

## Review

## Metal-mediated radical perfluoroalkylation of organic compounds



Sebastián Barata-Vallejo, Alberto Postigo\*

Departamento de Química Orgánica, Facultad de Farmacia y Bioquímica, Universidad de Buenos Aires, Junín 954, CP1113 Buenos Aires, Argentina

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## ABSTRACT

The incorporation of fluoroalkyl groups, and particularly the trifluoromethyl group, in pharmaceutical molecules has a profound impact on their physical and biological properties, mainly because of the unique metabolic stability, lipophilicity, and electron-withdrawing nature of the fluoroalkyl substituent. The relevance of the CF<sub>3</sub>-containing substrates provides the driving force for the development of more efficacious and versatile synthetic protocols for these molecules.

In this account, the latest radical trifluoromethylation and perfluoroalkylation reactions with the aid of metals of both aliphatic and aromatic compounds will be discussed. The aim of this account is to review the recently emerging literature (2010–present) on perfluoroalkyl-group addition or substitution reactions performed through radical and radical-ion pathways with the intervention of metals or metalorganic species.

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## 1. Introduction

Performing substitution or addition reactions of organic substrates with perfluoroalkyl groups (R<sub>f</sub>) by classical polar mechanisms has always been challenging, especially with perfluoroalkyl halides R<sub>f</sub>X [1]. However, novel electrophilic and nucleophilic trifluoromethylation and perfluoroalkylation reagents have recently been developed [2], thus allowing chemists to achieve the perfluoroalkyl group addition or substitution reactions on organic substrates through conventional polar routes.

Another relevant synthetic strategy employed to accomplish perfluoroalkyl group substitution or addition reactions of organic substrates involves generating the electrophilic perfluoroalkyl radicals (R<sub>f</sub>•), and enable them to react with proper radical acceptors [3].

**Abbreviations:** Ar, aromatic; ACCN, 1,1'-azobis(cyclohexanecarbonitrile); AgOTf, silver triflate; ATRA, atom transfer radical addition; BTF, benzotrifluoride; bpy, 2,2'-bipyridine; DBU, 1,8-diazabicyclo-7-undecene; DCM, dichloromethane; DMF, dimethylformamide; EPR, electron proton resonance; ET, electron transfer; HAT, hydrogen atom transfer; MeCN, acetonitrile; MeOH, methanol; NaTEMPO, 2,2,6,6-tetramethylpiperidine-N-oxide sodium; NMP, N-methyl-2-pyrrolidone; Ph, phenyl; Phen, phenanthroline; R<sub>f</sub>, perfluoroalkyl; R<sub>f</sub>X, perfluoroalkyl halide; SET, single electron transfer; S<sub>H</sub>Ar, homolytic aromatic substitutions; TBAF, tetrabutyl ammonium fluoride salt; TBHP, butylhydroperoxide; TEMPO, 2,2,6,6-tetramethylpiperidine-N-oxide; TMSCF<sub>3</sub>, trifluoromethyltrimethylsilane; TMSCF<sub>2</sub>H, trimethylsilyldifluoroethane; Xantphos, 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene.

\* Corresponding author. Tel.: +54 11 4964 8200; fax: +54 11 4964 8350.

E-mail addresses: [apostigo@ffyb.uba.ar](mailto:apostigo@ffyb.uba.ar), [alberto.postigo@ub.edu.ar](mailto:alberto.postigo@ub.edu.ar) (A. Postigo).

As for classical methods to generate  $R_f$  radicals, spontaneous [4] or photoinduced [1] Electron Transfer (ET) reactions between a perfluoroalkyl halide  $R_fX$ , and a nucleophilic radical acceptor (e.g.  $S_{RN}1$  reactions), or direct irradiation methods [3,5] have been known for quite some time. Other methods developed for the generation of  $R_f$  radicals encompass redox processes (through sulfur salts) based on ET which have deserved special attention [6].

On the other hand, the participation of transition metals or metalorganic species could offer a viable alternative to the generation of perfluoroalkyl radicals by means of the ET character that metals alone and some metalorganic species possess. The recent growth in using transition metals in radical perfluoroalkylation reactions brings about the advantages of these metals as ET agents for initiating radical reactions or generating perfluoroalkyl radicals which add to unsaturated centers or substitute aromatic moieties.

Lately, advantages in using aqueous media have been incorporated to the organic chemist's armamentarium for appending perfluoroalkyl moieties onto organic compounds through the involvement of metallic species and radical reactions.

This review intends to cover recently emerging literature on radical perfluoroalkylation reactions performed through the aid of metals, exploring the benefits and advantages of transition metals in radical perfluoroalkylation reactions, as opposed to conventional polar reactions involving the same metallic species. In doing so, the latest metal-mediated radical perfluoroalkylation reactions performed in aqueous media or water shall be presented, expanding the scope of metal-mediated radical perfluoroalkylation reactions.

## 2. Aromatic substrates

Sulfinatehalogenation reactions (e.g.  $R_fX + Na_2S_2O_4$ ) have long been employed to accomplish perfluoroalkyl-group substitution of aromatic and heteroaromatic nuclei in *aqueous media* through an ET initiation. These reactions have recently been reviewed by Xiao and collaborators [6] and encompass a large array of aromatic compounds, ranging from activated arenes (anisole, aniline, naphthalene, phenanthrene derivatives), to heterocycles (pyrrol, indole, coumarin, carbazole derivatives) and a variety of perfluoroalkyl sources. Although these reactions do not employ metals or metal complexes, they have been seminal to the development of other perfluoroalkylating reagents that necessitate the use of coordination metals and employ sulfur inorganic salts in IV oxidation state.

There are numerous methods for the construction of alkyl- $R_f$  bonds. In contrast, the generation of aryl- $R_f$  linkages remains synthetically challenging, particularly *via* transition metal catalysis. The first original copper-promoted perfluoroalkylation of aromatic halides was reported by McLoughlin and Thrower in 1968 and later communications followed [7]. Since then, a number of methods for preparation of  $[CuCF_3]$  species and their reactions with aryl halides have been reported through non-radical methods.

A recent review by Grushin and collaborators [8] summarizes all metal complex-mediated reactions for synthesizing trifluoromethylated and perfluoroalkyl-substituted arenes, with a large variety of Pd(II) trifluoromethyl complexes and Cu-promoted (Cu(I)) trifluoromethyl group *ipso* substitution of haloarenes. Also, the trifluoromethylation of haloarenes in organic solvents catalyzed by Ni was used for the aromatic carbon-halogen bond activation and has been summarized by Grushin et al. The mechanism for these reactions include: (i) oxidative addition of polyfluorohaloalkanes to metals and their complexes, (ii) transmetalation, (iii) decarboxylation and decarbonylation of metal perfluoroalkylcarboxylates and perfluoroacyls.

The oxidative addition of polyfluorohaloalkanes to metals often proceeds in aprotic organic solvents. The Pd-transmetalation

process, where a Ph- $CF_3$  reductive elimination was achieved through the trifluoromethyl palladium aryl  $[(Xantphos)Pd(Ph)(CF_3)]$  constitutes a breakthrough for transmetalation processes [9]. However, this alternative is costly and the ligands employed in various Pd-catalyzed reactions cost more than the metals themselves, the reactions are carried out in harmful organic solvents, and difficult to scale up. Cu-mediated decarboxylation and decarbonylation reactions may involve the presence of difluorocarbene intermediates and fluoride anion which can result in unwanted side reactions. In the past, radical metal-promoted perfluoroalkylation reactions were scarcely invoked as possible reaction pathways for perfluoroalkyl group substitution or addition reactions. Exceptions constitute the employment of metals for enabling chain lengths in radical perfluoroalkylation reactions of aromatic nuclei with perfluoroalkyl halides, where catalytic amounts of Cu(II) salts increase the reaction rates, as a redox chain is superimposed with a radical chain in the perfluoroalkyl group substitution of arenes [10,11].

Although the involvement of transition metals to effect perfluoroalkylation reactions has relied in the past on the employment of costly organocatalysts and/or harsh reaction conditions, alternative metal-mediated perfluoroalkylation strategies of organic substrates have been sought after.

Only recently have radical pathways emerged as feasible mechanisms for effecting the trifluoromethylation and perfluoroalkylation of organic substrates through the intervention of metals. It is to be noted that though some metal compounds are employed in the perfluoroalkylation reactions, the metals are not directly involved in the  $R_f-Ar$  bond forming step, but are needed to form the perfluoroalkyl radical instead.

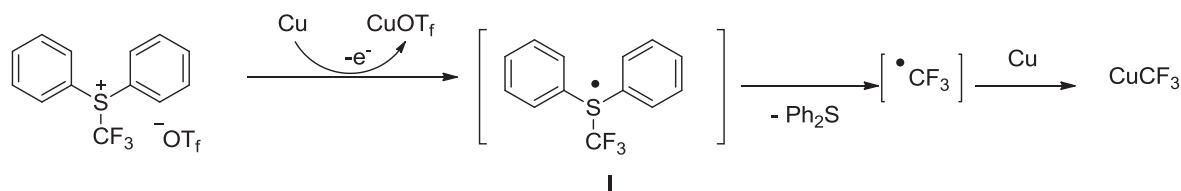
A recent review on radical trifluoromethylation reactions [12] carried out, most of them, with the assistance of metals, metal complexes, or metal-coordinated photocatalysts in organic solvents attests to the relevance of the subject. All these reactions were studied in organic media. Most invariably, all metal-mediated perfluoroalkyl-group substitutions of arenes necessitate the presence of formal leaving groups on the ring, and the reactions proceed fairly well only in aprotic dipolar organic solvents. However, recent examples have appeared in the literature where homolytic aromatic substitutions ( $S_HAr$ ) with  $CF_3$  or perfluoroalkyl groups occur in aqueous environments by a radical process (*vide infra*) [13].

In the following sections, the participation of metals such as Cu, Ag, Zn, Ti, Ru, and Re, will be shown to facilitate the generation of  $R_f$  radicals and effect the perfluoroalkyl group substitution of the arene or heteroarene ring. The radical pathways will account for the substitution products observed and the better regioselectivity encountered when radical transformations are employed as opposed to polar reactions involving the same metallic species.

### 2.1. Cu- and Ag-mediated perfluoroalkylation reactions

Copper-mediated trifluoromethylation reactions of arenes have very recently been reviewed by Shen and collaborators [14]. Some of these reactions are proposed to occur by radical mechanisms. The sort of reactions depicted therein encompasses *ipso* and homolytic aromatic substitutions ( $S_HAr$ ) with  $CF_3$  group.

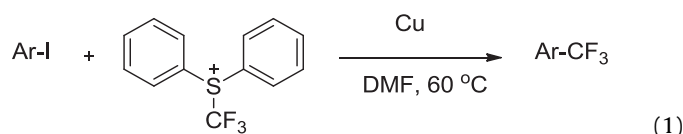
Among the perfluoroalkylating reagents that can efficiently accomplish fluorination of arenes are: the Langlois reagent (sodium trifluoromethanesulfinate,  $NaSO_2CF_3$ ) [15], the Togni reagent (a hypervalent benziodoxolone salt) [16], and the Umemoto reagent (*S*-(trifluoromethyl)diphenylsulfonium triflate) [17,18]. Though the latter two reagents have been conceived to operate through polar mechanisms, new reactions have been developed involving radicals with the electrophilic Togni reagent and the nucleophilic Umemoto reagent. Although these reagents have been initially developed to perform perfluoroalkylation reactions without the



**Scheme 1.** Proposed mechanism for generation of  $\text{CuCF}_3$  (Ref. [20]).

assistance of metals, recent protocols have been uncovered with these reagents in conjunction with metals or metal complexes that expanded the scope of these transformations to a large array of substrates and milder conditions.

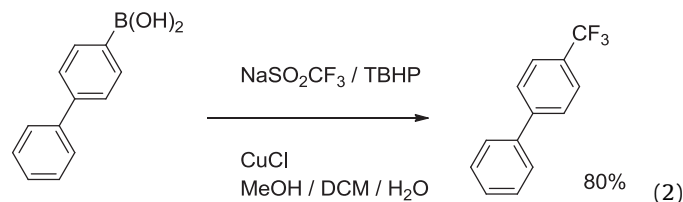
Although these latter reagents (Umamoto's and Togni's) have been extensively developed and applied on a large array of aromatic substrates, they are still limited to polar reactions. For instance, Umamoto and colleagues have reported a  $\text{S}_{\text{H}}\text{Ar}$  reaction of aniline with *S*-(trifluoromethyl)diphenylsulfonium salts and onium derivatives to render 2-, and 4- $\text{CF}_3$ -substituted anilines in global yields ranging from 46% to 76% [19]. On the other hand, iodo-substituted heteroaromatic compounds undergo smooth and regioselective trifluoromethylation by *S*-(trifluoromethyl)diphenylsulfonium salts in the presence of copper, according to Eq. (1) [20] in high yields.



The mechanism of this reaction was explored by Vicić and co-workers, who characterized the thermally stable  $\text{L}^1\text{CuCF}_3$  complexes which could trifluoromethylate organic halides under mild conditions [21]. Xiao and co-workers [20] demonstrated by  $^{19}\text{F}$  NMR analysis that  $\text{CuCF}_3$  is generated under reactions conditions employing *S*-(trifluoromethyl)diphenylsulfonium and Cu. On the basis of their analysis, they proposed that  $\text{CuCF}_3$  is generated by the mechanism depicted in Scheme 1.

The *S*-(trifluoromethyl)diphenylsulfonium triflate is first reduced by copper *via* single electron transfer (SET). Intermediate I (Scheme 1) decomposes readily to generate  $\text{CF}_3$  radicals, which further produce  $\text{CuCF}_3$ . The proposed radical mechanism with the Cu participation [20] seems to be superior in terms of regioselectivity, as opposed to the polar reaction carried out in the absence of Cu by the nucleophilic *S*-(trifluoromethyl)diphenylsulfonium salts, where various  $\text{CF}_3$ -substituted regioisomers are obtained [19].

Recently, Sanford and collaborators have developed a mild protocol for the copper-mediated trifluoromethylation of aryl and heteroaryl boronic acids using  $\text{NaSO}_2\text{CF}_3$  (Langlois reagent) and *tert*-butylhydroperoxide (TBHP) as radical initiator [22]. In this account, arylboronic acids were treated with the Langlois reagent, copper, and TBHP, in aqueous-organic solvent mixtures. The best results for  $\text{CF}_3$ -substitutions were obtained when using  $\text{CuCl}$ , in a mixture of  $\text{MeOH}/\text{DCM}/\text{water}$ , according to Eq. (2).



For electron-poor aryl boronic acids such as 4-(cyanophenyl)boronic acid, substitution yields were sluggish.

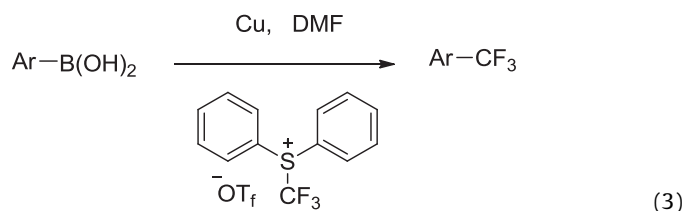
However, replacement of  $\text{CuCl}$  by  $(\text{MeCN})_4\text{CuPF}_6$  and  $\text{NaHCO}_3$  increased the substitution yields substantially [22].

Also recently, Grushin and collaborators have introduced a non-radical pathway to achieve the trifluoromethylation of aromatic compounds through aryl boronic acids and  $\text{CuCF}_3$  obtained from fluoroform ( $\text{CF}_3\text{H}$ ) and the copper complex  $[\text{K}(\text{DMF})][\text{Cu}(\text{O}^t\text{Bu})_2]$  [23]. However, this copper complex approach [23] affords trifluoromethylated arenes from the respective arylboronic acids in lower yields as compared with the radical pathway methodology [22]. Of note is the fact that the radical strategy used by Sanford employs readily available reagents and involves an aqueous solvent system.

Buchwald and colleagues [24] have recently achieved the trifluoromethylation of arylboronic acids in the presence of  $\text{Cu}(\text{II})$  salts and ligands (phenanthroline) employing the Ruppert-Prakash reagent ((trifluoromethyl)trimethylsilane,  $\text{TMSCF}_3$ ), [25] in 1,2-dichloroethane as solvent. Their protocol affords also substitution of the boronic moiety by H, lowering the  $\text{CF}_3$ -substitution global yields. The mechanism of this reaction is non-radical in nature.

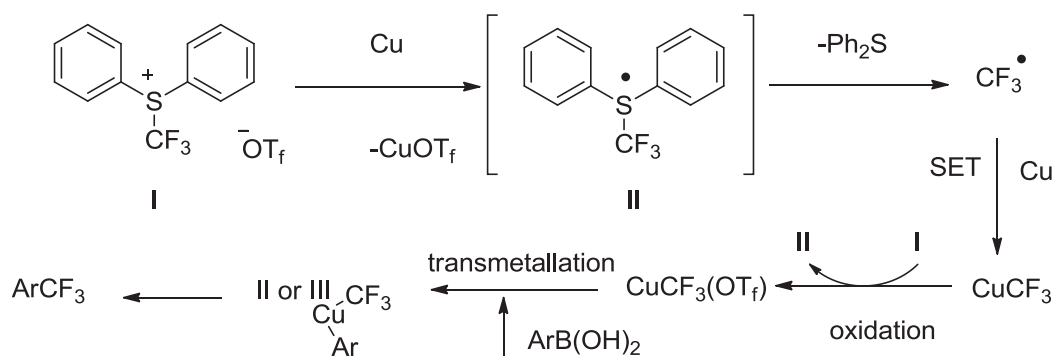
An improvement of the reaction from Eq. (1) is illustrated in the recent work by Baran and collaborators where no-metal catalysis is employed in the generation of the perfluoroalkyl radicals from the Langlois reagent in the presence of TBHP [26]. Thus, the authors managed to perform  $\text{S}_{\text{H}}\text{Ar}$  on heteroarylboronic acids, with  $\text{NaSO}_2\text{CF}_3$  initiated by TBHP, in aqueous media, in the absence of metal catalysis, in excellent yields.

The trifluoromethylation of arylboronic acids through the Umamoto reagent *S*-(trifluoromethyl)diarylsulfonium salt) in the presence of Cu was recently revisited by Xiao and collaborators [18]. In these reactions no ligands were necessitated for the Cu catalysis. Both electron-rich and electron-poor arylboronic acids reacted toward the reagent and produced trifluoromethylated compounds (*cf.* with Eq. (2)). Aryl boronic acids bearing CN, CHO,  $\text{NO}_2$  and OH groups were all suitable substrates for this reaction. The general reaction is illustrated in Eq. (3).



The authors [18] proposed a mechanism for this reaction, according to Scheme 2, where the  $\text{CuCF}_3$  intermediate is formed through a single electron transfer (SET) process and is oxidized to  $\text{Cu}(\text{II})$  or  $\text{Cu}(\text{III})$ -complex by the Umamoto reagent *S*-(trifluoromethyl)diarylsulfonium triflate, I, in Scheme 2). The  $\text{Cu}(\text{II})$  or  $\text{Cu}(\text{III})$  complex then undergoes transmetalation with the arylboronic acid to form an aryl- $\text{Cu}(\text{II})$  or  $\text{Cu}(\text{III})$  intermediate, which, by a facile reductive elimination, affords the substitution arene product [18].

Thus, arylboronic acids can efficiently be trifluoromethylated either employing the Langlois reagent (Eq. (2), [22]) or the Umamoto reagent (Eq. (3), [18]) *via* radical mechanisms with the intervention of Cu. These two strategies seem superior to the polar



**Scheme 2.** Proposed mechanism for the trifluoromethylation of arylboronic acids (Ref. [18]).

protocols reported by Grushin [23] and Buchwald [24] from arylboronic acids, in terms of yields and regioselectivity.

The perfluoroalkylation of arenes and arylbromides has recently been accomplished by using arylboronates esters and the complex [(Phen)CuR<sub>f</sub>], where R<sub>f</sub> can be C<sub>n</sub>F<sub>2n+1</sub> (*n* = 1–3) [27]. Disubstituted or trisubstituted arenes and a range of aryl bromides are converted regioselectively to an arylboronate ester *in situ*, and this ester readily undergoes perfluoroalkylation under mild conditions with the stable preformed copper reagent [(Phen)CuR<sub>f</sub>]. These reactions are carried out under air, and in DMF as solvent [27].

In organic solvents, the fluorosulfonyl difluoromethyl iodide FSO<sub>2</sub>CF<sub>2</sub>I and Cu metal couple has been employed in the *ipso* substitution of iodoarenes with CF<sub>3</sub> group, according to Scheme 3.

Mechanistic probes for this reaction include a radical anion scavenger such as *p*-DNB, and a radical inhibitor such as hydroquinone, which suppress partially the reaction. The radical nature of the reaction has been uncovered through trapping of the fluorosulfonyl dimethyl radical with 2,3-dimethyl-2-butene. However, the trifluoromethylated arene is believed to arise from a CuCF<sub>3</sub> intermediate substitution of the iodoarene (*vide infra*).

The introduction of the CF<sub>2</sub>H moiety onto an aromatic substrate confers the molecule interesting properties, as this group is isosteric and isopolar with the OH functionality (bio-isosteres of alcohols and thiols), and offers an alternative to more traditional hydrogen bond donors. The CF<sub>2</sub>H moiety also allows the pharmacophore to display better membrane permeability, being reasonably lipophilic.

Methods for the introduction of CF<sub>2</sub>H groups onto arenes are laborious, and often involve harsh reagents (SF<sub>4</sub> or (R<sub>2</sub>N)SF<sub>3</sub>), or several steps [28]. Recently, Hartwig and collaborators have introduced a copper-mediated protocol for the difluoromethylation of aryl and vinyl iodides [29]. Though difluoromethyl-copper complexes are much less stable than trifluoromethyl-copper complexes and decompose to tetrafluoroethane and

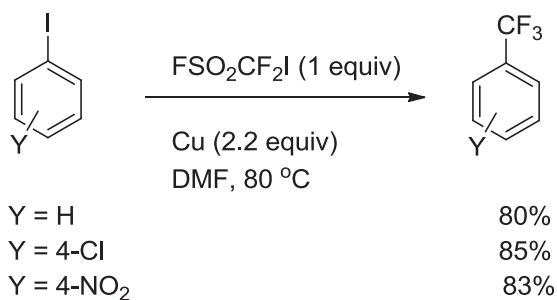
*cis*-difluoroethylene, new strategies have come up to circumvent this issue and effect the difluoromethylation reactions of arenes. The source of CF<sub>2</sub>H is trimethylsilyldifluoroethane (TMSCF<sub>2</sub>H). This latter reagent is synthesized by NaBH<sub>4</sub> reduction of the Ruppert–Prakash reagent (TMSCF<sub>3</sub>) [29]. The authors achieved the difluoromethylation of a series of aryl iodides, according to Scheme 4.

Mechanistic studies conducted by the authors [29] could not rule out radical pathways, and further investigations on the mechanism are claimed to be necessary. From the point of view of reagents and reaction conditions, the Hartwig protocol [29] seems to be superior to other methods known in the literature.

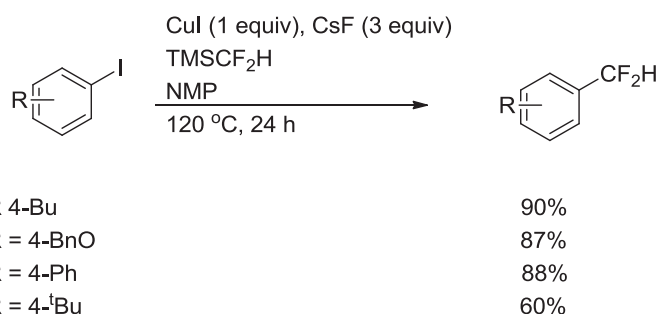
Hu and collaborators [30] have very recently accomplished the silver-mediated aromatic trifluoromethylation-iodination reaction (through an aryne intermediate) in MeCN as solvent. Although through studying the mechanism of the reaction the presence of radicals could not be uncovered, the protocol used turned out to be unprecedented for the synthesis of *o*-trifluoromethylated iodoarenes that are otherwise difficult to obtain by traditional methods.

Sanford and co-workers [31] have recently reported that a combination of AgOTf, KF, and TMSCF<sub>3</sub> can be used for the C–H trifluoromethylation of aromatic substrates under mild conditions. AgCF<sub>3</sub> was generated *in situ* from the reaction of AgF with TMSCF<sub>3</sub> in MeCN as solvent. The authors [31] concluded that the reaction has a radical nature, since addition of 1 equiv. of TEMPO (2,2,6,6-tetramethylpiperidine-*N*-oxide), led to a dramatic reduction in the yield of the substitution product. The proposed free radical pathway for the Ag-mediated trifluoromethylation of arenes is illustrated in Scheme 5.

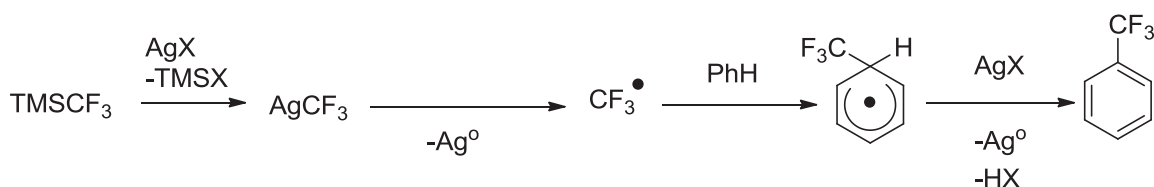
This radical methodology [31] for obtaining CF<sub>3</sub>-substituted arenes employing the Ruppert–Prakash reagent and Ag is unprecedented, since the protocol by Hu and collaborators [30] necessitates the formation of the aryne intermediate (through an arene



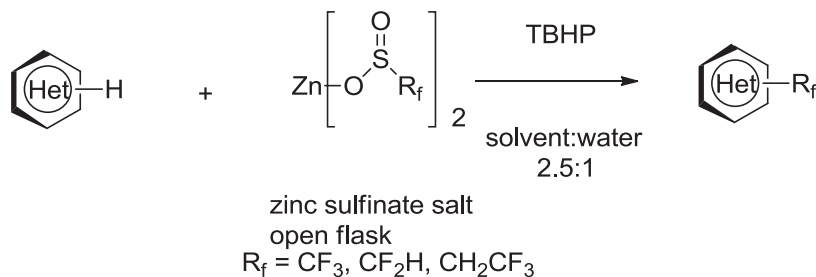
**Scheme 3.** Trifluoromethylation of iodoarenes employing FSO<sub>2</sub>CF<sub>2</sub>I/Cu in DMF (Ref. [28]).



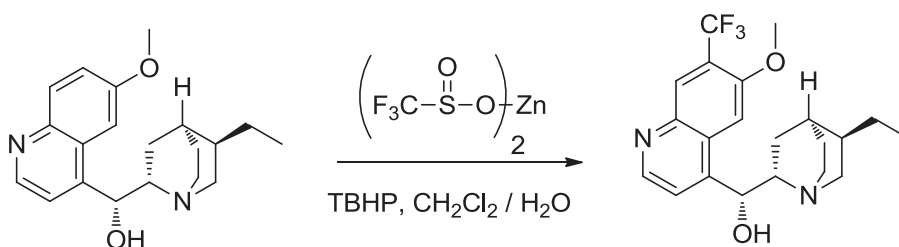
**Scheme 4.** Difluoromethylation of iodoarenes by copper catalysis (Ref. [29]).



**Scheme 5.** Radical pathway for the Ag-mediated trifluoromethylation reaction (Ref. [31]).



**Scheme 6.** Homolytic aromatic substitution of heteroarenes with zinc bis(perfluoroalkylsulfonates) (Ref. [32]).



**Scheme 7.** Homolytic aromatic substitution of dihydroquinine with  $CF_3$  moiety by the use of the trifluoromethylsulfinate zinc salt in aqueous mixtures, initiated by DTHP (Ref. [32]).

conveniently *o*-disubstituted) and affords *o*-trifluoromethyl iodoarenes by a non-radical process.

## 2.2. Zn-mediated trifluoromethylation and perfluoroalkylation reactions

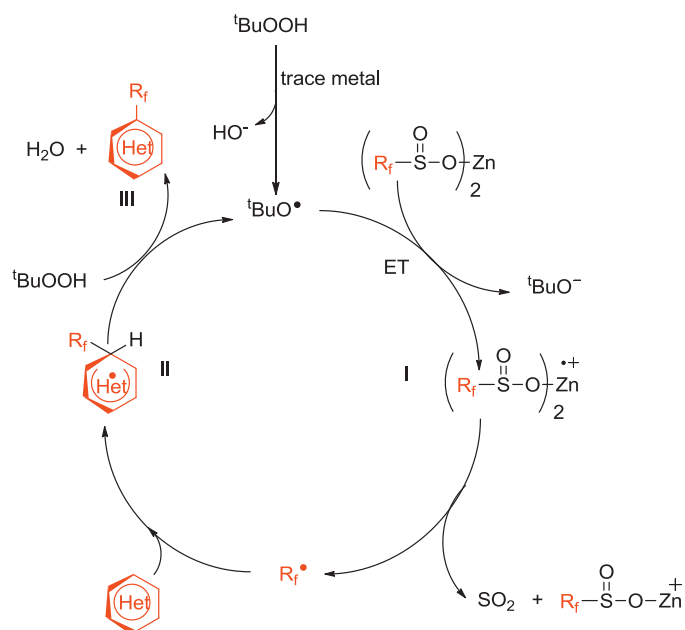
Also recently, Baran and collaborators [32] have developed a new family of perfluoroalkylating reagents based on the zinc bis(perfluoroalkylsulfonates). The C–H functionalization of heterocycles with perfluoroalkyl and other groups results in products that cannot be efficaciously generated by the protocols reported in the past [10]. The advantage of this methodology involves carrying out the reaction in aqueous mixtures, under mild radical thermal initiation conditions (TBHP) as depicted in Scheme 6.

An interesting example is presented in the same paper [32] when dealing with the dihydroquinine trifluoromethylation reaction, where homolytic substitution occurs in the electron-rich aromatic nucleus of the dihydroquinine, according to Scheme 7.

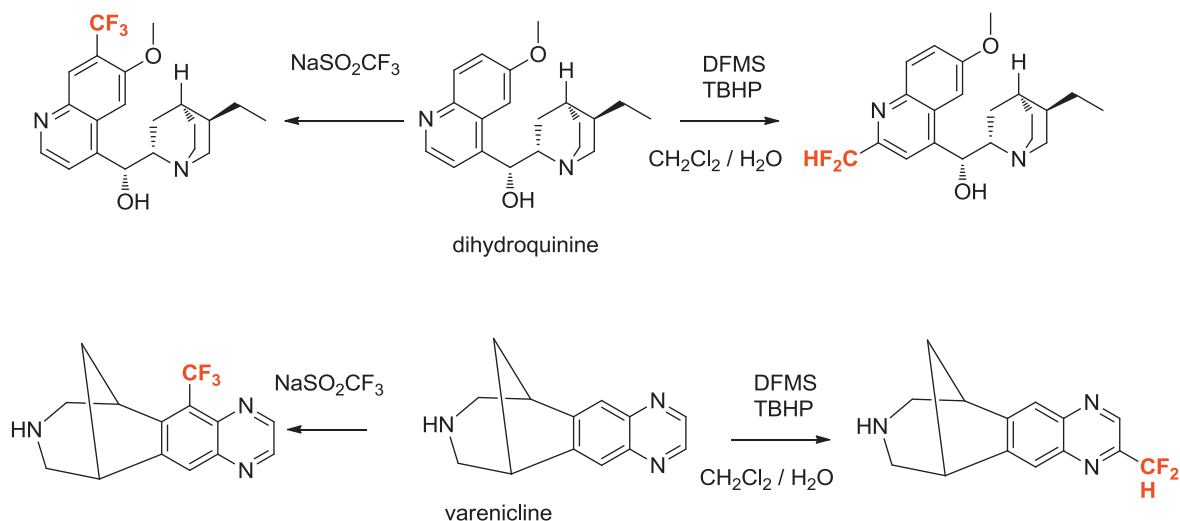
The authors [32] comment on the advantages of using these sulfinate salts over the Langlois reagent ( $NaSO_2CF_3$ ), the mildness of the reaction, and the one-pot operation, also on the ability to conduct the reaction under open air. Although the authors do not postulate a plausible mechanism, we believe that the intervention of the metal is crucial, and a putative mechanistic radical proposal is illustrated in Scheme 8.

In the mechanism proposed by us (see Scheme 8), the *tert*-butoxyl radicals (generated from trace metal-induced decomposition of TBHP) undergo an ET process with zinc bis(perfluoroalkylsulfonates) to afford *tert*-butoxide anion and the radical cation of the zinc salt I (Scheme 8), which decomposes

to  $R_f$  radicals, sulfur dioxide, and the electrophilic  $R_fSO_2Zn^+$  species.  $R_f$  radicals add to the heteroaromatic ring to afford a substituted cyclohexadienyl-type radical intermediate II (Scheme 8) which loses a H atom with the aid of further



**Scheme 8.** A putative mechanism for the perfluoroalkylation of heteroarenes employing perfluoroalkylsulfinate zinc salts.



**Scheme 9.** Regiochemical orthogonality between trifluoromethylation and difluoromethylation of dihydroquinine and varenicline with the Langlois reagent ( $\text{NaSO}_2\text{CF}_3$ ) and difluoromethylsulfinate zinc salt, respectively (Ref. [33]).

TBHP and produces the perfluoroalkyl-substituted arene **III**. This proposed mechanism would account for the stoichiometric excess of the zinc *bis*(perfluoroalkylsulfonates) and the TBHP needed in relation to heteroarenes [32]. Clearly from the mechanistic proposal, for each equivalent of  $\text{R}_f$  radicals formed, an unproductive  $\text{R}_f\text{SO}_2\text{Zn}^+$  species is generated. According to the stoichiometry employed by the authors [32], TBHP is also used in large excess (3–5 equiv), likely needed to initiate the ET process to zinc *bis*(perfluoroalkylsulfonates) and also required in the re-aromatization step of the cyclohexadienyl-type radical intermediate, as indicated in Scheme 8.

The same research group came up with a practical methodology to incorporate the  $\text{CF}_2\text{H}$  moiety onto organic substrates [33]. The use of the difluoromethylsulfinate zinc salt,  $\text{Zn}(\text{SO}_2\text{CF}_2\text{H})_2$ , or DFMS, in aqueous organic media in the presence of TBHP is able to achieve the difluoromethylation of a large series of heteroaromatic compounds in fairly good yields. An interesting example of the reaction is given in Scheme 9.

The  $\text{Zn}(\text{SO}_2\text{CF}_2\text{H})_2$  reagent was evaluated through a broad cross section of heteroaromatic compounds bearing a large array of sensitive functional groups present on the ring, such as carboethoxy, halogen atoms, amino, cyano, carboamido, and carbonyl groups, resulting in difluoromethylated products, with intact functionalities in reasonable yields [30].

Also, the site selectivity illustrated in Scheme 9 for the difluoromethylation reaction as compared to that of the trifluoromethylation reaction of both dihydroquinine and varenicline is remarkable [33]. For both dihydroquinine and varenicline, C–H trifluoromethylation takes place on the most electron-rich position of the molecule, whereas difluoromethylation takes place at electron-poor sites adjacent to heteroatoms. Although the authors do not comment on the “fine tuning” of the difluoromethylation reaction,

we believe that hydrogen bonding from the  $\text{CF}_2\text{H}$  group to the N atom is playing a key role in the substitution pattern observed. This aspect of the regiochemistry, although not discussed in the original paper, was uncovered by carrying out the reaction in two different solvent systems, as depicted in Scheme 10.

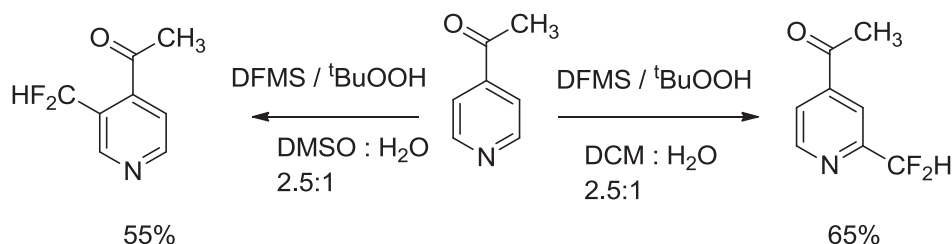
In the less polar  $\text{DCM}:\text{H}_2\text{O}$  solvent mixture, difluoromethylation takes place next to the N atom on the 4-acetylpyridine ring, whereas in the more polar hydrogen-bonded solvent system, substitution occurs at the 3-position of the ring.

Thus, the employment of the Baran reagent ( $\text{Zn}(\text{SO}_2\text{R}_f)_2$ ) is able to accomplish trifluoromethylation, difluoromethylation and perfluoroalkylation reactions of a large number of arenes, heteroarenes, and pharmacophore precursors in very high yields and regioselectivity. These transformations are achieved through radical pathways under mild radical initiation conditions in aqueous media, and surpass all other perfluoroalkylation reagents thus far proposed, enhancing the armamentarium of radical transformations available to Chemists. The Baran reagent is always used under radical conditions and fails to operate by polar mechanism.

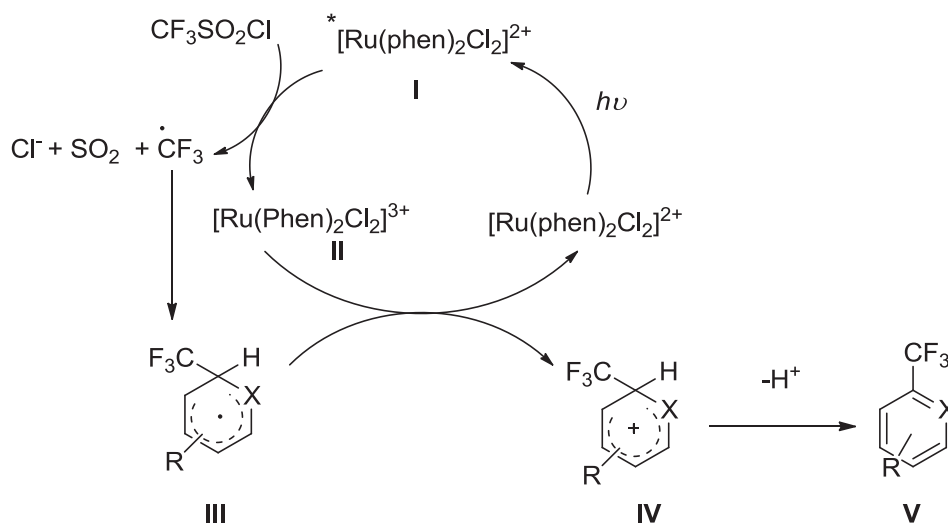
### 2.3. Ru-, Re-, and Ti-mediated perfluoroalkylation reactions

The trifluoromethylation of arenes was also accomplished with trifluoromethylsulfonyl chloride as the  $\text{CF}_3$  radical precursor and the catalyst  $[\text{RuCl}_2(\text{PPh}_3)_2]$ , being arene the solvent of the reactions [34]. These constitute homolytic aromatic substitution reactions ( $\text{S}_\text{H}\text{Ar}$ ), where a H atom of the arene is replaced by a  $\text{CF}_3$  group. MacMillan and Nagib developed a photoredox catalyst to achieve the trifluoromethylation of heteroarenes with  $\text{CF}_3\text{SO}_2\text{Cl}$ . A plausible mechanism is depicted in Scheme 11 [35].

The excited Ru photocatalyst **I** (Scheme 11) undergoes an ET process to  $\text{CF}_3\text{SO}_2\text{Cl}$ , rendering  $\text{CF}_3$  radicals from reduction



**Scheme 10.** Site selectivity in the difluoromethylation reaction of 4-acetylpyridine (Ref. [33]).



**Scheme 11.** Trifluoromethylation of arenes employing  $[\text{Ru}(\text{phen})_2\text{Cl}_2]$  and  $\text{CF}_3\text{SO}_2\text{Cl}$  (Ref. [34]).

of  $\text{CF}_3\text{SO}_2\text{Cl}$ , and an oxidized Ru complex (**II**, Scheme 11). Homolytic aromatic substitution ( $\text{S}_{\text{H}}\text{Ar}$ ) of the arene ring with the  $\text{CF}_3$  affords the cyclohexadienyl  $\text{CF}_3$ -substituted radical intermediate **III** which, in turn, is oxidized by the Ru(III) species to afford a Wheland- $\text{CF}_3$ -substituted intermediate **IV**, which finally deprotonates to a trifluoromethyl-substituted heteroarene **V** (Scheme 11).

MacMillan and collaborators [36] demonstrated the conversion of  $\text{CF}_3\text{I}$  to  $\text{CF}_3$  radicals in the presence of a photocatalyst  $\text{Ru}(\text{bpy})_3^{2+}$ , visible light, and a reductant. Thus, arylboronic acids were transformed into the corresponding trifluoromethyl-substituted arenes in reasonable yields. This protocol was improved by Sanford and colleagues by introducing the cross coupling of arylboronic acids with  $\text{CF}_3\text{I}$  through a photoredox and copper catalysis, obtaining excellent yields of trifluoromethyl-substituted aromatic nuclei. The catalyst was the visible light activated complex  $[\text{Ru}(\text{bpy})_3\text{Cl}_2 \cdot \text{H}_2\text{O}]$ , and the solvent was DMF [13]. Thus, a large series of arenes and heteroarenes has been trifluoromethylated in fairly good yields [13]. The postulated mechanism involves the Ru complex in different oxidation states, and copper as the cross-coupling agent. This radical-like protocol for obtaining  $\text{CF}_3$ -substituted arenes proved to be very convenient, as a standard 20W light-bulb was used to initiate the reaction, and both photocatalyst and  $\text{CF}_3\text{SO}_2\text{Cl}$  are readily commercially available compounds. The re-generation and re-utilization of the catalyst warrants the protocol good industrial applications.

The protocol confers the photocatalytic methodology an advantage over the use of metallic species alone in scale-up processes

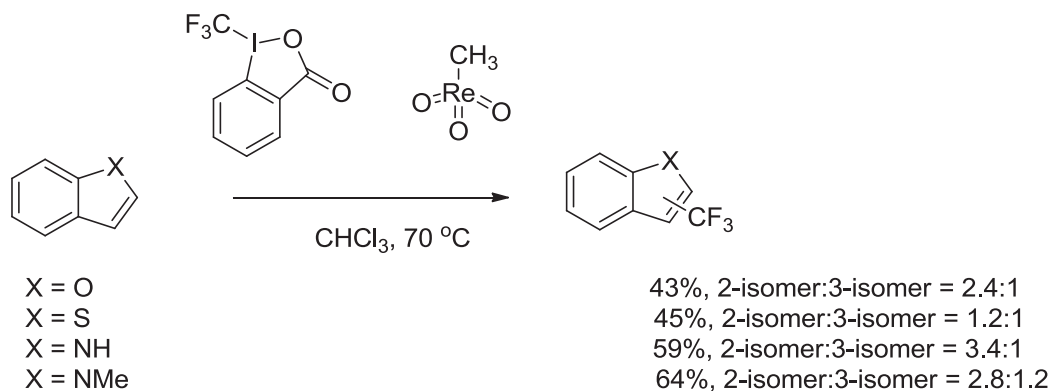
and so the radical nature of the reaction over classical polar transformations.

Togni's reagent (3,3-dimethyl-1-(trifluoromethyl)-1,2-benziodoxol) had been introduced as a trifluoromethylating reagent of arenes [37], such as phenol. However, substitution of phenol by this latter reagent affords a mixture of the *o*-, *m*-, and *p*- $\text{CF}_3$  substituted isomers, with no control on the regioselectivity [37]. The mechanism of these reactions is of a polar nature.

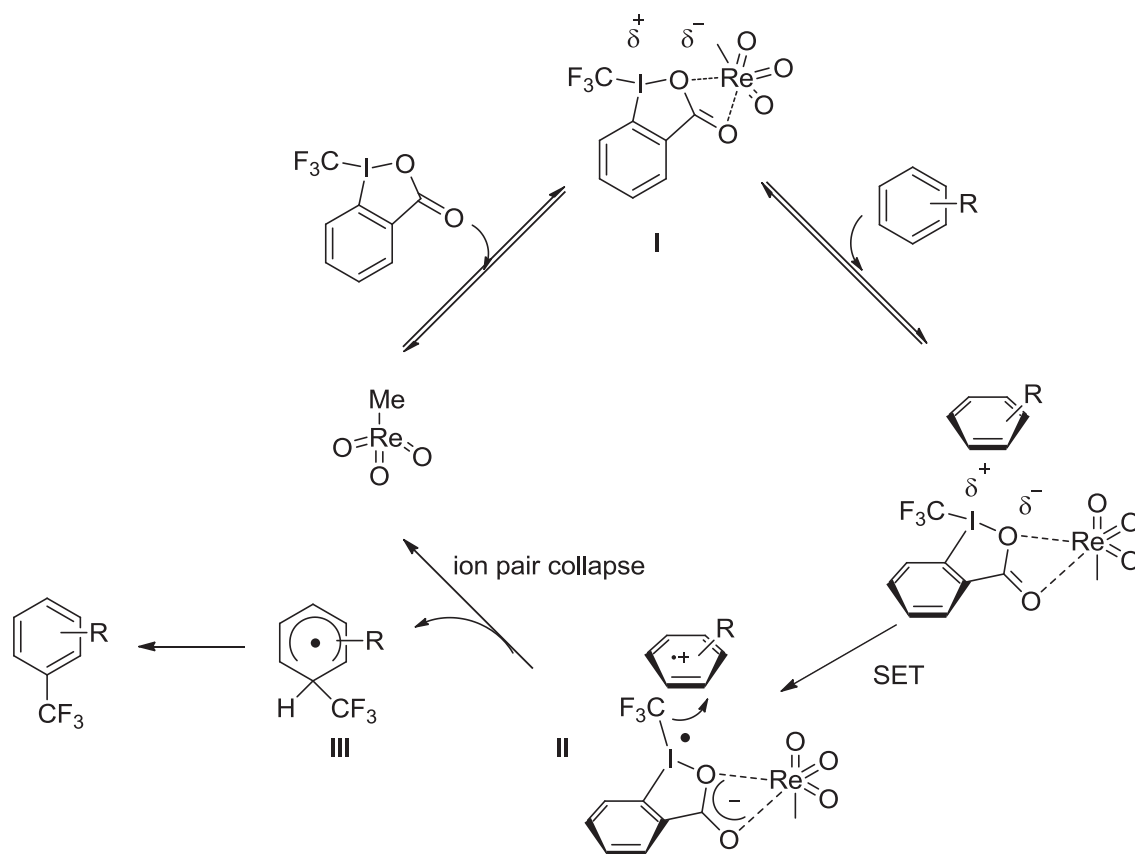
Later on, Togni and collaborators [38] utilized the methyltrioxorhenium complex as catalyst for the trifluoromethylation of various aromatic and heteroaromatic compounds using the hypervalent iodine reagent 1-(trifluoromethyl)1,2-benziodoxol-3(1*H*)-one (Togni's reagent). The scope of the reaction was further extended to oxygen-, sulfur-, and nitrogen-containing heterocycles, according to Scheme 12.

The authors inspected the mechanism of the above reaction monitoring its progress to completion, observing a pattern attributable to that of a radical process. In order to unambiguously check the involvement of a radical species, the authors [38] followed the reaction by EPR and observed that the composition of the radical mixture is not the same throughout the reaction. The conjunction of the Togni reagent and the rhenium complex endows the reaction with some degree of regioselectivity (Scheme 12) otherwise unobserved in the absence of the methyltrioxorhenium complex [38].

The first stage of the reaction includes the activation of the Togni reagent with coordination with the Re catalyst **I** (Scheme 13), making a hypervalent iodine reagent more electrophilic and allowing



**Scheme 12.** Trifluoromethylation of heteroarenes with Re catalyst (Ref. [38]).



**Scheme 13.** Reaction mechanism for the rhenium-catalyzed trifluoromethylation of arenes with Togni reagent (Ref. [38]).

the single electron transfer (SET) from the benzene molecule, which generates an aromatic radical cation **II** coupled with the reduced Togni reagent. The cage-pair **II** would collapse with an effective transfer of  $\text{CF}_3^-$  to give a radical intermediate, which transfers a  $\text{CF}_3$  radical closing the cycle. The termination step would be the decomposition of the cyclohexadienyl radical **III** leading to  $\text{CF}_3$ -substituted product formed only in the last step of the reaction, as illustrated in Scheme 13 [38].

A redox system for the perfluoroalkylation of arenes and  $\alpha$ -methylstyrenes derivatives using titanium oxide as photocatalyst has been developed by Yoshida and collaborators [39]. The authors [39] were able to perfluoroalkylate a series of aromatic substrates, and a few heteroaromatic compounds without formal leaving groups in reasonable yields. Photoirradiation of titanium dioxide excites electrons from the valence band to the conduction band. Making use of the holes and electrons, a redox process takes place affording the perfluoroalkylated arenes.

### 3. Aliphatic substrates

Activated and unactivated alkenes are among the most abundant and commonly used carbon feedstocks in the synthesis of commodity chemicals. For this reason, a myriad of catalytic reactions are available for the functionalization of alkenes that form carbon–carbon, and carbon–heteroatom bonds.

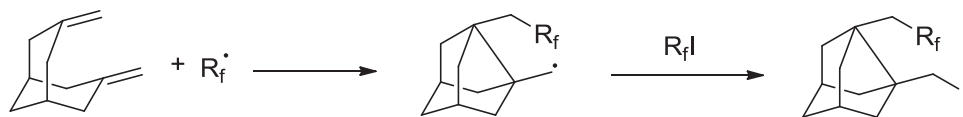
The free radical addition of  $\text{R}_f\text{I}$  to carbon–carbon multiple bonds results in a radical addition adduct, which further reacts with more  $\text{R}_f\text{I}$  to render a perfluoroalkyl-substituted iodoalkane or iodoalkene [33b]. These reactions are easily conducted under sulfinate-dehalogenation reaction conditions [6] (aqueous  $\text{Na}_2\text{S}_2\text{O}_4/\text{NaHCO}_3$ , in aqueous organic solvent mixtures), and do not necessitate the

intervention of metals. Many recent review articles do exist in the literature regarding this sort of transformations [6a,40–42] and will not be discussed herein.

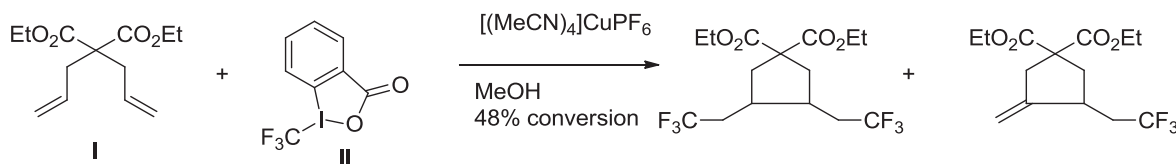
Among other perfluoroalkylating reagents that can efficiently accomplish fluorination of alkenes are those analogous employed for effecting perfluoroalkylation of aromatic substrates (*vide supra*, Section 2). the Ruppert-Prakash reagent ((trifluoromethyl)trimethylsilane,  $\text{TMSCF}_3$ ) [25], the Togni reagent (a hypervalent benziodoxolone salt) [16], and the Umemoto reagent (*S*-(trifluoromethyl)diphenylsulfonium triflate) [17,18]. Though the latter two reagents have been conceived to operate through polar mechanisms, new reactions have been developed involving radicals with the electrophilic Togni reagent and the nucleophilic Umemoto reagent and aliphatic substrates. Applications of these reagents onto aromatic substrates are discussed in the previous section. Although these reagents have initially been developed to perform perfluoroalkylation reactions without the assistance of metals, recent protocols have been uncovered with these reagents in conjunction with metals or metal complexes that expanded the scope of these reactions to a large array of substrates and milder reaction conditions.

Recently, Studer and collaborators reported the transition metal-free trifluoromethylaminoxylation of alkenes, where by the use of the Togni reagent and the reducing sodium salt of TEMPO (sodium 2,2,6,6-tetramethylpiperidine-*N*-oxide) achieved the simultaneous formation of both a carbon–carbon and a carbon–oxygen bonds from a large array of terminal alkenes in THF as solvent [43]. Although this strategy does not necessitate the use of metals, it is remarkable from the mechanistic point of view, since the generation of  $\text{CF}_3$  radicals occurs through an SET from the Togni reagent and NaTEMPO, a persistent radical.





**Scheme 14.** Mechanism for the reaction of 3,7-dimethylene-bicyclo[3.3.1]nonane (Ref. [46]).



**Scheme 15.** Use of Togni reagent in the trifluoromethylation of alkenes (Ref. [48a]).

While earlier studies focused on stoichiometric amounts of trifluoromethylation and perfluoroalkylation reactions of multiple bonds, recent attention has been diverted to transition metal catalyzed trifluoromethylation reactions of unsaturated centers, which usually are carried out under milder conditions and exhibit improved yields, selectivity, and functional group tolerance. These reactions usually proceed by radical pathways. Good examples have been reported with regards to Pd- or Cu-mediated trifluoromethylation of various unsaturated carbon centers [44,45]. In the following sections, radical perfluoroalkylation reactions of unsaturated centers with the participation of Cu, Zn, Fe, Ni, Pd, Ru, Ir, Ti, Re, In, and Si will be discussed.

### 3.1. Cu- and Zn-mediation in radical perfluoroalkylation reactions

Radical cyclizations of 3,7-dimethylenebicyclo[3.3.1]nonane with perfluoroalkyl iodides in the presence of Cu, selectively lead to the corresponding 3,7-noradamantanes. The reaction pathway involves an ET from Cu to  $R_fI$  leading to a proposed perfluoroalkyl radical, such as that depicted in Scheme 14. The reaction is carried out in MeCN as solvent. These radicals add to 3,7-dimethylenebicyclo[3.3.1]nonane affording the perfluoroalkyl-substituted noradamantanes, according to Scheme 14 [46].

These cyclization reactions are only feasible through radical pathways with the involvement of Cu species as ET agents.

The Cu-promoted trifluoromethylation of primary and secondary alkylboronic acids has been recently informed by Fu and collaborators with the use of the Ruppert-Prakash reagent ( $TMSCF_3$ ) [47]. Although the latter does not represent a reaction of a radical nature, this Cu-catalyzed cross coupling of alkylboronic acid derivatives turned out to be unprecedented, since transmetalation takes place on  $sp^3$ -hybridized carbon atoms instead of the more traditional  $sp^2$ - or  $sp$ -hybridized carbon centers.

Buchwald and Wang independently employed the Togni reagent (a hypervalent benziodoxolone salt) as an effective source of  $CF_3$  radicals for the trifluoromethylation of alkenes, relying on the Cu

catalysis [48]. For instance, the trifluoromethylation of diethyl diallyl malonate **I** as a cyclization radical clock (Scheme 15) with Togni reagent **II** in the presence of Cu, provided a mechanistic prove for a radical reaction, as observed for the cyclized cyclopentane products obtained [48a].

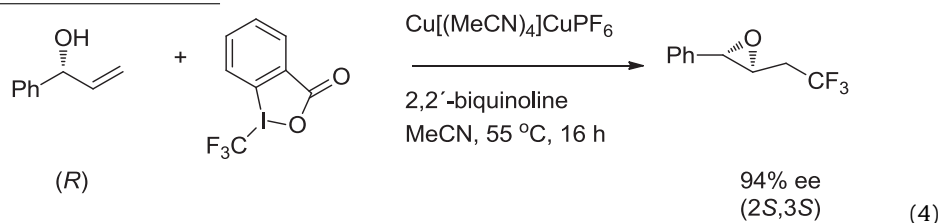
These useful radical transformations afford trifluoromethyl-substituted cyclopentane rings that cannot be obtained by polar mechanism from the reagents proposed.

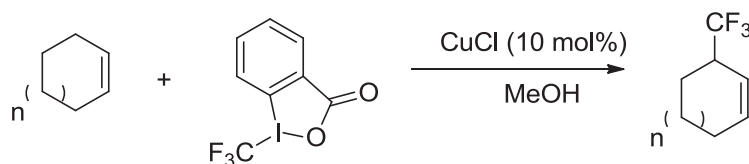
Concurrently, Wang and collaborators [48b] were able to accomplish the allylic trifluoromethylation of a series of alkenes, both activated and unactivated, with the Togni reagent, in the presence of CuCl in MeOH as solvent. Some examples are given in Scheme 16.

In order to explore the radical nature of the above reaction, the authors [48b] employed the well-known radical scavenger TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy) and obtained the TEMPO- $CF_3$  adduct. These allylic positions can easily be trifluoromethylated in the presence of Cu by a radical mechanism.

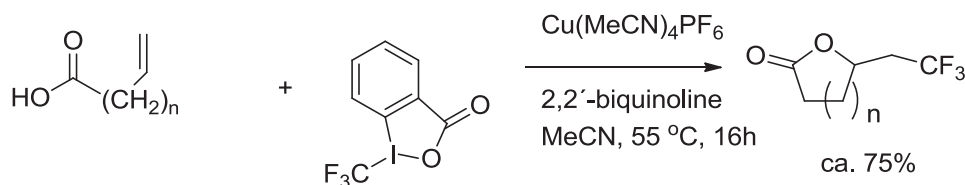
The Togni reagent was also employed for the Cu-catalyzed oxytrifluoromethylation of unactivated alkenes, rendering a myriad of oxygen-containing rings with trifluoromethyl appendices [49]. A series of unsaturated aliphatic and aromatic acids undergoes the desired transformation to afford the corresponding trifluoromethylated lactones in good yields, according to Scheme 17.

With regard to the scope of the alkene moiety, monosubstituted and geminal-disubstituted alkenes were excellent substrates for this reaction. Aryl and alkyl substituents on the carbon-carbon double bond were well-tolerated. As for the size of the ring formed,  $\delta$ -,  $\gamma$ -, and even  $\beta$ -lactones proved to be accessible [49]. The authors also tested primary alcohols and phenols which served as suitable substrates for these reactions, affording oxo-rings in good yields. Allylic alcohols were also investigated, giving rise to 3-trifluoromethyl-substituted-1,2-epoxides; these latter considered versatile intermediates. Interestingly, when (*R*)-1-phenyl-prop-2-ene-1-ol was investigated, the product obtained retained the enantiomeric excess, as depicted in Eq. (4) below:





**Scheme 16.** Use of Togni reagent for the allylic trifluoromethylation (Ref. [48b]).



**Scheme 17.** Cu-catalyzed oxytrifluoromethylation (Ref. [49]).

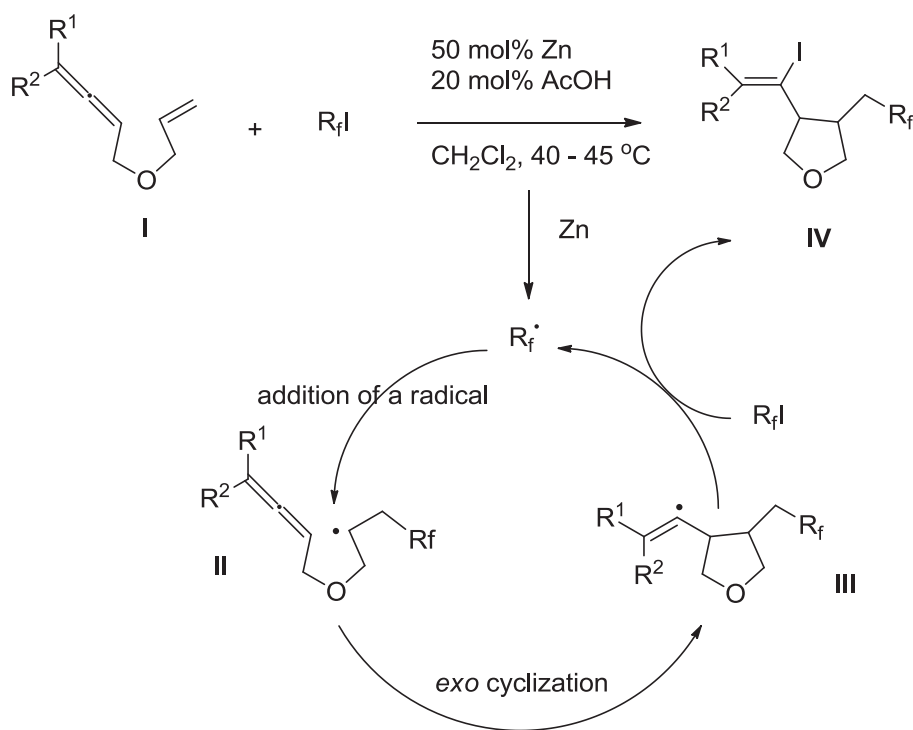
The authors [49a] argue in favor of an atom transfer-type radical addition pathway [49b] for the mechanism of the process in Eq. (4), because of the Cu(I)/pyridine-based bidentate ligand system [50]. Also, the addition of TEMPO inhibits the reaction completely [49a]. These transformations, *i.e.* cyclizations (Scheme 17) and epoxidation reactions (Eq. (4)), could not be achieved by a polar mechanism with Togni's reagent, which makes the radical pathway the strategy of choice.

Fu and Ma [42] have recently developed an intriguing radical addition/cyclization protocol of allene-enes in an alkene-to-allene fashion using zinc powder as cheap initiator to afford the highly selective formation of *exo*-cyclization products in moderate to good yields. Furthermore, using TBAF-promoted dehydroiodination reactions, the products were transformed into 3-(1-enylidene)heterocyclopentanes. The mechanism of the transformation is described in Scheme 18.

The initiation of the reaction with Zn forms the perfluoroalkyl radical which attacks the alkene moiety of allene **I** (Scheme 18) to form the radical intermediate **II**. An intramolecular radical *exo*-cyclization process yields the intermediate **III**, which upon atom transfer releases product **IV** (Scheme 18). These allene-to-alkene cyclization reactions are typical of radical transformations, and are difficult to obtain under polar pathways.

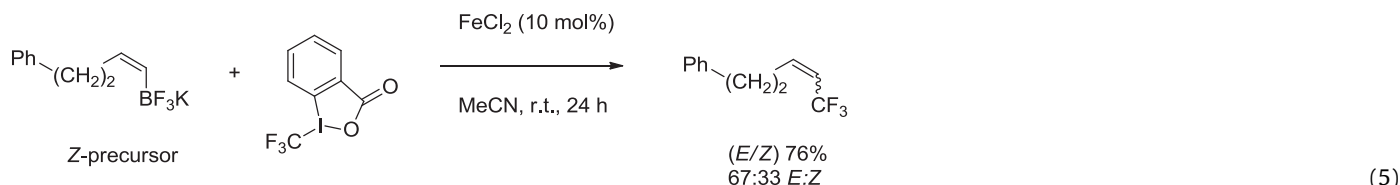
### 3.2. Iron-catalyzed fluoroalkylation

Very recently, Buchwald and collaborators [51] have introduced the Fe(II)-catalyzed trifluoromethylation of vinyltrifluoroborates, as a versatile entry to trifluoromethylallyl derivatives, with high *E* stereoselectivity. The authors argue against a transmetalation/reductive elimination mechanism through the borate precursors on the basis of the stereoconvergence of the *E* and *Z*



**Scheme 18.** Mechanism for the Zn-initiated radical addition/cyclization of allene-ene (Ref. [42]).

substrate isomers in favor of a mechanism involving a radical intermediate (Eq. (5)).



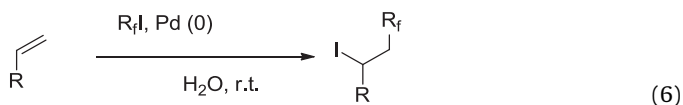
The authors [51] also undertook a study on the Lewis acid catalyst, and came up with  $\text{Sn}(\text{Tf})_2$  as the best candidate for achieving a high *E* stereoselectivity. This is quite remarkable from the mechanistic point of view since Togni's reagent does not effect substitution reactions of aliphatic substrates other than polar mechanisms.

### 3.3. Nickel and palladium-cross coupling/catalyzed fluoroalkylation reactions

$\text{Ni}(0)$ -catalyzed perfluoroalkylation of alkenes and alkynes with perfluoroalkyl chlorides afford perfluoroalkyl-reduced substituted alkanes and alkenes, respectively, in DMF as solvent [52]. This procedure utilizes the *in situ* formation of a  $\text{Ni}(\text{PPh}_3)_4$  species to effect a SET process to  $\text{R}_f\text{Cl}$ , and thus generate  $\text{R}_f$  radicals which add to the carbon–carbon multiple bonds. The authors [52] also apply this methodology to accomplish substitution of aromatic nuclei, such as anisoles and anilines.

Lanteri and collaborators [53] reported on the synthesis of perfluoroalkyl-phosphines, arsines, and selenides through Pd-cross coupling reactions with organostannanes. Cross coupling of selenium-stannanes were employed to generate perfluoroalkyl selenides in high yields with Pd [54]. Although these reactions were carried out in strictly anhydrous organic solvents, they are notorious from the point of view of transition metal coupling reactions.

The palladium-catalyzed Kharasch reaction of alkenes and alkynes proceed in a heterogeneous aqueous system, without the use of hydrophilic co-solvents or phase transfer catalysts. Thus, Oshima and collaborators [55] report the Pd(0)-catalyzed reaction of terminal alkenes with bromotrichloromethane in water as an effective reaction. When the authors attempt to conduct the reaction in an organic solvent such as benzene, no reaction occurs under the same conditions. The Pd(0) catalyst in aqueous media also effects the radical addition of iodoperfluoroalkanes toward terminal alkenes and alkynes at room temperature. This is illustrated in Eq. (6).



### 3.4. Ruthenium-, iridium-, titanium-, and rhenium-mediated radical fluoroalkylation reactions

The atom transfer radical addition of  $\text{CF}_3\text{I}$  to alkenes catalyzed by the complex  $[\text{Ru}_3(\text{CO})_{12}]$  is an example of a halogen atom transfer radical addition reaction (ATRA). Though the mechanism was not discussed in the original publication, Studer proposed that the metal can participate in the chain reaction, as shown in Scheme 19 [11a].

Thus, an active  $[\text{Ru}]$  complex abstracts an iodine atom to generate a trifluoromethyl radical and an oxidized  $[\text{Ru}-\text{I}]$  species. Trapping of the adduct radical with the  $[\text{Ru}-\text{I}]$  species affords the halogen atom transfer product.

Similar radical mechanisms can be suggested when using other metal catalysts, such as  $[\text{Fe}_3(\text{CO})_{12}]$  [56],  $[\text{Co}_2(\text{CO})_8]$  [56],  $[\text{Pd}(\text{Ph}_3)_4]$  [57],  $[\text{Ni}(\text{CO})_2(\text{PPh}_3)_2]$  [58],  $[\text{W}(\text{CO})_5\text{P}(\text{OEt})_3]$ ,  $[\text{Mo}(\text{CO})_5\text{PPh}_3]$ , [58],  $[\text{RuCl}_2(\text{PPh}_3)_2]$  [58b], etc. for the perfluoroalkyl addition to alkenes in organic solvents.

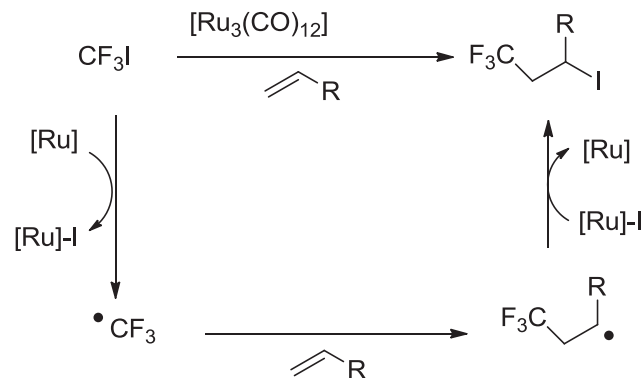
Photocatalysis was also employed effectively to perfluoroalkylate octanal with good yield and high enantioselectivity by means of an iridium catalyst and a commercial imidazolidinone to introduce a variety of perfluoroalkyl moieties at the 2-position of octanal, according to Scheme 20 [36]. Although these reactions take place in DMF as solvent, the authors do not conduct studies in other solvent systems.

These results are relevant since they constitute the first enantioselective organocatalytic  $\alpha$ -trifluoromethylation of aldehydes accomplished using a readily available iridium photocatalyst and a commercial imidazolidinone catalyst [36].

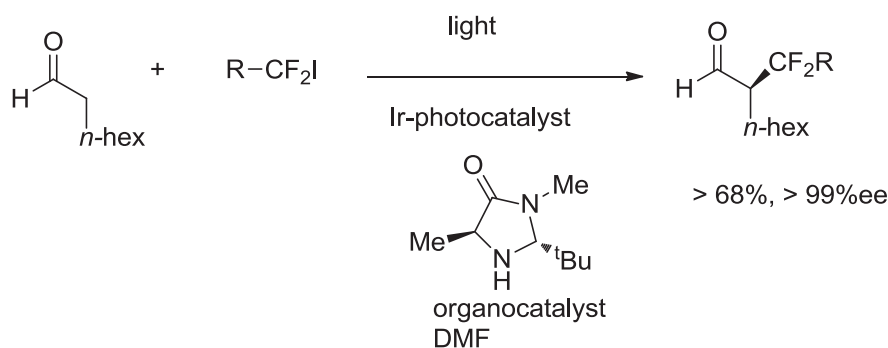
Although these results have nonetheless been recently reviewed [11] it would be useful to inspect at the mechanism, as depicted in Scheme 21.

Irradiation of Ir with a fluorescent light bulb leads to the corresponding excited Ir complex, which undergoes SET to  $\text{CF}_3$  to afford  $\text{CF}_3$  radicals along with oxidized organocatalyst. In a second catalytic cycle, the organocatalyst reacts with the starting aldehyde to afford chiral enamine **I** (Scheme 21). Diastereoselective addition of the  $\text{CF}_3$  radical onto the electron-rich enamine, affords a radical adduct **II** which, in turn, is oxidized by the Ir complex to iminium ion **III** (Scheme 21). This redox step results in the regeneration of the catalyst. Hydrolysis results then in the fluorinated aldehyde. Analogously to the photocatalytic perfluoroalkylation reactions conducted on arenes by Ru (Section 2.3.-), aliphatic aldehydes can be trifluoromethylated through the use of an Ir photocatalyst in very high yields.

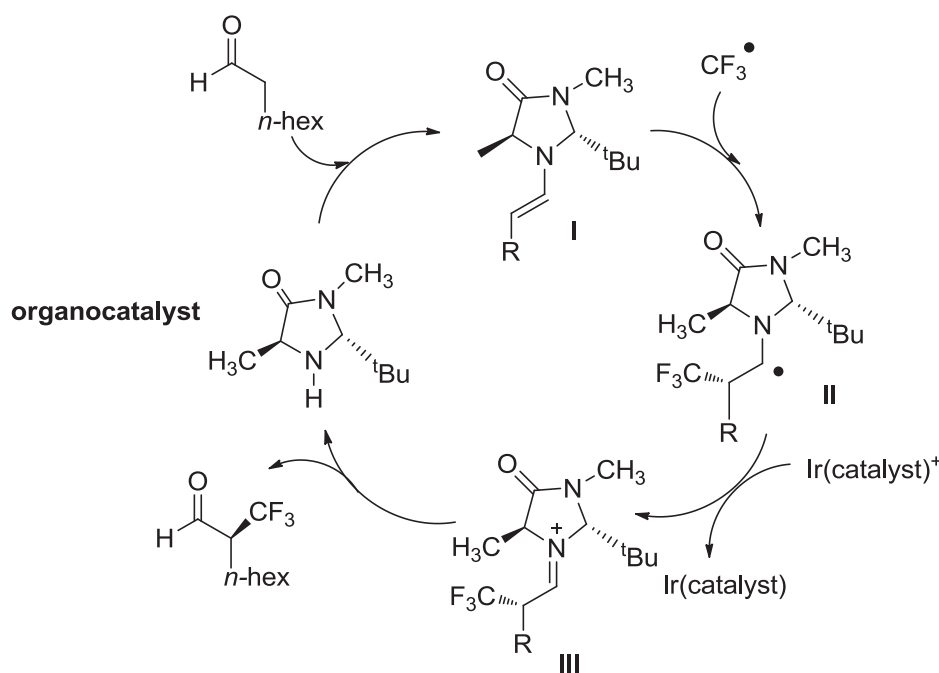
Zakarian and collaborators [59] have recently developed a Ru-catalyzed direct trifluoromethylation and perfluoroalkylation of *N*-acyloxazolidinones by a radical methodology, and high degree of stereocontrol. This method seemed improved with respect to the photocatalytic method developed by MacMillan (Scheme 21),



**Scheme 19.** Atom transfer radical addition of  $\text{CF}_3\text{I}$  to alkenes catalyzed by  $[\text{Ru}_3(\text{CO})_{12}]$  (Ref. [11]).

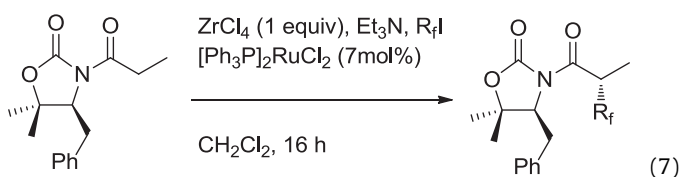


**Scheme 20.** Enantioselective  $\alpha$ -perfluoroalkylation of aldehydes (Ref. [36]).



**Scheme 21.** Catalytic cycle for the trifluoromethylation of aldehydes using an Ir complex (Ref. [11]).

and employs zirconium enolates. This method proves the formation of soft enolization (Zr) intermediates, which readily accept perfluoroalkyl radicals. Thus, *N*-acyl oxazolidinones obtained from unfunctionalized alkanolic acids undergo efficient and diastereoselective trifluoromethylation, with yields increasing for  $\beta$ -branched substrates, according to Eq. (7).

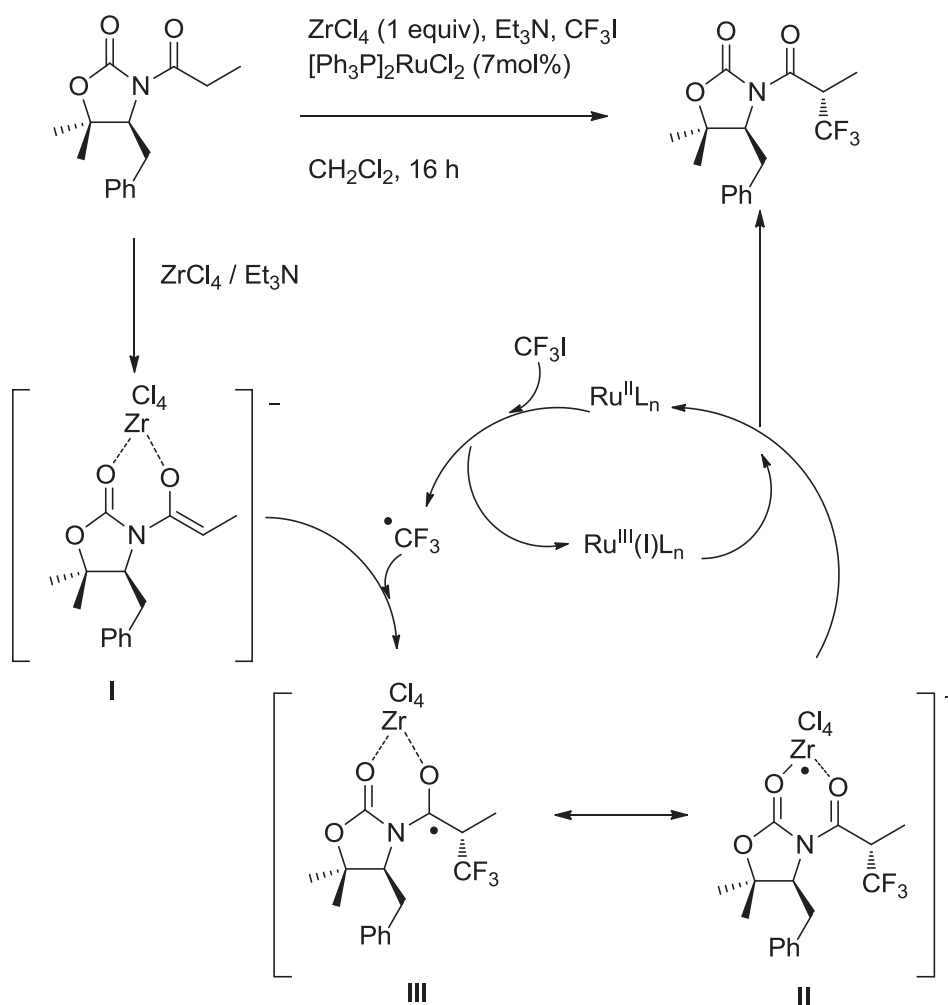


The proposed mechanism of the reaction is based on related Ru-catalyzed trichloromethylations [60] and involves an enolate formation confirmed by NMR studies using *N*-propionyl oxazolidinone,  $\text{ZrCl}_4$  and  $\text{CDCl}_3$ , according to Scheme 22. This enolate **I** (Scheme 22) undergoes an addition reaction with trifluoromethyl radicals generated by a redox process from iodotrifluoromethane and ruthenium (II) catalyst. The addition product is well represented by a resonance form **II** (Scheme 22) rather than a carbon-centered form **III**, and a potential biradical character of **I**

may facilitate the addition of  $\text{CF}_3$  radical. The ruthenium catalyst is recovered by a single electron transfer from intermediate **II** to Ru(III) species (Scheme 22).

Burton and collaborators [61] have accomplished the addition of perfluoroalkyl iodides to alkenes and alkynes in the presence of low-valent titanium catalyst generated *in situ* from  $\text{TiCl}_4$  and Zn, in dimethoxyethane as solvent. The reaction is postulated to occur through an ET process which generates the  $\text{R}_f$  radicals which add to the multiple bonds to form radical adducts that finally abstract iodine from  $\text{R}_f\text{I}$  to generate the ATRA product. In this paper, mechanistic evidence is supplied by conducting the reactions in the presence of *p*-DNB and galvinoxyl, and observing low yields of reaction, purporting the presence of radicals and radical anion intermediates [61].

Zakarian and collaborators [62] have also employed titanium enolates under ruthenium mediation to achieve the trichloromethylation of *N*-acyloxazolidinones, under a dual Ti-Ru catalysis. The mechanism proposed for the trichloromethylation is similar to that of Scheme 22 where  $\text{TiCl}_4$  is used instead  $\text{ZrCl}_4$ , and the trichloromethylated products are obtained with diastereoselectivity higher than 99:1. In another report [60], the leading author and colleagues described a practical method for highly



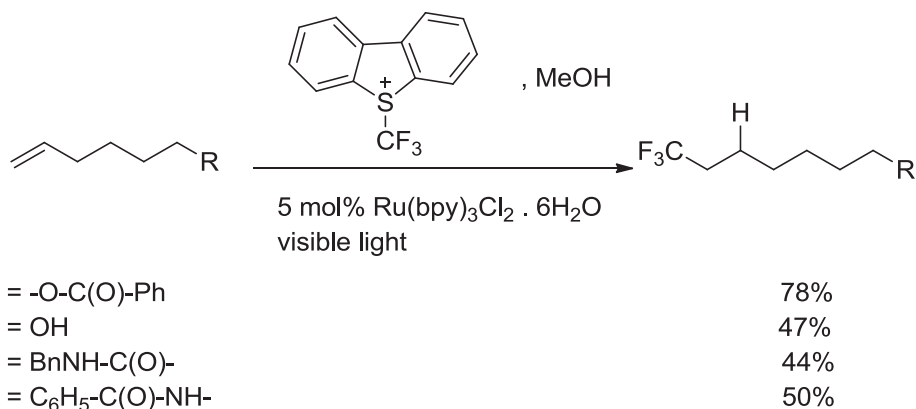
**Scheme 22.** Proposed mechanism of the trifluoromethylation reaction of Ru-catalyzed zirconium enolates from *N*-propionyl oxazolidinones (Ref. [59]).

stereoselective direct chloroalkylation of titanium enolates and its application in the total synthesis of neodysidenin that could be extended to the synthesis of other bioactive natural products of that class.

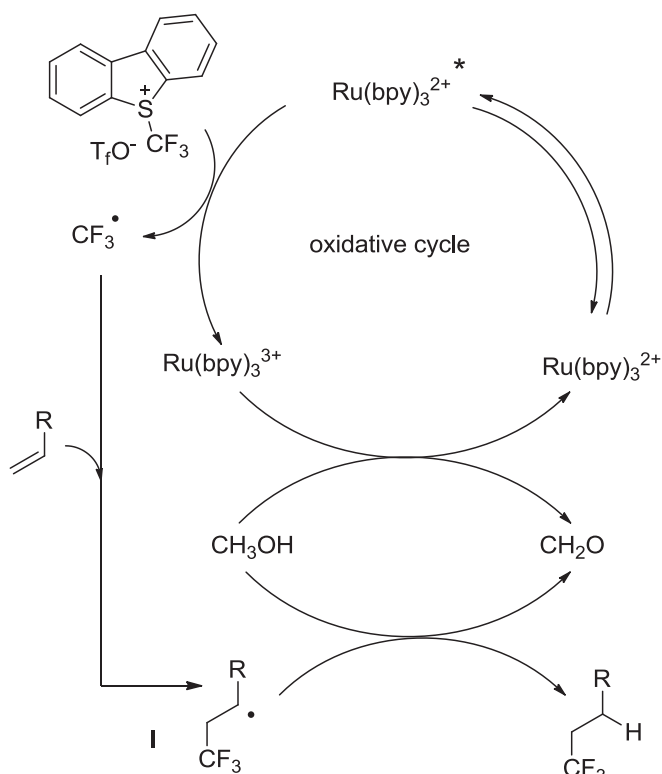
Another recent reaction employing a photocatalyst of Ru and visible light has been studied by Gouverneur and collaborators [63]. Thus, unactivated alkenes were hydrotrifluoromethylated in reasonable yields employing the Umemoto reagent

(*S*-(trifluoromethyl)diphenylsulfonium triflate) as the  $\text{CF}_3$  radical source, and methanol as the hydrogen donor. A wide range of substrates and functional groups were tolerated, including esters, unprotected and protected alcohols, protected amines, amides, imines, carbamates, enones, and oxazolidinones. The reaction is depicted in Scheme 23.

The visible-light excited  $\text{Ru}(\text{bpy})_3^{2+}$  photocatalyst reduced the Umemoto reagent (Scheme 24) to  $\text{CF}_3$  radicals (and



**Scheme 23.** Hydrotrifluoromethylation of unactivated alkenes (Ref. [63]).



**Scheme 24.** Proposed mechanism for the hydrotrifluoromethylation of carbon–carbon multiple bonds (Ref. [63]).

dibenzothiophene), which in turn add to the carbon–carbon double bond to generate the radical adduct of the addition product (**I**, Scheme 24). This radical adduct abstracts a H atom from methanol, to generate the hydrotrifluoromethylated product, and formaldehyde [63]. The mechanism proposed implies that SET reduction of the Umemoto reagent is concurrent with oxidation of the  $[\text{Ru}(\text{bpy})_3^{2+}]^*$  to  $\text{Ru}(\text{bpy})_3^{3+}$  (Scheme 24). Deuterium isotope effects demonstrate that the H atom arises indeed from the C–H bond of methanol.

Cho and collaborators have recently accomplished the radical-based trifluoromethylation of unactivated alkenes by visible light photoredox catalysis that shows a broad scope of high *E/Z*

selectivity [64]. Thus, they attempted the trifluoromethylation of alkenes containing a range of functional groups, including unprotected alcohol, aldehydes, ketones, esters, carbamates, amides, silyl ethers, sulfonates, etc., according to Scheme 25.

The authors [64] noted that although the reactions of terminal alkenes are regio- and stereoselective, those of internal alkenes generated a mixture of isomers. The authors proposed a mechanism where through the intervention of the base DBU, a SET takes place between the excited catalyst and the base, which in the presence of  $\text{CF}_3\text{I}$ ,  $\text{CF}_3$  radicals are generated, according to Scheme 26.

Radicals  $\text{CF}_3$  add to the terminal alkene to give radical adduct **I** (Scheme 26), which can either suffer a HAT to render product **II** or else be oxidized to carbocation species **III**. Product **II** can undergo a HI-based elimination to afford end-product **IV** (Scheme 26).

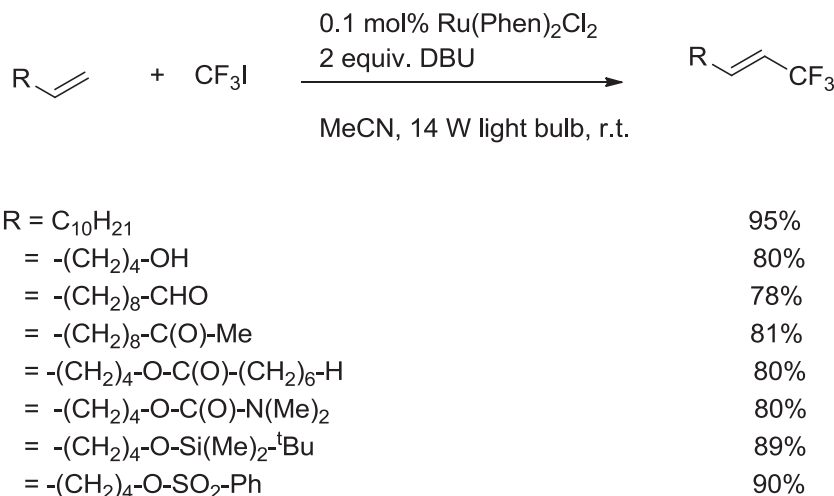
The photocatalytic strategy developed by MacMillan [36] and Cho [64] achieves trifluoromethylation reactions of aldehydes and alkenes in fairly good yields. This methodology is very convenient since the photocatalyst is re-generated in the course of the reaction, and can be recycled and re-used in large scale syntheses.

### 3.5. Indium-mediated trifluoromethylation reactions. selenoperfluoroalkylation reactions. Silicon-mediated perfluoroalkylation reactions of alkenes

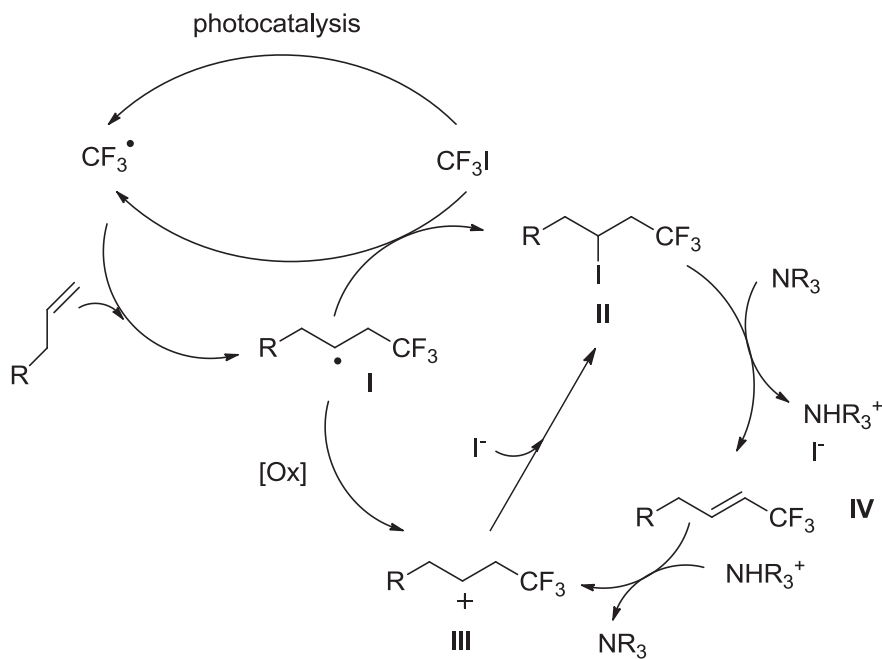
Indium has been demonstrated to be an efficient and promising metal for organic reactions in aqueous media [65]. Indium has recently been used as an ET agent in the perfluoroalkylation of aromatic aldehydes in DMF as solvent employing iodoperfluoroalkanes [66]. Some additives such as LiCl or LiBr are used to increase the reaction yields.

Aldehydes undergo perfluoroalkylation with the use of In reagents and perfluoroalkyl iodides by using 1 equiv. of indium, lithium chloride or sodium iodide, and ferrocene [66]. The reaction is depicted in Scheme 27.

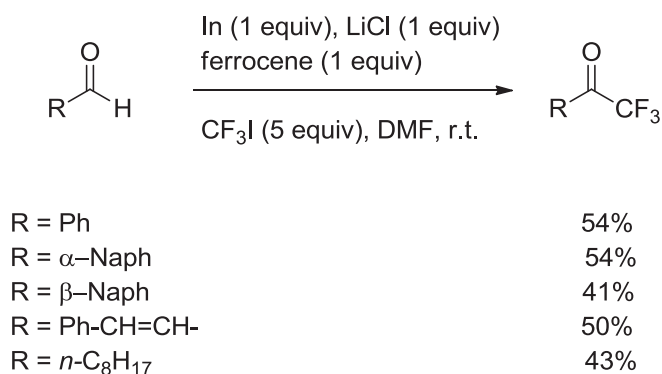
Under the optimized conditions there was no significant difference between iodide and bromide reagents in the perfluoroalkylation reaction. Perfluoroalkyl iodides afforded a higher chemical yield than the corresponding bromides. However, trifluoromethylation with  $\text{CF}_3\text{I}$  yielded no adduct whereas  $\text{CF}_3\text{Br}$  gave up to 60% yield of the trifluoromethylation product derived from benzaldehyde in DMF as solvent. This can be attributed to a SET from In to  $\text{CF}_3\text{Br}$ . The second step of the mechanism involves subsequent SET from  $\text{In}^1$  to the radical anion of  $\text{CF}_3\text{X}$  to afford the



**Scheme 25.** Ru-catalyzed trifluoromethylation of terminal alkenes (Ref. [64]).



**Scheme 26.** Proposed mechanism for the alkenyl trifluoromethylation (Ref. [64]).



**Scheme 27.** Trifluoromethylation of aldehydes with In (Ref. [67]).

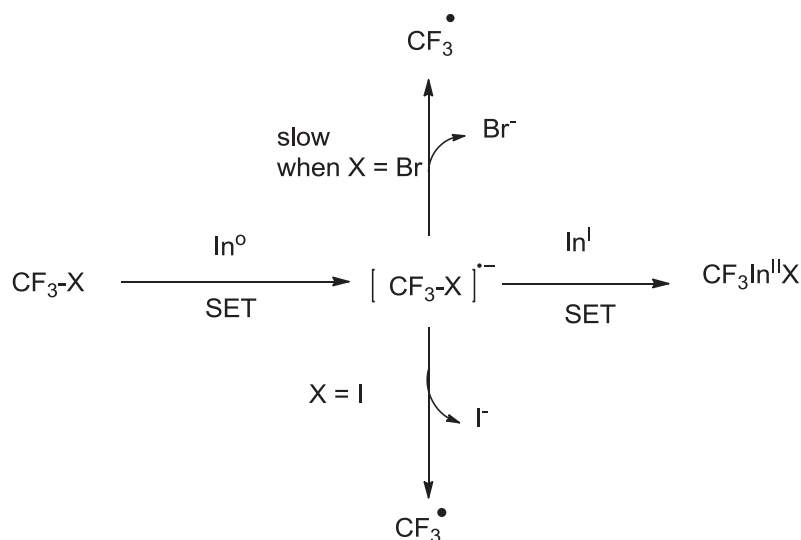
trifluoromethyl indium(II) species, according to [Scheme 28](#). Due to the dissociative nature of the  $\text{CF}_3\text{I}^{\bullet-}$  radical anion prior to the second SET, this results in the formation of trifluoromethyl radical and the Wurtz coupling product [66].

Thus, several aldehydes, such as naphthyl, cinnamic, and aliphatic aldehydes were trifluoromethylated with a combination of In, LiCl, ferrocene, and  $\text{CF}_3\text{I}$  [66].

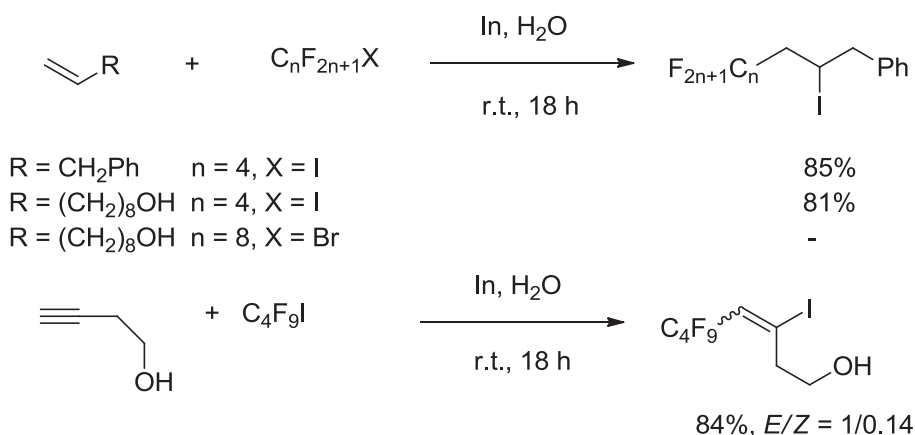
Takagi and collaborators [68] have accomplished the radical, indium-mediated perfluoroalkylation reaction of alkenes and alkynes in water. The reaction is a HAT sequence ([Scheme 29](#)) where an iodo-perfluoroalkylated compound is obtained.

The SET properties of In enables the radical initiation of the perfluoroalkylation reactions of both aldehydes and carbon–carbon multiple bonds.

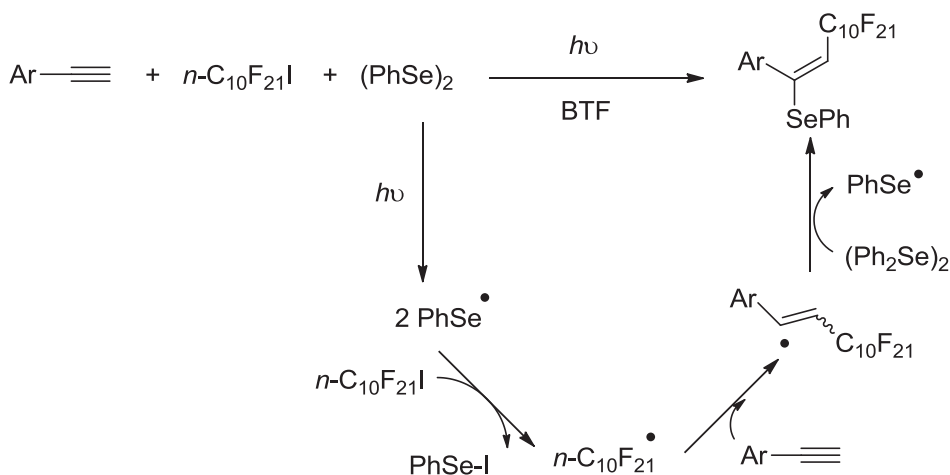
Ogawa and collaborators have developed a selenoperfluoroalkylation reaction of terminal alkynes [69] using the readily available



**Scheme 28.** Formation of the  $\text{CF}_3\text{In(II)X}$  intermediate in the trifluoromethylation of aromatic aldehydes (Ref. [67]).



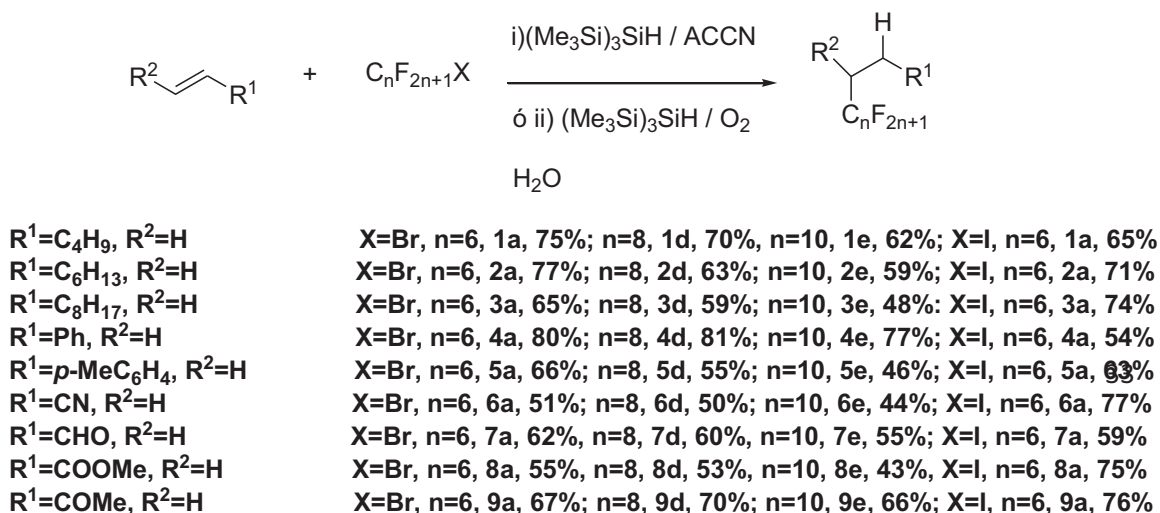
**Scheme 29.** Perfluoroalkylation of alkenes and alkynes in water, mediated by In (Ref. [68]).



**Scheme 30.** Mechanism for the selenoperfluoroalkylation of terminal alkynes in benzotrifluoride (BTF) as solvent (Ref. [69]).

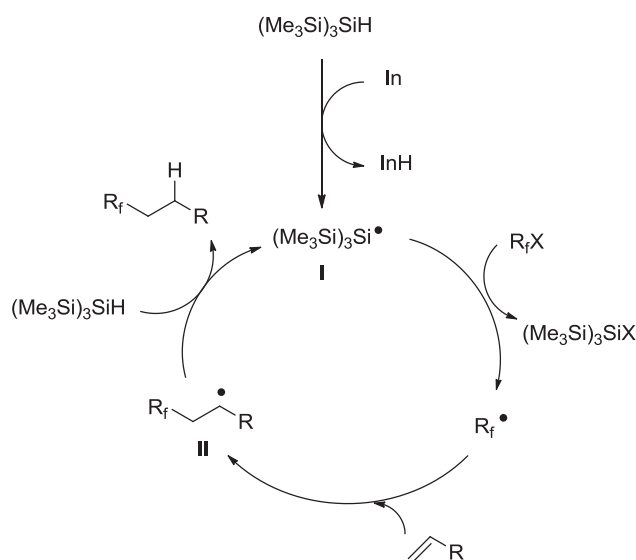
PhSe radicals from homolytic dissociation of PhSeSePh induced by photolysis. These PhSe radicals abstract iodine atom from  $n\text{-C}_{10}\text{F}_{21}\text{I}$  to afford perfluoroalkyl radicals that add to carbon–carbon multiple bonds, according to Scheme 30.

Barata-Vallejo and Postigo have accomplished the silane-mediated radical perfluoroalkylation reaction of activated and unactivated alkenes (Scheme 31) in water as solvent [70]. The radical sequence of the reaction is initiated by either



**Scheme 31.**  $(\text{Me}_3\text{Si})_3\text{SiH}$ -mediated radical perfluoroalkylation of aliphatic substrates in water (Ref. [70]).





**Scheme 32.** Mechanism for the perfluoroalkylation reaction of alkenes mediated by silanes (Ref. [70]).

1,1'-azobis(cyclohexanecarbonitrile) (ACCN) or oxygen. Both perfluoroalkyl iodides and bromides are used in the radical perfluoroalkylation reactions (Scheme 31). The mechanism of the reaction is depicted in Scheme 32.

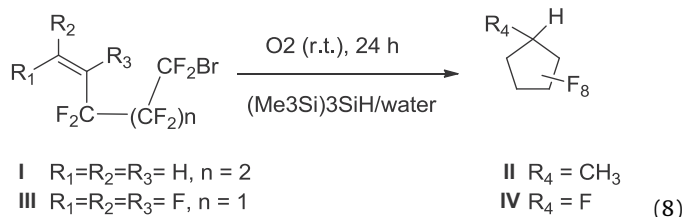
According to the mechanistic proposal of Scheme 32, silyl radicals **I** are generated from  $(\text{Me}_3\text{Si})_3\text{SiH}$  through some initiation method (ACCN or oxygen). These silyl radicals **I** abstract the halogen atoms from the perfluoroalkyl halides  $\text{R}_f\text{X}$ , to generate perfluoroalkyl radicals  $\text{R}_f^\bullet$  which add to the carbon–carbon double bond to afford a radical adduct intermediate **II**, which, in turn, abstracts a H atom from the silane, regenerating silyl radicals and propagating the chain. The mechanistic proposal was substantiated through the use of several radical probes, such as the radical cyclization/addition product derived from diallyl ether [70].

When 3,3,4,4-tetrafluoro-1,5-hexadiene is allowed to react in water with  $(\text{Me}_3\text{Si})_3\text{SiH}$ /dioxygen and  $\text{C}_2\text{F}_5\text{I}$ , the product in Scheme 33 is obtained in 61% yield (the 4-*exo* cyclization product), based on  $\text{C}_2\text{F}_5\text{I}$  [71,72].

This is a notorious example of the influence of water on radical cyclization reactions. Though cyclobutane is an uphill process due to considerable strain in ring formation, Dolbier [73] found

that fluorinated cyclobutanes appear to be less strained than their hydrocarbon counterparts and that fluorinated 4-pentenyl radicals **R1** (Scheme 33) cyclize both in a favored kinetic and thermodynamic manner [72]. The question why 4-pentenyl radical **R1** (Scheme 33) prefers to cyclize in an *exo* fashion to render the four-membered ring product in water is not yet clear, though the result points to a favored transition state stabilized by water molecules, unlike organic media.

In another account, 6-bromo-3,3,4,4,5,5,6,6-octafluoro-1-hexene **I** (Eq. (8)) [71] is subjected to reaction with  $(\text{Me}_3\text{Si})_3\text{SiH}$  and dioxygen as initiator in water, the *exo-trig* cyclization product 1,1,2,2,3,3,4,4-octafluoro-5-methylcyclopentane **II** (Eq. (8)) is obtained in 76% isolated yield [72,74].

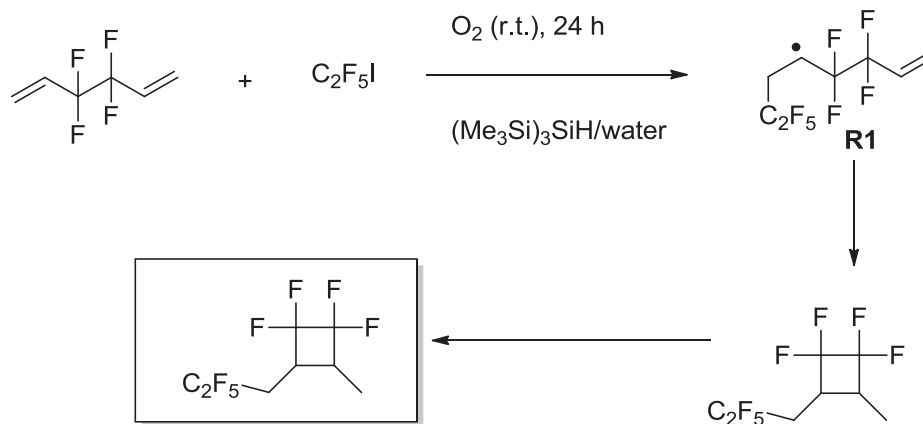


Though the measurement of the rate constants for cyclization in the heterogeneous water system is difficult to be obtained, the cyclohexane-cyclized product has not been observed in water under the reaction conditions reported. No uncyclized-reduced product is either observed [71,72a].

Analogously, cyclization of 5-bromo-1,1,2,3,3,4,4,5,5-nonafluoro-pent-1-ene **III** (Eq. (8)) in water triggered by  $(\text{Me}_3\text{Si})_3\text{SiH}$  and dioxygen leads to nonafluorocyclopentane, the *endo-trig* cyclization product **IV** (Eq. (8)) in 68% yield. The reaction carried out in organic solvent does not lead to cyclization product [71,72a]. These silicon-mediated cyclization reactions of perfluoroalkenes are facile processes initiated by a radical mechanism efficiently accomplished in water as solvent.

#### 4. Concluding remarks

Radical perfluoroalkylation and trifluoromethylation reactions of both aliphatic and aromatic substrates can be efficiently conducted through the aid of metals (transition metals, or main-group metals) which prove to enhance scope, regioselectivity, and stereoselectivity of the perfluoroalkyl radical addition and substitution reactions as compared to the same metal-mediated reactions carried out by polar mechanisms. Recent examples are given where through the redox properties of metal complexes or stand-alone



**Scheme 33.**  $(\text{Me}_3\text{Si})_3\text{SiH}$ -mediated perfluoroalkyl-substituted cyclobutanes in water (Ref. [72]).

metals, facile electron transfer events can operate to generate perfluoroalkyl and trifluoromethyl radicals, ensuing addition or substitution products. The sources of these fluoroalkylating radicals can be varied, and encompass putative perfluoroalkyl halides, the Ruppert-Prakash reagent, the Langlois reagent, Umemoto's, Togni's, and Baran's reagents. Very interesting examples regarding Zn complexes or perfluoroalkylsulfinate zinc salts are illustrated in aqueous media for the perfluoroalkylation reactions of numerous biological interesting substrates. Among the advantages of performing radical perfluoroalkylation reactions in the presence of metallic species, the following can be outlined:

- (i) The trifluoromethylation of arylboronic acids through the Umemoto reagent *S*-(trifluoromethyl)diarylsulfonium salt) in the presence of Cu does not necessitate the presence of ligands in the Cu catalysis, and is able to substitute aryl boronic acids bearing electron withdrawing groups with CF<sub>3</sub> substituents under radical conditions, where the polar methodology fails to do so.
- (ii) The combination of AgOTf, KF, and TMSCF<sub>3</sub> can be used for the C–H trifluoromethylation (by S<sub>H</sub>Ar) of aromatic substrates under mild conditions, generating CF<sub>3</sub>-substituted arenes regioselectively by a radical methodology. Utilization of the Ruppert-Prakash (TMSCF<sub>3</sub>) reagent on haloarenes by polar mechanisms is not regioselective, and the S<sub>H</sub>Ar of the ring cannot be achieved.
- (iii) The Baran reagent (Zn(SO<sub>2</sub>R<sub>F</sub>)<sub>2</sub>) is able to accomplish trifluoromethylation, difluoromethylation and perfluoroalkylation reactions of a large number of arenes, heteroarenes, and pharmacophore precursors in very high yields and regioselectivity. These transformations are achieved through radical pathways under mild radical initiation conditions in aqueous media, and surpass all other perfluoroalkylation reagents thus far proposed, thus enhancing the armamentarium of radical transformations available to chemists. The Baran reagent is always used under radical conditions and fails to operate by polar mechanism.
- (iv) The utilization of the Togni reagent in the presence of Cu can achieve oxytrifluoromethylation of unactivated alkenes, rendering a myriad of oxygen-containing rings with trifluoromethyl appendices by a radical mechanism where polar transformations cannot do so.
- (v) The employment of the Togni reagent in the presence of Cu with allylic alcohols gives rise to 3-trifluoromethyl-substituted-1,2-epoxides; these latter considered versatile intermediates that cannot be synthesized by a Cu-promoted polar trifluoromethylation reaction.
- (vi) The radical addition/cyclization protocol of allene-enes catalyzed by Zn renders selective formation of *exo*-cyclization products that cannot be achieved by polar mechanisms.
- (vii) Radical perfluoroalkylation and trifluoromethylation reactions through the employment of photocatalysts (*i.e.* Ru, Ir) have opened up strategies for large and industrial scale trifluoromethyl group substitution and addition reactions. The use of photocatalysts warrants a radical mechanism in operation, where the photocatalyst is regenerated in the process and can be re-used.
- (viii) The consecutive radical perfluoroalkylation of olefins in water mediated by silanes has broadened the synthetic methodologies for achieving hydroperfluoroalkylated alkanes and cycloalkanes in a consecutive manner. The perfluoroalkyl-substituted rings thus obtained cannot be synthesized by a polar pathway.

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