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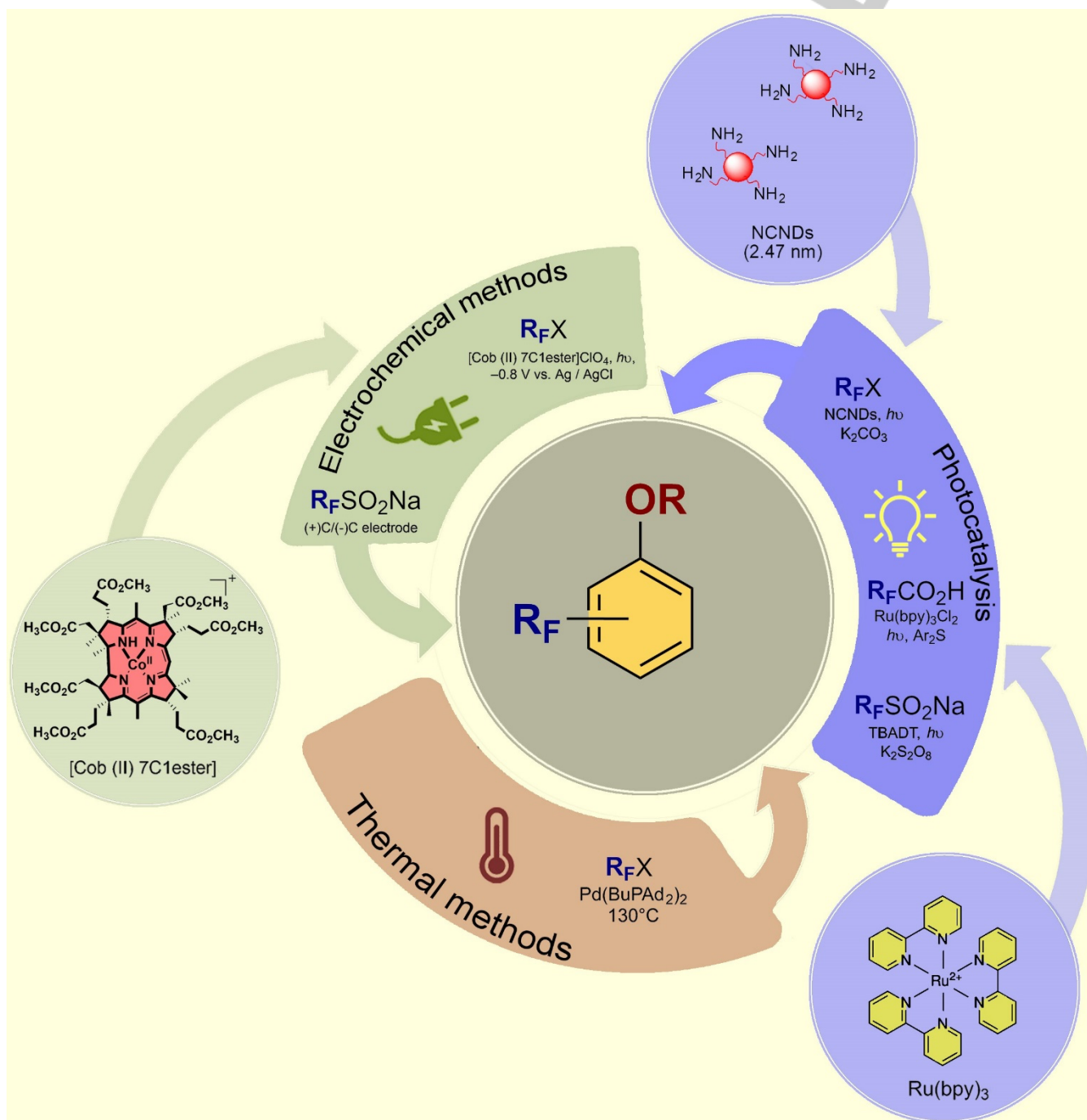
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Catalytic Fluoroalkylation Reactions of Alcoxy-subtituted (Hetero)Arenes

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Catalytic Fluoroalkylation Reactions of Alcoxy-subtituted (Hetero)Arenes

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Abstract: Electron-rich alcoxy-substituted (hetero)arenes and electrophilic fluoroalkyl moieties represent advantageous partners for substitution reactions due to their electronic match. Fluoroalkylation strategies of alcoxy-substituted (hetero)arenes are herein presented which depict photocatalytic and thermal methods. Photocatalytic methods rely on the use of diverse photocatalysts such as $Ru(bpy)_3Cl_2$, tetrabutylammonium decatungstate TBADT, N-doped carbon nanodots NCNDs, and vitamin derivatives which can partner with the Langlois reagent $NaSO_2CF_3$, CF_3CO_2H, and perfluoroalkyl iodides R_F-I as fluoroalkylating reagents. Also, electrocatalytic methods that make use of the cathodic reduction of CF_3SO_2Cl to generate CF_3 radicals can achieve trifluoromethylation reactions of alcoxy-substituted (hetero)arenes. On the other hand, thermal methodologies comprising $Pd(OAc)_2$ catalysis and using CF_3Br as trifluoromethylating source have been implemented.

1. Introduction

Alcoxy-substituted (hetero)arenes have found multiple applications in medicinal chemistry. Methoxy groups, in particular, are potential contributors to the antimetastatic effects of many drugs.[1] For instance, the inhibitors of the tubulin polymerization Colchine[2] and Combrestatin A-4 (Figure 1), or the seven-membered lactone rings[3] (Figure 1) with broad antiproliferative activity. The 4-anilino quinazoline derivative N´-(6,7-dimethoxy-2-methylquinazolin-4-yl)benzene-1,4-diamine (upper right, Figure 1), which targets the inhibition of the epidermal growth factor receptor (EGFR) by regulating cell proliferation, relies on its methoxy groups for an increased inhibitory activity.[1] Several alcoxy-substituted (hetero)arenes decorated with fluorine or fluoroalkyl groups are known or beginning to show a relevant enhancement in pharmacological activity, such as the commercial antidepressant Prozac; tafenoquine,[4] a medication used to prevent and to treat malaria, or fostamatinib (Figure 1),[5] a tyrosine kinase inhibitor medication for the treatment of chronic immune thrombocytopenia.
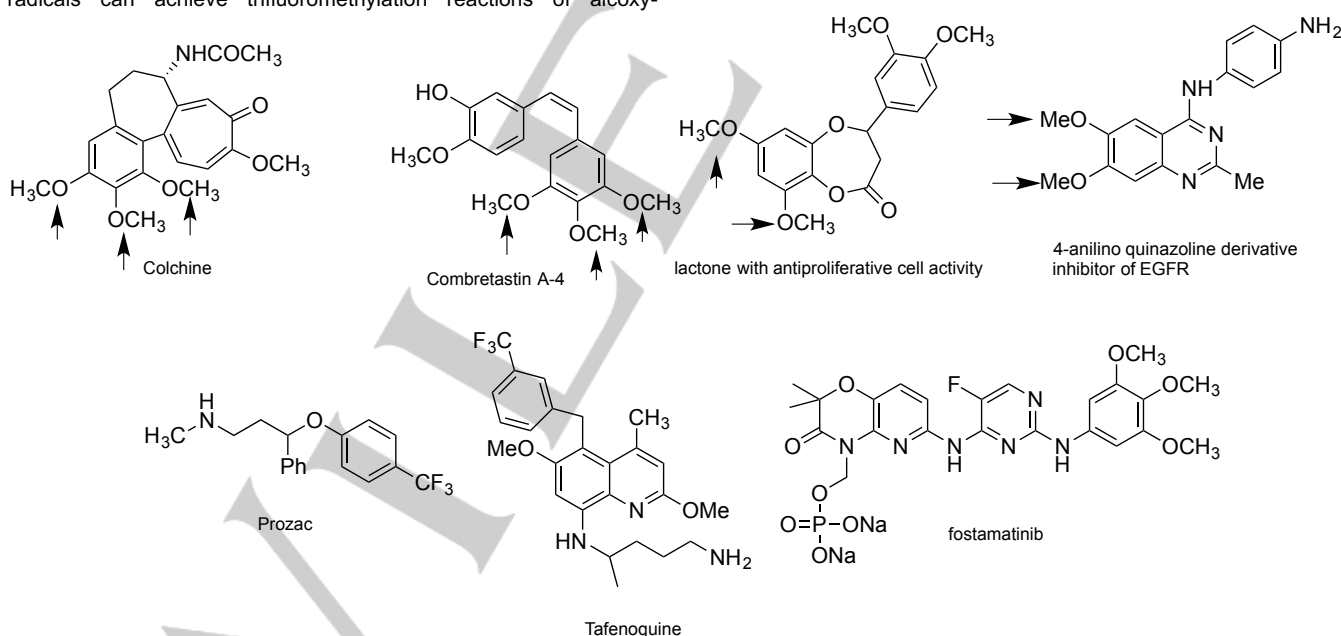

Figure 1. Bioactive compounds and commercial drugs bearing alcoxy groups. Arrows indicate the alcoxy groups crucial for the activity

Many of these drugs and drug candidates rely on the methoxy substituents as powerful electron-donating groups on their scaffolds to sustain high spin density framework areas for their activity.[1,6a]

On the other hand, fluoroalkyl substitution on compounds with already-known biological or pharmacological activity is known to impart enhanced bioavailability, resistance to oxidation and better membrane-permeability, which are all caused by the distinctive physicochemical properties of fluoroalkyl R_F substitution. The introduction of these fluoroalkyl R_F groups late

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in the reaction synthetic sequence is therefore a sought-after strategy. Consequently, the investigation of fluoroalkylation strategies on alcoxy-substituted (hetero)arenes becomes an enticing target for structure-activity relationship studies.

Although there are general fluoroalkylation strategies of (hetero)arenes that contemplate some alcoxy-substituted substrates among their substrate scope,[6b-d] special reports on this particular class of compounds have only been investigated in depth by few authors and will be herein discussed.

In the next sections, a study of the different methodologies for fluoroalkylation[6e,f] reactions of methoxy-substituted (hetero)arene derivatives is conducted, with emphasis on their reaction mechanisms, in order to show the different approaches undertaken by the authors to attain substitution of these compounds with R_F groups. At the end of the manuscript, a comparison between the different strategies will be exposed and critically analyzed.

Damian E. Yerien was born in Argentina and obtained his Biochemistry degree from University of Buenos Aires in 2014. He obtained his Ph.D. degree (2019) at the University of Buenos Aires studying synthetic and mechanistic aspects of radical perfluoroalkylation reactions through photoredox catalysis, under the direction of Prof. Dr. Al Postigo. He is currently a National Argentine Research Council postdoctoral scholarship holder and a Teaching Assistant at the Department of Chemical Sciences, Faculty of Pharmacy and Biochemistry, University of Buenos Aires..

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particular carbon- and sulfur-centered radicals reactivity, fluoroalkylation reactions by radical pathways and photocatalysis. .

Al Postigo was born in Argentina and obtained his M.Sc. degree from the University of Buenos Aires in 1986. He moved to Canada in 1990, and obtained his Ph.D. from McMaster University in 1994, under the direction of Prof. Dr. W. J. Leigh. After postdoctoral positions in Canada, he returned to Argentina and worked with Prof. Dr. R. Rossi at the University of Córdoba in the area of radical ion reactions. He held assistant and associate professorship positions at the University of Córdoba, University of Buenos Aires, and University of Belgrano. He is currently full professor of Organic Chemistry at the Department of Chemical Sciences, Faculty of Pharmacy and Biochemistry, University of Buenos Aires. His interests are in the areas of radical chemistry, both carbon-centered radicals and metal-centered radicals. He is devoted to studying radical reactions of these species in water and non-conventional media. .

2. Discussion

2.1. Photocatalytic Methods

Córsico and Ravelli[7a] have informed the trifluoromethylation of alcoxy-substituted (hetero)arenes employing tetrabutylammonium decatungstate (TBADT) as photocatalyst, the Langlois reagent ($NaSO_2CF_3$) as source of CF_3 radicals in the presence of $K_2S_2O_8$ as oxidant, in MeCN : water mixture, irradiating with a solar lamp (Scheme 1).
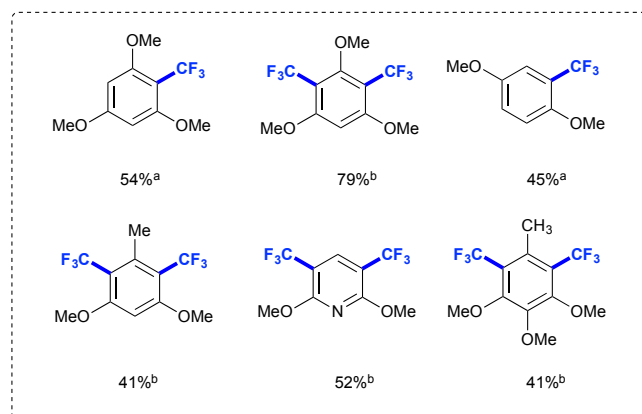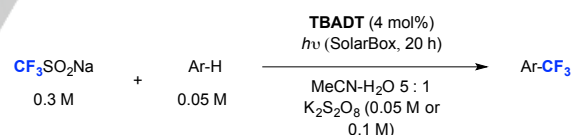

a.-Reaction Conditions use 0.05 M of K2S2O8. 4 hour-reaction. b.-Reaction Conditions use 0.1 M of K2S2O8 20-h reaction.

Scheme 1. Selected examples for trifluoromethylation of alcoxy-substituted (hetero)arenes

As observed from Scheme 1, when 0.05 M of $K_2S_2O_8$ as oxidant is used, the mono-substituted products derived from 1,3,5-trimethoxybenzene is obtained. Di-substituted products are obtained when $K_2S_2O_8$ is used in 0.1 M concentration.

The authors[7a] inspected the reaction pathway and proposed the following mechanism, illustrated in Scheme 2.
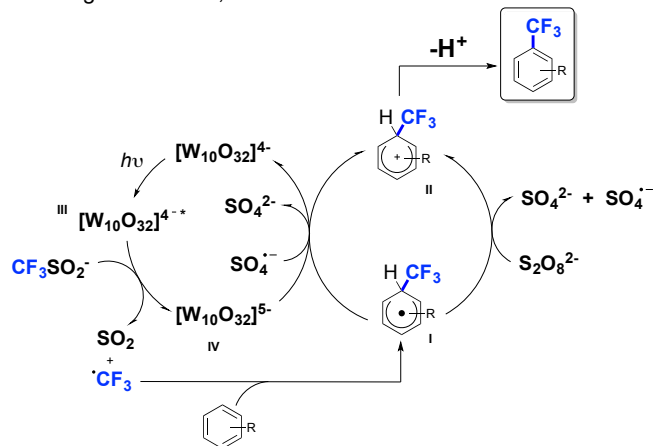
Scheme 2. Proposed reaction mechanism

The highly positive reduction potential of excited TBADT [E_{red}(TBADT*) = E_{red} (TBADT) + E_{exc} = 2.26 to 2.61 V vs. SCE] [7b] makes the ET process conceivable, and turns TBADT into a highly oxidizing species in its excited state (the oxidation potential of the Langlois reagent is instead 1.05 V vs SCE [7c]). Visible light-excited tetrabutylammonium decatungstate (TBADT)* (**III**, Scheme 2) oxidizes the Langlois reagent to CF_3 radicals (and SO_2). CF_3 radicals substitute the arene ring giving the cyclohexadienyl-substituted radical intermediate **I**, which is oxidized by sulfate radical anion to give the Wheland intermediate **II** that gets deprotonated to render the final product and sulfate anion. The reduced photocatalyst **IV** is oxidized to its photoactive state through oxidation with $K_2S_2O_8$ or the sufate radical anion. The strong oxidizing properties of TBADT* warrants oxidation of the Langlois reagent.

Rosso, Filippini and Prato[8a] have come up with a perfluoroalkylation reaction of methoxy-substituted arenes in the presence of N-doped carbon nanodots (CND) by microwave-assisted hydrothermal synthesis from arginine (Arg) and ethylenediamine, according to Figure 2.
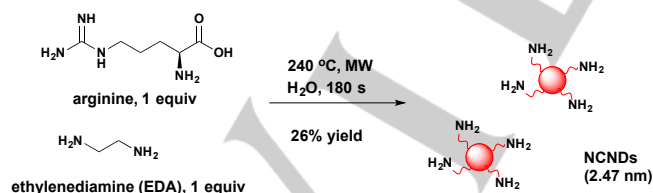

**Figure 2**. Synthesis of NCNDs (70–110 psi, 200 W)

The irradiation source was a light-emitting diode (LED, λ = 395 nm) strip, at ambient temperature, in DMF as solvent. The best reaction conditions obtained by the authors[8] consisted in using NCNDs (0.7 w/v), K_2CO_3 as base (1 equiv), perfluoroalkyl iodide R_F-I (6 equiv) in DMF (0.26 M) as solvent. The scope of the transformation is depicted in Scheme 3.
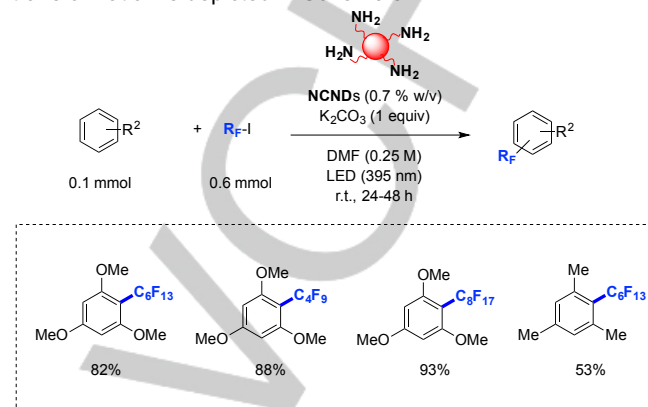
Scheme 3. Selected examples for the perfluoroalkylation of methoxy and methyl-substituted benzenes

The authors[8a] studied the reaction mechanism. Exclusion of light inhibited the reaction completely. In the absence of NCNDs, no reaction took place. Irradiation at 525 nm wavelength (wavelength where the photocatalyst NCNDs does not absorb) did not produce any fluorinated product. The presence of oxygen, or 2,2,6,6-Tetramethylpiperidine 1-oxyl (TEMPO), inhibited product formation, purporting to the radical nature of the reaction. The halogen-bonding character of the amino groups from NCNDs to promote the formation of electron-donor acceptor complexes (EDA complexes) was confirmed when using nBu-NH_2 as acceptor in the formation of halogen-bonded derivatives with R_F-I. Based on the above-mentioned experiments, the authors[8a] proposed the reaction mechanism illustrated in Scheme 4. Upon contact of R_F-I with NCNDs, an EDA complex **I** is formed (Scheme 4). This complex **I** is activated by light ensuing an ET between NCNDs and R_F-I (**II**, Scheme 4, redox potential of the excited NCND is -2.21 V vs SCE, sufficiently negative to reduce C_6F_{13}-I to C_6F_{13} radicals, being the reduction potential of C_6F_{13}-I – 1 V [8b]), affording radical R_F (and iodide anion) and the radical cation of NCNDs (**III**, Scheme 4). Radical R_F effects homolytic aromatic substitution onto the methoxy-substituted arene, giving a substituted cyclohexadienyl radical intermediate **IV**, which, in turn, is oxidized by **III** to carbocation intermediate **V**, which ultimately is deprotonated by the base to yield the R_F-substituted product.

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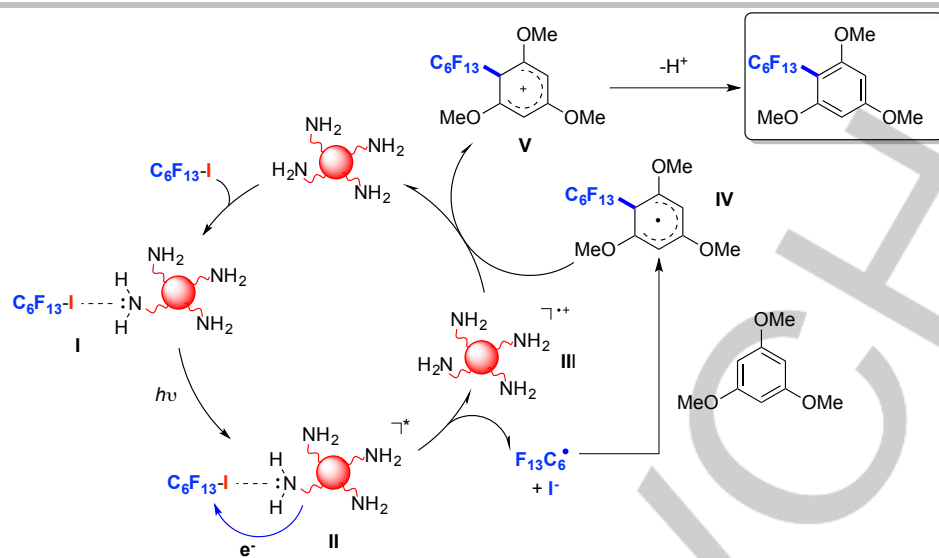
Scheme 4. Proposed reaction mechanism

Different commercial sources of CF_3 radicals are available in the literature, such as the Ruppert Prakash reagent CF_3SiMe_3,[9] the Langlois reagent $NaSO_2CF_3$,[10] CF_3-I, Umemoto´s reagent,[11] Togni´s reagents,[12] etc.

Jin, Yin and colleagues[13] used a diarylsulfoxide activator to produce CF_3 radicals from trifluoroacetic acid TFA through photocatalysis. This source of CF_3 radicals (i.e.: TFA) is rarely used on account of the high oxidation potential of TFA (> 2.5 V vs SCE) to produce the trifluoroacetate radicals. The proposed methodology is illustrated in Scheme 5.
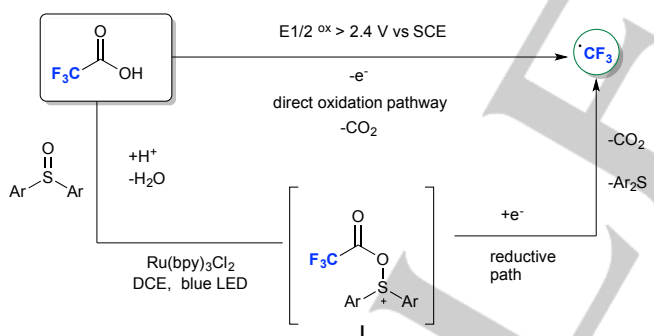
Scheme 5. Photocatalyzed production of CF_3 radicals from TFA

The activator used by the authors[13] was bis(4-chlorophenyl)sulfoxide, which upon oxidative ET from excited $Ru(bpy)_3Cl_2$ afforded intermediate **I** (Scheme 5). Intermediate **I** underwent electron reduction to afford CF_3 radicals, SO_2 and diarylsulfide.

The optimized reaction conditions for the trifluoromethylation or perfluoroalkylation of alcoxy-substituted arenes consisted in the use of 2 equiv of bis(4-chlorophenyl)sulfoxide, 1 mol% of $Ru(bpy)_3Cl_2$ as photocatalyst, dichloroethane DCE as solvent, 2 equivalents of TFA or the respective perfluoroalkylated carboxylic acid, irradiating with 427

nm LEDs. The scope of the transformation is depicted in Scheme 6.

Scheme 6. Selected examples for the perfluoroalkylation of methoxy-substituted (hetero)arenes
   a.-390 nm LED used

Control experiments such as the reactions in the presence of BHT or TEMPO did not form any arene-substituted product, which pointed out to the radical nature of the reaction. This is a

convenient method that allowed for the decarboxylation of trifluoroacetic acid and perfluoroalkykated carboxylic acids to provide the trifluoromethyl radical and the perfluoroalkyl radical,

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respectively, that ensue in homolytic substitution reactions of alcoxy-substituted arenes.

The use of vitamin B12 and its derivatives in catalytic systems in both aqueous and organic media is well documented.[14] Among the vitamin B12 derivatives is heptamethyl cobyrinate perchlorate [Cob (II) 7C1ester] ClO_4 (**1**, Figure 3), which has ester groups instead of peripheral amides present in cobalamin (i.e., vitamin B12). Derivative **1** is soluble in various organic solvents and is used as a catalyst for a wide variety of reactions such as methyl transfer reactions, halide coupling reactions, hydrogenation of C = C and C = X bonds.
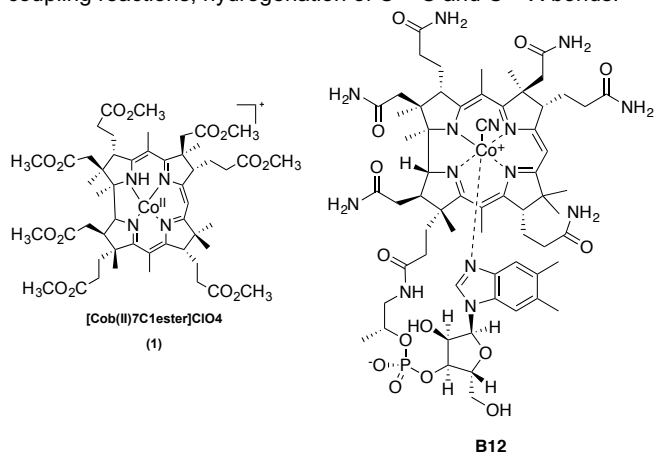
Figure 3. Structures of cobyrinate perchlorate 1 and vitamin B12

Hossain, Ono and Hisaeda[15a] undertook the perfluoroalkylation and trifuoromethylation reactions of methoxy-substituted (hetero)aromatic compounds using a vitamin B12 derivative as catalyst (cobyrinate perchlorate 1). The reactive cobalt (I) species from the vitamin B12 catalyst was prepared through a controlled potential electrolysis at –0.8 V vs. Ag / AgCl in methanol. This species, which reacted with perfluoroalkyl iodides to form Co-R_F complexes, under visible light irradiation released an R_F radical that reacted with (hetero)arenes, obtaining the perfluoroalkylated molecule through direct C-H functionalization.

The authors[15a] used perfluoroalkyl iodides R_F-I to introduce trifluoromethyl and perfluoroalkyl groups into aromatic rings via the formation of a radical intermediate in the presence of heptamethyl cobyrinate perchlorate [Cob (II) 7C1ester]ClO_4 **1** in an electrocatalytic reaction.

The model system was carried out using 1,3,5-trimethoxybenzene with n-C_3F_7-I using an electrochemical method. Cyclic voltammetry showed that the reduction potential of the central cobalt ion (Co(II)/Co(I)) in **1** was –0.61 V vs. Ag/AgCl in methanol. Therefore, –0.6 V vs. Ag/AgCl was used as the initial setup for the controlled potential electrolysis of 1,3,5-trimethoxybenzene using 9 equiv. of n-C_3F_7-I in the presence of 1 mol% of catalyst **1** in methanol as solvent at room temperature under visible light irradiation. Under these conditions, unreacted substrate remained and the perfluoroalkyl product was obtained in rather low yield (20%). A 100% conversion of the substrate was obtained after 9 h, setting the potential at -0.8 V vs. Ag / AgCl, giving the desired product in 84% yield.

Visible light irradiation was essential, as removing the light source only traces of the desired compound were obtained. In the absence of catalyst **1** there was no reaction. The optimized reaction conditions consisted in the use of a 5 x 10^{-2} M solution of

methoxy-substituted substrate, 9 equiv. of R_F-I, 1 mol% of catalyst **1**, at –0.8 V vs. Ag / AgCl (with n-Bu$_4$NClO$_4$ as electrolyte) in the presence of methanol as solvent for 9 h under visible light irradiation at room temperature.

Perfluoroalkylation reactions were carried out on 1,3,5-trimethoxybenzene, 1,4-dimethoxybenzene, 1,3,4-trimethoxybenzene, 1,2-dimethoxybenzene and 3,4-dimethoxytoluene substrates with a variety fluoroalkylating reagents (n-C_nF_{2n+1}-I, n = 1,3,4,6,8,10).

Due to the low solubility of n-$C_{10}F_{21}$-I under electrolysis conditions, the yield of the desired products were very low. Benzenes substituted with OMe / Me groups in different positions were well tolerated and afforded good yields of substitution products (Scheme 7). Moderate yields are obtained when heteroarenes such as 1-phenylpyrrole and 1,2-dimethylindole are used as substrates (not shown).
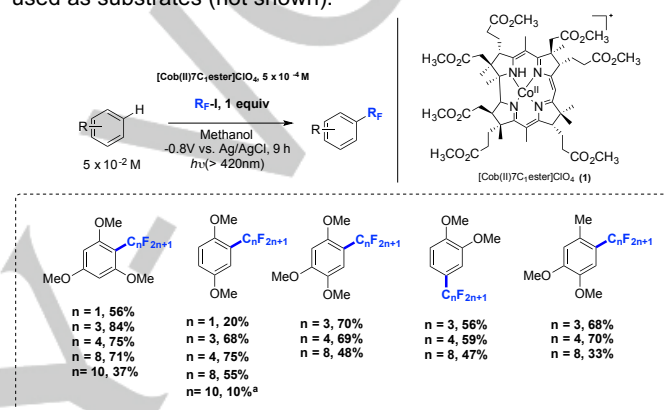

a.- [n-C10F21-I] = 0.33 eq. to substrate per 1.0 hour.

Scheme 7. Selected examples for the perfluoroalkylation of various methoxy-substituted arenes. [1] = 5.0×10^{-4} M; [Substrate] = 5.0×10^{-2} M; [n-C_nF_{2n+1}-I] = 1 eq. to substrate per 1.0 hour; [n-Bu$_4$NClO$_4$] = 0.1 M; Internal standard $C_{12}F_{10}$; under visible light (>420 nm).

Co(I)-species are typically generated *in-situ* by reduction of a stable Co(II)-species through a chemical, electrochemical or photoredox process and can be easily oxidized in the presence of oxygen.[15b] This one-electron reduction process of Co(II) to Co(I) has been profusely studied by means of pulse radiolysis techniques in aqueous solutions by Blackburn and collaborators.[15c] The cobalt ion (i.e., Co(I)) thus formed, which is known as a supernucleophilic species, combines with alkyl (R-X) or perfluoroalkyl halides (R_F-X) to form an (perfluoro)alkyl-cobalt complex (R_F-Co(III)). Visible light irradiation or heat then induces a homolytic cleavage of the carbon-cobalt σ- bond of the alkyl-cobalt complex to form an alkyl radical and Co(II) species. This general reaction mechanism is at the base of the catalytic activity of porphyrin-type and oxime cobalt complexes, along with vitamin B12 derivatives.[15b]

The authors postulated that the trifluoromethylation and perfluoroalkylation reactions proceeded via the formation of an intermediate radical (R_F). Its formation was tested using a radical inhibitor, *N-tert*-butyl-α-phenylnitrone PBN. A dramatic reduction in yield (18%) was observed upon addition of 1 equiv. of PBN to the substrate. This result suggested that the reaction likely involved a radical intermediate. Indeed, a PBN – spin adduct (PBN•C_3F_7) was detected by ESR experiment and GC-MS analysis when n-C_3F_7-I was employed. The authors[15a] proposed

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a mechanism based on experimental evidence as depicted in Scheme 8. The Co (I) species is generated from Co (II) by electrolysis potential controlled at - 0.8 V vs. Ag / AgCl. The Co (III) -R$_F$ complex is formed by the rapid reaction of Co (I) with R$_F$-I. The complex then released an R$_F$ radical under visible light irradiation. Finally, the generated R$_F$ radical reacted with non-activated substrates, such as arenes and heteroarenes, followed by a one-electron oxidation and proton loss to give the desired product (Scheme 8).
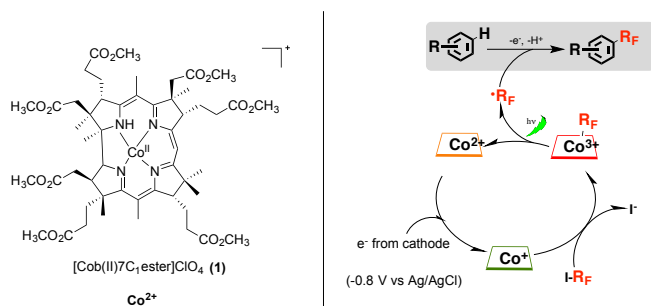
Scheme 8. Expected catalytic cycles of electrolysis for radical fluoroalkylation of aromatic compounds mediated by 1.

2.2. Thermal and Electrochemical Methods

Anodic generation of CF$_3$ radicals has been accomplished in the past using triflinate salts.[16] Heteroarenes were successfully functionalized using the Baran´s reagent Zn(SO$_2$CF$_3$)$_2$ in a divided cell setup by anodic oxidation.[17] However, cathodic generation of R$_F$ radicals is not a common strategy.

Judd, Kappe and Cantilo[18] have reported the electrochemical trifluoromethylation of (hetero)arenes through a cathodic process involving the electron-reduction of a complex between trifluoromethanesufonyl chloride (T$_f$Cl) and triethylamine (complex **I**, Scheme 9). The generation of the electrochemically-active trifluoromethylative complex is depicted in Scheme 9. Species **II** and **III** (Scheme 9) were shown by the authors[18] to be electrochemically unreactive species.
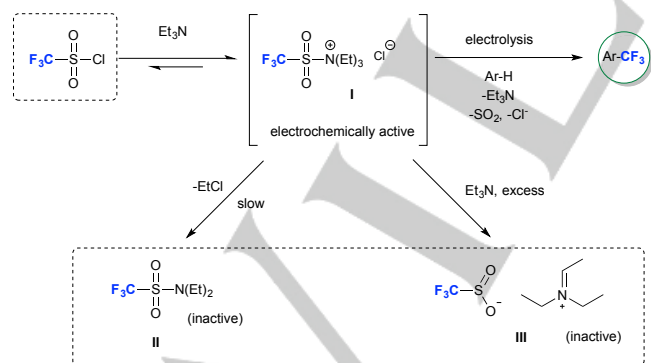
Scheme 9. Generation of electrochemically active trifluoromethyl complex

The optimized reaction conditions for the trifluoromethylation of alcoxy-substituted (hetero)arenes consisted in using a substrate concentration of 0.1 M, 3 equiv. of T$_f$Cl, 2 equiv. of *N,N,N*-triethylamine, 8 F/mol of current, 0.1 M in Et$_4$NBF$_4$ as electrolyte, in MeCN as solvent. As expected, at high conversions, certain amounts (~10%) of the bis-

trifluoromethylated product were also detected for mesityl substrate, which was the substrate employed for optimization of the reaction. The scope of the reaction in relation to the alcoxy-substituted arenes is illustrated in Scheme 10.
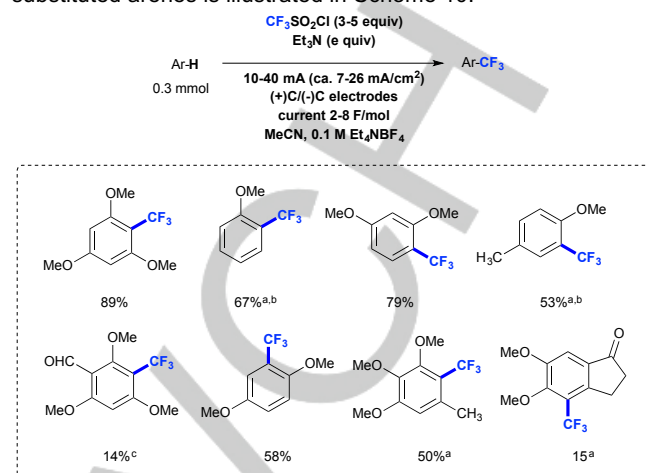
a.- Method A: 0.3 mmol scale, 3 equiv of TfCl, 3 mL of acetonitrile. b.-Obtained as a mixture of isomers. e.-Bis-trifluoromethylation product also obtained. c.- Method B: 0.6 mmol scale, 3 mL of acetonitrile, 5 equiv of TfCl.

Scheme 10. Selected examples for the cathodic electrochemical trifluoromethylation of methoxy-substituted arenes

The authors proposed a reaction mechanism such as that illustrated in Scheme 11.
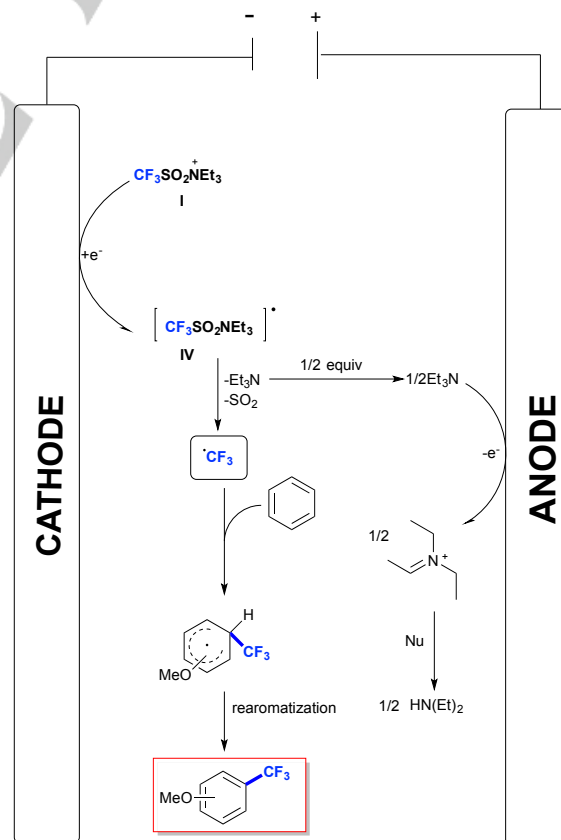
Scheme 11. Proposed reaction mechanism

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In the proposed mechanism, the transformation mainly takes place on the cathode surface of the carbon electrode. One-electron reduction of triflylammonium complex **I** (Scheme 11) results in neutral radical **IV**. Although cyclic voltammetry measurements of compound **IV** could not be obtained, DFT calculations showed that the reduction of the complex **IV** should be significantly favored compared to reduction of T_fCl, with a reduction potential that was ~0.5 V lower. Also, the authors[18] found that **IV** is likely the species being reduced and also the radical source. DFT calculations also confirmed that compound **II** (Scheme 9) has a very negative reduction potential and cannot

be involved in the electrochemical process. Decomposition of **V** affords the amine and SO_2 together with the CF_3 radical, which effects the arene substitution (Scheme 11).

Natte, Beller and colleagues[19] have achieved the trifluoromethylation of alcoxy-substituted arenes employing CF_3Br (1 – 3 bar) as source of the CF_3 group, $Pd(OAc)_2$ (10 mol%) and bis adamantly-butyl phosphine ($BuPAd_2$) (20 mmol) as ligand, Cs_2CO_3 (2 equiv) and TEMPO (1 equiv) as additives, in acetone as solvent, under N_2 atmosphere, at 140 °C for 40 h. The scope of the transformation is illustrated in Scheme 12.
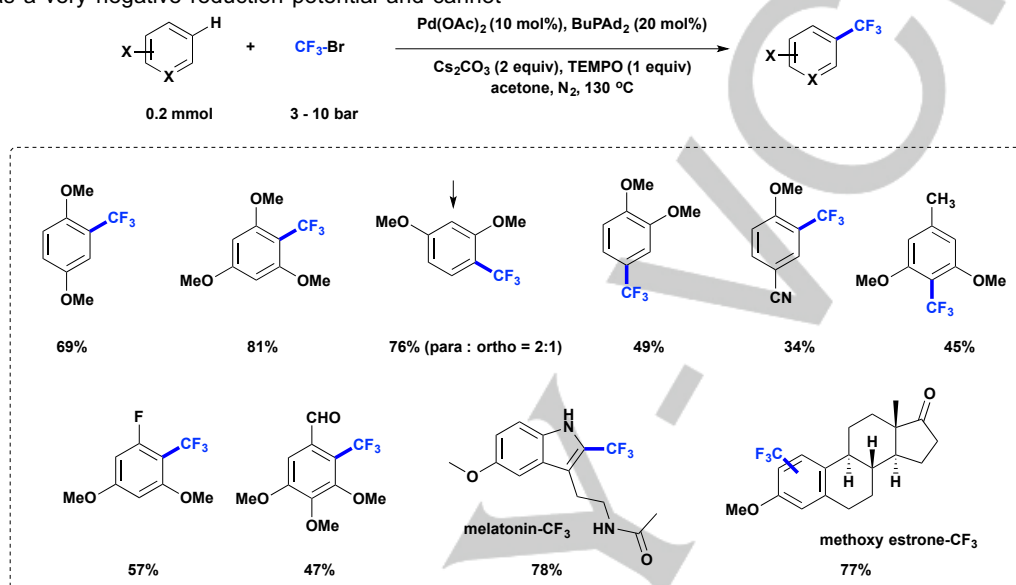
Scheme 12. Selected examples for the trifluoromethylation of (hetero)arenes

As observed from Scheme 12, good yields are obtained from methoxy-substituted (hetero)arenes. Specially, two bioactive compounds, melatonin and a methoxy-estrone, have been trifluoromethylated in good, isolated yields. The promoting effect of TEMPO in affording good yields of products has been observed before.[20] The authors[19] explored the reaction mechanism (Scheme 13). A mixture of $Pd(OAc)_2$ and $BuPAd_2$ suspended in toluene saturated with CF_3Br gave an EPR signal, attributed to a CF_3 radical, which reacts with the arene. Reaction with $PdBrL_2$ leads to $HPdL_2Br$ (**I**), which is detected by NMR spectroscopy. The quenching with Cs_2CO_3 converts $HPdL_2Br$ (**I**) into the active species PdL_2 (**II**) and closes the catalytic cycle. The role of the specific $Pd0L_2$ complex **II** is to cleave the CF_3-Br bond homolytically to release the CF_3 radical. The role of TEMPO is rationalized as single-electron reducing and oxidizing agent, which intervenes within the different palladium species.
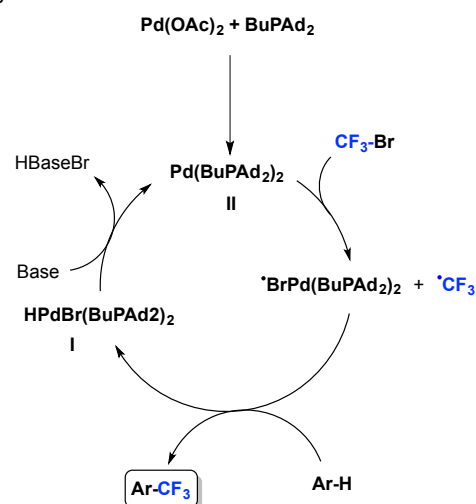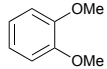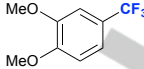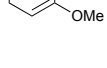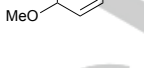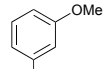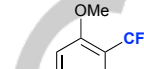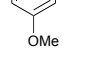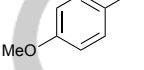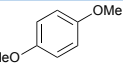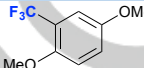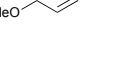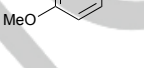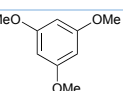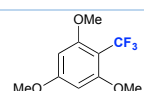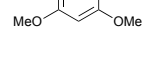

Scheme 13. Proposed reaction mechanism

3.-Summarizing Table
Next, a comparison between the different trifluoromethylation methods of methoxy-substituted arenes described in the text is illustrated in Table 1 for 1,2-dimethoxybenzene, 1,3-dimethoxybenzene, 1,4-dimethoxybenzene, and 1,3,5-trimethoxybenzene.

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Table 1. Comparison of yields obtained for the trifluoromethylation of 1,2-dimethoxybenzene, 1,3-dimethoxybenzene, 1,4-dimethoxybenzene, and 1,3,5-trimethoxybenzene through different method

entry	Methoxy arene	methodology	CF_3 SOURCE	Product	% yield	Ref.
1	OMe / OMe (1,2)	Ru(bpy)$_3$Cl$_2$, hu, Ar$_2$S, DCE	CF_3CO_2H	MeO / MeO / CF$_3$	47	[13]
2		Pd(OAc)$_2$, BuPAd$_2$, Cs$_2$CO$_3$,TEMPO, 130 ºC Acetone	CF_3Br		49	[19]
3	OMe / OMe (1,3)	Et$_3$N, (+)C/(-)C electrode, Et$_4$NBF$_4$, MeCN	CF_3SO_2Cl	OMe / CF$_3$ / MeO	79	[18]
4		Pd(OAc)$_2$, BuPAd$_2$, Cs$_2$CO$_3$,TEMPO, 130 ºC Acetone	CF_3Br		76[a]	[19]
5	OMe / MeO (1,4)	TBADT, hu, K$_2$S$_2$O$_8$, MeCN : H$_2$O	$NaSO_2CF_3$	F$_3$C / OMe / MeO	45	[7]
6		Ru(bpy)$_3$Cl$_2$, hu, Ar$_2$S, DCE	CF_3CO_2H		56[b]	[13]
7		Pd(OAc)$_2$, BuPAd$_2$, Cs$_2$CO$_3$,TEMPO, 130 ºC Acetone	CF_3Br		69	[19]
8		Et$_3$N, (+)C/(-)C electrode, Et$_4$NBF$_4$, MeCN	CF_3SO_2Cl		58	[18]
9		[Cob (II) 7C1ester]ClO$_4$, hu, −0.8 V vs. Ag / AgCl MeOH	CF_3-I		20	[15]
10	MeO / OMe / OMe (1,3,5)	Pd(OAc)$_2$, BuPAd$_2$, Cs$_2$CO$_3$,TEMPO, 130 ºC Acetone	CF_3Br	OMe / CF$_3$ / MeO / OMe	81	[19]
11		Et$_3$N, (+)C/(-)C electrode, Et$_4$NBF$_4$, MeCN	CF_3SO_2Cl		89	[18]
12		Ru(bpy)$_3$Cl$_2$, hu, Ar$_2$S, DCE	CF_3CO_2H		67	[13]
13		TBADT, hu, K$_2$S$_2$O$_8$, MeCN : H$_2$O	$NaSO_2CF_3$		54[c]	[7]
14		[Cob (II) 7C1ester]ClO$_4$, hu, −0.8 V vs. Ag / AgCl MeOH	CF_3-I		56	[15]

a.   Ratio para : ortho = 2 : 1

b.   390 nm LED

c.   Reaction Conditions use 0.05 M of K2S2O8. 4 hour-reaction.

The methods depicted in Table 1 could be considered convenient to be adopted as perfluoroalkylation routes, depending on the necessities and availability of the particular laboratory. Diverse strategies such as those employing photocatalysis relying on Ru(bpy)$_3$Cl$_2$ (entries 1,6, and 12, Table 1) or TBADT (entries 5 and 13, Table 1) photocatalysts and CF_3CO_2H and $NaSO_2CF_3$ as trifluoromethylating sources respectively, or the biomimetic vitamin B12 derivative (entries 9 and 15) partnered with trifluoromethyl iodide rendered fluoroalkylated products. Thermal methods employing Pd(OAc)$_2$ as catalyst (entries 4, 7 and 10, Table 1) and BuPAd$_2$ as ligand using CF_3Br as CF_3 source, although with different environmental demands, also supplied the fluorinated products in good yields. Electrochemical methods (entries 3, 8, and 11, Table 1) consisting in the cathodic reduction of CF_3SO_2Cl to obtain the incipient CF_3 radical are able to substitute alcoxy-substituted (hetero)arenes in good yields.

As observed from Table 1, all methods afforded comparable yields of trifluoromethylated products, with slight differences among a few substrates. For instance, while for 1,2-dimethoxybenzene and 1,3-dimethoxybenezene all reported methods seem comparable, for 1,4-dimethoxybenzene the vitamin B12-photocatalyzed protocol afforded lower yields of trifluoromethyl-substituted product. Regarding 1,3,5-trimethoxybenzene, the photocatalyzed methods render lower product yields than the electrochemical or thermal protocols. However, not all methods are comparable in terms of environmental demand, chemical waste, and reaction conditions. For instance, thermal methods[19] necessitate harsh reaction conditions such as elevated temperatures; electrolytic methods[18] consume large amounts of current and instrumental setups, which can only be implemented in equipped laboratories.

On the other hand, photocatalytic methods,[7,8,13] employed for fluoroalkylation of alcoxy-substituted (hetero)arenes, although more environmentally benign, also vary significantly in terms of reactions conditions. Photocatalytic methods requiring an oxidant[7] are sensitive to the presence of oxidizable groups pre-assembled on the molecule. Photocatalytic methods relying on commercially available inexpensive fluoroalkylating reagents, such as trifluoracetic acid[13] are promising, and less expensive than other methods needing the Langlois reagent[7] or perfluoroalkyl iodides.[8] A compromise should be made between product yields and environmental demand of the protocols to be employed. Of note, are photocatalytic methods relying on *N*-doped carbon nanodots.[7] which afford fluoroalkylation products

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from methoxy-substituted arenes employing nonmetal-based photocatalysts.

4.-Summary and Outlook

Alcoxy-substituted (hetero)arenes which encompass candidates with specific biological activity can be fluoroalkylated through photocatalytic and thermal methods. Photocatalytic methods represent advantages over thermal ones, as milder reaction conditions can be applied. Regarding the fluoroalkylating reagents employed in photocatalytic methods, the Langlois reagent, perfluorocarboxylic acids R_F-COOH, and perfluoroalkyl halides R_F-X have been reported as sources of the fluoroalkyl radical. On the other hand, thermal methods employ Pd catalysts and CF_3Br as trifluoromethylating source. Electrochemical methods have also been reported, specially, the cathodic reduction of CF_3SO_2Cl as CF_3 source. All these approaches, although different in nature and environmental demand, contribute to the realm of perfluoroalkylation strategies that can be applied to this special family of organic compounds.

One other approach that has to be considered or reinforced in the future is fluoroalkylation strategies in environmentally friendlier reaction media, such as aqueous mixtures of organic solvents or water itself as reaction medium. Also, the role of biomimetic catalysts such as vitamin B12 derivatives or other unmodified vitamins in the perfluoroalkylation reactions of (hetero)aromatic compounds should be further explored.

5.-Acknowledgements

6.-Authors contributions
All authors contributed equally

7.-Conflict of Interests
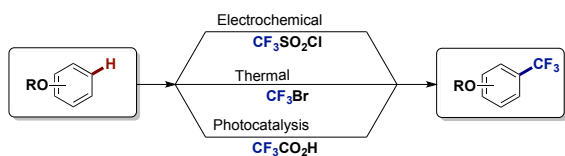The authors declare no competing interests.

Keywords: Alcoxy-substituted (hetero)arenes • fluoroalkylation strategies • photocatalytic fluoroalkylation • thermal fluoroalkylation methods; electrochemical fluoroalkylation methods • radical fluoroalkylation methods

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Entry for the Table of Contents

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