibility of up-scaling the late-stage aminotrifluoromethylation.[48]

Next, the authors have also studied the photocatalytic reaction using different organic[48] nitriles as *N*-nucleophiles in a mixture of organic nitriles and CH_2Cl_2 in (1:9) ratio affording the corresponding aminotrifluoromethylated products in moderate to good yields as is depicted in Scheme 15.

R	Yield (%)
Et	75
CH_2OCH_3	53
sec-Pr	62
c-Pr	77
c-Hex	67

Scheme 15. Ru(bpy)$_3$$^{2+}$-photocatalyzed trifluoromethylation of olefins with Umemoto´s reagent
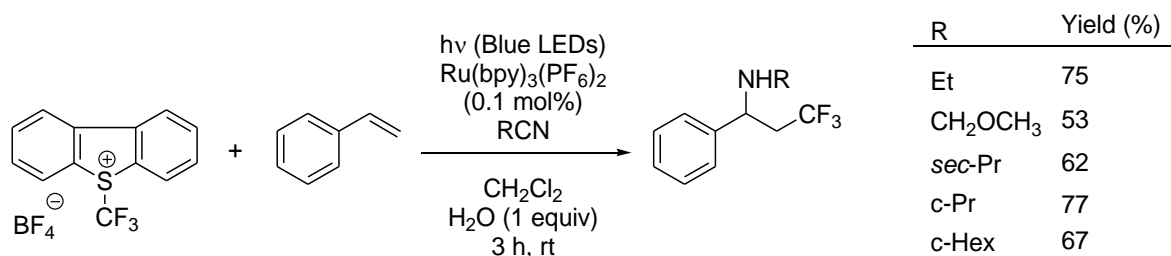
A plausible reaction mechanism via single-electron transfer (SET) process is shown in Scheme 16.[48] First, irradiation of the photocatalyst with visible light affords the photocatalyst in its excited state which reduces the Umemoto's reagent to generate the trifluoromethyl radical (CF$_3$·). Addition of CF$_3$· to the alkene affords the radical intermediate **A** (Scheme 16) which is oxidized to the carbocation **B** by [Ru(bpy)$_3$]$^{3+}$ closing the photocatalytic cycle according to *path (a)* (see Scheme 16). However, another possible pathway for the oxidation of intermediate **A** (Scheme 16) can be proposed, i.e., radical propagation (*path (b)*) providing intermediate **B** (Scheme 16). Finally, intermediate **B** reacts with organic nitriles (RCN), and following hydrolysis through a Ritter-Type amination, affords the desired products.

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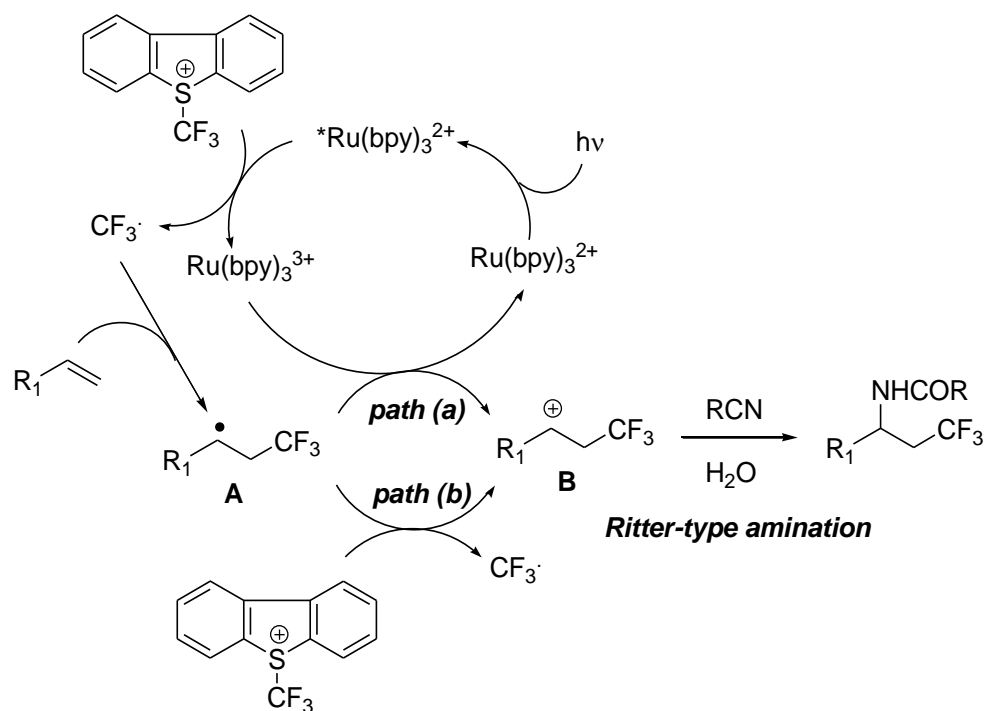
Scheme 16. Mechanism via single-electron transfer (SET) process.

The reaction appears to proceed through sequential single-electron transfer photoredox processes. Upon irradiation, excited $Ru(bpy)_3^{2+*}$ reduces Umemoto's reagent to provide trifluoromethyl radical that adds to alkenoic acids rendering intermediate **A** (Scheme 16). Oxidation of intermediate **A** by $Ru(bpy)_3^{3+}$ produces a α-trifluoromethyl-substituted carbocation intermediate **B** (Scheme 16) with high regioselectively. DFT computational studies on intermediate **B** reveal the most favorable conformation between the trifluoromethyl and the aryl groups which is arranged in an *anti*-fashion presumably because of steric repulsion. Subsequent intramolecular nucleophilic addition of the COOH group to the carbocationic center affords the *trans*-lactone trifluoromethylated.[48]

The hydroxy- and oxytrifluoromethylation of terminal and internal alkenes using the above-mentioned methodology, i.e., Umemoto's reagent as the $CF_3^.$ source and *fac*-Ir(ppy)$_3$

under visible light as the photoredox catalyst had also been informed.[63] The

hydroxytrifluoromethylation of styrene with H_2O affords the desired product in 97 % yield;

when the photocatalyst is $Ru(bpy)_3^{2+}$ the same product is obtained in 96 % yield. Electron-

donating and electron-withdrawing substituted styrene derivatives, as well as α-alkyl and α-

aryl substituted styrenes react efficiently affording the respective products in good yields

and with noticeable diastereoselectivity.

The photocatalytic oxytrifluoromethylation reaction of terminal alkenes affords the

trifluoromethylated ether products in moderate to good yields when O-nucleophiles such as

alcohols and carboxylic acids are used (Scheme 17).[63]
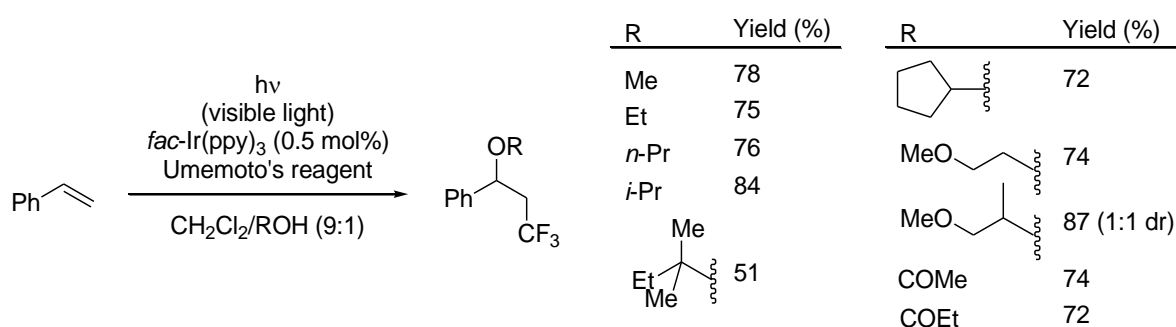
Scheme 17. Photocatalytic oxytrifluoromethylation reaction of terminal alkenes

Finally, studies on diasteroselective oxytrifluoromethylation of *trans*-stilbene were

carried out with a series of O-nucleophiles such as MeOH, EtOH, *i*-PrOH and AcOH and

similar d.r. were obtained. It is likely that the photocatalytic reactions go through the

common 3,3,3-trifluoro-1,2-diphenylpropyl intermediate with the same configuration.[63]

Recently, Akita and co-workers have developed a highly regio- and

diasteroselective trifluoromethyl lactonization of both terminal and internal alkenoic acids

by photoredox catalysis.[52] The use of $Ru(bpy)_3^{2+}$ and visible light as the photocatalyst and

Umemoto's reagent as a $CF_3^.$ radical source (mechanism for CF_3 radical production as in

Scheme 20, *vide infra*) is key in the present carbolactonization. The photoredox reaction of

4-aryl-4-pentenoic acid derivatives with electron-donating and electron-withdrawing

groups affords selectively the *exo* five-membered ring trifluoromethylated lactones in good

yields. The results are depicted in Scheme 18. Furthermore, the present photocatalytic

system has been extended to 5-phenyl-5-hexenoic acid as the terminal alkene and the

construction of a six-membered ring lactone is obtained in 69 % yield.[52]

R	Yield (%)
Ph	90
p-MeOC$_6$H$_4$	82
p-FC$_6$H$_4$	83
p-ClC$_6$H$_4$	79
p-BrC$_6$H$_4$	76
H	60
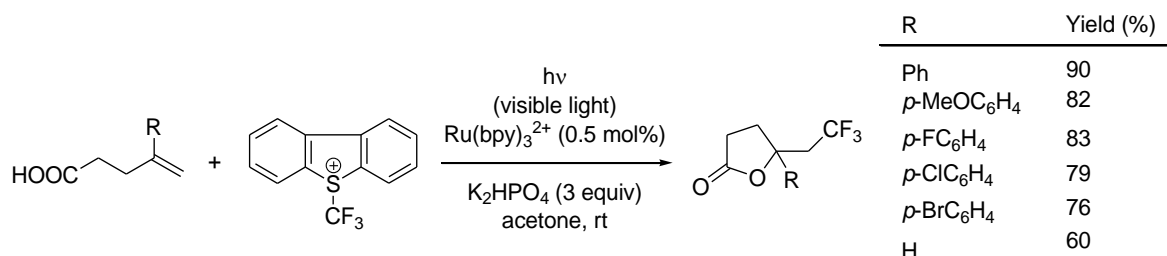
Scheme 18. Lactonization with ulterior trifluoromethylation of alkenoic acids through

photoredox catalysis employing Ru(bpy)$_3^{2+}$ and visible light

The photoredox-catalyzed trifluoromethylative cyclization of internal alkenoic acids

proceeds with high *endo*- diasteroselectivity providing the corresponding trifluoromethyl

lactones in good to excellent yields.[52] The reaction tolerates many functionalized groups

including trifluoromethyl and also a heteroaryl such as the benzothiophenyl group. Several

selected examples are shown in Scheme 19.
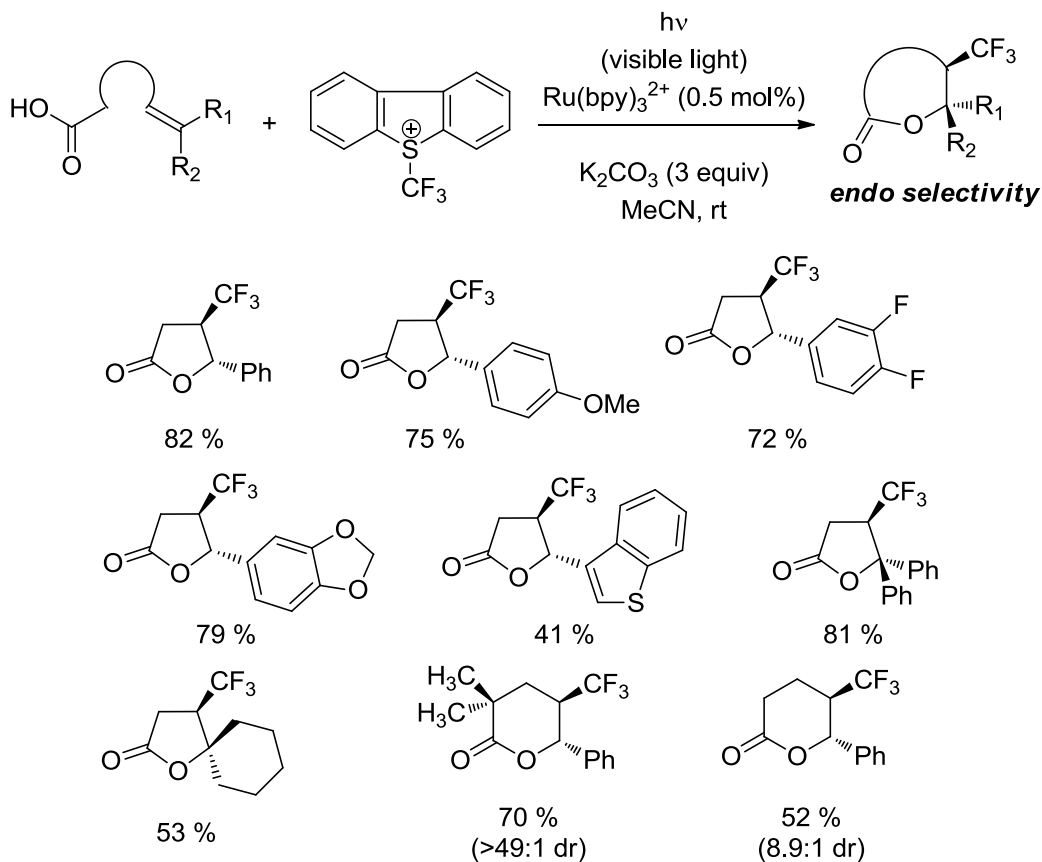
Scheme 19. Examples for the trifluoromethylative cyclization of internal alkenoic acids

The diasterocontrol of the photocatalytic reaction has been tested with (*S*)-4-phenyl-2-methyl-3-butenoic acid affording the trifluoro-substituted *endo*-lactone derivatives in 60 % yield as a mixture of only two of four possible diastereomers (3.3:1 dr) as shown in eq. 1.[52] Performing the reaction at -78 °C improved the diasteroselectivity (2.4:1 dr at room temperature). This result suggests that the stereofacial introduction of the CF$_3$ group is key for the selectivity outcome of the reaction.
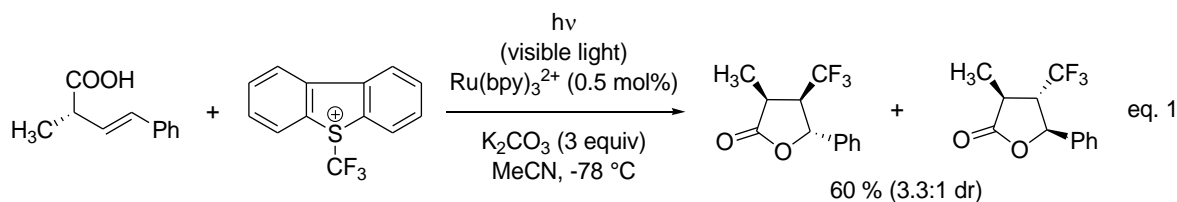
A reaction mechanism for this interesting highly *endo-* and diasteroselective photocatalytic reaction has been proposed and is illustrated in Scheme 20.[52][52]
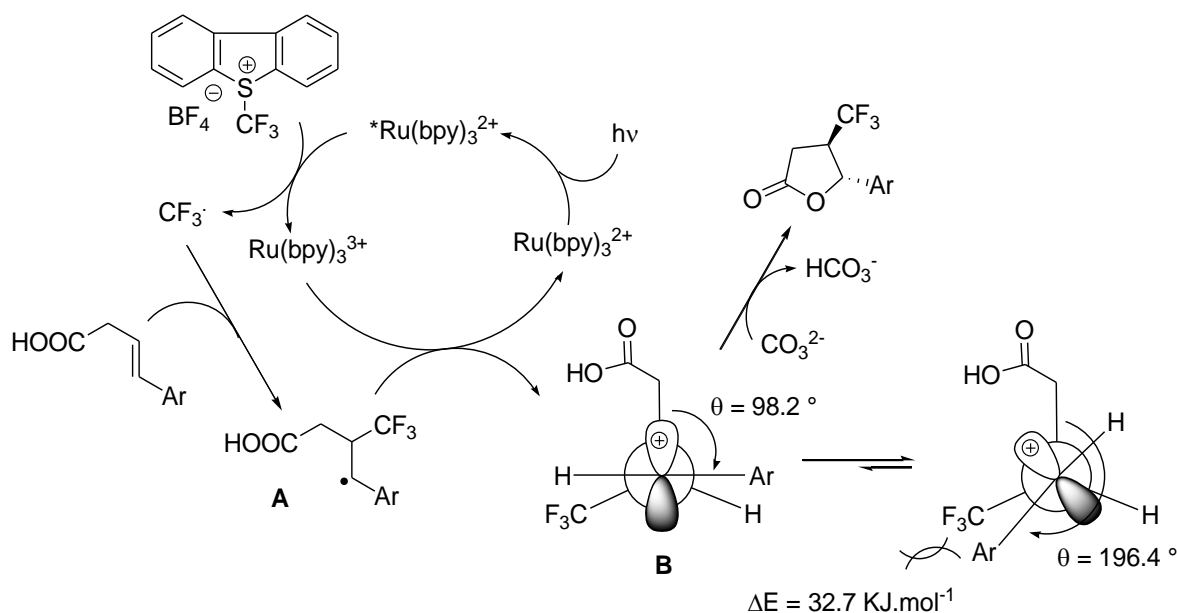
Scheme 20. Proposed mechanism for the highly *endo-* and diasteroselective photocatalytic reaction of alkenoic acids

In the above mechanism (Scheme 20), the excited $*Ru(bpy)_3^{2+}$ catalyst reduces the Umemoto´s reagent to CF_3 radical (and oxidized $Ru(bpy)_3^{3+}$). These CF_3 radicals add to the olefin generating the trifluoromethylated benzyl radical **A** (Scheme 20), which is further oxidized by $Ru(bpy)_3^{3+}$ to cation **B** (Scheme 20). Stereofacial intramolecular nucleophilic attack of the OH to the cationic center and further deprotonation by the base (CO_3^{2-}) affords

trifluoro-substituted *endo*-lactone derivatives in a highly *endo*- and diasteroselective manner.

Recently, the same authors have developed and disclosed highly efficient and stereoselective photocatalytic deboronated trifluoromethylation of potassium vinyltrifluoroborates using Togni's and Umemoto's reagents as trifluoromethyl radical source and Ir(ppy)$_3$ or Ru(bpy)$_3$(PF$_6$)$_2$ as the photocatalysts under visible light.[53] The best results in terms of yields and selectivity are obtained with Togni's reagent and Ru(bpy)$_3$(PF$_6$)$_2$ (5 mol%) in MeOH at room temperature under irradiation with blue LEDs which are shown in Scheme 21. The use of alkenyl boronic acids as the substrates under the photocatalytic process affords the trifluoromethyl products in moderate yields and without stereoselectivity.[53]

(a) Trifluoromethylation of (E)-styrylboronic acids
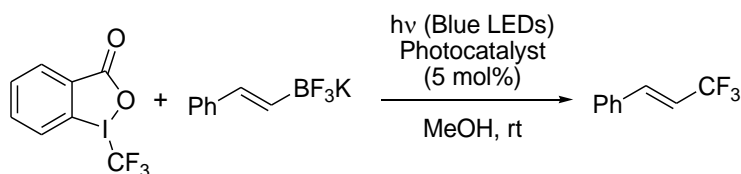
BX_n	Photocatalyst	Yield (%)	*E/Z*
$B(OH)_2$	$Ir(ppy)_3$	53	57/43
BF_3X	$Ir(ppy)_3$	85	94/6
BF_3X	$Ru(bpy)_3(PF_6)_2$	81	98/2

(b) Scope of trifluoromethylation of vinylborates
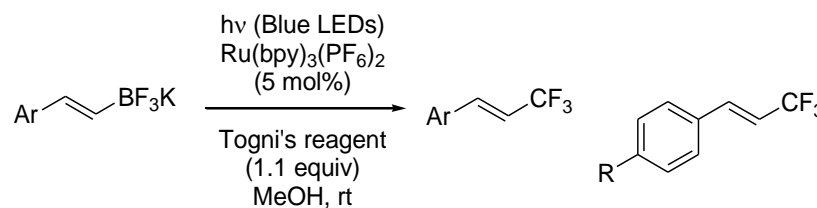
R	Yield (%)	*E/Z*
Me	81	92/8
MeO	88	99/1
Cl	72	94/6
Br	81	95/5
CF_3	79	98/2
CF_3O	69	95/5
CN	78	96/4

81 % (*E/Z* = 97/3)   68 % (*E/Z* = 96/4)   93 % (*E/Z* = 96/4)   63 % (*E/Z* = 96/4)

68 % (*E/Z* = 97/3)   69 % (*E/Z* = 97/3)   71 % (*E/Z* = 98/2)   60 % (*E/Z* = 63/37)

79 % (*E/Z* = 73/27)   56 % (*E/Z* = 98/2)   68 % (*E/Z* = 98/2)   68 % (*E/Z* = 97/3)
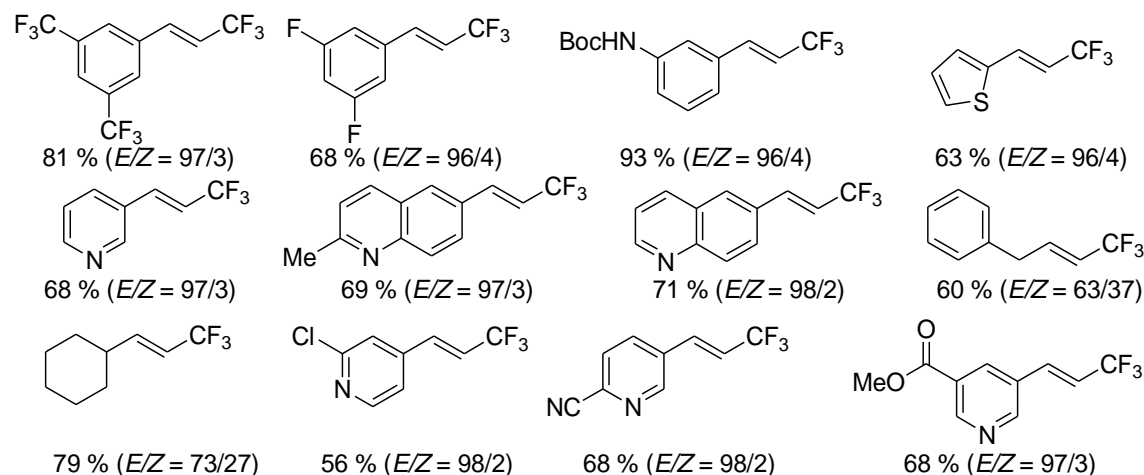
Scheme 21. Use of alkenyl boronic acid as the substrates under the photocatalytic process

The α-trifluoromethyl styrene products are formed starting from (*E*)-styrylborates bearing a variety of electron-rich and electron-deficient groups. Also, vinylborates containing heteroaryl groups are trifluoromethylated efficiently in good yields and with noticeable *E/Z* selectivity. The mechanism of this reaction has recently been reviewed.[53b]

An efficient one-step protocol to obtain α-trifluoromethyl ketones from propargylic alcohols and trifluoroiodomethane has recently been developed by visible-light photoredox catalysis by Cho and collaborators.[82] The photoreaction takes place with both photocatalyst, i.e. Ru(bpy)$_3$Cl$_2$ and *fac*-Ir(ppy)$_3$ affording comparable results, however, the former was selected due to its lower cost and clean reaction profile. A variety of propargylic alcohols connected to an aromatic ring efficiently undergoes the cascade catalysis to provide the corresponding β-trifluoromethyl ketones in moderate to good yields (Scheme 22a).[82] Changing the aryl substituent to an aliphatic group as well as internal propargyl alcohols do not improve the selectivity or reactivity of the process and generates mixtures of unidentified compounds or trifluoromethylated allylic alcohols.

(a) Substrate scope for the synthesis of β-trifluoromethyl ketones.

R	Yields (%)
H	80
Me	74
OH	55
OMe	70
F	70
Cl	52
Br	45

65 %

84 %

75 %

45 %
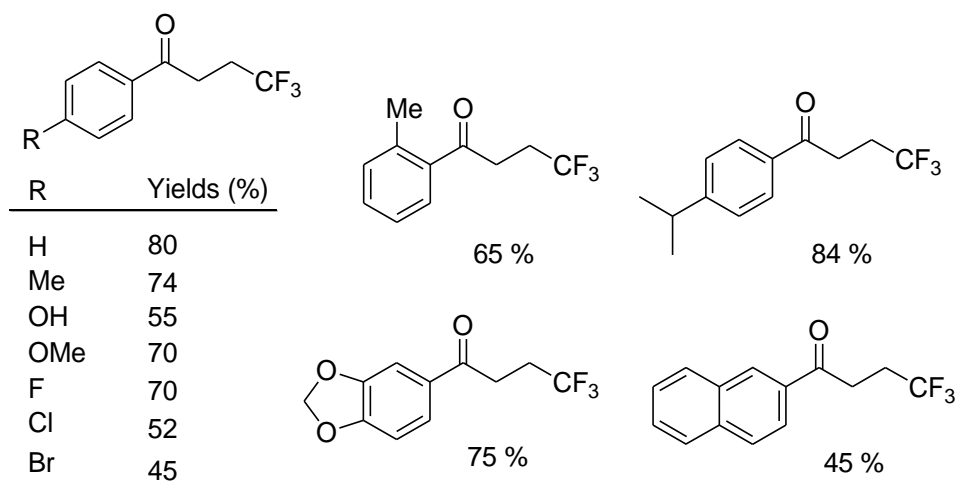
**(b) Plausible reaction mechanism.**
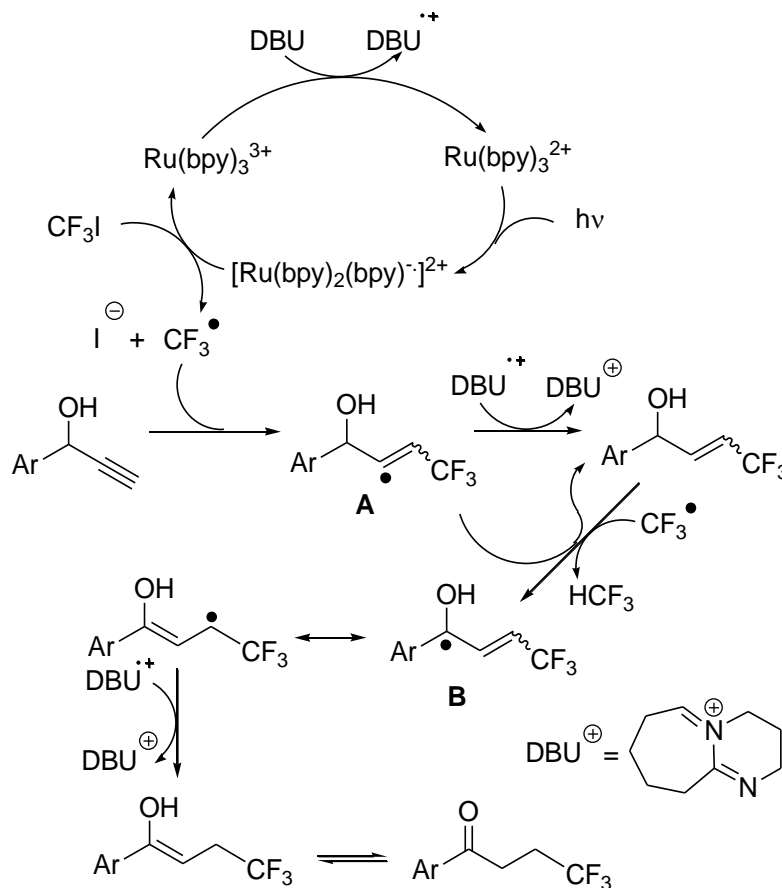
Scheme 22. β-trifluoromethyl ketones by photoredox catalysis

The proposed mechanism for the preparation of β-trifluoromethyl-ketones is depicted in Scheme 22b and involves a radical chain process.[82] Visible-light photoexcitation of the photocatalyst produces $[Ru^{III}(bpy)_2(bpy)^{\cdot-}]^{2+}$ which is oxidatively quenched by single-electron transfer to CF_3I to produce the key intermediate $CF_3^{\cdot}$, $[Ru^{III}(bpy)_3]^{2+}$, and iodide ion. Ulterior addition of the $CF_3^{\cdot}$ radical to the alkyne forms the trifluoromethylated vinyl radical species (**A**, Scheme 22). Hydrogen atom abstraction of the radical species from the ammonium radical cation $(DBU^{+\cdot})$ provides the allyl alcohol. Formation of a resonance-stabilized allyl radical **B** (Scheme 22) is proposed to be formed by hydrogen abstraction from radical **A** and radical $CF_3^{\cdot}$. Ultimately, radical **B** (Scheme 22) is terminated by hydrogen abstraction to afford the enol which, after keto-enol tautomerization, affords the β-trifluoromethyl ketone.[82]

A novel photocatalytic trifluoromethylarylation/1,4-aryl shift/desulfonylation cascade reactions of tosyl amide derivatives using CF_3SO_2Cl as CF_3 radical source and $Ru(bpy)_3Cl_2$ as the photocatalyst was described by Chang, Xia and co-workers.[83] The photocatalytic reaction takes place under blue LEDs irradiation in the presence of the photocatalyst (5 mol%) and a base such as K_2HPO_4 in MeCN at room temperature under N_2 atmosphere. Replacement of $Ru(bpy)_3Cl_2$ by $Ir(ppy)_3^{3+}$ did not improved the yields as well as when Togni's reagent was used instead of CF_3SOCl as the CF_3 radical source. The reaction scope was studied using α,β-unsaturated imide alkenes containing various electron-donor and electron-withdrawing substituents in *para* position and the corresponding products were obtained in moderate to good isolated yields. A substituent in *meta* position of the imide gave a mixture regioisomers in a ratio 2:5 in 36 % yield while a

substituent in *ortho* position gave a complex reaction mixture. The results are shown in Scheme 23.
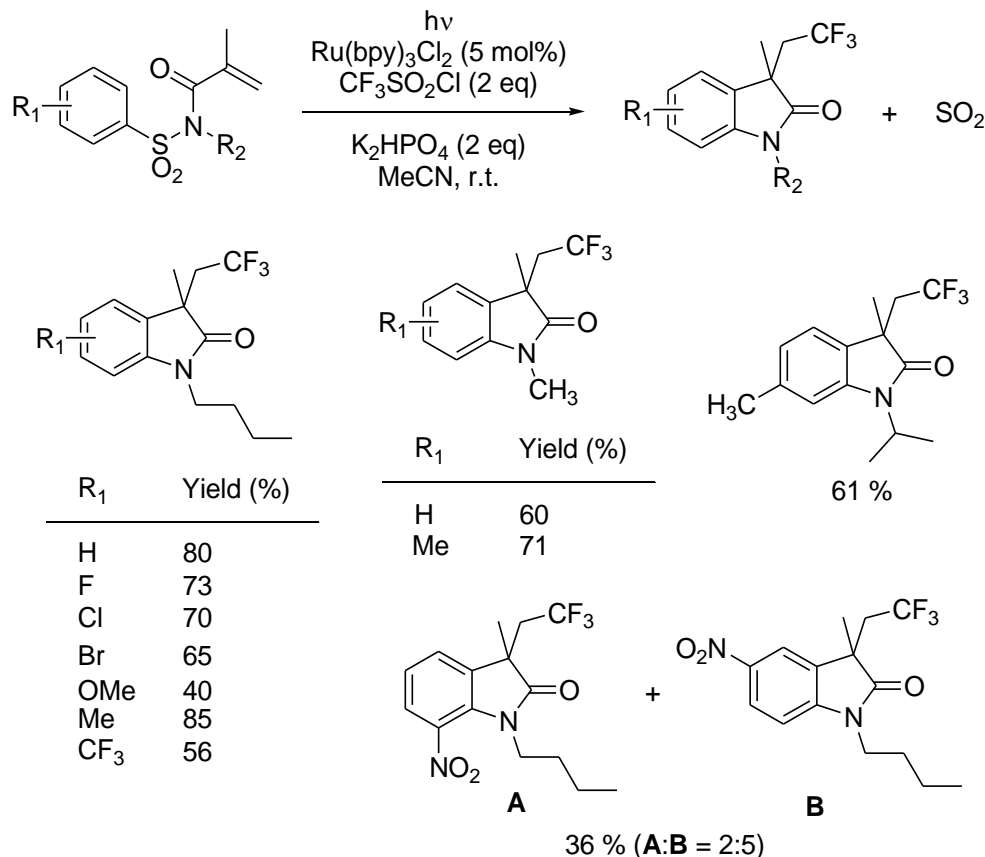
Scheme 23. Trifluoromethylation of α,β-unsaturated imide alkenes.

Interestingly, when the *N* substituent was changed from alkyl to aryl groups, only a 1,4-aryl shift was observed rather than the radical cyclization.[83] The photocatalytic reaction operates efficiently with the protocol mentioned above, but it is not necessary the use of a base. The effect of substituents of the sulfonamide group as well as of the aryl group bounded to the N atom has been examined and the corresponding products are obtained in moderate to good yields (see Scheme 24). Electron-donating groups at the *para* or *meta*

position are compatible with the reaction; in contrast, the presence of electron-withdrawing

groups decrease the efficiency of the reaction.
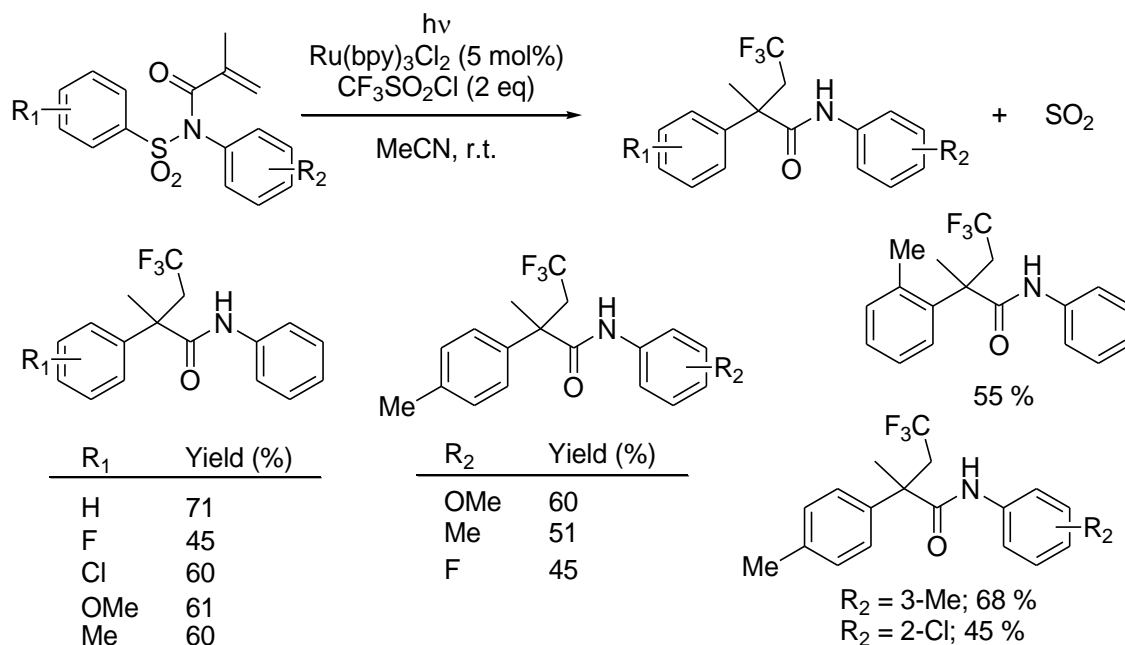
Scheme 24. Trifluoromethylation of α,β-unsaturated *N*-arylimide alkenes.

The application of the photocatalytic reaction to the preparation of trifluoromethylated

isoquinolonedione derivatives is also successful and the respective products are obtained in

moderate to good yield as depicted in Scheme 25.[83] Methyl *para*-substituted, and fluoro-

para-substituted-aryl substrates or substrates bearing substituents at *N* atoms can also be

tolerated under the reported reaction conditions.
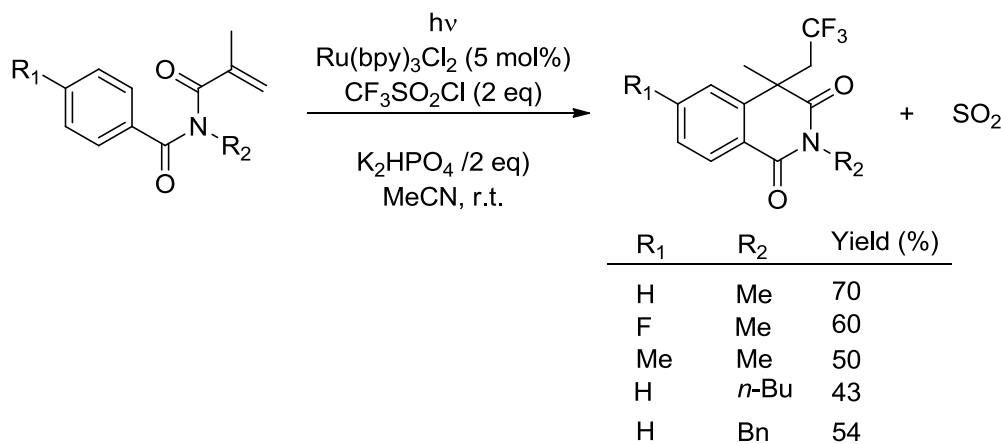
Scheme 25. Photocatalytic preparation of trifluoromethylated isoquinolonedione derivatives.

A plausible mechanism of the protocol is proposed in Scheme 26.[83] An oxidative quenching cycle is postulated that begins with visible-light irradiation of the photocatalyst to the excited state $[Ru(bpy)_3^{2+}]^*$ which promotes the reduction of CF_3SO_2Cl to generate CF_3 radical after release of chloride and SO_2. The CF_3 radical is trapped by the α,β-unsaturated imine alkenes to afford the intermediate **A** (Scheme 26) after the formation of a new $C(sp^3)$-CF_3 bond. When X is SO_2 aryl migration/desulfonylation cascade reaction occurs to form intermediate **B**, due to the instability of intermediate **A** (Scheme 26). At this stage, intermediate **B** abstracts a hydrogen atom from the solvent to afford the corresponding amide when an aryl group is bounded to the N atom, whereas when the substituent is an alkyl group, cyclization of amidyl radical to the aryl ring of intermediate **B** is the favoured pathway leading to the formation of intermediate **C** (Scheme 26). This last intermediate is then oxidized to the carbocation **D** which collapses to the product after releasing a proton. For X = CO, the intramolecular radical cyclization of **E** (Scheme 26)

leads to the intermediate **F** (Scheme 26), which produces *iso*quinolidione derivatives after oxidation and deprotonation.
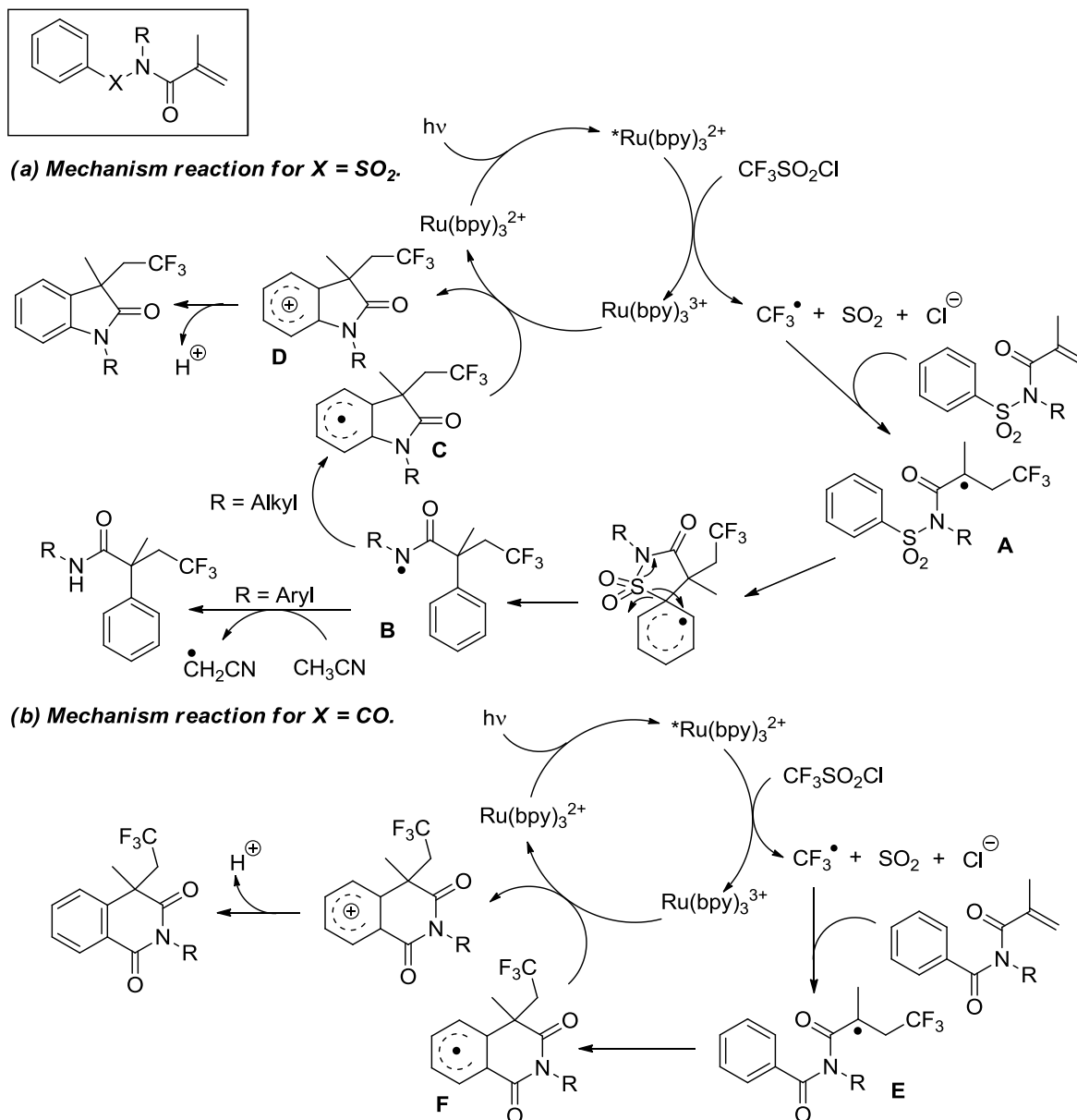
Scheme 26. Reaction mechanism of the trifluoromethylation of α,β-unsaturated imide alkenes.

1.2.-TRANSITION METAL-PHOTOCATALYTIC FLUOROALKYLATION OF (HETERO)ARENES

Transition-metal catalysis can be considered a very valuable tool in organic synthesis on account of the number of reactions that can be performed. A recent review article on transition-metal-mediated thermal perfluoroalkylation reactions of heteroarenes attests to the relevance of the subject.[84]

1.2.1.-ARENES

The use of semiconductors as photocatalysts, has been reported by Iizuka and Yoshida.[66] Irradiation of TiO_2 promotes electrons from the metal valence band to the conduction band, leaving holes in the valence band. It becomes possible to use these electrons and holes for one-electron reductions and oxidations, respectively.

Iizuka and Yoshida[66] have reported the development of a new redox system using TiO_2 as a photocatalyst to perform perfluoroalkylation reactions of arenes that form carbon–carbon bonds. Perfluoroalkyl radicals are formed by injection of an electron from the conduction band of TiO_2. The resulting radical reacts with the substrate to provide a new radical species (**A,** Scheme 27a), which is oxidized to the corresponding cation intermediate **B** as depicted in Scheme 27a.
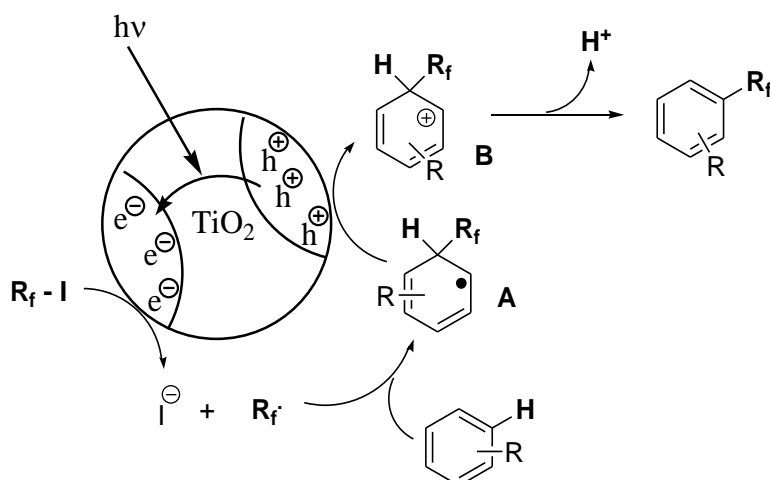
Scheme 27a. TiO$_2$-photocatalyzed perfluoroalkylation of arenes

Aromatic perfluoroalkylations of *p*-xylene, benzene and 1,4-dichlorobenzene with perfluoroalkyl iodide by TiO$_2$-photocatalysis have been studied in a solvent system consisting of a mixture of CH$_3$CN/CH$_3$OH in the presence of NaBF$_4$. The reactivity of these arenes in the production of perfluorohexyl-substituted arenes is consistent with the electrophilicity of the perfluoroalkyl radical. The scope of the reaction is illustrated in Scheme 27b.
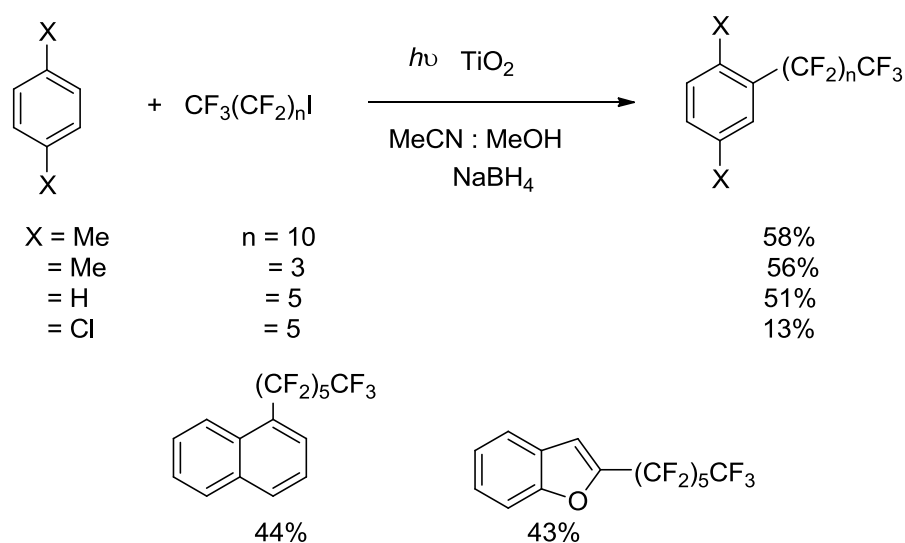
Scheme 27b. Scope of the TiO$_2$-photocatalyzed perfluoroalkylation reaction

1.2.2.-HETEROARENES

It has been reported that microreactors, owed to their high surface-to-volume ratios, can be very useful as process parameters can easily be controlled (e.g., heat and mass-transfer, gas-liquid characteristics, residence time control), which leads to a safer handling of hazardous compounds.[85-89] Due the large absorptivity of photoredox catalysts, a considerable amount of light is absorbed within the first few hundreds of micrometers of the light path, enabling the scaling-up of the reactions.[34-39] A series of experiments have been conducted by Noeel and collaborators[90] to evaluate the scope of the continuous-microflow trifluoromethylation method. Next, the authors[90] have extended their focus by developing a continuous flow method for the photocatalytic perfluoroalkylation of heteroarenes using perfluoroalkyl iodide (RCF_2I).

With the optimal conditions in hand, the authors have evaluated the method by perfluoroalkylating a selection of five-membered heteroarenes with different perfluoroalkyl iodides and ethyl 2-bromo-difluoroacetate (Scheme 28). The construction of perfluoroalkylated *N*-methylpyrrole and a number of indole analogues is possible within several minutes (t_R=10 min) and the target compounds are delivered in good yields (53–88%). Besides, 3-methylindole also reacts with perfluoro-2-iodopropane and ethyl 2-bromo-difluoroacetate, giving the corresponding products in very good yields (99% and 72%).
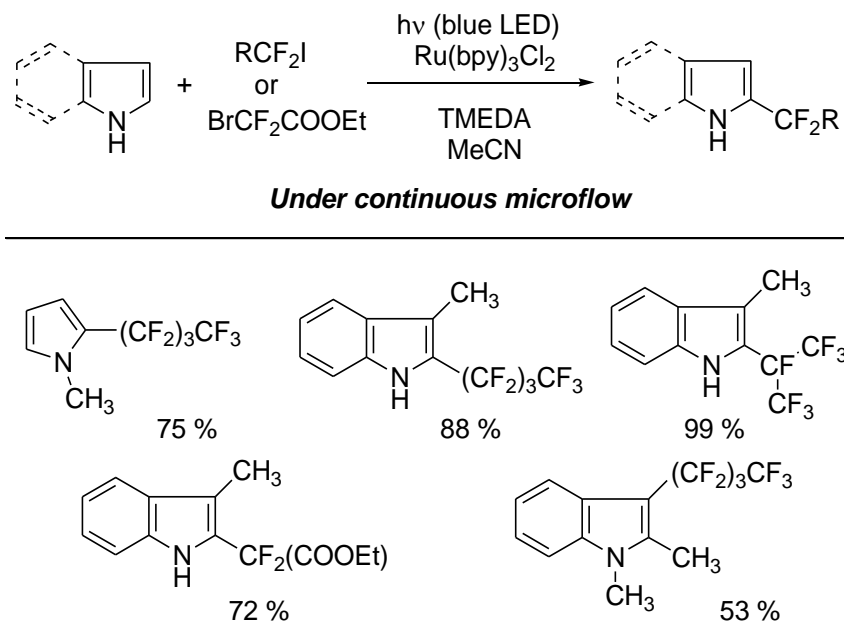
Scheme 28. Perfluoroalkylation of indole derivatives employing perfluoro-2-iodopropane and ethyl 2-bromo-difluoroacetate under Ru(bpy)$_3$Cl$_2$ photocatalysis

Yu and co-workers have introduced for the first time the visible-light-promoted somophilic *iso*cyanide insertion using an iridium photocatalyst.[91] This efficient synthetic approach provides a rapid entry to 6-perfluoroalkylated phenanthridine derivatives as depicted in Scheme 29. The reactions proceed at room temperature with *fac*-Ir(ppy)$_3$ under blue light in the presence of NaH$_2$PO$_4$ in DMF providing the phenanthridine derivatives in good yields.

(a) Scope of isocyanide.
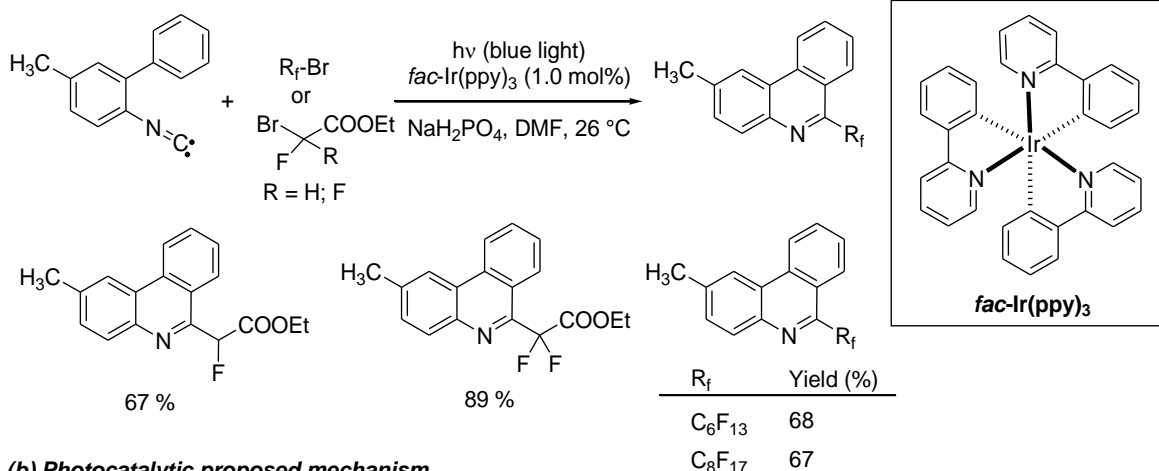
(b) Photocatalytic proposed mechanism.
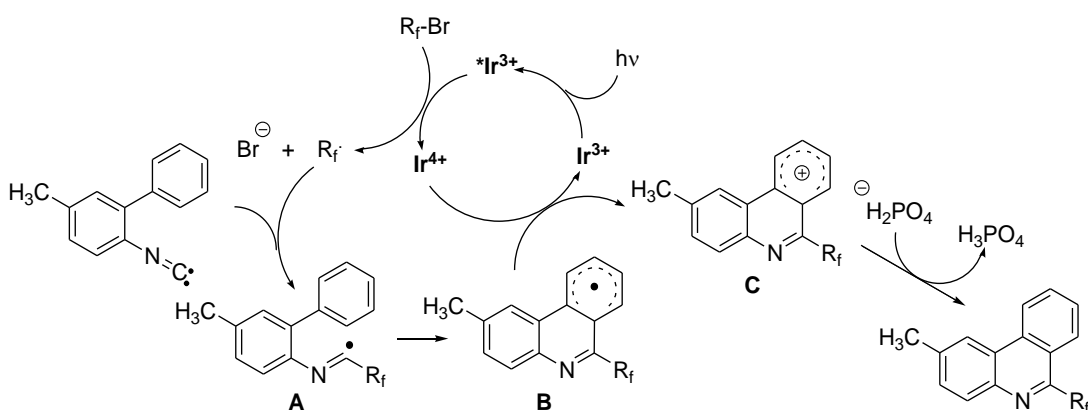
Scheme 29. Perfluoroalkylation of *iso*cyanides towards the synthesis of phenanthridine derivatives, and proposed mechanism of the photocatalyzed *fac*-Ir(ppy)$_3$$^{3+}$-reaction

Although this is not a direct fluoroalkylation of an aromatic nucleus, a homolytic aromatic substitution results in the production of fluoroalkyl-substituted phenanthridines.

Recently, the same authors have developed both a stepwise and a one-pot procedure for the preparation of mono- and difluoromethyl phenanthridine derivatives in good to excellent yields involving a perfluoroalkylation and decarboxylation sequence.[92] The photoredox fluoromethylation reaction takes place upon visible irradiation of the photocatalyst *fac*-Ir(ppy)$_3$$^{3+}$ in the presence of KHPO$_4$ in DMF at room temperature.

Depending on the selected procedure, basic hydrolysis with K_2CO_3 in MeOH of the carboxylated derivatives affords the expected phenanthridine derivatives. The reaction shows a broad substrate scope. Scheme 30 illustrates several selected examples.
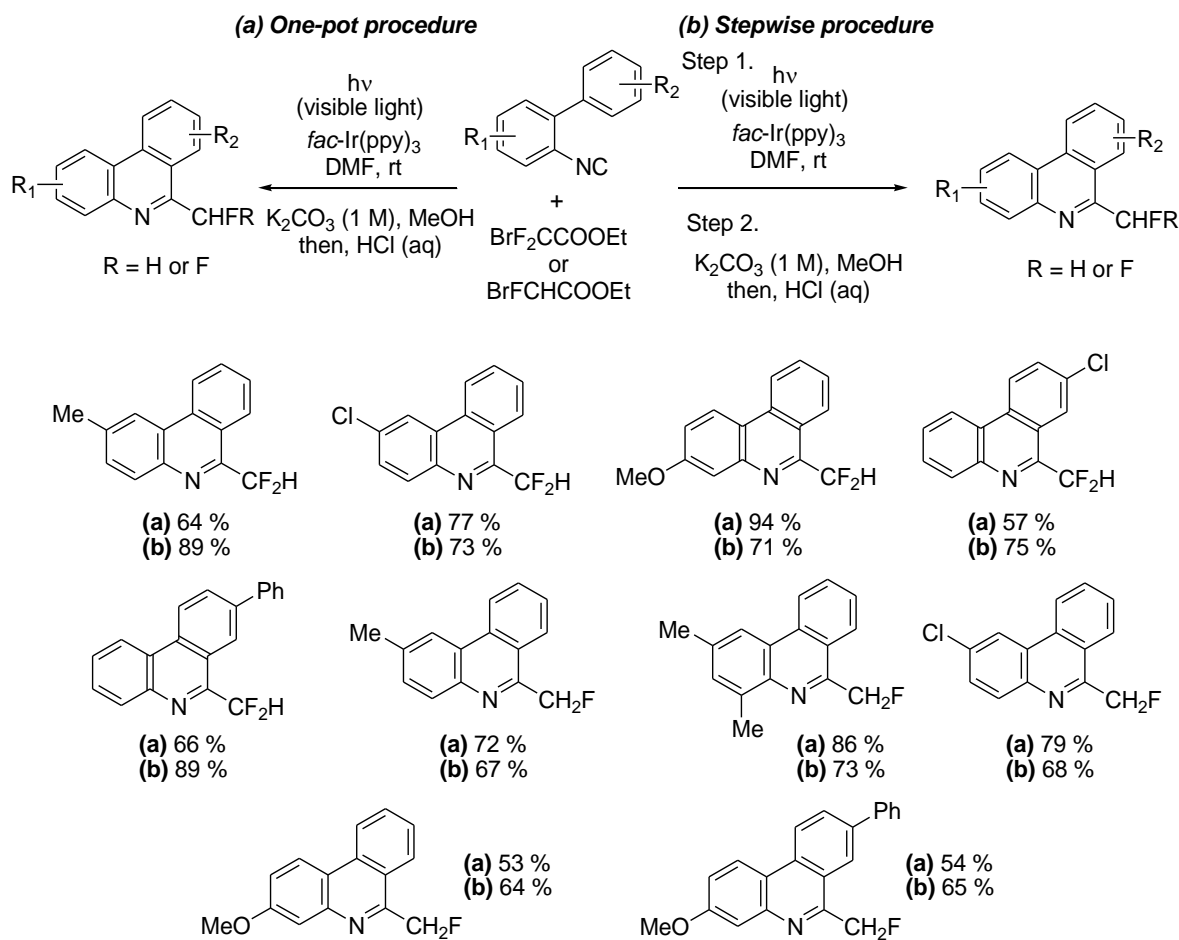
Scheme 30. Fluoromethylation reaction by visible irradiation of the photocatalyst *fac*-Ir(ppy)$_3$$^{3+}$ in the presence of KHPO$_4$ in DMF

Desulfonylation (not shown) is accomplished by Mg and was found to proceed smoothly at room temperature, affording the difluoromethyl, and monofluoromethyl derivatives in good yields (Scheme 30).[92]

Wang and co-workers have developed a novel method for visible light photoredox-catalyzed difluoromethylation of electron-rich heteroarenes such as pyrrol, indole, furane, and thiophene under very mild reaction conditions.[93] The photocatalytic reaction of heteroarenes is carried out with the Prakash and Hu's reagents, $PhSO_2CF_2I$, as the difluoromethyl source in the presence of $Ru(bpy)_3Cl_2.6H_2O$ and visible light, a base such as K_2HPO_4, in dichloromethane at 40 °C. Heteroarenes such as substituted pyrrol, furane and thiophene are difluoro(phenylsulfonyl)methylated in satisfactory to good yields and selected examples are shown in Scheme 31.[93] Generally, the reaction proceeds with electron-rich and electron-poor groups attached to the heteroarene moieties. Another interesting feature of the regioisomers obtained is the predominantly functionalization at the electron-rich C-5 position (C-5:C-2 = 3.3:1) for the case of 4-methyl-thiazole, further corroborating the preference of this novel method for attack at the electron-rich position. This suggests that the putative difluoro(diphenylsulfonyl)methyl radical generated by photoredox reduction of $PhSO_2CF_2I$ is an electrophilic radical.[93]
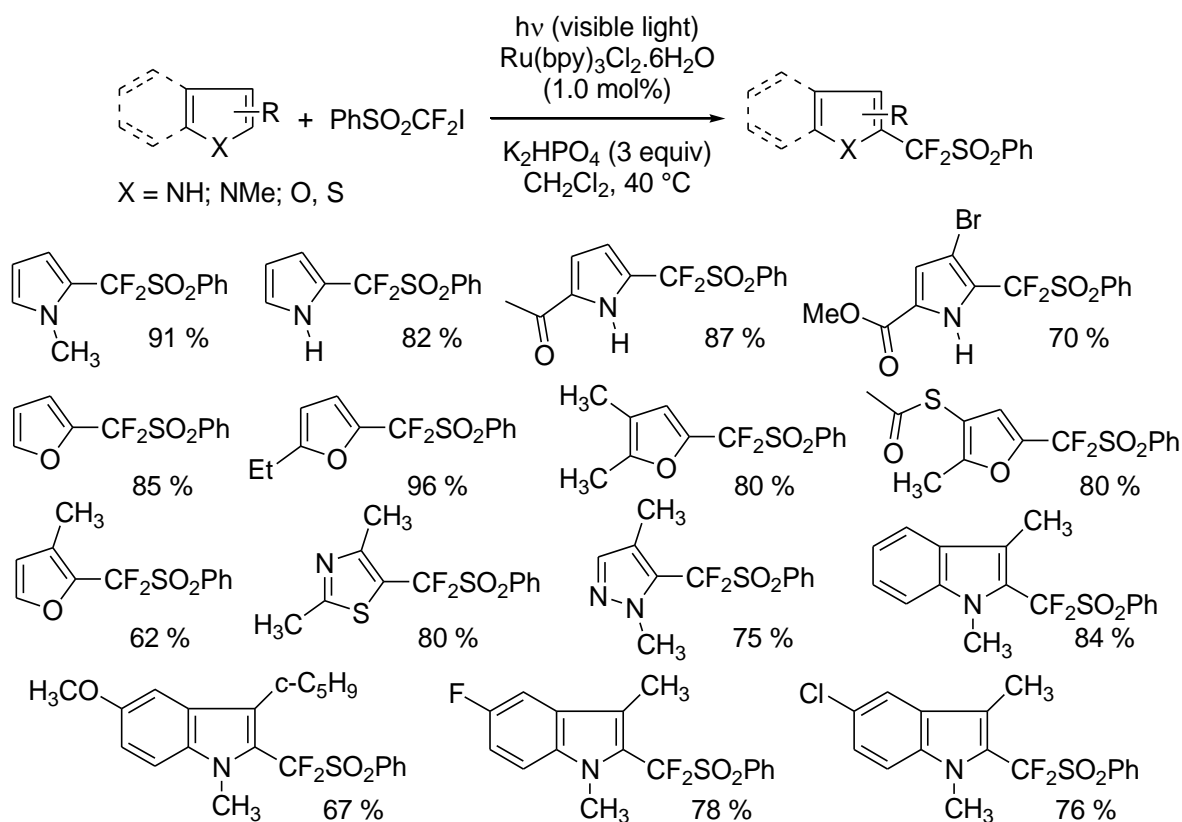
Scheme 31. Difluoromethylation of heteroarenes with $PhSO_2CF_2I$, as the difluoromethyl source in the presence of $Ru(bpy)_3Cl_2.6H_2O$ and visible light

You and co-workers have reported and developed for the first time the application of cyclometalated Pt^{II} complexes in photoredox catalytic trifluoromethylation of heteroarenes.[79] The Pt^{II} photocatalyst bears a 2-phenylpyridinate and non-photoactive acetylacetonate ancillary ligands. The oxidative quenching photoredox catalysis was investigated over a range of heteroarenes in MeCN as solvent and at room temperature to provide the trifluoromethylated heteroarenes in good yields (Scheme 32). A sacrificial electron-donor, such as tetramethyl-ethylene-diamine, TMEDA, is required and the photocatalytic reaction is completed within 10 - 24 h. With the optimized conditions in

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hand, the Pt(II) complex shows catalytic activities similar to the other well-establish

photoredox catalyst, such as Ru(bpy)$_3$Cl$_2$ and Ir(ppy)$_2$(dtbbpy)PF$_6$.
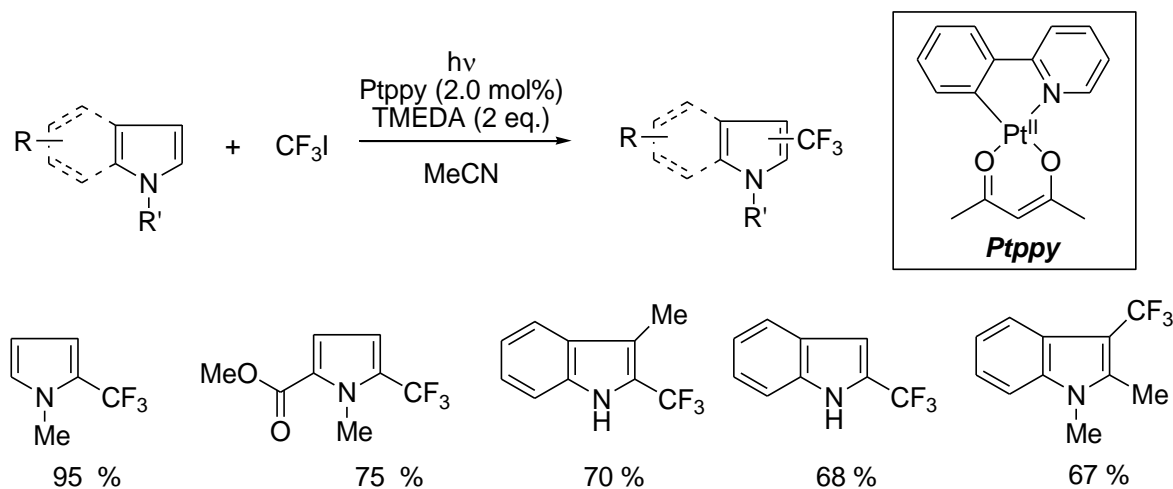
Scheme 32. Cyclometalated Pt^{II} complexes in photoredox catalytic trifluoromethylation of

heteroarenes

2.-PHOTOORGANOCATALYSIS (POC)

Photoorganocatalysts are generally small molecules that harvest enough energy in their

excited states enabling them to generate intermediates otherwise difficult to attain. This can

be done either via atom transfer or via a redox process.[9] The excited state potential energy

surface reached by these excited POC overcomes the high energy barriers of thermal

reactions, catalytic or not, which can only be accessed employing extremely aggressive

reagents or harsh reaction conditions.

The related cost, potential toxicity, and availability of the ruthenium and iridium

salts are disadvantages of these metal-based methods. Through the possibility of using

green light, the most abundant part of solar light, it can be speculated that red to orange

dyes could be used successfully in photoredox catalysis, and the choice of appropriate

reaction conditions would additionally permit the cooperative involvement of asymmetric organocatalysis.

In the last decade organocatalysis, together with metal and enzyme catalysis, are complementary protocols in organic synthesis for achieving asymmetric catalysis. [94,95]

Excellent review articles do exist on photoorganocatalysis.[9] However, few perfluoroalkylation reactions by photoorganocatalysis have been informed. In the reactions reviewed in the next sections, an organic molecule under irradiation catalyzes a reaction where a fluoroalkyl moiety is introduced in the structural organic backbone. Useful photoorganocatalysts consist of aromatic ketones, quinones, heterocycles, dyes; intermediates formed are radicals, radical ions and ions from precursors such as alkanes, alkenes, amines, ethers, etc. The key characteristic of the method is the smooth generation of highly reactive intermediates under mild conditions.

2.1.-FLUOROALKYLATION OF ALIPHATIC SYSTEMS BY POC

2.1.1.-FLUOROALKYLATION OF SP^3 CARBON ATOMS BY POC

Zeitler and collaborators[96] have established a methodology compatible with the stereospecific incorporation of polyfluorinated alkyl substituents on aliphatic aldehydes (Scheme 33), which are important elements in drug design to modulate specific properties.
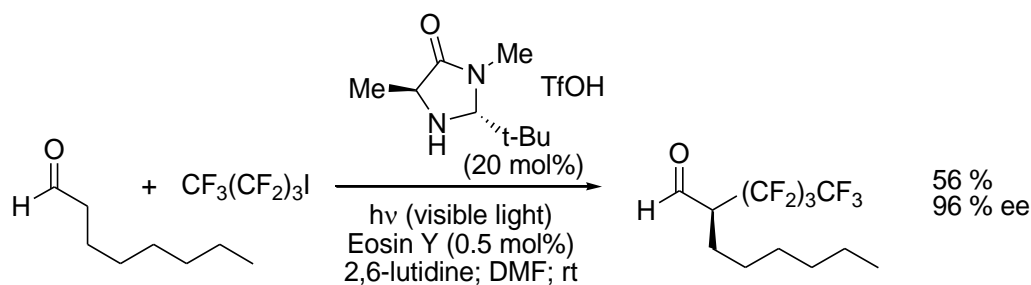
Scheme 33. Stereospecific incorporation of polyfluorinated alkyl substituents on aliphatic aldehydes

It is not yet quite clear the mechanistic picture of this reaction.[96] After visible light excitation, eosin Y acts as a photoredox catalyst, populating its more stable triplet state and enabling single-electron transfer (SET; Scheme 34).|[97]   As has been shown for the chemistry of $Ru^{2+}*$, excited eosin Y (^{3}**EY***) can undergo both reductive and oxidative quenching pathways.[98] These results are comparable to those of MacMillan and coworkers (*vide supra*); therefore it can be inferred that eosin Y acts a reductant—relying on the sacrificial donor (i.e.: enamine) as the initial electron reservoir[99] —to yield the electron-deficient alkyl radical by means of SET with an alkyl halide. Addition of this radical to the electron-rich enamine (regenerated within the organocatalytic cycle) unites both activation pathways. In the catalytic cycle the oxidation of the amino radical to the iminium species affords the electron for the reductive quenching of the dye excited state ^{3}EY*.[100,96] The authors then focused their efforts to the determination of the quantum yield of the reaction to gain further information on its efficiency.[101]

(a) Proposed mechanism.
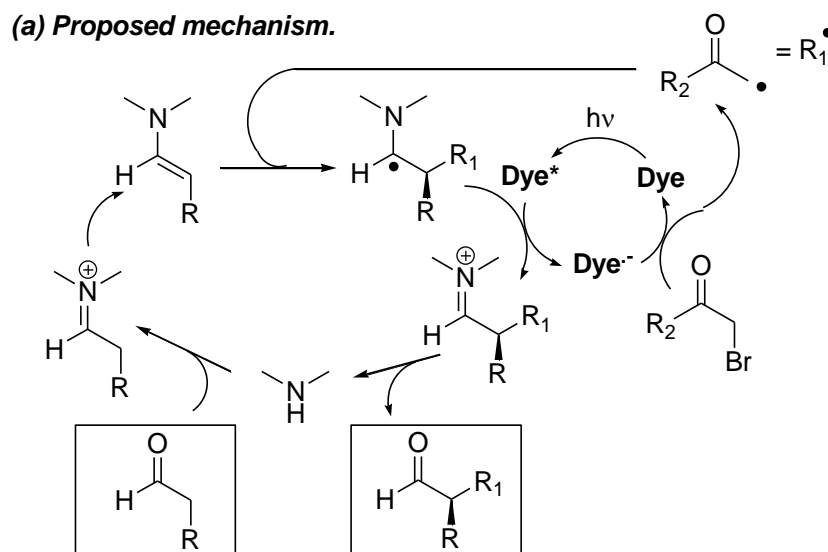
(b) Photoredox cycles of Ru[II] and Eosin Y.
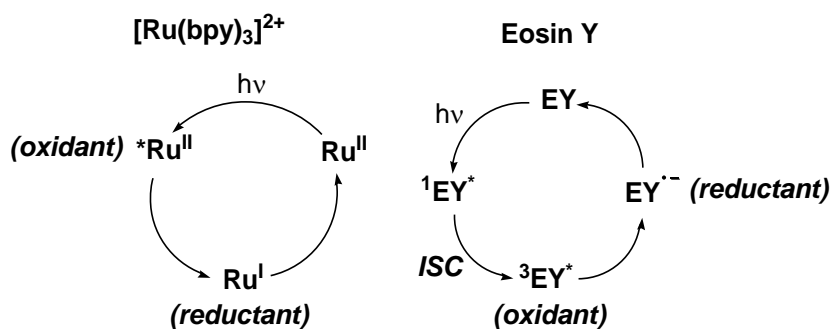
Scheme 34. Reductive and oxidative quenching known for excited eosin Y

Melchiorre and collaborators[102] have very recently reported that the reaction of methyl ester of the 1-indanone-2-carboxylate with perfluorohexyl iodide in chlorobenzene/C_8F_{18} as solvent under irradiation by white light-emitting diodes (LEDs) (Scheme 35), in the presence of the commercially available cinchona-derived PTC catalyst and Cs_2CO_3 (2 equiv), so as to form the corresponding chiral enolate of type **IV**, provided the corresponding product in good chemical yield.

As detailed in Scheme 35,[102] a variety of electron-withdrawing substituents are well tolerated, independently of their position. The authors[102] next found that the system is

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amenable to using other perfluoroalkyl iodides (Scheme 35c). Both shorter and longer

perfluorinated chains can be installed in indanone derivatives in a good yield and with a

high stereocontrol (*ee* ranging from 90% to 94%). Notably, trifluoromethyl-containing

quaternary stereocenters can be forged with high fidelity when reacting β- ketoesters with

CF$_3$I (Scheme 35d).

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(a) General enantioselective photocatalytic reaction.

R_f = C_6F_{13}; C_4F_9; C_3F_7; $C_{10}F_{21}$
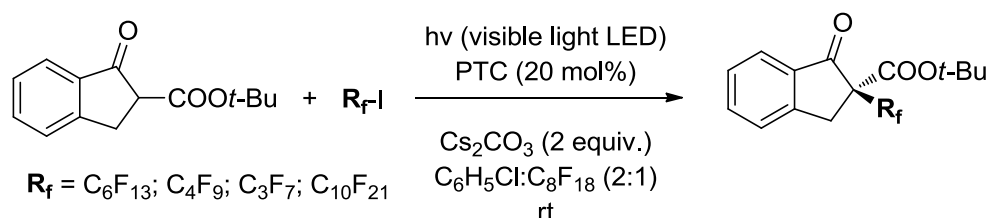
(b) Substituent effect on the enantioselective photocatalytic reaction.

R	Yield (%)	ee (%)	R	Yield (%)	ee (%)
H	71	93	5-MeO	38	86
5-F	63	87	4-CF$_3$	61	90
5-Cl	70	86	6-Me	55	83
5-Br	60	88	6-Br	55	83

(c) Reactivity of different perfluoroalkyl iodides.

R_f	Yield (%)	ee (%)
C$_4$F$_9$	62	90
C$_{10}$F$_{21}$	68	93
C$_8$F$_{17}$	60	94

(d) Enantioselective trifluoromethylation.

50 % (ee = 90 %)   53 % (ee = 84 %)   38 % (ee = 78 %)

PTC =
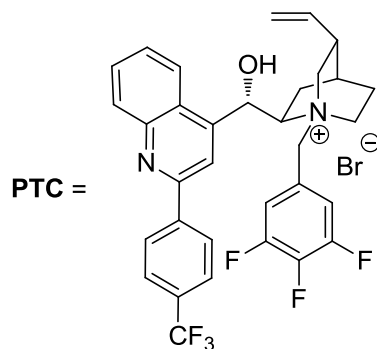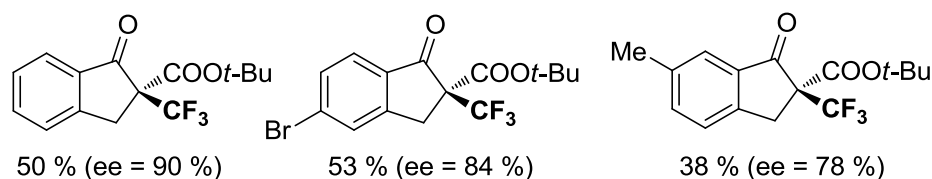
Scheme 35. Trifluoromethyl-containing quaternary stereocenters by photoorganocatalysis

As for the mechanism of this asymmetric photochemical perfluoroalkylation, the authors propose[102] a radical chain propagation pathway, as depicted in Scheme 36. The chain reaction commences by irradiation of the EDA complex of type **A**, formed upon the

aggregation of the chiral enolate **B** with R_FI. Electron transfer triggered by visible-light promotes the formation of the electron-deficient perfluoroalkyl radical through the reductive cleavage of the C−I bond within **C**. Consistent with a SET pathway, the model reaction is completely inhibited when performed in the presence of a redox trap such as 1,4-dinitrobenzene (0.2 equiv). The electrophilic perfluoroalkyl radical is next trapped by the chiral enolate **B** in a stereocontrolled fashion. The resulting ketyl intermediate **D** will then abstract an iodine atom from **C**, thereby regenerating R_F• [103]. The adduct **E** is not stable and collapses to release the product and the PTC catalyst (**PTC**$^+$). At the present level of investigation, an alternative electron transfer process, where the ketyl intermediate **D** reduces R_FI to directly afford the final product, cannot be excluded.
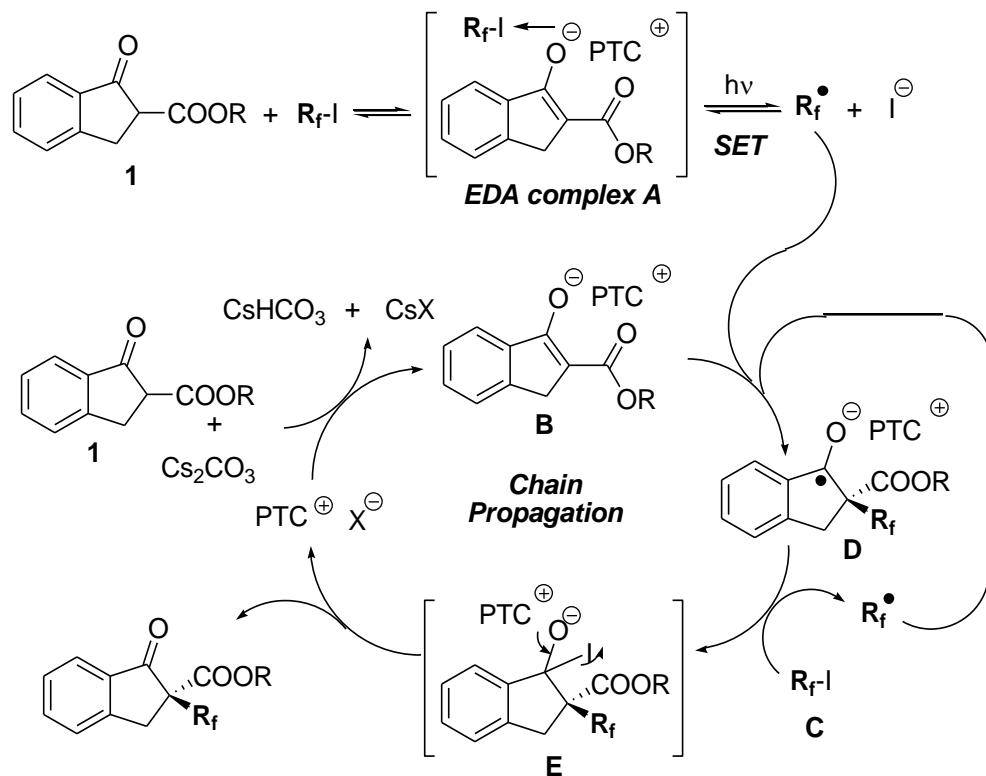
Scheme 36. Proposed reaction mechanism

2.1.2.-FLUOROALKYLATION OF *SP*^2 CARBON ATOMS BY POC

Nicewicz and co-workers have developed the hydrotrifluoromethylation of styrenes and unactivated aliphatic alkenes through an organic photoredox system.[104] The method relies in a single electron oxidation of sodium trifluoromethanesulfinate (Langlois reagent) by *N*-methyl-9-mesitylacridinium as a photoredox catalyst. The transformation has a broad substrate scope, including mono-, di- and trisubstituted aliphatic and styrenyl alkenes, with high regioselectivity in all the cases examined. The trifluoromethylated products are obtained as exclusively anti-Markovnikov regioisomers. The photoreaction takes place satisfactorily in a 9:1 $CHCl_3$ – TFE mixture and methyl thiosalicylate employed in substoichiometric quantities are used as hydrogen atom donor for aliphatic alkenes while stoichiometric quantities of thiofenol are required for the styrenyl alkenes. Scheme 37 illustrates the trifluoromethylation reaction of alkenes.[104]

(a) Substrate scope of the hydrotrifluoromethylation of aliphatic alkenes.
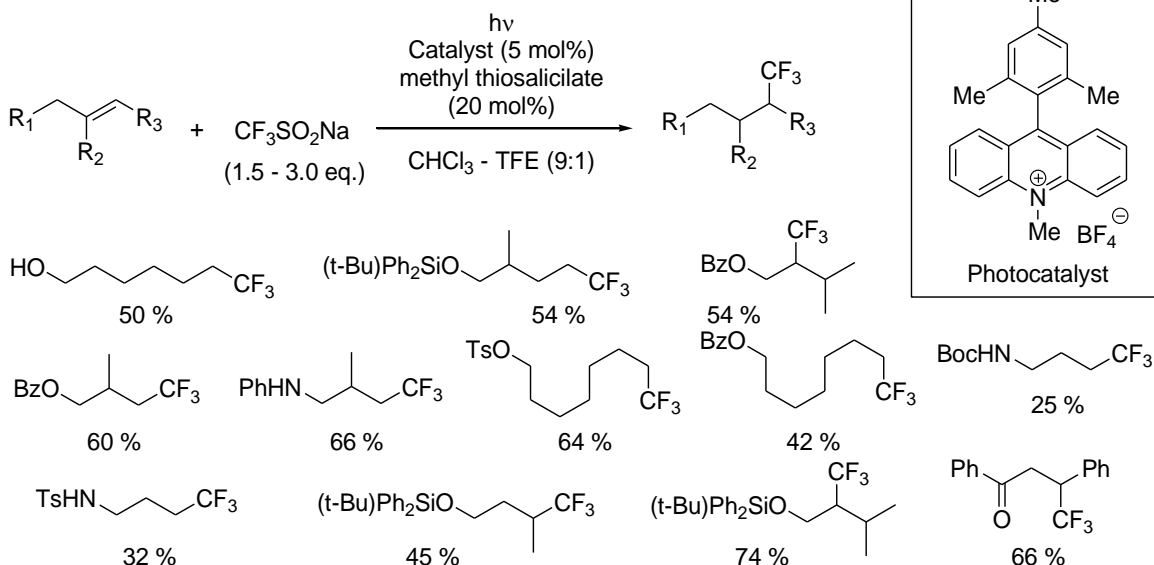
(b) Substrate scope of the hydrotrifluoromethylation of styrene derivatives.
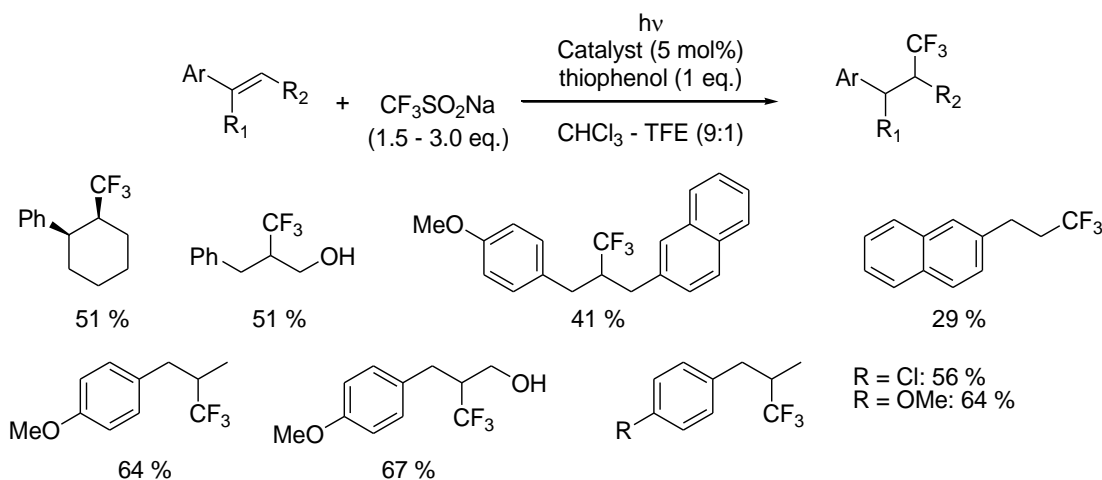
Scheme 37. Hydrotrifluoromethylation of aliphatic alkenes and styrene derivatives.

A plausible reaction mechanism is depicted in Scheme 38. Excitation of the organic photocatalyst *N*-methyl-9-mesityl acridinium leads to the oxidation of the Langlois reagent and generation of the electrophilic trifluoromethyl radical after the expulsion of SO_2.[104] Addition of the electrophilic radical to the alkene provides intermediate **A** with anti-Markovnikov selectivity. Since the cosolvent trifluoroethanol is essential for reactivity,

hydrogen atom transfer from TFE to the intermediate **A** occurs efficiently. Next, the radical

intermediate **B** abstracts a hydrogen atom from methyl salicylate or thiophenol, depending

on the alkene derivatives used, to give the thiyl radical (Ar-S$\cdot$). Oxidation of the

photocatalyst by thiyl radical closes the catalytic cycle and provides the formation of the

corresponding thiolate (Ar-S$^-$) that, under a proton transfer process, regenerates the thiol.

An alternative mechanism whereby the intermediate **A** reacts directly with a thiol is

difficult to rule out.[104]
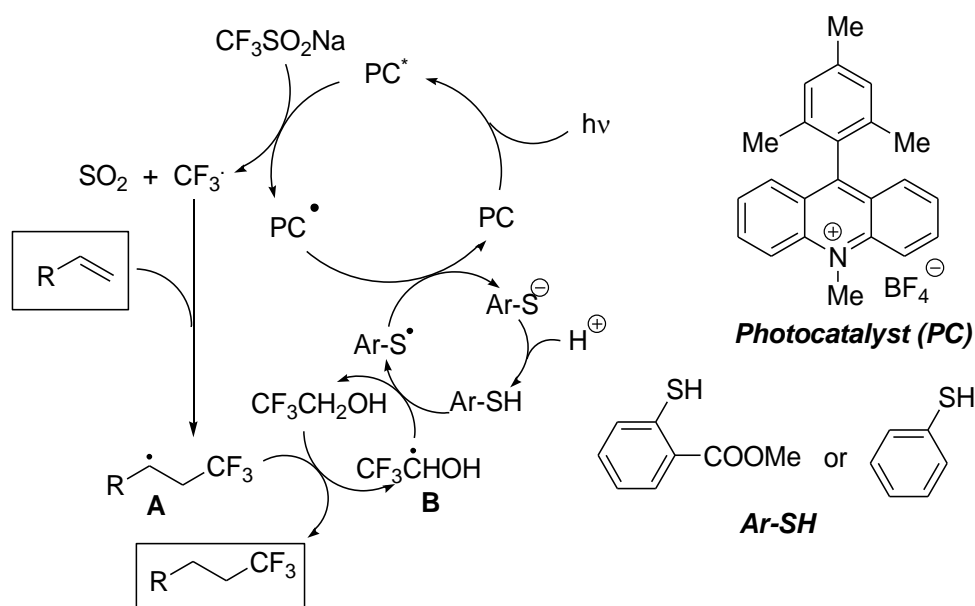
Scheme 38. Plausible reaction mechanism of the hydrotrifluoromethylation of alkenes

Scaiano and co-workers have studied the photocatalytic trifluoromethylation

reaction of terminal alkenes and alkynes using Methylene Blue (2 mol%) as the

photoorganic catalyst and Togni(I)'s reagent as the CF_3 radical source.[105] The photoreaction

is carried out in the presence of a sacrificial amine such as TMEDA or DBU (2 eq.),

depending on the substrate, in DMF under Argon atmosphere at room temperature. The

scope of the reaction is illustrated in Scheme 39.

Hydrotrifluoromethylation of terminal alkenes.

67 %   48 %

83 %   40 %

Hydrotrifluoromethylation of terminal alkynes.

70 % (*E/Z* = 4:1)   66 % (*E/Z* = 10:1)

79 % (*E/Z* = 6:1)
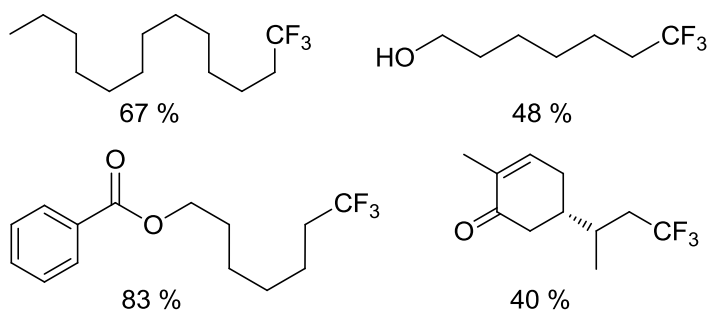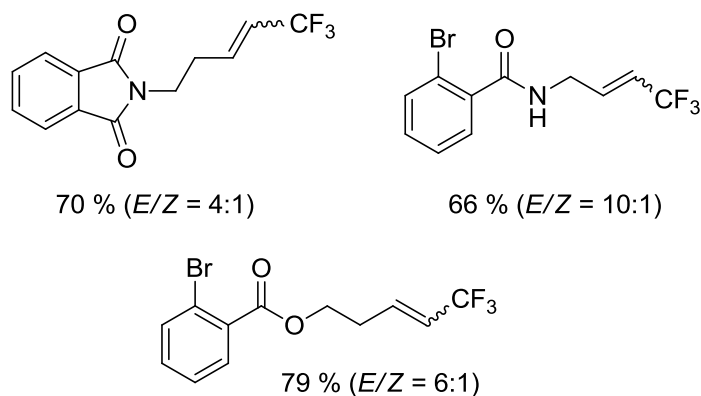
Scheme 39. Trifluoromethylation of heterocyclic compounds and hydrotrifluoromethylation of terminal alkenes and alkynes

The hydrotrifluoromethylation reaction of alkenes affords the expected products in moderate yields while for the same reaction on alkynes the yields obtained are good and a noticeable regioselectivity in favour of the *E* regioisomers is observed as depicted in Scheme 39.

Laser Flash Photolysis experiments and trapping of CF_3 radical with 4-hydroxy-TEMPO, a known radical trapping, allows to propose a possible mechanism for the catalytic formation of CF_3 radical shown in Scheme 40.
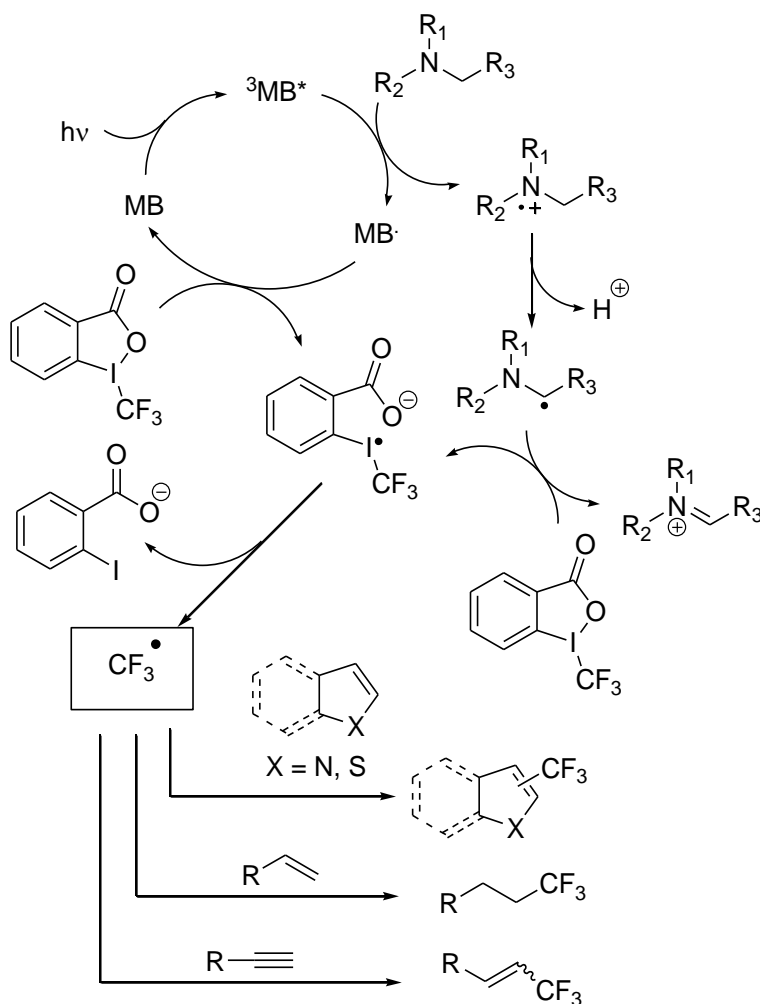
Scheme 40. Trifluoromethylation employing methylene blue as POC

Irradiation of Methylene Blue (MB) with λ higher than 400 nm provides the triplet excited state (^{3}MB*) that reacts with the sacrificial amine (TMEDA or DBU) to form the semi reduced MB radical and an α-amino radical. Both of these species can in turn reduce Togni's reagent, resulting in the release of a CF_3 radical and the formation of 2-iodobenzoate. Finally, reaction of CF_3 radical with heteroarenes or alkenes or alkynes provides the trifluoromethylated products in moderate to good yields.

2.2.-FLUOROALKYLATION OF AROMATIC SYSTEMS BY POC

2.2.1.-ARENES

The first report on a metal-free photoredox perfluoroalkylation reaction of arenes and heteroarenes[106] has been introduced by Itho and colleagues, who have accomplished the fluoroalkylation of (hetero)arenes though the use of R_fSO_2Na (perfluoroalkyl sulfinate salts), in the presence of photocatalyst anthraquinone-2-carboxylic acid and TFA as additive in yields ranging from 70-90%.[106]

Once the optimized reaction conditions for trifluoromethylation are met,[106] the scope and limitations of the reaction can be explored in Scheme 41. Electron-rich arenes afford the corresponding products in good yields. In addition, some substituted heteroarenes are also obtained in good yields. In contrast, trace amounts of products are found when benzene is used as substrate, and nitrobenzene does not react at all. Various sodium perfluoroalkylsulfinates can be employed in the study and it was found that pentafluoroethyl (C_2F_5) and heptafluoropropyl (C_3F_7) groups can be substituted on 1,3,5-trimethoxybenzene in good yields. Furthermore, $C_6F_{13}SO_2Na$ and $C_8F_{17}SO_2Na$ also react with 1,3,5-trimethoxybenzene to afford the corresponding products in good to high yields.

Ar-**H** + **R$_f$**-SO$_2$Na → Ar-**R$_f$**

(4.0 eq.)

(5 mol%)

TFA (6 mol%)
MeCN; r.t.; Ar

R$_f$	Yield (%)
C$_2$F$_5$	79
C$_3$F$_7$	83
C$_6$F$_{13}$	76
C$_8$F$_{17}$	92

76 %
2-CF$_3$:4-CF$_3$ = 1:2

44 %

75 %

73 %

89 %

76 %
4-CF$_3$:5-CF$_3$ = 6:5

69 %

82 %

55 %

62 %
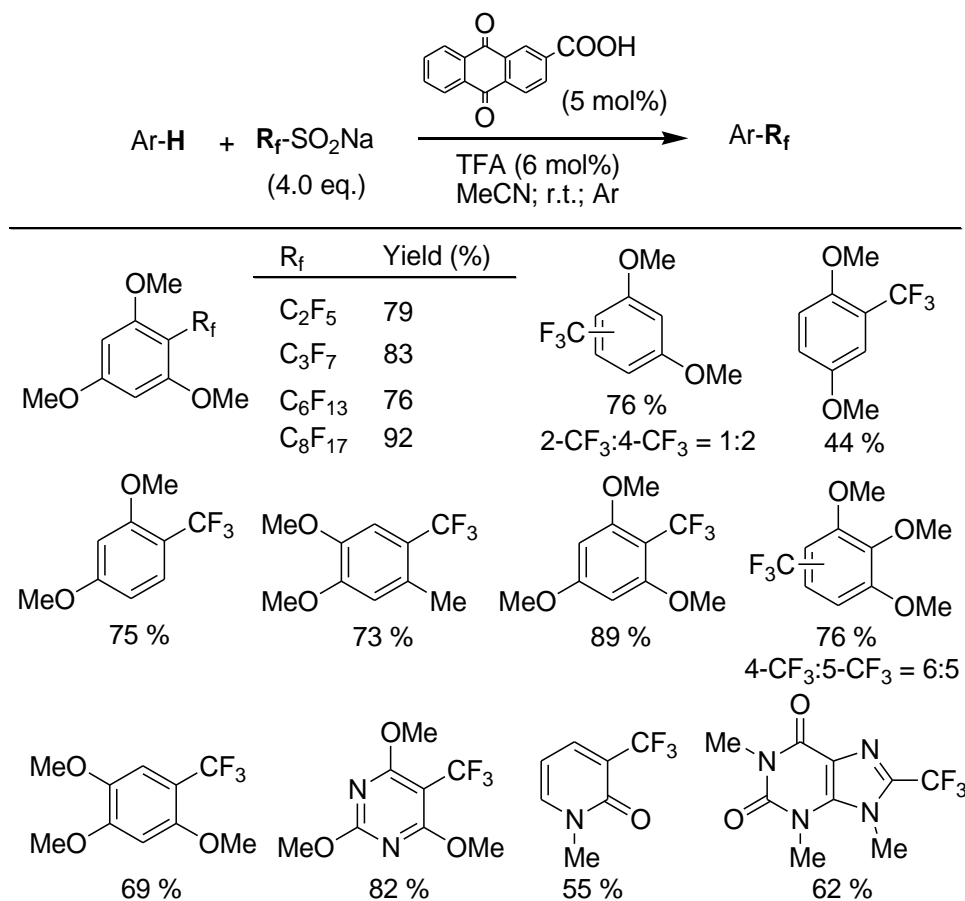
Scheme 41. Anthraquinone-2-carboxylic acid photoorganocatalyzed trifluoromethylation of organic substrates

The mechanism of the proposed transformation is depicted in Scheme 42a.[106] AQN in its ground and excited redox states can function as an electron transfer mediator, becoming important for the formation of the electron-poor perfluoroalkyl radical (R$_f$); this radical acts as an oxidant of the substrate.

The photoinduced downhill electron transfer from R$_f$SO$_2^-$ to the excited state of AQN (AQN*) is expected to efficiently generate Rf• and AQN•— radicals on the basis of their redox potentials. Facile oxidation of AQN•— by SO$_2$ produced by cleavage of R$_f$SO$_2$• regenerates the ground state of AQN. It can be considered that a likely reaction pathway

involves the radical addition of R_f to an electron-rich position of the aromatic ring, followed by oxidation of the generated radical **A** to cation **B** by R_f radical followed by deprotonation (Scheme 42a).[106] The latter reaction can be considered as a hydrogen abstraction reaction of **A** by R_f rather than an electron-transfer reaction facilitated by proton transfer, as is shown in Scheme 42a.
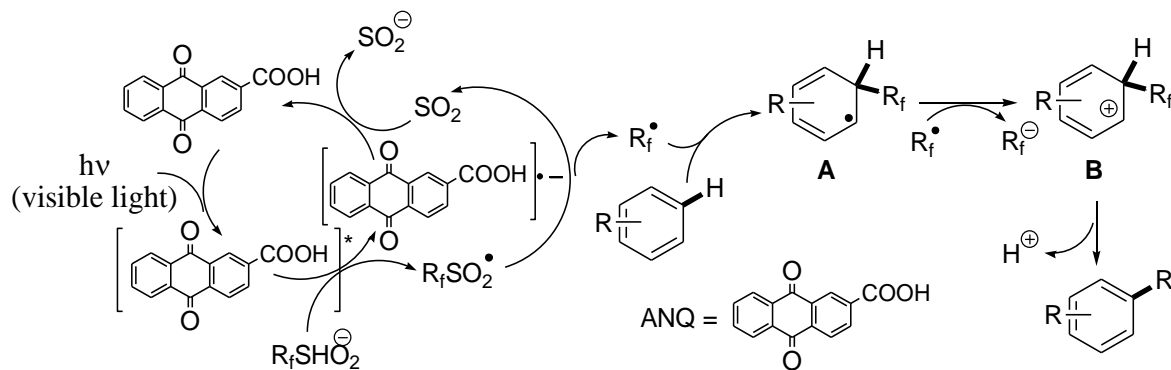
Scheme 42a. Mechanism for the anthraquinone-2-carboxylic acid photoorganocatalyzed trifluoromethylation of organic substrates

Scaiano and co-workers have studied the photocatalytic trifluoromethylation reaction of electron − rich heterocyclic compounds using Methylene Blue (2 mol%) as the photoorganic catalyst and Togni(I)'s reagent as the CF_3 radical source.[104] [105] The photoreaction is carried out in the presence of a sacrificial amine such as TMEDA or DBU (2 eq.), depending on the substrate, in DMF under Argon atmosphere at room temperature. The reaction mixture is irradiated with two warm white LEDs. The trifluoromethylation of various substituted indoles proceeds with high efficiency, however, no trifluoromethylation of the aromatic portion of the indole substrates is observed. Besides, the photoreaction of pyrrole and thiophene derivatives also proceeds in moderate yields.[105] These results are shown in Scheme 42b. Umemoto's reagent is also used to carry out the photocatalytic

reaction of 3-methyl indole but the trifluoromethylated product is obtained in low yield (35 %).[105]

Trifluoromethylation of heterocyclic compounds.

70 %   79 %   52 %

42 %   44 %   63 %
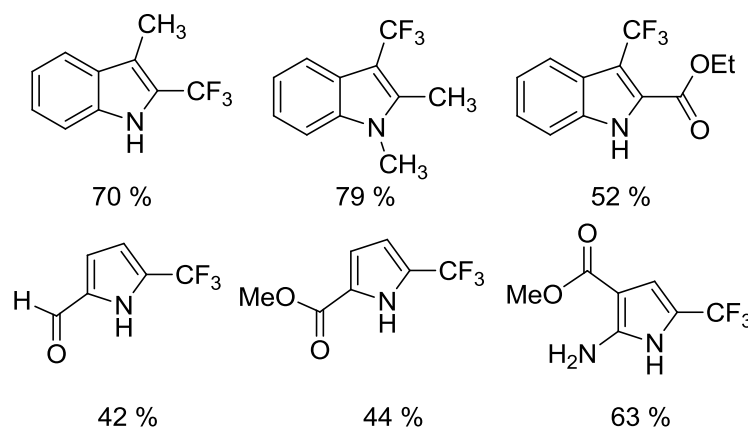
Scheme 42b. Trifluoromethylation of heterocycles with Methylene Blue as photocatalyst

3. MISCELLANEOUS

Direct photoredox catalytic formation of carbon-fluoride (C-F) bonds is a challenging task taking into account that recent reports of fluorine incorporation using photoredox catalysis focus on adding trifluoromethyl groups via C-C bond formation. Despite both the significant interest in photoredox catalysis and the pharmaceutical, agrochemical, and radiochemical importance,[107] the only reports of fluorine incorporation deals with electrochemical redox fluorination using fluoride.[108] There has not been photoredox catalytic methods for C-F bond formation, probably due to the lack of fluorine atom transfer reagents. For years, F_2, hypofluorites and XeF_2 were the few reagents available.[108] [109]

There exist very interesting reports on the photocatalyzed construction of C-F bond formation reactions via C-H functionalization (unactivated sp^3 C-H bond that is not

adjacent to a carbonyl group).[110] However, they are considered beyond the scope of the present review. In the following section, an example of decarboxylation-fluorination will be described.

Recently, Sammis and co-workers have reported the photochemical fluorination of alkyl radicals with Selectfluor providing alkylfluorides in good to excellent yields.[111]

Last year, the same authors have reported an interesting photocatalytic fluorination reaction of aryloxyacetic acids using $Ru(bpy)_3(PF_6)_2$ as the photocatalyst and Selectfluor as the fluorine source.[112] The reaction takes place efficiently under visible light irradiation in the presence of NaOH in either H_2O or $H_2O/MeCN$ mixtures depending on substrate solubility. The optimized condition leads to the photoredox decarboxylative fluorination of a range of aryloxyacetic acid derivatives in good to excellent yields showing access to a broader scope of substrates with electron-rich and electron-poor substituents as well as heteroarenes. Some examples of the photocatalytic fluorination reaction are illustrated in Scheme 43.[112]
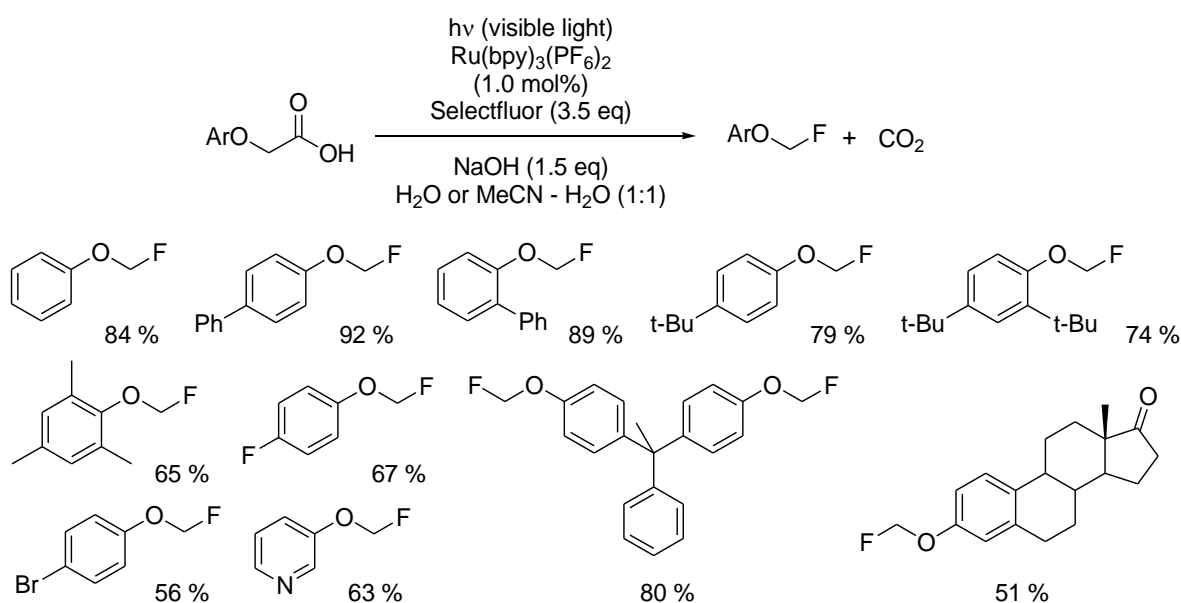
Scheme 43. Photoredox decarboxylative fluorination of a range of aryloxyacetic acid derivatives

The photocatalytic cycle that promotes the fluorination of aryloxyacetic acid derivatives commences with the excitation of $Ru(bpy)_3^{2+}$ to yield a singlet excited state that very fast undergoes an intersystem crossing to active triplet excited manifold. A single-electron transfer between the triplet excited state and Selectfluor provides the Selectfluor radical-cation and $Ru(bpy)_3^{3+}$ processes that is confirmed by transient absorption spectroscopy.[112] The strong oxidant $Ru(bpy)_3^{3+}$ reduces the aryloxyacetate to the radical intermediate **A** closing the photocatalytic cycle. Extrusion of CO_2 from **A** affords the radical intermediate **B**. Delivery of fluoride from Selectfluor radical-cation to **B** provides the corresponding fluoromethyl aryl ether. The plausible reaction mechanism is depicted in Scheme 44.
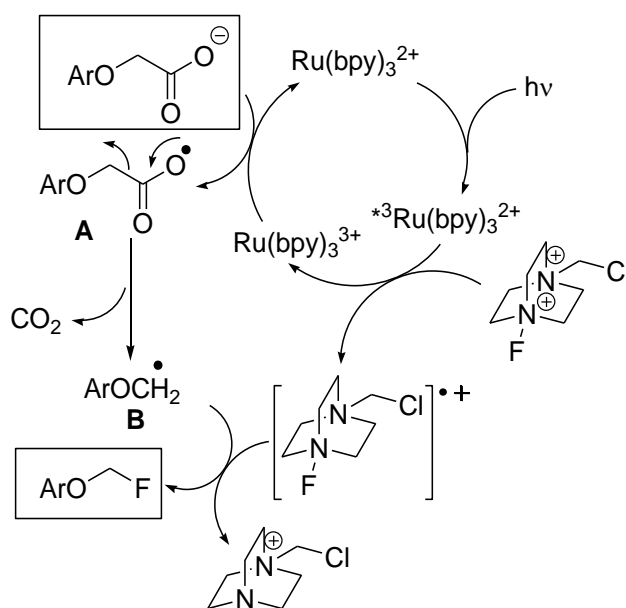
Scheme 44. Photocatalytic cycle that promotes the fluorination of aryloxyacetic acid derivatives

MacMillan and co-workers have developed a photocatalytic decarboxylation-fluorination of aliphatic carboxylic acids to provide alkyl fluorides in good to excellent yields.[113] The photoreaction occurs under visible light with Ir[dF(CF$_3$)ppy]$_2$(dtbbpy)PF$_6$ as the photocatalyst and Selectfluor as the fluorine source in the presence of Na$_2$HPO$_4$ in a mixture of H$_2$O and MeCN (1:1; v/v). Some selected examples are shown in Scheme 45a.[113]

The reaction mechanism is depicted in Scheme 45b. The authors hypothesized that an initial reduction of a sacrificial quantity of Selectfluor reagent through *Ir(III) by means of a single electron transfer (SET) process should provide the oxidizing Ir[dF(CF$_3$)ppy]$_2$(dtbbpy)$^{2+}$ (Ir^{IV}) species. Stern-Volmer fluorescence quenching confirmed the SET process. Base-mediated formation of an alkyl carboxylate followed by an SET oxidation using the transiently formed Ir^{IV} species should follow.[113] This process can be thought of to afford a carboxyl radical, which after extrusion of CO$_2$ should provide the SOMO species RCH$_2^.$. Then, direct F-transfer from Selectfluor to the alkyl radical provides the alkyl fluoride with concomitant formation to the corresponding Selectfluor radical cation. The Selectfluor radical cation would replace Selectfluor in subsequent photoredox cycles as an appropriate electron acceptor in the conversion of excited-state *Ir^{III} to the requisite Ir^{IV} species.[113]

(a) Scope of the photocatalytic reaction.

79 %   87 %   82 %   70 %

99 %   71 %   81 %   82 %

96 %   76 %   92 %   90 %
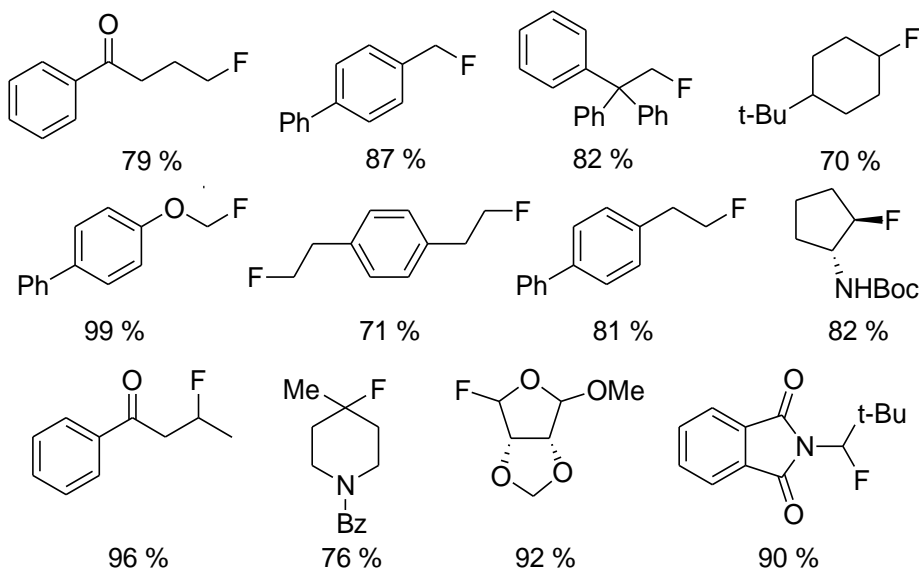
(b) Proposed reaction mechanism.
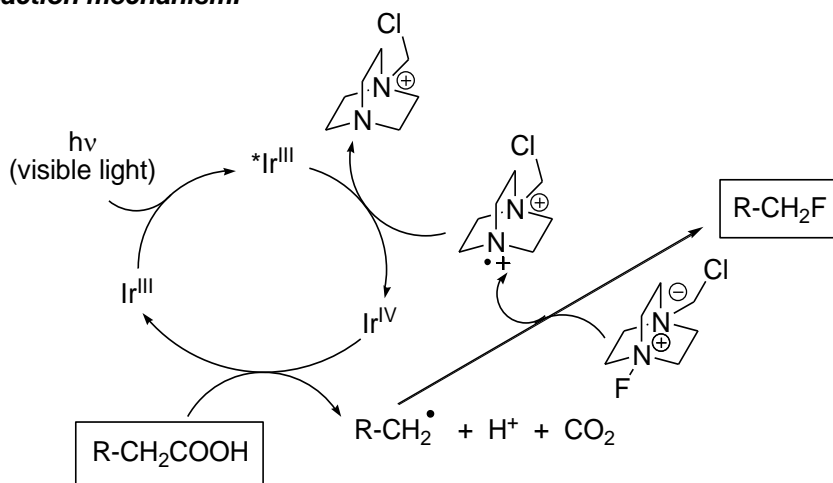
Scheme 45. Photocatalytic decarboxylation-fluorination of aliphatic carboxylic acids to provide alkyl fluorides

Carreira and co-workers have developed a cobalt-catalyzed photochemical synthesis of allylic trifluoromethane from styrene derivatives with 2,2,2-trifluoromethyl iodide.[114] This alternative bond construction strategy that complements existing approaches provides trifluoroethylated styrene derivatives in moderate to good yields and as a single

diastereomer with *trans* configuration. The photoreaction is performed with blue LED lights in the presence of cobalt catalyst (20 mol%) and *i*-Pr$_2$Net (2 eq.) in 1:1 MeCN/DMSO mixture at room temperature. The mild conditions of the reaction allow a wide range of functional groups to be tolerated including amines, aldehydes, thioethers, alcohols, and pyridines. Sterically more demanding 1,2-disubstituted styrene derivatives are also suitable substrates. However, aliphatic olefins did not undergo trifluoroethylation. Scheme 46 illustrates the cobalt-catalyzed photoreaction.[114]
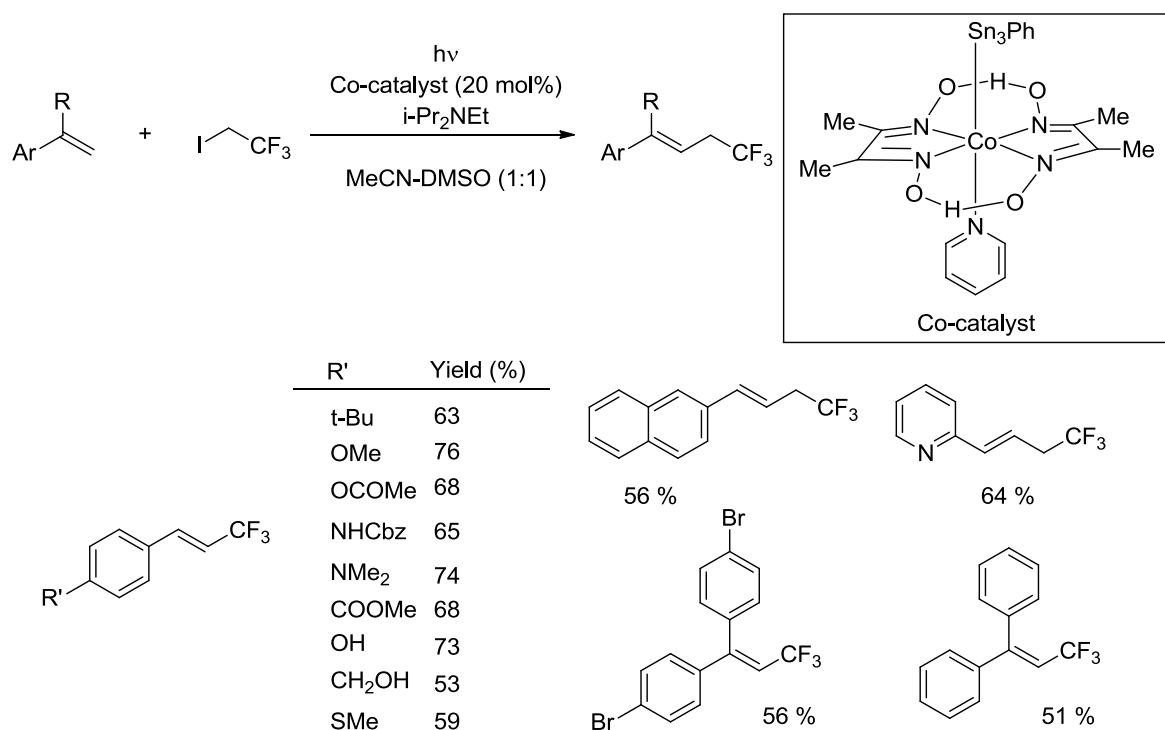
Scheme 46. Photocatalytic trifluoroethylation of styrene derivatives.

Next, the authors have studied the same reaction in a flow reactor photobox employing 48 high-power light-emitting diodes (LEDs) and a mesoscale glass microreactor. This methodology reduced the reaction time from 24 h (batch protocol) to 30

min (flow protocol), however, the conversion did not exceed the 65 % which is similar to

that obtained in batch protocol.[114]

4.-SUMMARY

Table 1. Photocatalysts and their use in the fluoroalkylation of organic substrates

Photocatalyst	R_f source/additive	substrate	product type
$[Ru(bpy)_3]^{2+}$	Umemoto reagent/ Methanol	$R\text{—}CH_2$	$R\text{—}CF_3$
	R_fI	$R\text{—}CH_2$	$R\text{—}R_f$ (I) ATRA
	Umemoto reagent/ MeCN / H_2O	$Ar\text{—}CH_2$	$Ar\text{—}CF_3$ (NHAc) ATRA
	Togni reagent MeOH	$Ar\text{—}BF_3K$	$Ar\text{—}CF_3$
	CF_3I/TMEDA	$R\text{—}CH$	$R\text{—}CF_3$ (I) ATRA
	CF_3SO_2Cl/KHPO$_4$ MeOH	$O\text{=}C(CH_3)\text{—}CH_2$, $R\text{—}N\text{—}R'$	$O\text{=}C(CH_3)\text{—}CF_3$, $R\text{—}N\text{—}R'$
	R_fI/TMEDA/MeCN	Het-H	Het-R_f
$Ir(ppy)_3$	Umemoto reagent CH_2Cl_2/ROH	$Ar\text{—}CH_2$	$Ar\text{—}CF_3$ (OR)
	Togni reagent MeOH	$Ar\text{—}BF_3K$	$Ar\text{—}CF_3$
	CF_3I/ DBU	$R\text{—}CH$	$R\text{—}CF_3$
	CF_3I/ t-BuOK	$R\text{—}CH$	$R\text{≡}CF_3$

Ir(ppy)$_2$(dtb-bby)$^+$	R$_f$I	(aldehyde, H–CO–CH$_2$–R)	(aldehyde, H–CO–CHR$_f$–R)
Ptppy(acac)	CF$_3$I/ DBU	R–CH=CH$_2$	R–CH=CH–CF$_3$
Eosin Y	CF$_3$I/ TMEDA	Het-H	Het-CF$_3$
	R$_f$I / 2,6-lutidine/DMF	(aldehyde, H–CO–CH$_2$–R)	(aldehyde, H–CO–CHR$_f$–R)
N-methyl-9-mesityl-acridinium	CF$_3$SO$_2$Na/ TFE / CHCl$_3$	R$_1$–CH=CH–R$_2$	R$_1$–CH$_2$–CHR$_f$–CHR$_2$
methylene blue	Togni reagent	Het-H	Het-CF$_3$
Anthranilic-2-carboxylic acid	R$_f$SO$_2$Na	Ar-H	Ar-R$_f$

Table 2. Photoredox properties of photocatalysts PC

PC	E$_{1/2}$ PC$^+$/PC (V vs SCE)	E$_{1/2}$ PC/PC$^-$ (V vs SCE)	E$_{1/2}$PC$^+$/PC* (V vs SCE)	E$_{1/2}$ PC*/PC$^-$ (V vs SCE)	Ref.
[Ru(bpy)$_3$]$^{2+}$	+1.69	-0.91	-0.21	0.99	115
Ir(ppy)$_3$	+0.77	-2.19	-1.73	+0.31	116
Ir(ppy)$_2$(dtb-bby)$^+$	+1.21	-1.51	-0.96	+0.66	77
Pt(ppy)	+0.57	-2.38	-2.07	+0.26	79
Rose Bengal	+0.74	-1.03	-0.68	+0.99	117, 9
Eosin Y	+0.89	-1.09	-1.60	+1.18	9
Methylene	+0.011	-0.23			9

blue					
N-methyl-9-mesityl-acridinium	+1.56	-0.57	-0.49	+1.88	104, 118

5.-CONCLUSIONS

The active area of photocatalysis has found applications in fluoroalkylation reactions. The employment of transition metal organocatalysts capable of absorbing light in the visible regions has enabled the production of trifluoromethyl, perfluoroalkyl, and fluorine radicals that can substitute both aliphatic and aromatic compounds very efficiently without the need of chemical initiators under more benign conditions. A new promising and expanding area of research is the use of ordinary laboratory dyes in the absence of transition metals, as electron exchange species, that absorb visible radiation or even solar light to trigger fluoroalkyl radical production. In this respect, photoorganocatalysis can be regarded as a more environmentally friendly option to classical Ru or Ir photoorganocatalysis, and future work should be directed towards the employment of dyes and visible light for the production of fluoroalkyl radicals capable of substituting organic substrates.

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[100] Remarkably, in contrast to most photocatalytic processes MacMillan_s system does not require any sacrificial oxidant or reductant by its design; both oxidation and reduction steps are productive and lead to the formation of the desired product.

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