Carlota Odena Juan

ACCESS TO NEW COMPLEXES OF (Cat)[Cu(CF_3)$_2$] AS EFFICIENT TRIFLUOROMETHYLATING AGENTS IN THE ACTIVATION OF ARYL HALIDES

FINAL DEGREE THESIS

Directed by Dra. Mónica H. Pérez Temprano and Dra. Sara Martínez de Salinas Uzquiza

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1. Abstract

Herein, we describe a rapid, selective and *in-situ* synthesis of the bis-(trifluoromethyl)cuprate complexes through a transmetalation reaction using analogous silver complexes. Subsequently, its potential as trifluoromethylating agents in the formation of C–CF_3 bonds using different aryl halides as model substrates has been evaluated. It is important to mention that this is the first time that the capability of these species has been demonstrated, since their reactivity has been neglected to date.

En aquest treball s'ha desenvolupat la síntesi in-situ de manera ràpida i selectiva dels complexos tipus bis-(trifluorometil)cuprat a través d'una reacció de transmetal·lació utilitzant complexes de plata anàlegs. Posteriorment, s'ha avaluat la seva capacitat com agents trifluorometilants en la formació d'enllaços C–CF_3 utilitzant diferents halurs d'aril com a substrats model. És important destacar que és la primera vegada que s'ha pogut demostrar el potencial d'aquestes espècies, ja que la seva reactivitat no havia sigut estudiada amb profunditat fins al moment.

2. Introduction

Since the middle 20th century, one of the research fields of most interest in chemistry has been and still is the formation of carbon–carbon bonds. These transformations are fundamental to synthesize, quickly and efficiently, natural products, agrochemicals, polymers and especially pharmaceutical products. In particular, in the last few years, the incorporation of trifluoromethyl (CF_3) group onto organic scaffolds has received special attention from the synthetic community.[1] The trifluoromethyl group is a prevalent structural motif in pharmaceuticals and agrochemicals (**Figure 1**) due to its unique capability to modify physical, chemical and biological properties of organic molecules.[2] For example, two of the top-selling drugs on the US market are trifluoromethyl derivatives, Januvia® (Sitagliptin) and Celebrex® (Celecoxib), made more than $9 billions in sales during 2013.

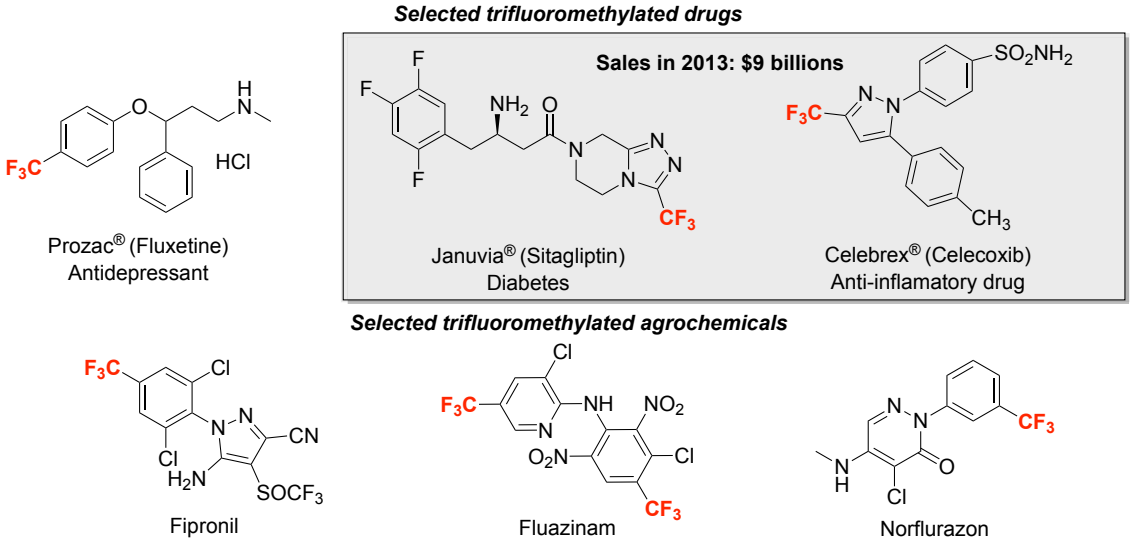


Figure 1. *Selected trifluoromethylated compounds.*

The Swarts reaction[3], discovered in 1892, which involves the treatment of benzotrichlorides with HF or SbF_5, remains the most prevalent method for the industrial-scale synthesis of trifluoromethyl arenes and certain heteroarenes. Although this method is effective in the bulk production of simple benzotrifluorides, its utility on the laboratory scale for the synthesis of complex molecules and late-stage functionalization is limited by the low functional group compatibility and toxic reagents (**Figure 2a**). Therefore, over the past years, tremendous efforts have been devoted towards the development of alternative

strategies for late stage installation of this privileged functional group into diversely decorated molecules using transition metal (TM) catalysts (**Figure 2b**).[1]

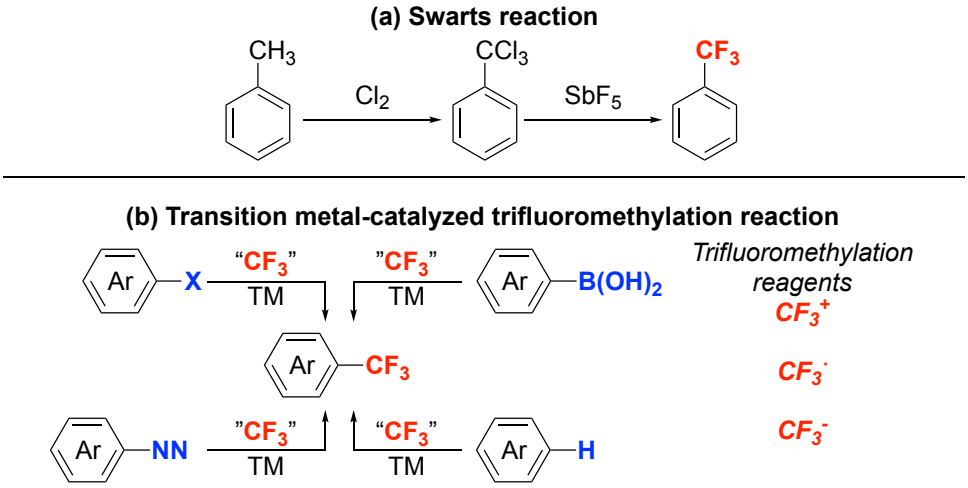
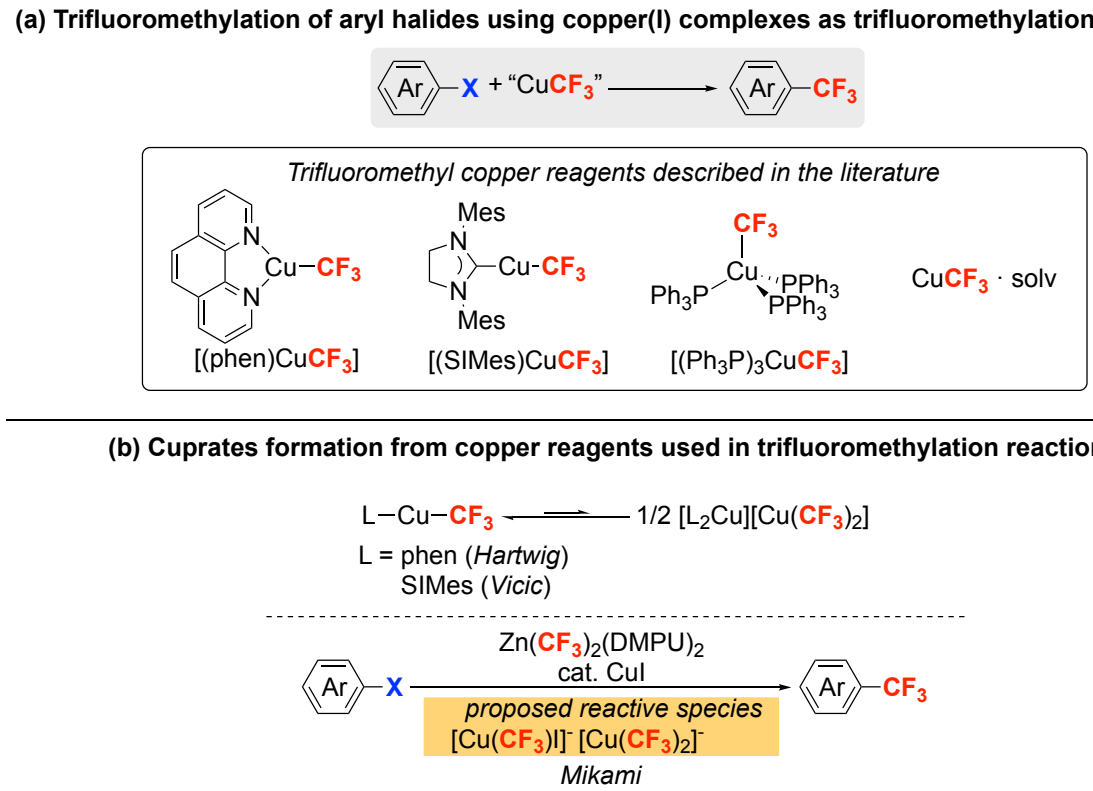


Figure 2. *Described synthetic methods for obtaining trifluoromethylated derivatives.*

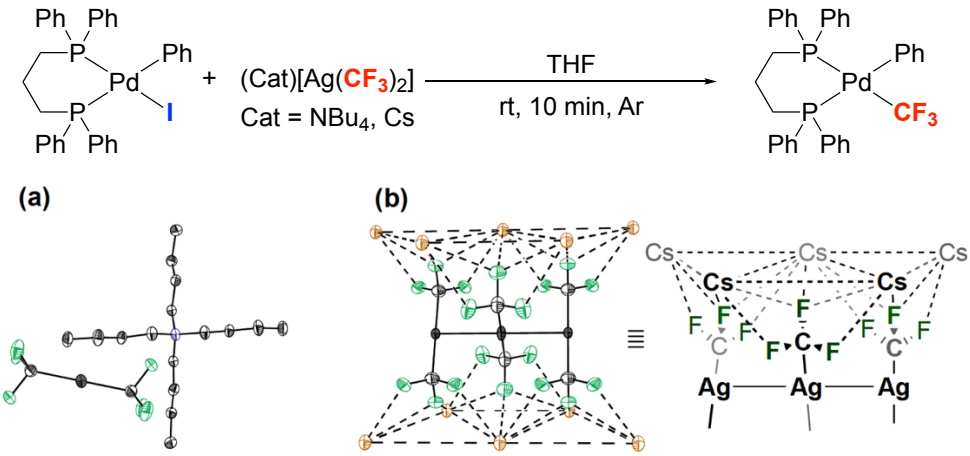
Among the different methods described in the literature, those that use trifluoromethylated copper complexes stand out, since they are capable of functionalizing efficiently aryl halide derivatives (**Scheme 1a**).[4] In most of these works, the authors use neutral copper species as trifluoromethylating sources, coordinated to different types of ligands or formed *in-situ* and stabilized by polar solvents. However, the reactivity of the trifluoromethylated derivatives such as (Cat)[Cu(CF_3)$_2$] or Gilman reagents[5] has been hardly explored in this type of reactions. Although the groups of Vicic[4a,b] and Hartwig[4c] have described the formation of this type of complexes in equilibrium with neutral copper(I) species in the trifluoromethylation reactions of aryl halides, their participation in these transformations has not been investigated (**Scheme 1b**). In this context, the Mikami group has explored the trifluoromethylation of aryl iodides by using cuprates, combining a copper(I) salt with a zinc transmetalating agent as the initial source of CF_3.[4f,g] However, the complex mixture of compounds observed by the authors in the reaction media made it impossible to determine the actual potential of these proposed reactive species (**Scheme 1b**).



Scheme 1. *Functionalization of aryl halides with copper(I) trifluoromethyl sources.*

Therefore, this *Project* aims at investigating the efficient and selective access to the complexes (Cat)[Cu(CF_3)$_2$] to determine their potential in the functionalization of different types of aryl halides. For this purpose, (Cat)[Ag(CF_3)$_2$] complexes, previously developed by the research group of Dr. Pérez-Temprano, were used.[6] Pérez-Temprano and co-workers reported that these species have a great capacity to transfer trifluoromethyl groups to transition metals, such as palladium (**Scheme 2**).

In this study, two silver complexes with different cations (Cs or NBu_4) will be used to establish the influence of the cation in the subsequent reactivity. It is worth mentioning the different bonding situation between these ionic species. The X-ray structure of (NBu_4)[Ag(CF_3)$_2$] shows a linear bis-(trifluoromethyl)argentate paired together with the NBu_4 cation. In sharp contrast, (Cs)[Ag(CF_3)$_2$] presents a rather unique structure, with the silver atoms forming linear chains and the cesium cations interacting with twelve different fluorine atoms (**Scheme 2**).[6]



Scheme 2. *Transfer of the CF_3 group from (Cat)[Ag(CF_3)$_2$] to Pd^{II}. X-ray structures of (Cat)[Ag(CF_3)$_2$],* ***(a)*** *(Cat = NBu_4) and* ***(b)*** *(Cat = Cs).*

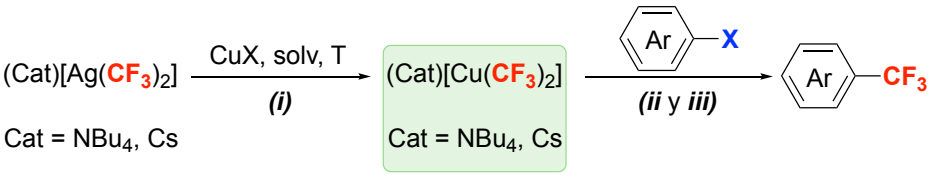
3. Objectives

Considering the insights presented before, this *Final Degree Thesis* aims at studying the potential of ionic copper(I) species in the trifluoromethylation reactions of aryl halides. To achieve this goal, the following objectives are proposed:

(i) To study the access to (Cat)[Cu(CF_3)$_2$] from copper(I) sources, using different silver salts (Cat)[Ag(CF_3)$_2$] as transmetalating agents.

(ii) To evaluate the reactivity of the species (Cat)[Cu(CF_3)$_2$] in the trifluoromethylation reactions of different representative aryl halides.

(iii) To gather key information in an attempt to elucidate the mechanism involved in the trifluoromethylation reaction of organic substrates.

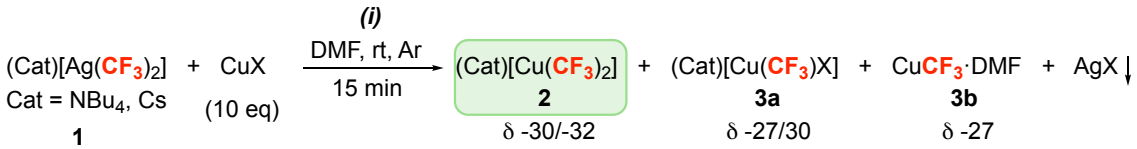


4. Results and Discussion

4.1. Synthesis of copper complexes type (Cat)[Cu(CF_3)$_2$]

The access to (Cat)[Cu(CF_3)$_2$] (Cat = Cs (**2$_{Cs}$**) or NBu_4 (**2$_{NBu4}$**)) complexes was carried out through the transmetalation reaction of copper(I) salts and the silver complexes, (Cat)[Ag(CF_3)$_2$] (Cat = Cs (**1$_{Cs}$**) or NBu_4 (**1$_{NBu4}$**)). As discussed in the

Introduction of the present *Research Work*, Mikami and co-workers have described that the combination of a copper(I) salt with a transmetalating agent "$ZnCF_3$" can result in a complex mixture of compounds "$CuCF_3$".[4f,g] These species could be assigned to: (a) $[Cu(CF_3)_2]^-$ (**2**) whose chemical shift values in ^{19}F NMR range from –30 to –32 ppm; (b) $[Cu(CF_3)(X)]^-$ (**3a**) (δ = –27 to –30 ppm) or $CuCF_3$•S (**3b**) (S = coordinating nitrogenous solvents such as DMF, NMP, ACN…) whose δ in ^{19}F NMR is assigned to values close to –27 ppm.[1b,4] With this information as a starting point, we begin establishing the general conditions for the transmetalation reaction: (i) the use of 10 equivalents of CuX; (ii) the use of DMF as solvent, based on the studies described in the literature of the trifluoromethylation reaction with different aryl halides;[7] and (iii) mild reaction conditions, including short reaction time, 15 minutes, and room temperature (rt).



Scheme 3. *General procedure of the transmetalation reaction with 10 equivalents of the copper source.*

Different copper(I) sources were tested to explore the reactivity of this transformation. The used copper(I) salts were CuX (X = I, Br and Cl) and $[Cu(NCMe)_4][BF_4]$ in order to see the influence of the halogen or, in the case of $[Cu(NCMe)_4][BF_4]$, the presence of the acetonitrile ligand in the copper coordination sphere (**Figure 3**).

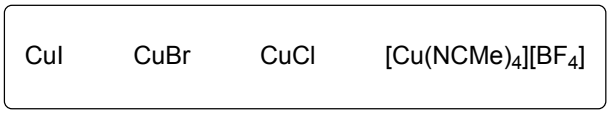


Figure 3. *Copper source used in the transmetalation reaction.*

Table 1. *Transmetalation reaction with different copper sources.*

Entry	Ag source	Cu source	δ specie 3	Ratio 2:3
1	$\mathbf{1}_{Cs}$	$[Cu(NCMe)_4][BF_4]$	-26.04	2:98
2	$\mathbf{1}_{NBu4}$	$[Cu(NCMe)_4][BF_4]$	-26.05	0:100
3	$\mathbf{1}_{Cs}$	CuBr	-26.75	1:99
4	$\mathbf{1}_{NBu4}$	CuBr	-26.71	1:99
5	$\mathbf{1}_{Cs}$	CuCl	-26.46	0:100
6	$\mathbf{1}_{NBu4}$	CuCl	-26.46	0:100
7	$\mathbf{1}_{Cs}$	CuI	-26.95	66:34
8	$\mathbf{1}_{NBu4}$	CuI	-26.86	52:48

In all cases, by ^{19}F NMR, a maximum of two species in the region corresponding to "$CuCF_3$" (from δ –25 to –32 ppm) were observed. One of the species unambiguously corresponds to the cuprate $[Cu(CF_3)_2]^-$ (**2**) ($\delta \approx$ –30.7 ppm in all cases) and the other specie whose δ is in the range from –26.04 to –26.95 ppm could not be conclusively identified as specie **3a** or **3b**.

When using $[Cu(NCMe)_4][BF_4]$ and CuBr as copper(I) salts, a mixture of different major species, including Cu(III) salts ($\delta =$ –33.84 ppm) in the case of $[Cu(NCMe)_4][BF_4]$, were obtained. For this reason, the use of both copper sources was discarded for the trifluoromethylation reaction of aryl halides (Entries 1 – 4, **Table 1**).

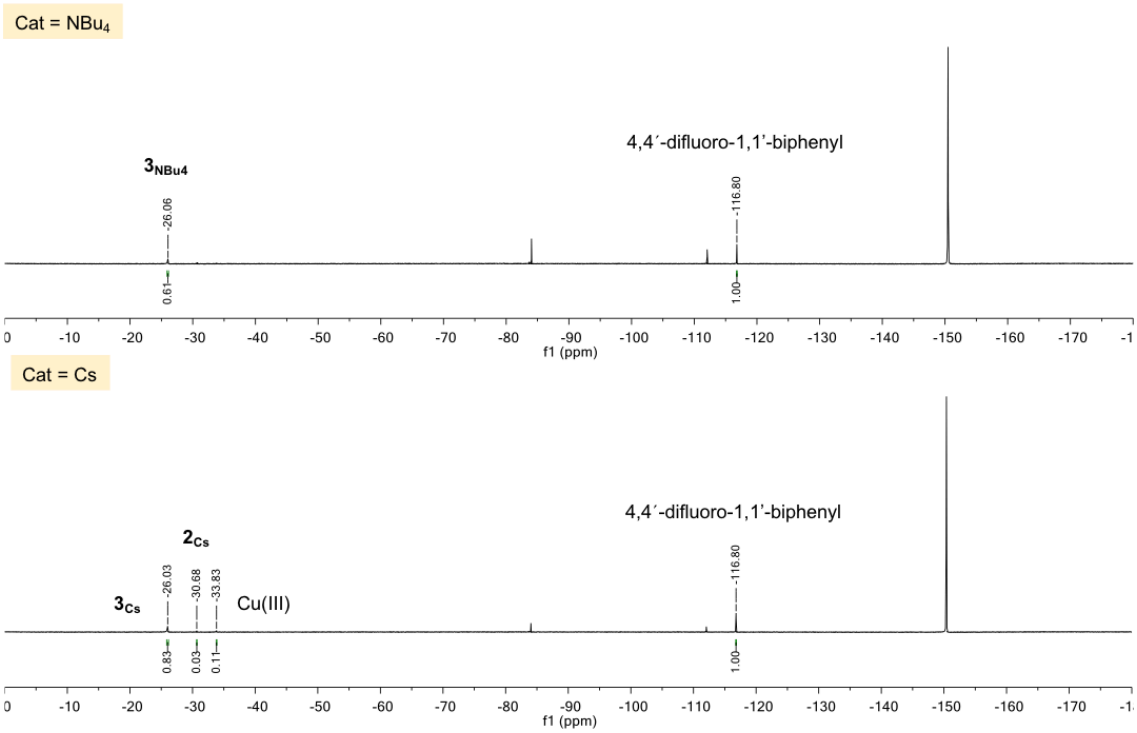


Figure 4. *^{19}F NMR spectra of the reactions of (Cat)[Ag(CF$_3$)$_2$] (**1**) with 10 equivalents of [Cu(NCMe)$_4$][BF$_4$] using 4,4'-difluoro-1,1'-biphenyl as internal standard.*

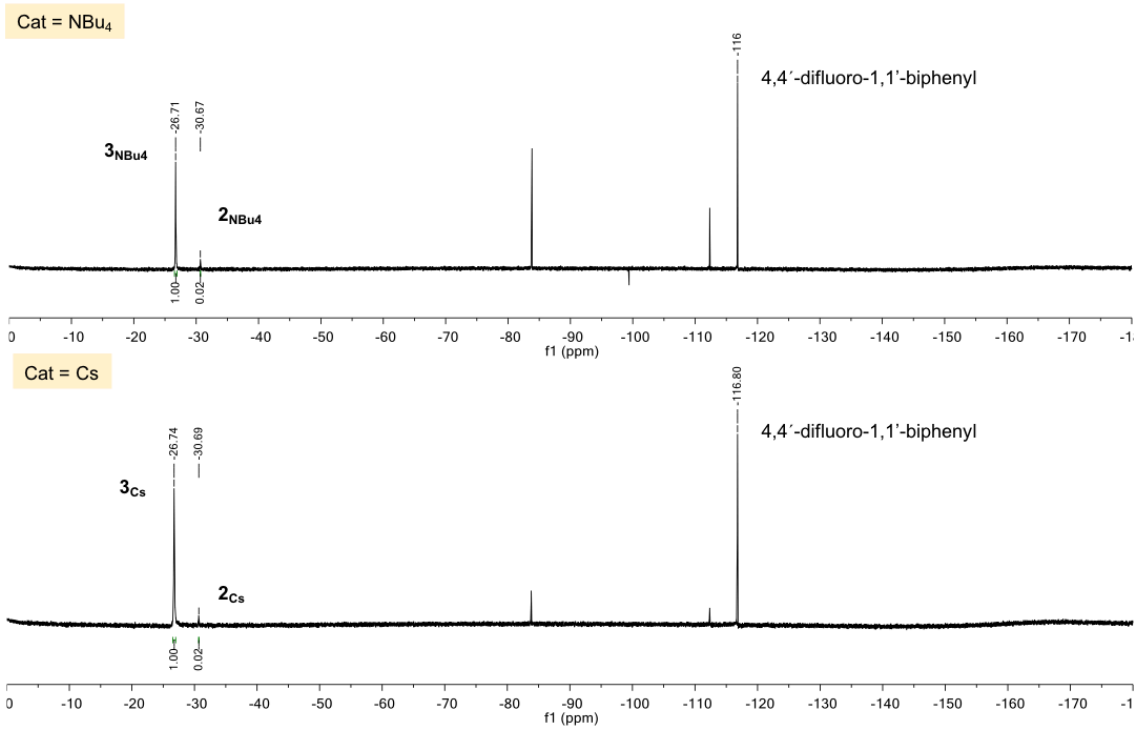


Figure 5. *^{19}F NMR spectra of the reactions of (Cat)[Ag(CF$_3$)$_2$] (**1**) with 10 equivalents of CuBr using 4,4'-difluoro-1,1'-biphenyl as internal standard.*

On the other hand, as seen on **Figure 6**, when performing the same reaction with CuCl, the specie **3** was formed quantitatively without detecting the cuprate (Cat)[Cu(CF_3)$_2$] (**2**) (Entries 5 and 6, **Table 1**).

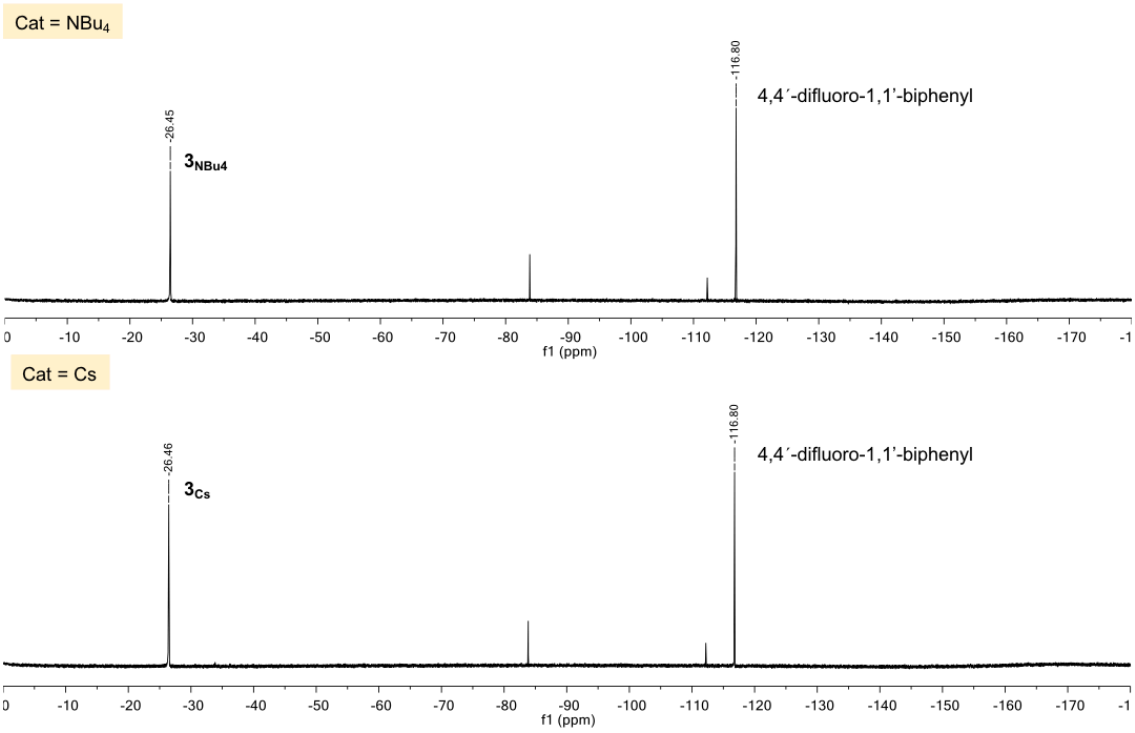


Figure 6. *^{19}F NMR spectra of the reactions of (Cat)[Ag(CF_3)$_2$] (**1**) with 10 equivalents of CuCl using 4,4'-difluoro-1,1'-biphenyl as internal standard.*

Finally, the reaction of the complexes (Cat)[Ag(CF_3)$_2$] (**1**) (Cat = Cs or NBu_4) with 10 equivalents of CuI in DMF during 15 minutes at room temperature led to a mixture of the species (**2**:**3**) in proportion [66:34 (Cat = Cs); 52:48 (Cat = NBu_4)] (Entries 7 and 8, **Table 1**).

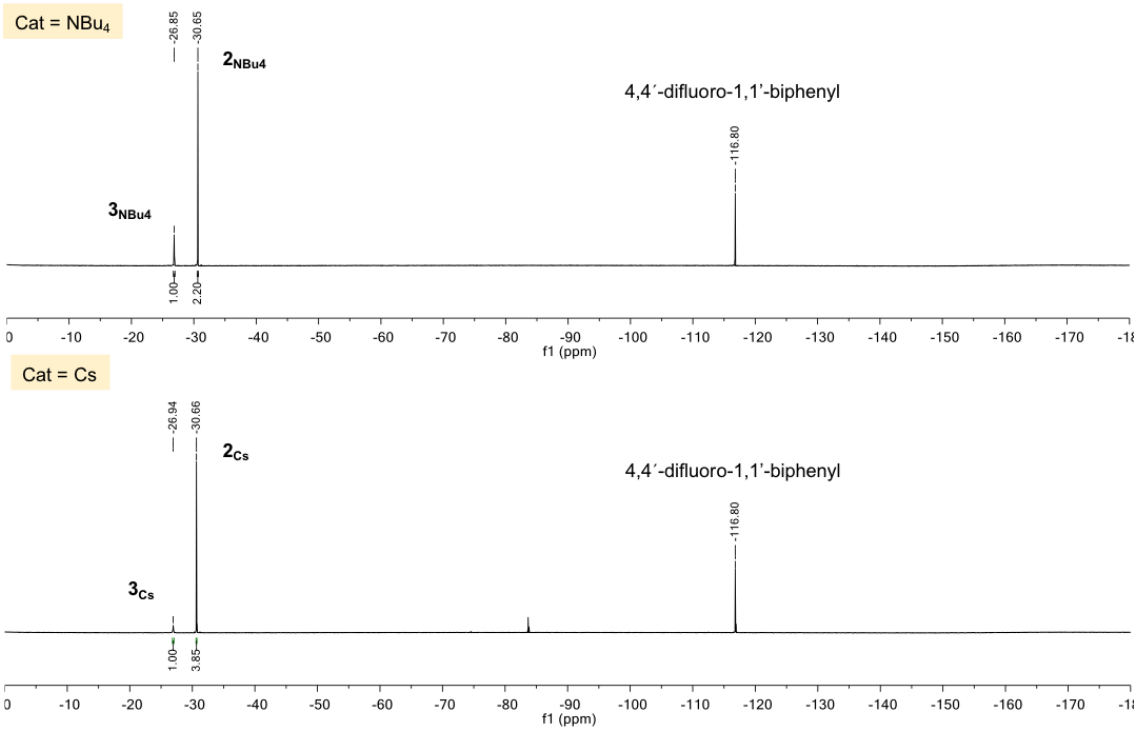
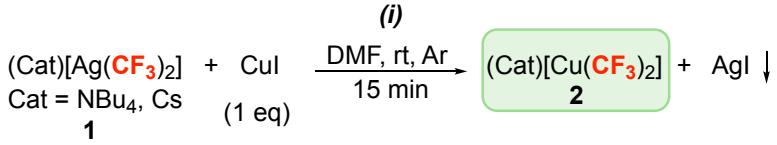


Figure 7. *^{19}F NMR spectra of the reactions of (Cat)[Ag(CF$_3$)$_2$] (**1**) with 10 equivalents of CuI using 4,4'-difluoro-1,1'-biphenyl as internal standard.*

In view of these results, we evaluated the transmetalation reactions using stoichiometric amounts of CuI, in order to find a more selective synthesis for the complexes (Cat)[Cu(CF$_3$)$_2$] (**2**). CuI was used as copper source since it is the salt that led to more proportion of the desired cuprate specie **2**. Thus, using 1 equivalent of CuI, the complexes (Cat)[Cu(CF$_3$)$_2$] (**2**) (Cat = Cs or NBu$_4$) were obtained quantitatively, confirming their structure through ^{19}F NMR (δ = –30.66 ppm in both cases). These compounds have not been isolated due to their instability, since when using the common Schlenk techniques, a rapid decomposition of them was observed. It is important to note that this is the first time that these bis-(trifluoromethyl)cuprate species can be prepared *in-situ* quantitatively under mild reaction conditions (**Scheme 4**).



Scheme 4. *General procedure of the transmetalation reaction with 1 equivalent of CuI.*

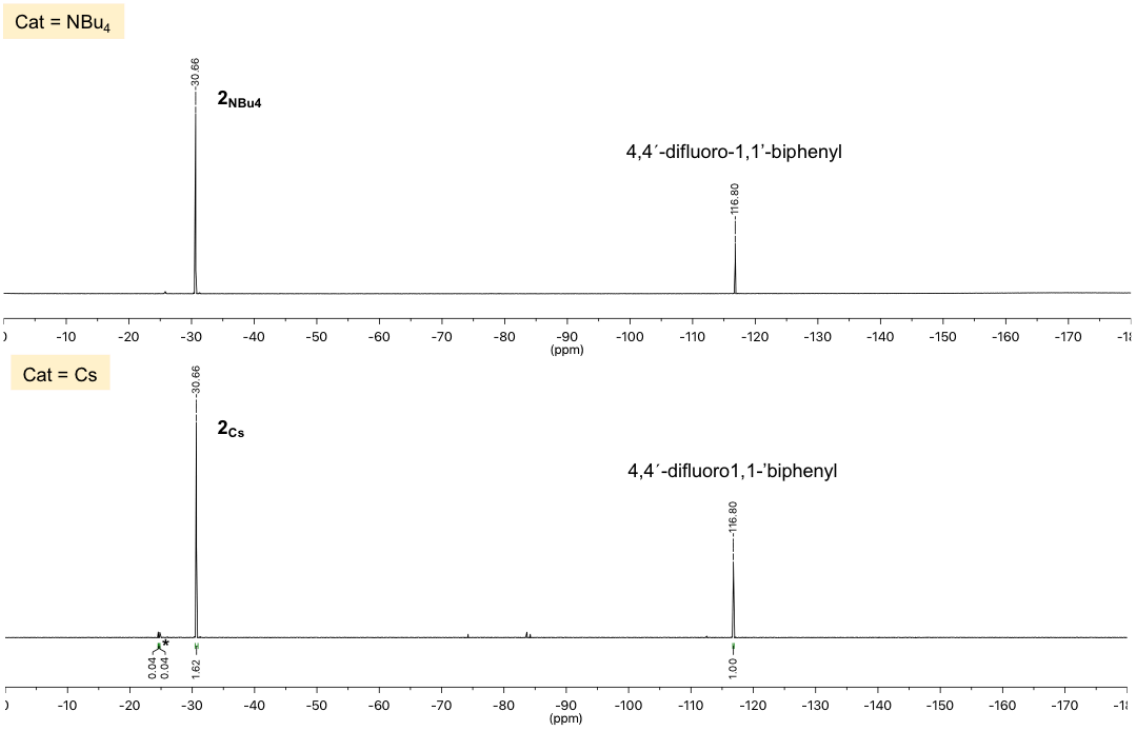


Figure 8. *^{19}F NMR spectra of the reactions of (Cat)[Ag(CF_3)$_2$] (**1**) with 1 equivalent of CuI using 4,4'-difluoro-1,1'-biphenyl as internal standard. *4% of the complex **1$_{Cs}$** did not react in the indicated time.*

4.2. Study of the reactions of C–CF_3 bond formation using "$CuCF_3$" to functionalize aryl halides

Once the synthetic route to the complexes (Cat)[Cu(CF_3)$_2$] (Cat = Cs (**2$_{Cs}$**) or NBu_4 (**2$_{NBu4}$**)) was established, we turned our attention towards the main objective of the present *Research Work*: to establish the potential of these cuprate species as trifluoromethylating agents in the reaction of C–CF_3 bond formation using different aryl halides as starting materials.

To perform a first evaluation of the reactivity, the organic substrate 4-iodobiphenyl (**4$_I$**) was chosen as model since the Csp^2–I bond is the most accessible within the aryl halides.[7] Moreover, Vicic et al. have recently performed an exhaustive evaluation of the efficiency of the most active "$CuCF_3$" species to date (**Figure 9**), using this substrate as model to establish an objective comparison of their reactivity.[1j]

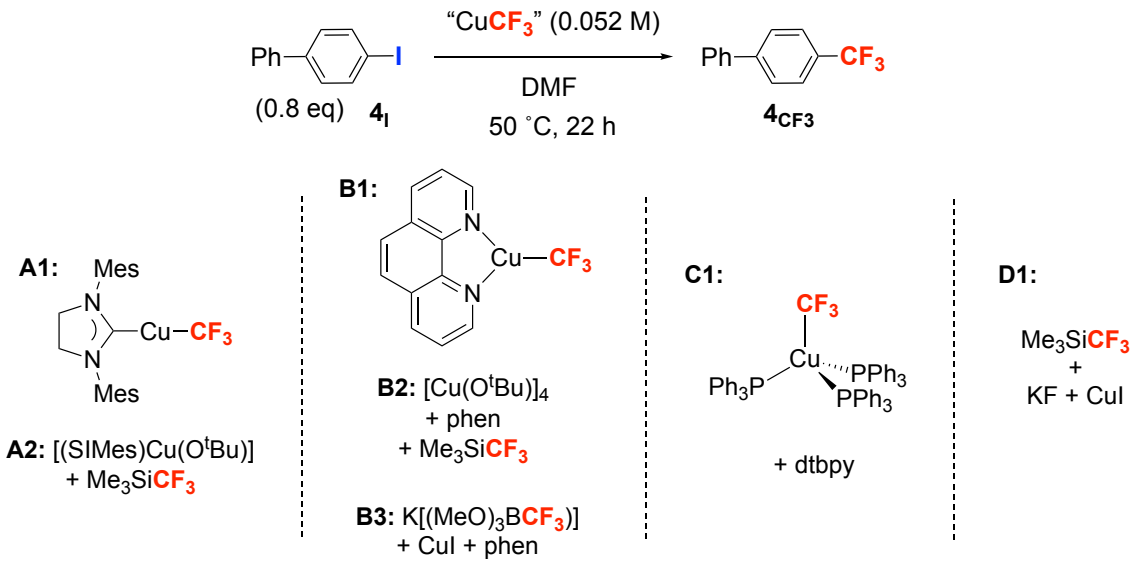
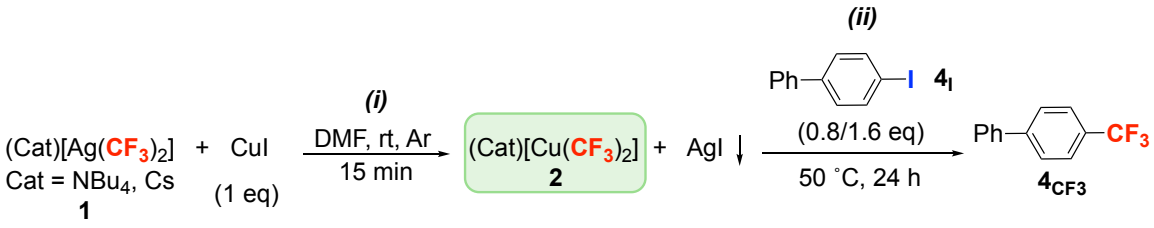


Figure 9. *Copper complexes used in the trifluoromethylation reaction of 4-iodobiphenyl.*

When using the **B1** and **B2** complexes, the best results afforded approximately 65% and 50% of the desired product after 24 hours. On the other hand, **B3** led to 30% of product at 24 hours and the other complexes did not reach more than 10% conversion in this time.

With these precedents as reference, we proceeded to study the potential of (Cat)[Cu(CF_3)$_2$] (**2**) (Cat = Cs or NBu_4) complexes in the activation reaction of 4-iodobiphenyl under the same reaction conditions established by Vicic and collaborators.[1j]

Firstly, the conditions of the transmetalation reaction previously described were used (1 equivalent of CuI, 15 minutes at room temperature and DMF as solvent). Then, once (Cat)[Cu(CF_3)$_2$] (**2**) (Cat = Cs or NBu_4) species were formed, 0.8 or 1.6 equivalents of the substrate were added, and the reaction mixture was heated at 50 ºC for 24 hours (**Scheme 5**). It is important to mention that the substrate and copper source "$CuCF_3$" ratio described by Vicic et al. is 0.8:1. In our case, as the complexes contain two trifluoromethyl groups, different ratios were tested (0.8:1 and 1.6:1).



Scheme 5. *Trifluoromethylation reaction of 4-iodobiphenyl (**4**$_I$) using 1 equivalent of CuI in the transmetalation reaction.*

In all the evaluated cases, the yields observed by ^{19}F NMR of 4-trifluoromethylbiphenyl (**4**$_{CF3}$) are excellent and, therefore, the potential of the bis-(trifluoromethyl)cuprate species (**2**) is superior to the copper species described by Vicic (**Table 2**). It should be noted that the activity of these complexes is independent of the nature of the cation.

Table 2. *Trifluoromethylation reaction of 4-iodobiphenyl (**4**$_I$) using 1 equivalent of CuI in the transmetalation reaction.*

Entry	Ag source	Eq substrate	**4**$_{CF3}$ yield (%)[a]
1	**1**$_{Cs}$	0.8	100
2	**1**$_{Cs}$	1.6	90
3	**1**$_{NBu4}$	0.8	100
4	**1**$_{NBu4}$	1.6	83

[a]The conversion value is calculated using two internal standards (see *Experimental Section*)

Finally, it is important to remark that when using 1.6 equivalents of substrate (Entries 2 and 4, **Table 2**), the bis-(trifluoromethyl)cuprate (**2**) species are capable of transferring the two trifluoromethyl groups. During the reaction, the accumulation of a reaction intermediate $[Cu(CF_3)I]^-$ (**3a**$_I$) was observed, in the range of –28.06 ppm a –28.29 ppm,[4f,g] by ^{19}F NMR. Taking into account the amount of this specie that is formed, it can be confirmed that it is also capable of transferring the trifluoromethyl group. For example, in **Figure 10** we can observe the specie **3a**$_I$, δ = –28.15 ppm (3 h) and δ = –28.29 ppm (24 h), in the reaction

of the complex $(NBu_4)[Ag(CF_3)_2]$ ($\mathbf{1}_{\mathbf{NBu4}}$) with 1 equivalent of CuI and 1.6 equivalents of substrate ($\mathbf{4}_{\mathbf{I}}$) (Entry 4, **Table 2**).

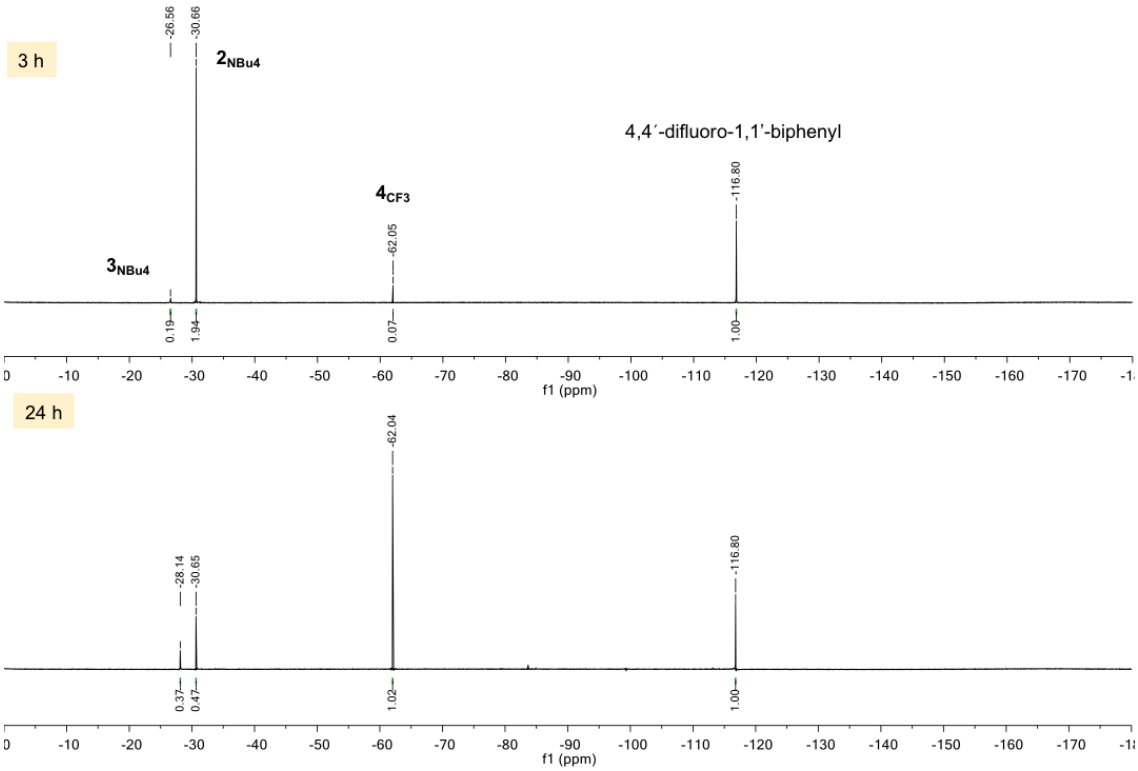
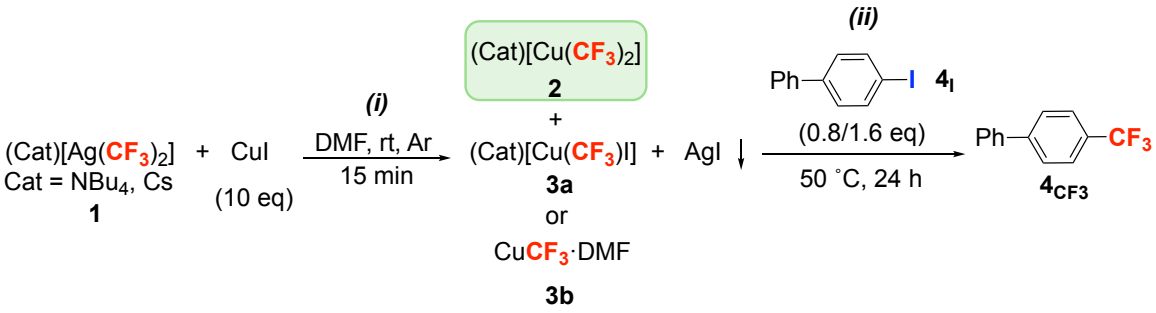


Figure 10. *^{19}F NMR spectra at 3 and 24 hours of the reaction of $(NBu_4)[Ag(CF_3)_2]$ ($\mathbf{1}_{\mathbf{NBu4}}$) with 1 equivalent of CuI and 1.6 equivalents of substrate ($\mathbf{4}_{\mathbf{I}}$). Both reactions were carried out independently with different amounts of internal standard.*

These preliminary results unambiguously confirm, for the first time, the ability of the bis-(trifluoromethyl)cuprate species as trifluoromethylating agents in the activation of substrates with Csp^2–I bonds.

Intrigued by the potential activity of **3**-type species, we decided to mimic the reaction conditions previously described, but using 10 equivalents of CuI in order to assess the effect of the presence of species **3** in the reaction media.



Scheme 6. *Trifluoromethylation reaction of 4-iodobiphenyl (**4**$_I$) using 10 equivalents of CuI in the transmetalation reaction.*

Table 3 shows that almost 100% of product conversion is achieved at 24 hours in all cases.

Table 3. *Trifluoromethylation reaction of 4-iodobiphenyl (**4**$_I$) using 10 equivalents of CuI in the transmetalation reaction.*

Entry	Ag source	Eq substrate	4_{CF3} yield (%)[a]
1	$\mathbf{1}_{Cs}$	0.8	100
2	$\mathbf{1}_{Cs}$	1.6	93
3	$\mathbf{1}_{NBu4}$	0.8	100
4	$\mathbf{1}_{NBu4}$	1.6	100

[a]The conversion value is calculated using two internal standards (see *Experimental Section*)

In order to understand how the proportion between the "$CuCF_3$" species changes in the activation reaction of 4-iodobiphenyl (**4**$_I$) using 10 equivalents of CuI and (Cs)[Ag(CF_3)$_2$] ($\mathbf{1}_{Cs}$), a monitorization of the reaction by ^{19}F NMR was performed. At 3 hours a 73% of $\mathbf{4}_{CF3}$ is already observed, while complex $\mathbf{2}_{Cs}$ has decreased from an initial 60% to 12% and the complex $\mathbf{3}_{Cs}$, from an initial 40% to 29%. This data confirms that specie $\mathbf{2}_{Cs}$ is active in the trifluoromethylation of the aryl iodide (**4**$_I$), while more experiments would be necessary to determine the implication of the specie $\mathbf{3}_{Cs}$ in the reaction. It is worth mentioning the variation of the chemical shift of specie $\mathbf{3}_{Cs}$ during the reaction, from –27.02 ppm to –28.18 ppm, due to the formation of $[CuI_2]^-$. Hu and co-workers described that the amount of $[CuI_2]^-$

can affect the chemical shift of **3a**-type species, thus it is proposed that a more appropriate way of denominating these species would be $\{[Cu(CF_3)I]_x\}^{x-}$ $\{[CuI_2]_y\}^{y-}$.[8]

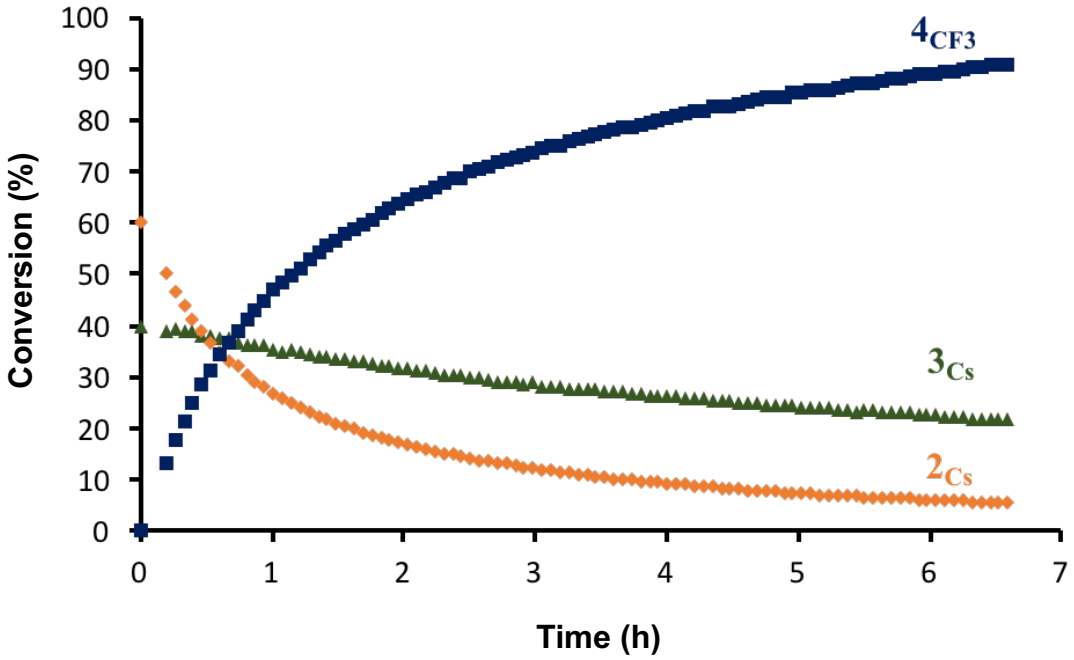
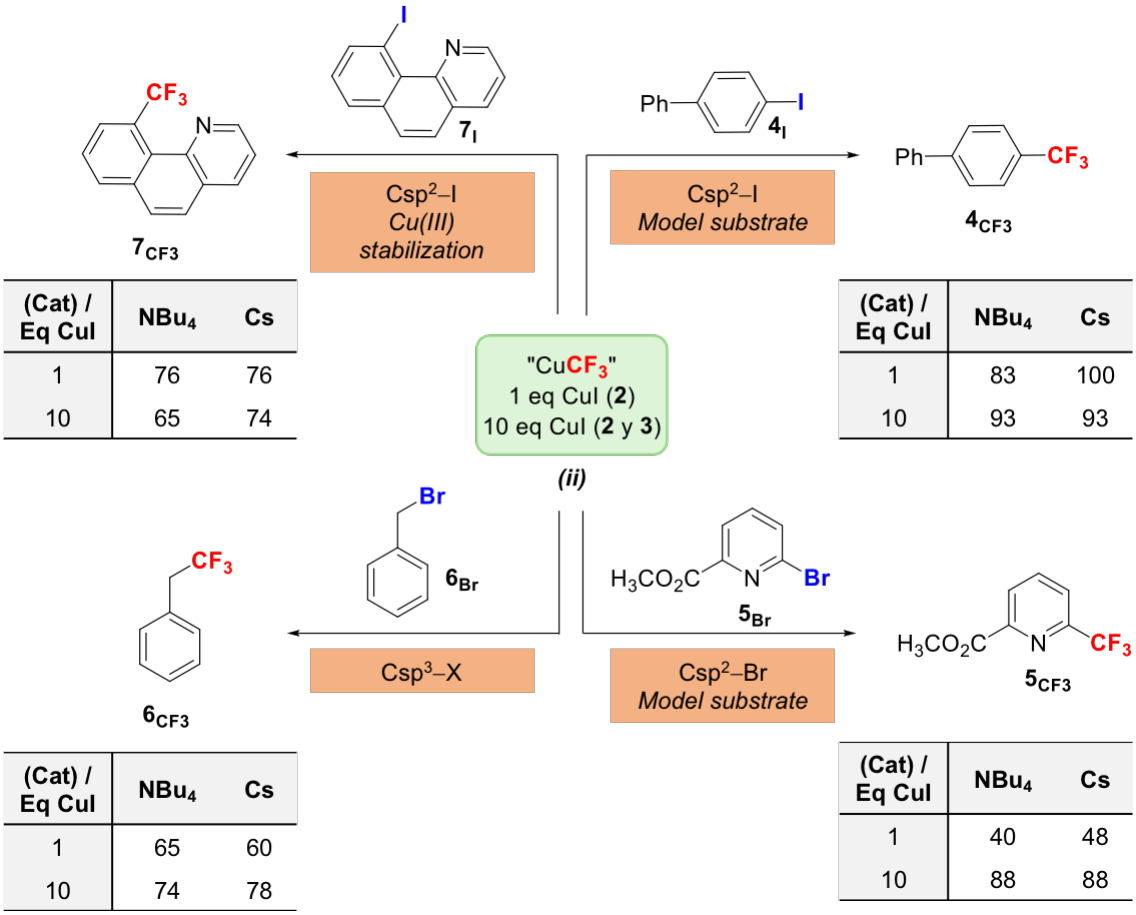


Figure 11. *Formation of* $\mathbf{4}_{CF3}$ *in the activation reaction of* $\mathbf{4}_{I}$ *using (Cs)[Ag(*CF_3*)*$_2$*] and 10 equivalents of CuI in DMF at 50 ºC.*

Once the trifluoromethylation capability of the "$CuCF_3$" species was verified using the model substrate, we decided to study its reactivity with different representative organic molecules such as methyl-6-bromopyridine-2-carboxylate ($\mathbf{5}_{Br}$), benzyl bromide ($\mathbf{6}_{Br}$) or 10-iodobenzo*[h]*quinoline ($\mathbf{7}_{I}$). From now on, the reactivity study is carried out with 1 or 10 equivalents of CuI and 1.6 equivalents of substrate to establish a comparison between the results.



(Cat) / Eq CuI	NBu_4	Cs
1	76	76
10	65	74

(Cat) / Eq CuI	NBu_4	Cs
1	83	100
10	93	93

(Cat) / Eq CuI	NBu_4	Cs
1	65	60
10	74	78

(Cat) / Eq CuI	NBu_4	Cs
1	40	48
10	88	88

Scheme 7. *Evaluation of the capability of "$CuCF_3$" (**2** and **3**) as trifluoromethylating agents in the C–CF_3 bond formation using different representative aryl halides.*

The substrate methyl-6-bromopyridine-2-carboxylate ($\mathbf{5_{Br}}$) was chosen not only for (a) the evaluation of the capability of copper species (**2**) to activate Csp^2–Br bonds, but also (b) to determine the efficiency of our system by comparing the obtained results with the ones reported by Hartwig and co-workers, who used different "$CuCF_3$" species to functionalize this same substrate.[9]

In this case, the reaction conditions are similar to the previously described, but they were carried out at 80 ºC to establish an objective comparison with the precedents.[9]

Table 4. *Trifluoromethylation reaction of methyl-6-bromopyridine-2-carboxylate (**5**$_{Br}$) using 1 and 10 equivalents of CuI in the transmetalation reaction.*

Entry	Ag source	Eq CuI	Eq substrate	**5**$_{CF3}$ yield (%)[a]
1	**1**$_{Cs}$	1	1.6	48
2	**1**$_{Cs}$	10	1.6	88
3	**1**$_{NBu4}$	1	1.6	40
4	**1**$_{NBu4}$	10	1.6	88

[a]The conversion value is calculated using two internal standards (see *Experimental Section*)

Hartwig et al. reported a 96% conversion to **5**$_{Br}$ using 0.8 equivalents of substrate, (Phen)$CuCF_3$ as "$CuCF_3$" source, DMF as solvent at 80 ºC for 8 hours.[9] In our first preliminary studies we performed the reaction with more diluted concentrations (0.052 vs 0.12 M), 1.6 equivalents of substrate **5**$_{Br}$ and 24 hours. In this case, the conversion values obtained using 1 equivalent of CuI were moderate (Entries 1 and 3, **Table 4**) and this can be explained due to the unknown potential reactivity of the $[Cu(CF_3)Br]^-$ species formed during the reaction ($\delta \approx -27.10$ ppm) (**3a**$_{Br}$), that have not been described to date. These mixed species, although more reactive *per se* than the bis-(trifluoromethyl)cuprate, could decompose in the reaction media at this temperature before activating the Csp^2–Br bond. On the other hand, it should be mentioned that the obtained yields using 10 equivalents of CuI (Entries 2 and 4, **Table 4**) are similar to those reported by Prof. Hartwig.[9]

Inspired by the obtained results in the activation of Csp^2–I and Csp^2–Br bonds, we decided to extend the study and explore the functionalization of a substrate containing a Csp^3–X bond. For this, we chose the benzyl bromide (**6**$_{Br}$) as model. The reactions were carried out at 50 ºC for 24 hours under the same reaction conditions used for the 4-iodobiphenyl (**4**$_{I}$).

Table 5. *Trifluoromethylation reaction of benzyl bromide (**6_{Br}**) using 1 and 10 equivalents of CuI in the transmetalation reaction.*

Entry	Ag source	Eq CuI	Eq substrate	6_{CF3} yield (%)[a]
1	$\mathbf{1_{Cs}}$	1	1.6	60
2	$\mathbf{1_{Cs}}$	10	1.6	78
3	$\mathbf{1_{NBu4}}$	1	1.6	65
4	$\mathbf{1_{NBu4}}$	10	1.6	74

[a]The conversion value is calculated using two internal standards (see *Experimental Section*)

In all cases the obtained yields were similar when using 1 or 10 equivalents of CuI (> 50%). These data suggest in this particular case that $[Cu(CF_3)Br]^-$ (**$3a_{Br}$**) species are also capable to transfer the second CF_3 molecule at 50 ºC (Entries 1 and 3, **Table 5**). These results are comparable to those obtained using other "$CuCF_3$" complexes.[4a,b,10] At the end of the reactions, one specie at δ = –34.01 ppm was observable by ^{19}F NMR, which is associated to Cu(III) species, in particular $[Cu(CF_3)_4]^-$ complexes, inactive in the activation of aryl halides.[4f]

Finally, a more specific substrate was studied, the 10-iodobenzo*[h]*quinoline (**7_I**). This scaffold presents a unique structure capable of stabilizing metals in high oxidation states.[11] In the case that the reaction mechanism would take place through oxidative addition-reductive elimination steps,[7] this type of substrate could be used as model to isolate highly reactive Cu(III) species. Therefore, the first step was to evaluate the activation of **7_I** by species **2** and **3**. These preliminary studies were performed with the optimal reaction conditions (1 or 10 equivalents of CuI, DMF, 50 ºC, 24 hours and 0.052 M "CF_3").

Table 6. *Trifluoromethylation reaction of 10-iodobenzo[h]quinoline (**7$_I$**) using 1 and 10 equivalents of CuI in the transmetalation reaction.*

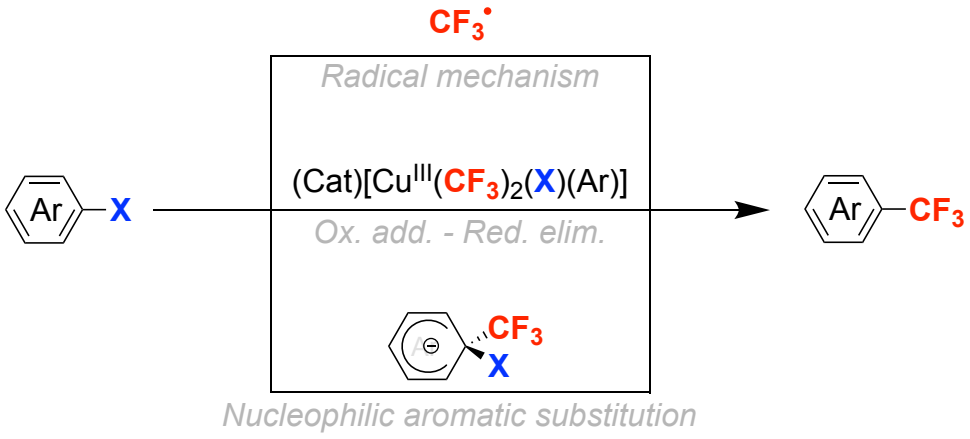
Entry	Ag source	Eq CuI	Eq substrate	7_{CF3} yield (%)[a]
1	$\mathbf{1}_{Cs}$	1	1.6	76
2	$\mathbf{1}_{Cs}$	10	1.6	65
3	$\mathbf{1}_{NBu4}$	1	1.6	76
4	$\mathbf{1}_{NBu4}$	10	1.6	74

[a]The conversion value is calculated using two internal standards (see *Experimental Section*)

In all cases, the obtained yields were promising,[12] so this substrate or similar ones could be used as model in a more exhaustive study in order to gain further insight of the reaction mechanism.

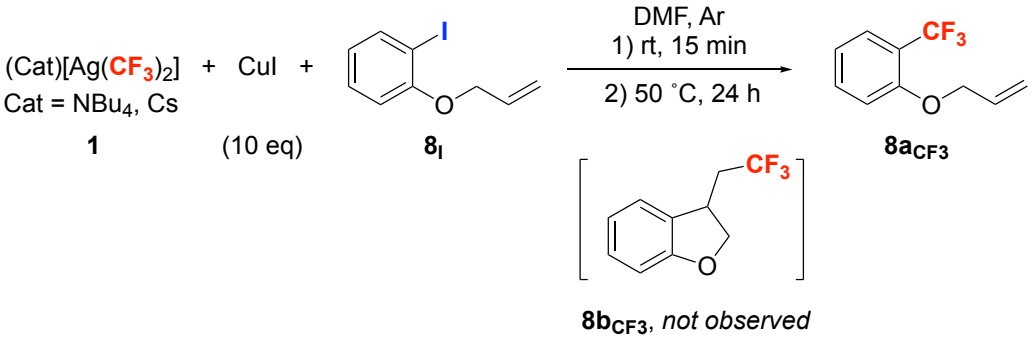
4.3. Preliminary studies of the mechanism of the trifluoromethylation reaction

Among the different proposed mechanisms for the activation reactions of Csp^2–X through "$CuCF_3$" complexes, it could be highlighted the radical mechanism, the nucleophilic aromatic substitution and the oxidative addition-reductive elimination (**Scheme 8**).[7]



Scheme 8. *Different proposed mechanisms for the activation reactions of Csp^2–X through "$CuCF_3$" complexes.*

In order to evaluate the presence of radical species, the trifluoromethylation reaction of the substrate 1-(allyloxy)-2-iodobenzene (**8$_I$**) was performed.[4c,7,13] The aryl radical derived from this iodoarene cyclizes with a rate constant of 10^{10} s^{-1}.[14] Thus, in case that the trifluoromethylation took place thought an aryl radical, the product **8b$_{CF3}$** would be observed. However, if the product **8a$_{CF3}$** is obtained, the presence of radical species can be discarded. Both compounds can be easily identified by ^{19}F NMR since the product **8a$_{CF3}$** appears as a singlet signal at –61.4 ppm, while **8b$_{CF3}$** is represented by a triplet signal at –65.2 ppm.



Scheme 9. *Trifluoromethylation reaction of 1-(allyloxy)-2-iodobenzene (**8$_I$**) using 10 equivalents of CuI in the transmetalation reaction.*

The trifluoromethylation reaction was carried out reproducing the optimal conditions for the rest of the iodized substrates. In this case, only 10 equivalents of CuI were tested to promote the formation of species **2** and **3** in the reaction media.

Table 7. *Trifluoromethylation reaction of 1-(allyloxy)-2-iodobenzene (**8$_I$**) using 10 equivalents of CuI in the transmetalation reaction.*

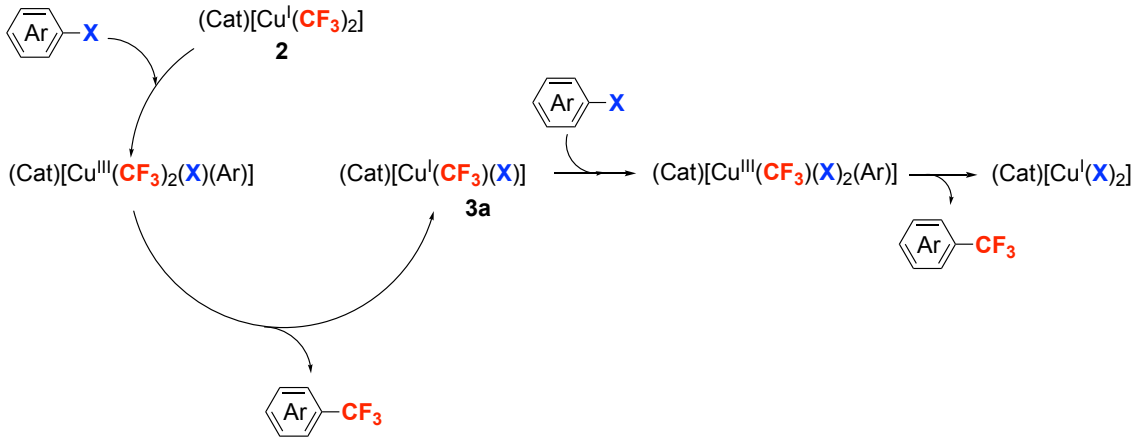
Entry	Ag source	Eq CuI	Eq substrate	8a$_{CF3}$ yield (%)[a]
1	**1$_{Cs}$**	10	1.6	86
2	**1$_{NBu4}$**	10	1.6	74

[a]The conversion value is calculated using two internal standards (see *Experimental Section*)

Compound **8b$_{CF3}$** was not observed by ^{19}F NMR and the obtained yields for **8a$_{CF3}$** (**Table 7**) are comparable to those obtained previously. These results show that

these reactions proceed without the intermediacy of an aryl radical from electron transfer and expulsion of the iodide.[4c,7]

The mechanism represented in **Scheme 10** is proposed as a possible oxidative addition-reductive elimination mechanism, based on the literature precedents.[7,15] The real nature of the intermediates, its geometry or the presence of other steps among the represented ones, remains unknown to date. More experiments are necessary to gain further insights on this proposed mechanism, for example, substrate $\mathbf{7_I}$ could be used as model for a deeper investigation of the suggested (Cat)[$Cu^{III}(CF_3)_2X(Ar)$] intermediate.



Scheme 10. *Oxidative addition-reductive elimination mechanism proposed by us.*

5. Conclusions

In summary, from this *Research Work* we can conclude that the proposed objectives have been achieved. In particular:

(i) A synthetic route that allows the *in-situ*, rapid and selective access to complexes of the bis-(trifluoromethyl)cuprate type has been established.

(ii) The ability of these complexes as trifluoromethylating agents in the C–CF_3 bond formation reactions has been evaluated using different representative aryl halides. The obtained results show the efficiency of these species, whose reactivity has been overlooked to date.

(iii) Preliminary studies of the reaction mechanism have been carried out and the involvement of radical species can be discarded.

Future studies related to this *Project* could be:

(i) Identification of specie **3** using techniques such as mass spectrometry.
(ii) Evaluation of other representative aryl halides.
(iii) Study of the reaction mechanism including the synthesis of possible reaction intermediates of Cu(III).

6. Experimental Section

6.1. Materials and Methods

Commercially available reagents AgF, AgOAc, NBu_4OAc, CsF, KF, Me_3SiCF_3, CuI, CuCl, CuBr, 4,4'-difluoro-1,1'-biphenyl, 4-iodobiphenyl, methyl-6-bromopyridine-2-carboxylate, benzyl bromide, 2-iodophenol, allyl bromide and K_2CO_3 were used without further purification directly as received from the commercial supplier and stored under inert gas and/or low temperature when required.

If necessary, the solvents (THF, DMF) were used from a solvent purification system *pure-solv* (SPS-400, *Innovative Technology*) and stored under argon with activated molecular sieves 4 Å.

The copper source $[Cu(NCMe)_4][BF_4]$[16] and the organic compounds 10-iodobenzo*[h]*quinoline[11] and 1-(allyloxy)-2-iodobenzene[17] were synthesized according to previous literature procedures.

All the silver complexes are light-sensitive, so the reactions are performed in the dark to avoid photodecomposition.

6.2. Most used reagents

Table 8. *Most used reagents*

Reactive	Purity	Toxicological information
CuI	99.999%	
4,4'-difluoro-1,1'-biphenyl	97%	
4-iodobiphenyl	97%	
DMF	100%	

Apart from wearing protective gloves/protective clothing/eye protection/face protection, preventive measures for a safe handling are:

- **4,4'-difluoro-1,1'-biphenyl**. Avoid breathing dust/fume/gas/mist/ vapours/spray.
- **4-iodobiphenyl**. Avoid release to the environment.
- **DMF**. Keep away from heat/sparks/open flames/hot surfaces. — No smoking. Avoid breathing dust/fume/gas/mist/vapours/spray.

6.3. General Procedures

All reactions were conducted in an argon-filled glovebox (mBraun Unilab 4420) with concentrations of O_2 and H_2O < 0.1 ppm or oven-dried glassware (at 100 ºC overnight and cooled under vacuum prior use) using Schlenk techniques under argon atmosphere.

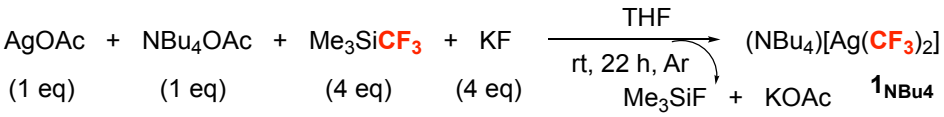
The reactions described in this report have been monitored by fluorine-19 nuclear magnetic resonance spectroscopy (^{19}F NMR). This same technique has been used for the characterization of copper complexes and trifluoromethylated organic compounds. NMR spectra were obtained on a Bruker 400 MHz. ^{1}H, ^{13}C and ^{19}F NMR chemical shifts are reported in parts per million (ppm), relative to

tetramethylsylane (TMS) for ^{1}H and ^{13}C with the residual solvent peak used as an internal reference and relative to $CFCl_3$ (Freon) and 4,4'-difluoro-1,1'-biphenyl as internal standard for ^{19}F. In the ^{19}F spectra registered in non-deuterated solvents, a coaxial tube containing acetone-d_6 was used to maintain the lock ^{2}H signal. Multiplicities are reported as follows: singlet (s), doublet (d), broad doublet (bd), triplet (t), doublet of quadruplet of quadruplets (dqq) and multiplet (m). The monitorization of the reaction and the product quantification were determined by internal calibration using 4,4'-difluoro-1,1'-biphenyl (δ –116.8 ppm) and fluorobenzene (δ –113.15 ppm) with 32 scans for data acquisition.

High Resolution Mass Spectrometry (HRMS) data was recorded on an LCT-Premier (Waters) or a MicroTOF Focus (Bruker Daltonics) mass spectrometers using ESI ionization technique and tetrahydrofuran as solvent.

6.4. Synthesis and characterization of (Cat)[Ag(CF$_3$)$_2$]

6.4.1. (NBu$_4$)[Ag(CF$_3$)$_2$] (**1$_{NBu4}$**)



In an argon atmosphere glovebox, a schlenk was charged with AgOAc (50 mg, 0.29 mmol), NBu$_4$OAc (90.3 mg, 0.29 mmol) and KF (67.4 mg, 1.16 mmol) and dissolved in 20 mL of THF. A solution of Me_3SiCF_3 (171.5 μL, 1.16 mmol) in 10 ml of THF was added and this mixture was stirred 22 h until the signal at –21.40 (2d, $^{2}J_{109Ag,F}$ = 132.8 Hz, $^{2}J_{107Ag,F}$ = 115.1 Hz) ppm corresponding of (NBu$_4$)[Ag(CF$_3$)(OAc)] had completely disappeared. The white suspension was filtered of at –20 ºC and the solution was then reduced to dryness under vacuum at this temperature. The white oil was recrystallized in a mixture of cold THF (1 mL) and cold hexane (20 mL) affording a crystalline white solid (120 mg, 83% yield). It was stored inside the glovebox at –32 ºC to avoid decomposition.

^{1}H NMR (500 MHz, DMF-d_7, 25 ºC): δ 3.25 (m, 8H, NC*H*$_2$), 1.70 (m, 8H, NCH$_2$C*H*$_2$), 1.43 (m, 8H, NCH$_2$CH$_2$C*H*$_2$), 1.02 (t, $^{3}J_{H,H}$ = 7.4 Hz,12H, CH$_3$).

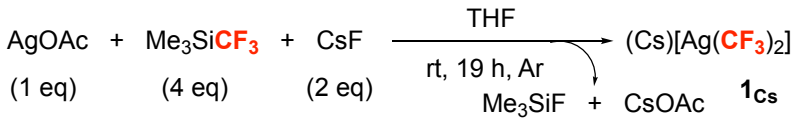
^{13}C NMR (126 MHz, DMF-d_7, 25 ºC): δ 155.85 (dqq, $^{1}J_{C,109Ag}$ = 257.0 Hz, $^{1}J_{C,F}$ = 371.0 Hz, $^{3}J_{C,F}$ = 8.1 Hz), 155.70 (dqq, $^{1}J_{C,107Ag}$ = 257.0 Hz, $^{1}J_{C,F}$ = 371.0 Hz, $^{3}J_{C,F}$ = 8.1 Hz), 59.33 (broad triplet, N*C*H$_2$), 24.61 (s, NCH$_2$*C*H$_2$), 20.82 (broad triplet, 8H, NCH$_2$CH$_2$*C*H$_2$), 14.19 (s, CH$_3$).

In this particular case, the highly symmetric environment around ^{14}N allows the observation of the *J* couplings ^{13}C–^{14}N.

^{19}F NMR (470 MHz, DMF-d_7, 25 ºC): –25.19 (2d, $^{2}J_{109Ag,F}$ = 100.5 Hz, $^{2}J_{107Ag,F}$ = 87.0 Hz) ppm.

HRMS-electrospray (-) in tetrahydrofuran (m/z): [M]$^-$ calcd for C_2AgF_6, 244.8955 and 246.8952; found 244.8950 and 246.8949.

6.4.2. (Cs)[Ag(CF$_3$)$_2$] (**1$_{Cs}$**)



In an argon atmosphere glovebox, two duplicate reactions were carried out. The schlenks were charged equally with AgOAc (50 mg, 0.3 mmol) and CsF (73 mg, 0.49 mmol) and each one was dissolved in 30 mL of THF. A solution of Me$_3$SiCF$_3$ (142 μL, 1.04 mmol) in 10 mL of THF was added dropwise to each schlenk and the mixtures were stirred overnight. After 16 h, inside the glovebox, a schlenk was charged with CsF (108 mg, 0.71 mmol) and it was dissolved in 10 mL of THF. Outside the glovebox, each duplicate yellow suspension was filtered through cannula to the schlenk containing the CsF suspension and a solution of Me$_3$SiCF$_3$ (47 μL, 0.32 mmol) in 5 mL of THF was added dropwise to the schlenk. The mixture was stirred around 3 h until the reaction was completed and the signal of –21.15 ppm (2d, $^{2}J_{109Ag,F}$ = 133.4 Hz, $^{2}J_{107Ag,F}$ = 115.8 Hz) corresponding to (Cs)[Ag(CF$_3$)(OAc)] had completely disappeared. At this point, the resulting yellow suspension was filtered through cannula at –20 ºC and the solution was then reduced to dryness under vacuum at this temperature. The yellow oily residue was recrystallized in a mixture of cold THF (1 mL) and cold hexane (20 mL) and the resulting yellow solid was washed with cold hexane (2 x 10 mL). The

yellow solid (192 mg, 85% yield) was stored in the dark at –32 ºC to avoid decomposition.

^{13}C NMR (126 MHz, THF-d_8, 25 ºC): δ 154.10 (dqq, $^{1}J_{C,109Ag}$ = 256.5 Hz, $^{1}J_{C,F}$ = 371.6 Hz, $^{3}J_{C,F}$ = 7.5 Hz), 152.09 (dqq, $^{1}J_{C,107Ag}$ = 256.5 Hz, $^{1}J_{C,F}$ = 371.6 Hz, $^{3}J_{C,F}$ = 7.5 Hz) ppm.

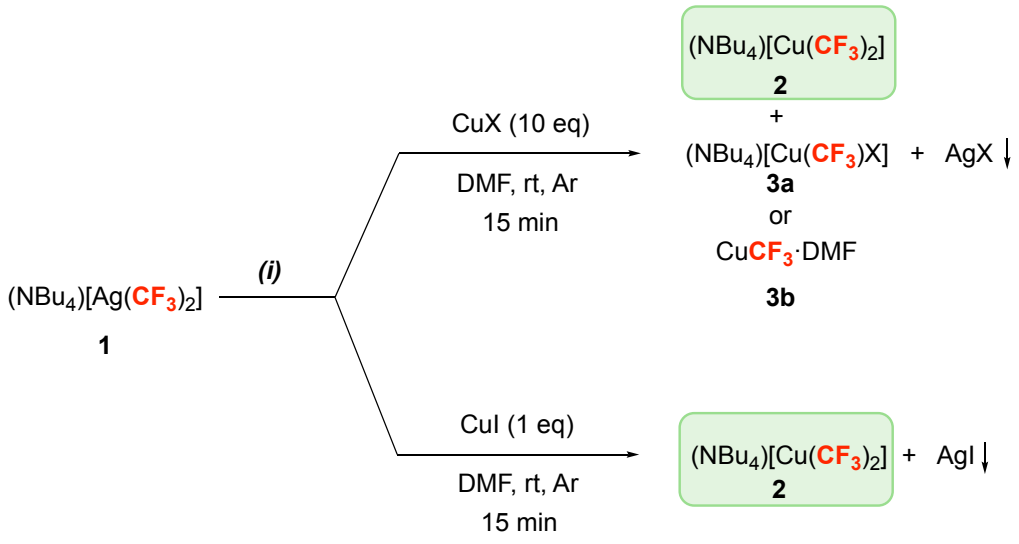
^{19}F NMR (470 MHz, THF-d_8, 25 ºC): –24.67 (2d, $^{2}J_{109Ag,F}$ = 98.6 Hz, $^{2}J_{107Ag,F}$ = 88.9 Hz) ppm.

HRMS-electrospray (-) in tetrahydrofuran (m/z): $[M]^-$ calcd for C_2AgF_6, 244.8955 and 246.8952; found 244.8970 and 246.8971.

6.5. "$CuCF_3$" species from the transmetalation reaction of (Cat)[$Ag(CF_3)_2$] with different copper sources

6.5.1. (NBu_4)[$Cu(CF_3)_2$] (**2**$_{NBu4}$)

In an argon atmosphere glovebox, a crimped vial was charged with (NBu_4)[$Ag(CF_3)_2$] (7.6 mg, 0.016 mmol), the corresponding copper source (1 and 10 equivalents with respect to **1**$_{NBu4}$) and a known amount of the internal standard, 4,4'-difluoro-1,1'-biphenyl. The mixture was dissolved in 0.6 mL of DMF and stirred at room temperature for 15 minutes. The solution was then filtered using a 0.2 mm PTFE filter and transferred to an NMR tube to be analyzed by ^{19}F NMR.



For CuX = CuI (10 eq), the following spectroscopic data were obtained:

^{19}F NMR (400 MHz, acetone-d_6 insert, 25 ºC) δ = –26.86 (s) (**3$_{NBu4}$**), –30.66 (s) (**2$_{NBu4}$**) ppm.

For CuX = CuI (1 eq), the following spectroscopic data were obtained:

^{19}F NMR (400 MHz, acetone-d_6 insert, 25 ºC) δ = –30.66 (s) (**2$_{NBu4}$**) ppm.

For CuX = CuBr (10 eq), the following spectroscopic data were obtained:

^{19}F NMR (400 MHz, acetone-d_6 insert, 25 ºC) δ = –26.71 (s) (**3$_{NBu4}$**), –30.68 (s) (**2$_{NBu4}$**) ppm.

For CuX = CuCl (10 eq), the following spectroscopic data were obtained:

^{19}F NMR (400 MHz, acetone-d_6 insert, 25 ºC) δ = –26.46 (s) (**3$_{NBu4}$**) ppm.

For CuX = $[Cu(NCMe)_4][BF_4]$ (10 eq), the following spectroscopic data were obtained:

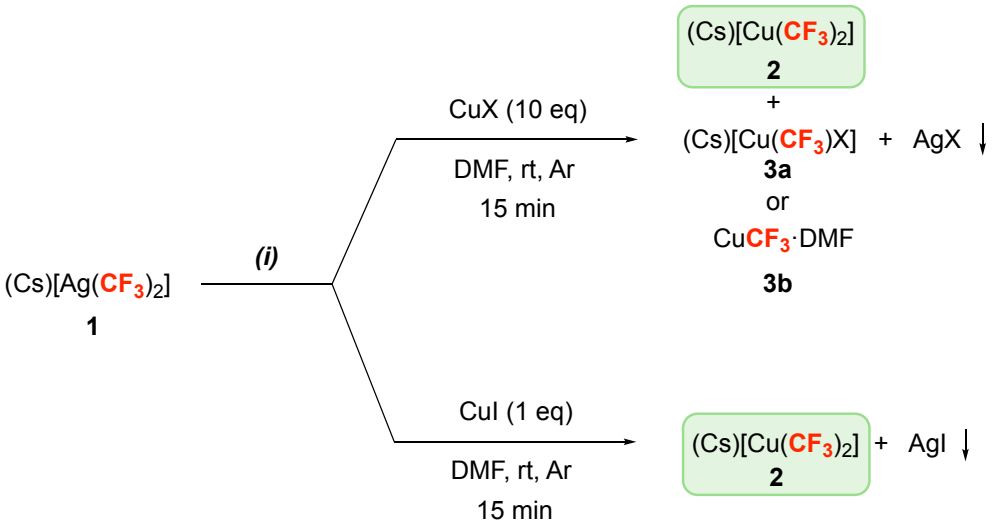
^{19}F NMR (400 MHz, acetone-d_6 insert, 25 ºC) δ = –26.05 (s) (**3$_{NBu4}$**), –30.69 (s) (**2$_{NBu4}$**), –33.84 (s) (Cu(III)), –83.70 (d), –84.04 (s), –112.06 (s), –150.43 (s), –150.48 (s) ppm. The signals that range from –83.70 to –150.48 ppm are decomposition products.

Temperature stability of the "$CuCF_3$" compounds formed from 1$_{NBu4}$

In order to know the stability of the "$CuCF_3$" species respect to the temperature, two types of experiments were carried out. After performing the transmetalation reaction with 10 equivalents of CuI at room temperature (Page 29), the filtered solutions were stirred at different temperatures (50 or 120 ºC). At 50 ºC, in 3 hours the specie $[Cu(CF_3)_2]^-$ (**2$_{NBu4}$**) had decreased by 30% and the specie containing one trifluoromethyl group (**3$_{NBu4}$**) by 36% and at 24 hours by 58% and 43% in total, respectively. At 120 ºC, the specie **2$_{NBu4}$** had decreased by 92% and the specie **3$_{NBu4}$**, by 72%.

6.5.2. (Cs)[Cu(CF_3)$_2$] (**2$_{Cs}$**)

In an argon atmosphere glovebox, a crimped vial was charged with (Cs)[Ag(CF_3)$_2$] (5.9 mg, 0.016 mmol), the corresponding copper source (1 and 10 equivalents with respect to **1$_{Cs}$**) and a known amount of the internal standard, 4,4'-difluoro-1,1'-biphenyl. The mixture was dissolved in 0.6 mL of DMF and stirred at room temperature for 15 minutes. The solution was then filtered using a 0.2 mm PTFE filter and transferred to an NMR tube to be analyzed by ^{19}F NMR.



For CuX = CuI (10 eq), the following spectroscopic data were obtained:

^{19}F NMR (400 MHz, acetone-d_6 insert, 25 ºC) δ = –26.94 (s) (**3$_{Cs}$**), –30.65 (s) (**2$_{Cs}$**) ppm.

For CuX = CuI (1 eq), the following spectroscopic data were obtained:

^{19}F NMR (400 MHz, acetone-d_6 insert, 25 ºC) δ = –30.66 (s) (**2$_{Cs}$**) ppm.

For CuX = CuBr (10 eq), the following spectroscopic data were obtained:

^{19}F NMR (400 MHz, acetone-d_6 insert, 25 ºC) δ = –26.75 (s) (**3$_{Cs}$**), –30.70 (s) (**2$_{Cs}$**) ppm.

For CuX = CuCl (10 eq), the following spectroscopic data were obtained:

^{19}F NMR (400 MHz, acetone-d_6 insert, 25 ºC) δ = –26.46 (s) (**3$_{Cs}$**), –33.84 (s) (Cu(III)) ppm.

For CuX = $[Cu(NCMe)_4][BF_4]$ (10 eq), the following spectroscopic data were obtained:

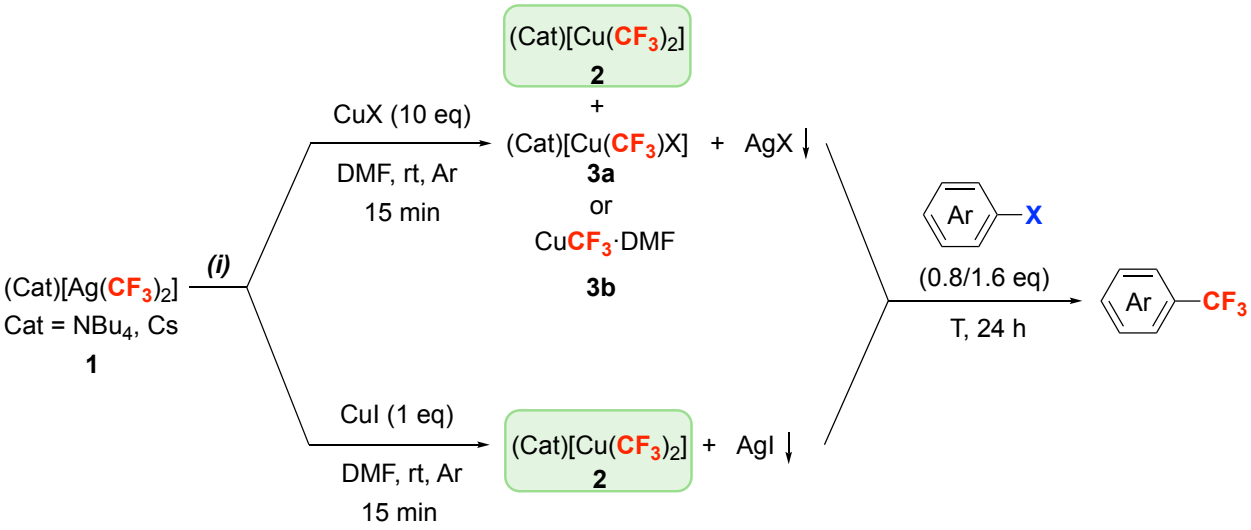
^{19}F NMR (400 MHz, acetone-d_6 insert, 25 ºC) δ = –26.03 (s) (**3_{Cs}**), –30.68 (s) (**2_{Cs}**), –33.83 (s) (Cu(III)), –84.04 (s), –112.05 (s), –116.80 (s), –150.34 (s), –150.40 (s) ppm. The signals that range from –84.04 to –150.48 ppm are decomposition products.

Temperature stability of the "$CuCF_3$" compounds formed from 1_{Cs}

In order to know the stability of the "$CuCF_3$" species respect to the temperature, two types of experiments were carried out. After performing the transmetalation reaction with 10 equivalents of CuI at room temperature (page 31), the filtered solutions were stirred at different temperatures (50 or 120 ºC). At 50 ºC, in 3 hours the specie $[Cu(CF_3)_2]^-$ (**2_{NBu4}**) had decreased by 15% and the specie containing one trifluoromethyl group (**3_{NBu4}**) by 14% and at 24 hours by 64% and 22% in total, respectively. At 120 ºC, the specie **2_{NBu4}** had decreased by 99% and the specie **3_{NBu4}**, by 98%.

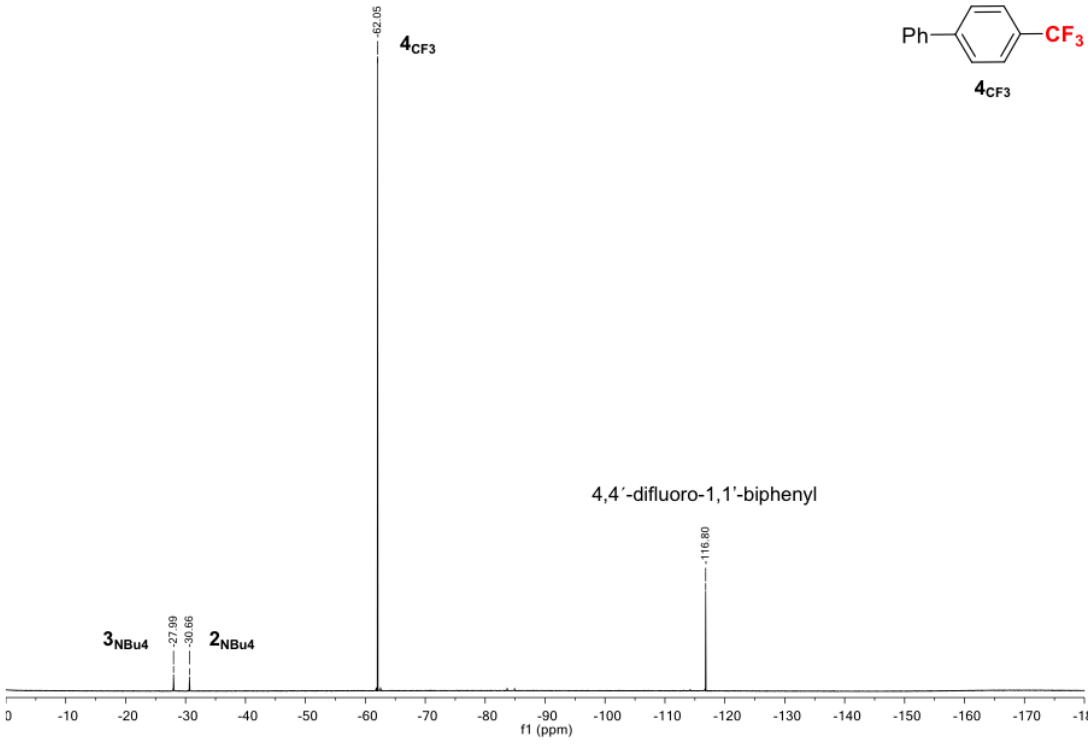
6.6. Synthesis and characterization of trifluoromethylated organic compounds 4_{CF3}, 5_{CF3}, 6_{CF3}, 7_{CF3} and 8_{CF3}

In an argon atmosphere glovebox, a crimped vial was charged with $(Cat)[Ag(CF_3)_2]$ [5.9 mg (Cat = Cs), 7.6 mg (Cat = NBu_4), 0.016 mmol] and the corresponding copper source (1 and 10 equivalents with respect to **1**). The mixture was dissolved in 0.6 mL of DMF and stirred at room temperature for 15 minutes. The solution was then filtered using a 0.2 mm PTFE filter and transferred to another crimped vial, that contained the organic substrate [0.0128 mmol (0.8 equiv) or 0.0256 mmol (1.6 equiv)] and a known amount of the internal standard, 4,4'-difluoro-1,1'-biphenyl. The mixture was stirred at 50 ºC (substrates **4_I**, **6_{Br}**, **7_I** and **8_I**) or 80 ºC (substrate **5_{Br}**) for the corresponding time (24 hours) and it was directly transferred to an NMR tube to obtain the ^{19}F NMR spectra.



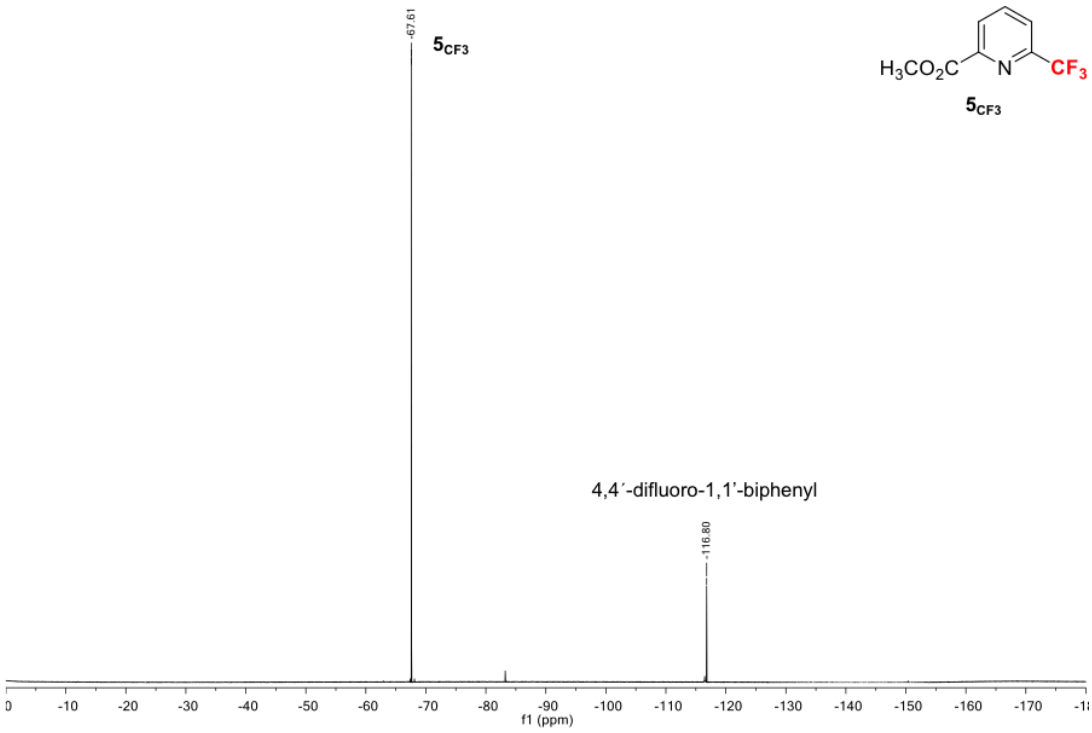
The quantification of the trifluoromethylated substrate is determined by taking into account the limiting reagent (aryl halide) with respect to the known amount of the internal standard.

6.6.1. Characterization of $\mathbf{4_{CF3}}$



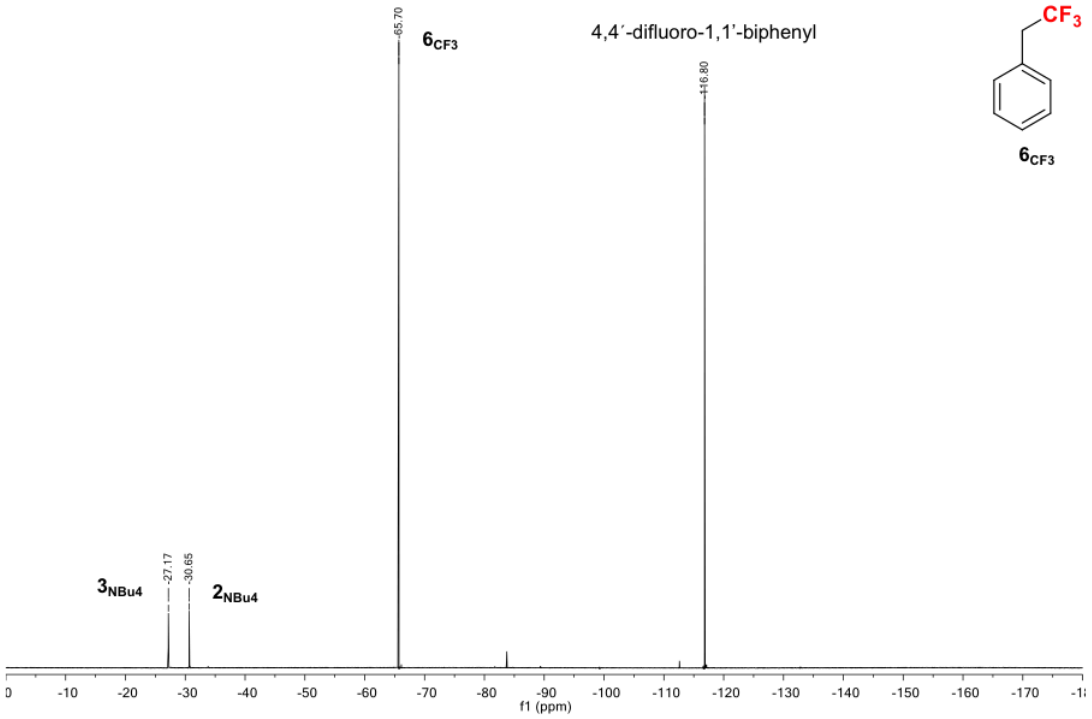
^{19}F NMR (400 MHz, acetone-d_6 insert, 25 ºC) δ –62.05 ppm.

6.6.2. Characterization of $\mathbf{5_{CF3}}$



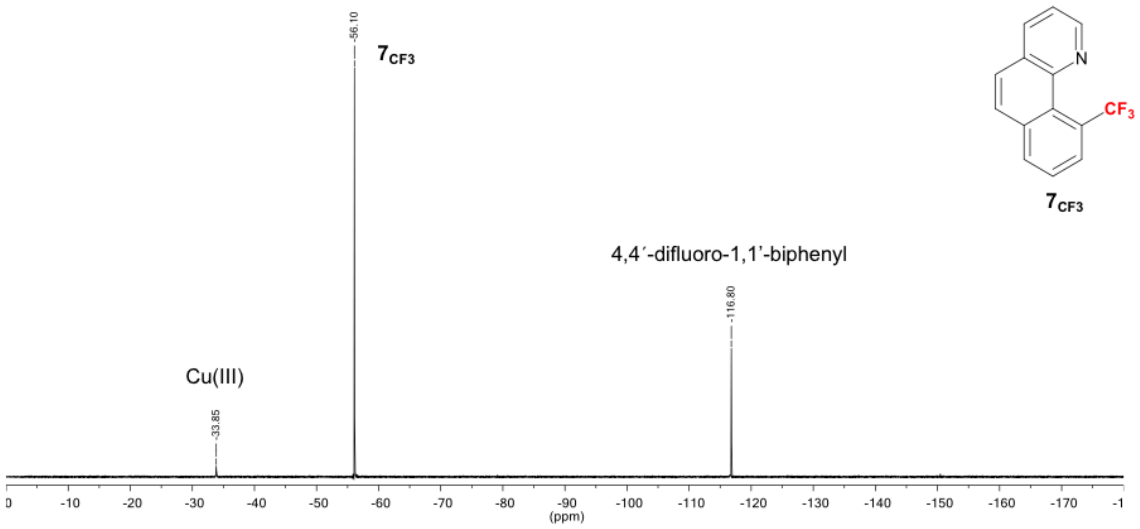
^{19}F NMR (400 MHz, acetone-d_6 insert, 25 ºC) δ –67.61 ppm.

6.6.3. Characterization of $\mathbf{6_{CF3}}$



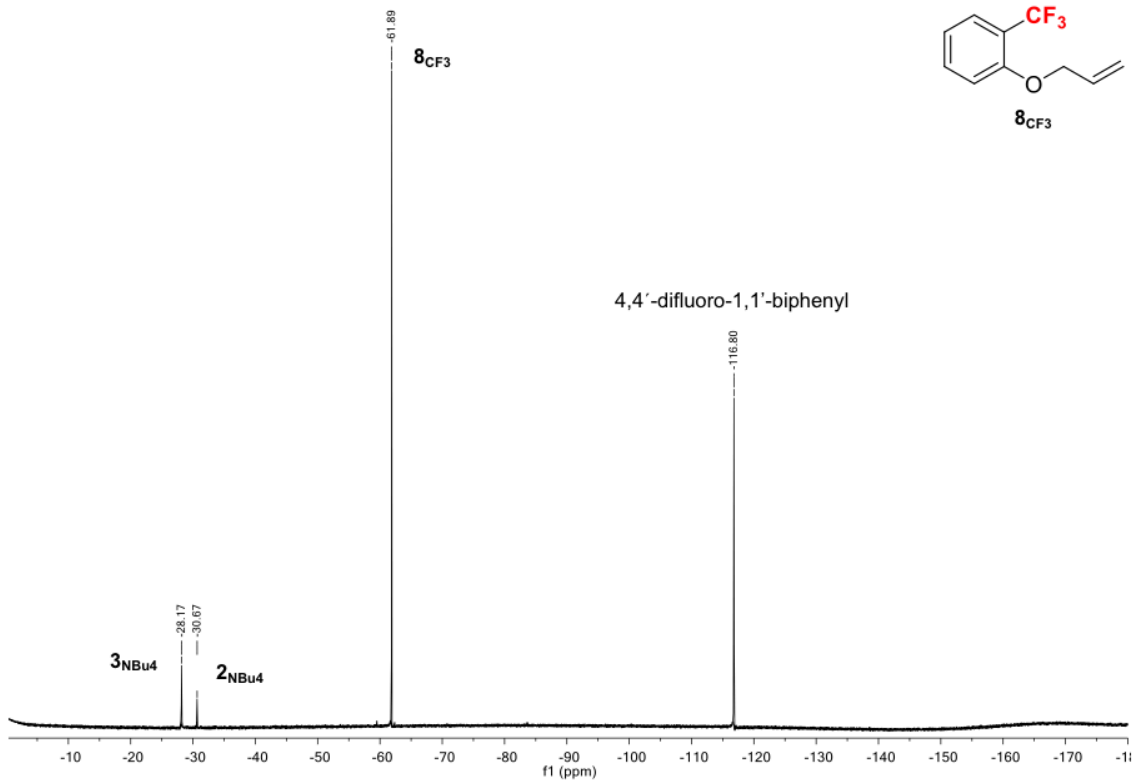
^{19}F NMR (400 MHz, acetone-d_6 insert, 25 ºC) δ –65.70 ppm.

6.6.4. Characterization of $\mathbf{7}_{CF3}$



^{19}F NMR (400 MHz, acetone-d_6 insert, 25 ºC) δ –56.10 ppm.

6.6.5. Characterization of $\mathbf{8}_{CF3}$



^{19}F NMR (400 MHz, acetone-d_6 insert, 25 ºC) δ –61.89 ppm.

7. Bibliography

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