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Comprehensive Study and Development of a Metal-Free and Mild Nucleophilic Trifluoromethoxylation.

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Abstract: Among the general interest in fluorinated compounds, trifluoromethoxylated molecules play a specific role. However, despite this interest, the development of efficient reagents to perform trifluoromethoxylation reactions remains a challenge. Here, 2,4-dinitro-trifluoromethoxybenzene (**DNTFB**) is used as a trifluoromethoxylating reagent to perform nucleophilic substitution under mild metal-free conditions with different leaving groups, including direct dehydroxytrifluoromethoxylation. A mechanistic study rationalized the reaction and subsequently proposed only three reaction conditions, depending on the reactivity of the starting substrates.

Introduction

Over the past few decades, fluorinated compounds have become extremely popular in many application areas, from materials^[1] to life sciences.^[2] This interest is mainly due to the specific properties brought by fluorinated groups to organic molecules.^[3] For example, significant modifications of the electronic properties as well as an increase of the lipophilicity of the compounds have been observed. In order to develop new products with very specific and modulated properties for specific applications, the search for innovative fluorinated groups has become very popular in recent years.^[4]

In this quest, trifluoromethylchalcogen groups have shown renewed interest.^[5] Specifically, the trifluoromethoxy group has recently attracted attention (Figure 1).^[6] Indeed, trifluoromethoxylated molecules have already found valuable applications in medicinal chemistry with riluzole (treatment of amyotrophic lateral sclerosis),^[7] pretomanid (anti-tuberculosis drug)^[8] and sonidegib (inhibitor of the Hedgehog signaling pathway)^[9] or in agrochemistry with thifluzamide (fungicide)^[10] and triflumuron (insect growth regulator).^[11] Even materials

science has used CF₃O-compounds, as exemplified by DMVC-OCF₃ (battery electrolyte additive).^[12]

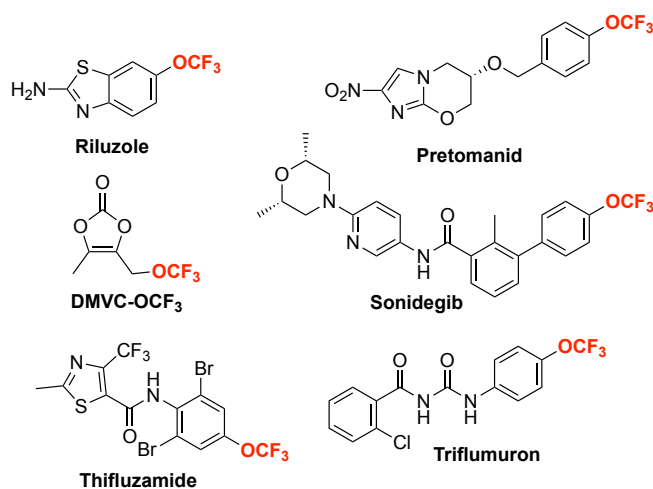


Figure 1. Examples of CF₃O-containing compounds.

Due to these successful applications, the chemistry of the CF₃O moiety has recently been reinvested in order to expand the still too limited synthetic toolbox available.^[5, 13] Specifically, direct trifluoromethoxylation, which is too rare, has been investigated in order to propose new efficient reagents.

Some radical reactions have been recently described using specific reagents.^[13b, 14] However, not only are these reagents expensive or explosive, but the reactions are limited to aromatic substrates and pose regioselectivity problems. Therefore, direct nucleophilic trifluoromethoxylation remains the most widely used reaction. Nevertheless, due to the easy collapse of the trifluoromethoxide anion into difluorophosgene and fluoride anion,

the design of specific reagents capable of generating CF_3O^- in situ is usually considered. Thus, several reagents have been described in the literature (Figure 2) with a certain efficiency but with drawbacks: high volatility (**TFMT**)^[15] or in gaseous form (**CF₃OMe**)^[16] costly and/or multi-step synthesis (**TFMS**)^[17] **TFBO**,^[17b, 18] **TFNf**^[19], synthesis from toxic reagents (**TFBz**)^[20] **CF₃OAg**^[21]. Very recently, Qing et al. updated the synthesis and use of **Phth-OCF₃**.^[22] For our part, we described, concomitantly with the Sanford group, the use of cheap 2,4-dinitrotrifluoromethoxybenzene (**DNTFB**) as an efficient source of a stable solution of CF_3O^- anion (**DDPyOCF₃**).^[23]

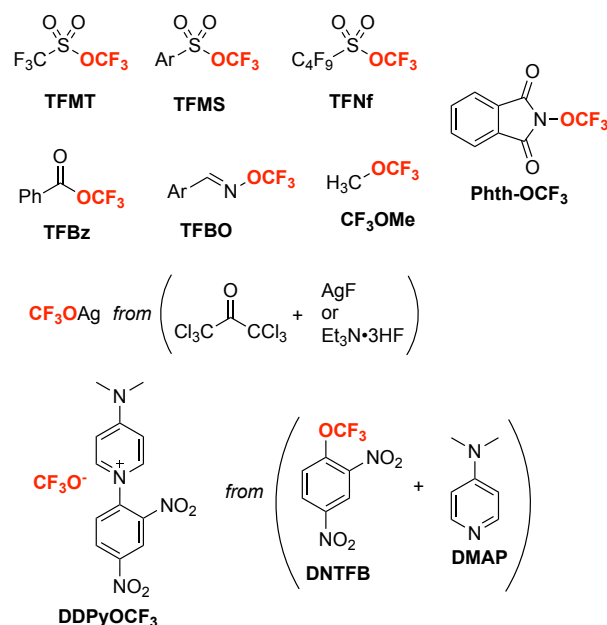


Figure 2. Reagents for direct nucleophilic trifluoromethoxylation.

All of these reagents were used to perform nucleophilic substitutions, but the majority of them required a stoichiometric amount of silver salts. **TFBO** was the first reagent to work under metal-free conditions.^[18] However, in addition to the problem of expensive access to the reagent, exacerbated by the need for overstepping the stoichiometry (5-6 equiv.), the reaction also requires excess base and, in some cases, the addition of HMPA. In addition, the majority of examples are primary alkyl iodides. In the case of **Phth-OCF₃**, no basic conditions were required, only Et_4NI or CsF was added. Again, primary alkyl iodides are the key substrates used and no real rationalization regarding the choice of additive (Et_4NI or CsF or $\text{Et}_4\text{NI}/\text{CsF}$) was provided.^[22]

While **DDPyOCF₃** was used by Sanford with a stoichiometric amount of silver salt to perform nucleophilic substitutions, primarily with benzyl bromides,^[23b] we demonstrated that similar substrates could also be trifluoromethoxylated under mild, metal-free conditions.^[23a] In our early work, the **DNTFB/DMAP** ratio was found to be a crucial parameter: an excess of **DNTFB** is required to provide a reservoir of the CF_3O^- anion to perform metal free substitutive trifluoromethoxylations. Based on this successful proof of concept, we decided to fully explore the reactivity of **DDPyOCF₃**, preformed in situ from **DNTFB/DMAP**, in metal-free nucleophilic substitutions with a wider variety of substrates and

leaving groups in order to provide a valuable and effective alternative to existing methods.

Results and Discussion

Since in our preliminary work concerning the study of **DDPyOCF₃** we established the efficient reactivity of the **DNTFB/DMAP** system with benzyl bromide,^[23a] we decided to first explore the influence of the leaving group under the same conditions (Table 1).

Table 1. Role of leaving groups in the S_N reaction with **DNTFB/DMAP**

Entry	X	Additive (equiv.)	2a (%) ^[a]
1	Br	-	81
2	I	-	68
3	OMs	-	82
4	Cl	-	5
5	Cl	Bu_4NI (0.1)	5
6	Cl	Bu_4NI (1)	13
7	Cl	Bu_4NI (3)	18
8	Cl	NaI (1)	3
9	Cl	KI (1)	65
10	Cl	RbI (1)	31
11	Cl	CsI (1)	49
12	Cl	$\text{KI} + 18\text{-crown-6}$ (1:1)	22
13	Cl	KI (2)	70
14	Cl	KI (3)	26
15	I	KI (2)	26

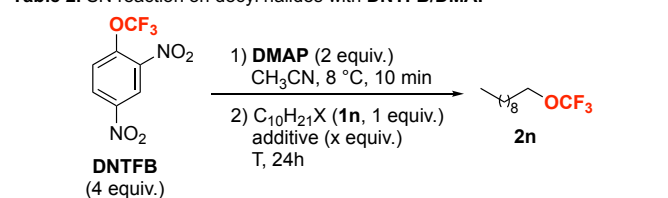
[a] Yields determined by ^{19}F NMR with PhCF_3 as internal standard.

While, unsurprisingly, good yields were also obtained from benzyl iodide (entry 2) or mesylate (entry 3), a disappointing result was observed with benzyl chloride (entry 4). Therefore, some additives were investigated in an attempt to improve the performance. Tetrabutylammonium iodide did not significantly lead to better results, regardless of the amount used (entries 5-7). For alkali iodides, NaI was ineffective (entry 8), while KI (entry 9) significantly improved the yield. Other alkali iodides RbI (entry 10) and CsI (entry 11) appeared less effective, although they promote the dissociation of ionic pairs. This negative effect of an overly dissociated counterion is confirmed by the worst result observed with $\text{KI}/18\text{-crown-6}$ as additive (entry 12). Finally, the optimal result was obtained with 2 equivalents of KI (entry 13) while a

higher amount was deleterious (entry 14). Compared to trifluoromethylations reaction based on **TFBO**,^[18] the reaction based on **DDPyOCF₃** works under milder conditions, without HMPA addition, and furnished a better yield. No alkyl chloride was tested with **Phth-OCF₃**.^[22]

After this initial reaction optimization, less reactive substrates were considered, as illustrated by the halodecanes (Table 2).

Table 2. SN reaction on decyl halides with **DNTFB/DMAP**



Entry	X	Additive (equiv.)	T (°C)	2n [a]
1	I	-	40	47
2	Br	-	40	11
3	I	-	80	94
4	Br	-	80	62
5	Cl	-	80	1
6	I	KI (2 equiv.)	80	93
7	Br	KI (2 equiv.)	80	92
8	Cl	KI (2 equiv.)	80	14
9	Cl	KI (3 equiv.)	80	22
10	Cl	KI (5 equiv.)	80	10
11	OMs	KI (2 equiv.)	80	90
12	OTs	KI (2 equiv.)	80	75

[a] Yields determined by ¹⁹F NMR with PhCF₃ as internal standard.

Unlike the benzyl series, modest to low yields were obtained with iodo- or bromodecane at 40 °C (entries 1-2). By increasing the temperature to 80 °C, excellent to satisfactory results were respectively observed (entries 3-4). On the other hand, chlorodecane could not be trifluoromethylated under these conditions, certainly due to the weaker nucleofugality of Cl. Inspired by the positive effect obtained previously with the addition of KI (Table 1, entry 13), similar conditions were tested. While logically no effect was observed with iododecane (entry 6), a significant improvement was obtained with bromodecane (entry 7). In the case of chlorodecane, a better, but still low, yield was obtained (entry 8). A larger excess of KI did not provide any relevant improvement (entries 9-10) and may even be detrimental (entry 10), possibly due to a solubility problem. Tosylate and mesylate also reacted under the same conditions to provide good to excellent yields (entries 11-12).

In order to rationalize the role of KI in the reaction, a mechanistic study was performed. First, we can logically assume that a Finkelstein reaction occurred to generate the most reactive iodine derivatives in situ. This assumption was confirmed by comparing similar results obtained using BnCl/KI or only BnI (Table 1, entries

13 and 2) or using bromodecane/KI or only iododecane (Table 2, entries 7 and 3). This was also confirmed by the rapid formation of iodo derivatives from bromodecane (Figure 3, blue curve) or from benzyl chloride (Figure 3, red curve) monitored by ¹H NMR. The role of this Finkelstein reaction was reinforced by the low yield obtained starting from chlorodecane, in the presence of KI. Indeed, the formation of the corresponding iododecane is very slow (Figure 3, green curve). Therefore, the competition between the substitution reaction and the thermal degradation of the CF₃O⁻ species is in favor of the undesired last case.

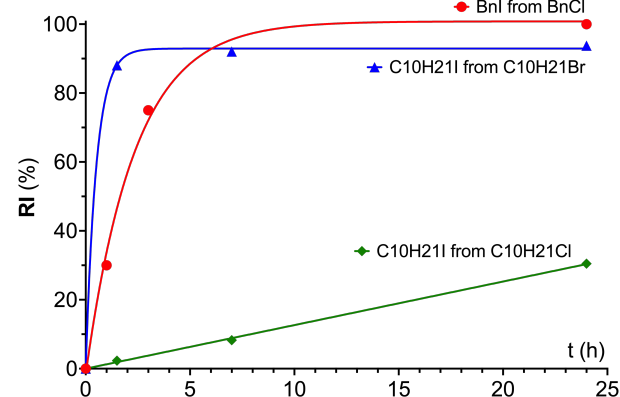


Figure 3. Follow-up by ¹H NMR of the formation of alkyl iodides.

However, this did not fully justify the necessary use of 2 equivalents of KI and the reason why other, more dissociated and therefore more reactive, iodide sources led to lower yields. In order to better understand this "potassium effect", an NMR study of the addition of KI to a solution of **DDPyOCF₃** (Figure 4) was carried out. In the ¹⁹F NMR spectra, a downfield shift and peak sharpening were observed (Figure 4A).^[24] A larger shift was observed in the ³⁹K NMR spectra between KI and newly formed species (Figure 4B). All these findings led us to consider the transient formation of CF₃OK.

To verify the importance of the formation of CF₃OK during the reaction, additional tests were performed (Scheme 1). First, CF₃OK turned out to be more stable at 80 °C than **DDPyOCF₃** (Scheme 1A). This could be explained by a closer ion pair in CF₃OK than in **DDPyOCF₃** leading to a "less free" CF₃O⁻ anion. Such thermal stability should help to promote the reaction since the reactive species CF₃O⁻ would disappear more slowly from the reaction medium. Second, some reactions with iododecane were performed in the presence of only 2 equivalents of **DNTFB** (i.e., without reservoir of CF₃O⁻ which counter-balances its degradation^[23a]) with and without KI (Scheme 1B). A better yield was clearly obtained in the presence of KI, demonstrating the importance of the CF₃OK species since the Finkelstein reaction could not play any role.

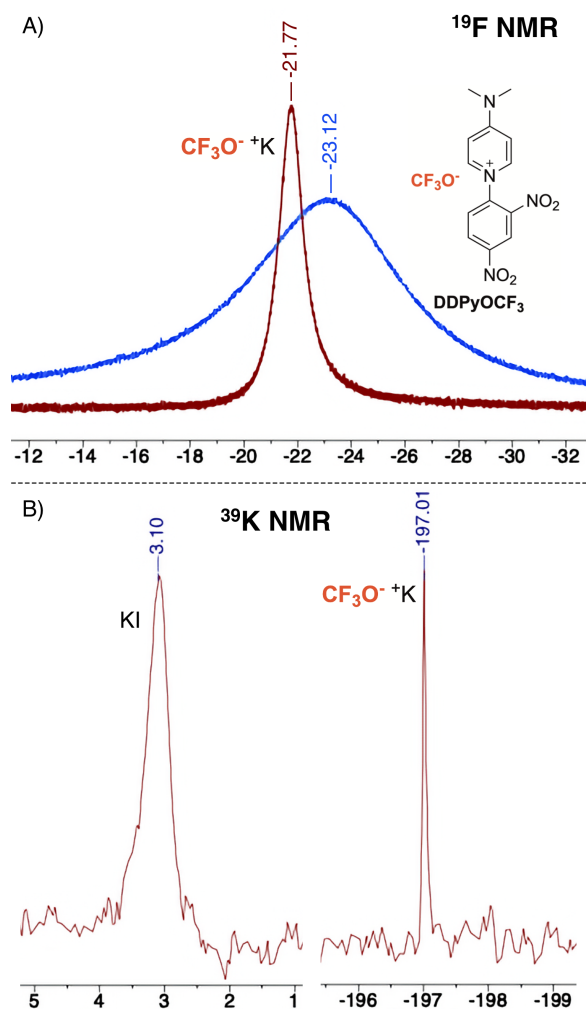
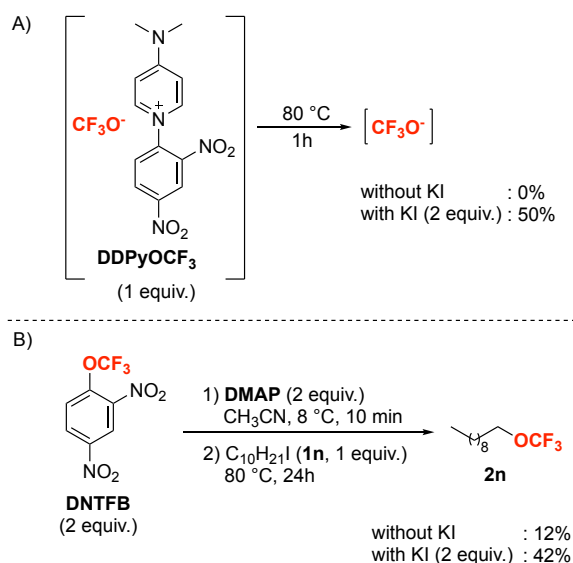


Figure 4. NMR spectra in CD₃CN of DDPyOCF₃, KI and a mixture of both. A) ¹⁹F NMR spectra of DDPyOCF₃ (blue) and of the mixture of DDPyOCF₃ and KI (red). B) ³⁹K NMR spectra of KI and of the mixture of DDPyOCF₃ and KI.



Scheme 1. Role of CF₃OK. A) Thermal stability of CF₃O⁻ species. B) Nucleophilic substitution on iododecane with or without KI addition. Yields determined by ¹⁹F NMR with PhCF₃ as internal standard.

At this stage, we finally had 3 reaction conditions: 40 °C (conditions 1); 40 °C with 2 equiv. KI (conditions 2); 80 °C with 2 equiv. KI (conditions 3). The comparison of these conditions, depending on the substrate, has been summarized in Figure 5. It became clear that the reactive (benzyl bromide) and less reactive (bromodecane) substrates did not require the same conditions; the optimal conditions for bromodecane even appeared deleterious for benzyl bromide. The same observations were made for the "moderately reactive" substrate (benzyl chloride) which required a compromise in terms of conditions (temperature used for benzyl bromide and additive used for bromodecane), the other conditions being detrimental.

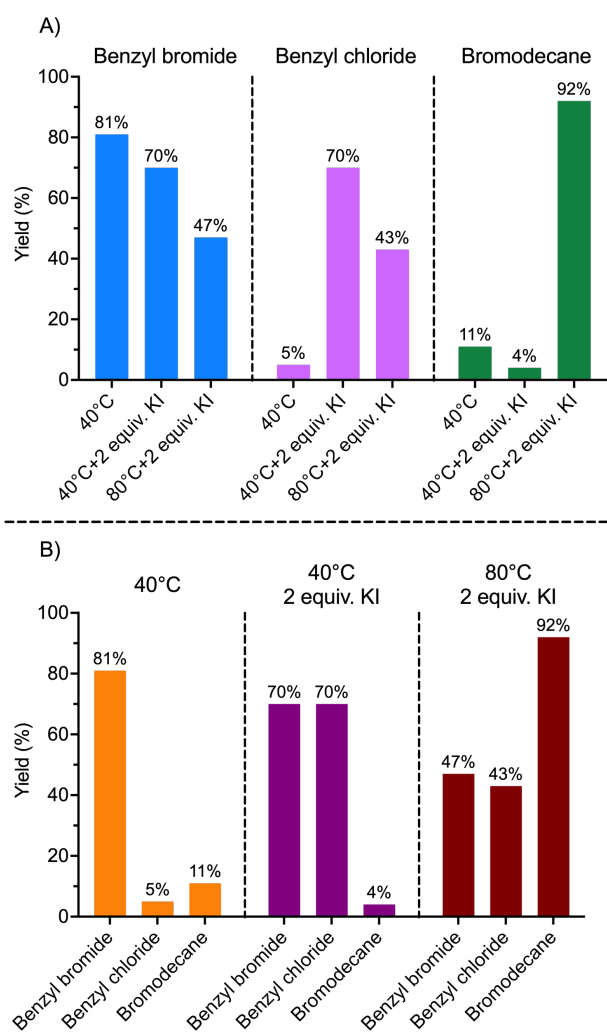
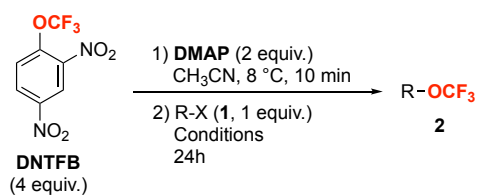
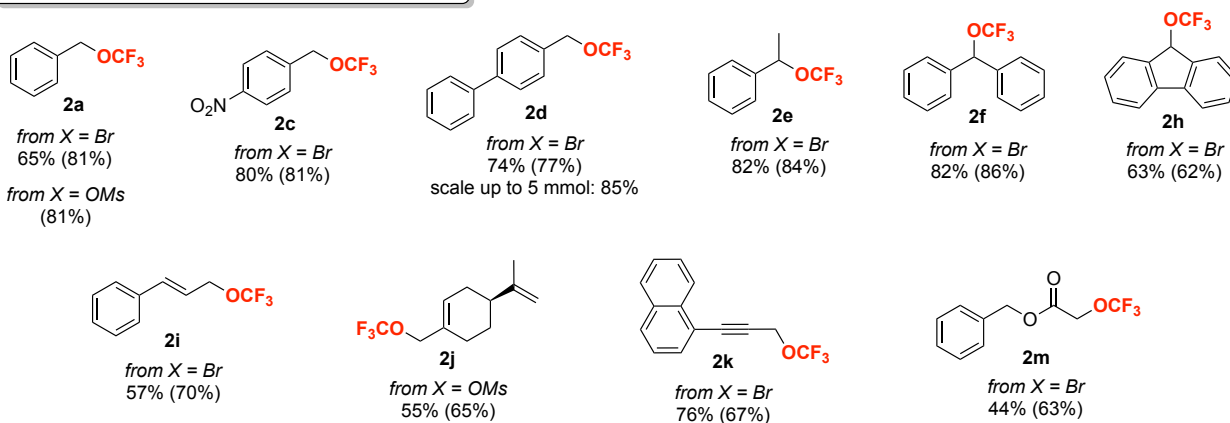


Figure 5. Comparison of reaction conditions. Conditions: DNTFB (4 equiv.) and DMAP (2 equiv.) premixed at 8 °C in CH₃CN, then addition of RX (1 equiv.) and finally KI (2 equiv.), heating for 24h. Yields determined by ¹⁹F NMR with PhCF₃ as internal standard. A) Comparison of conditions as a function of RX. B) Comparison of RX as a function of conditions.

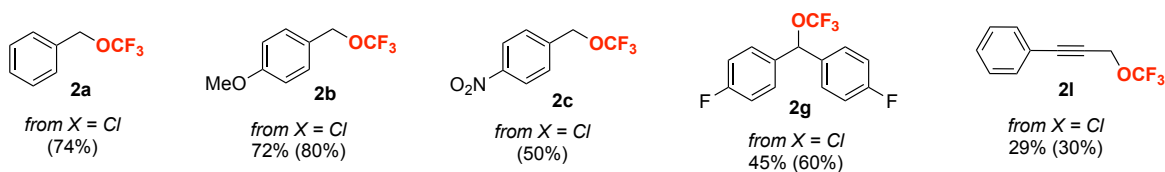


A)

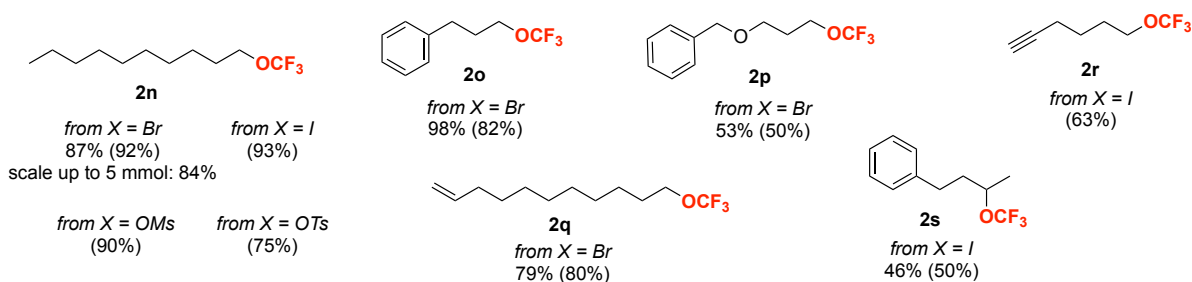
Conditions 1: 40°C (X=Br, OMs / activated substrates)



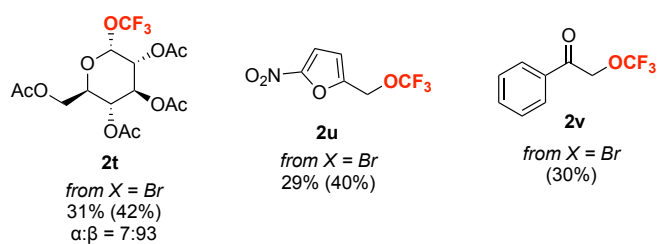
Conditions 2: 40°C + 2 equiv. KI (X=Cl / activated substrates)



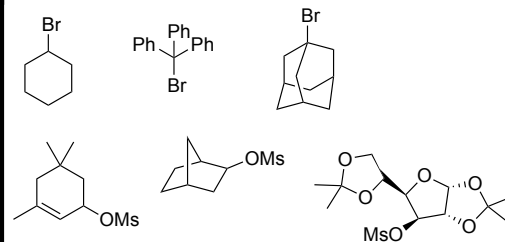
Conditions 3: 80°C + 2 equiv. KI (X=I, Br, OMs, OTs / non-activated substrates)



Specific conditions: RT (X=Br / activated and sensitive substrates)



B) Unsuccessful trifluoromethoxylation



Scheme 2. Scope of nucleophilic trifluoromethoxylation. Isolated yields (in parentheses, yields determined by ^{19}F NMR with PhCF_3 as internal standard).

From this comparative study, it appears that the addition of KI is detrimental to the most reactive substrate (benzyl bromide). This result could be rationalized by considering that while CF_3OK is more thermally stable, due to a less dissociated ionic pair, it is also less nucleophilic. In addition, iodinated derivatives of reactive substrates are certainly less thermally stable, as shown by the lower yields obtained starting from benzyl iodide (Table 1, entries 1-2 and 13, 15). Therefore, heating and KI addition may, depending on the substrate, have synergistic or opposite effects. In summary, with reactive substrates bearing a good leaving group, stabilization of CF_3O^- with potassium, and eventual formation of the iodo derivative by the Finkelstein reaction, are not necessary because the facile nucleophilic substitution is favored compared to the degradation of the trifluoromethoxide anion, whereas with non-activated substrates, the formation of CF_3OK is required to slow the decomposition of the anion in addition to in situ generation of the iodine derivative and heating to 80 °C to accelerate the substitution. With "intermediately reactive" substrates (showing an activated position but with a moderately effective leaving group), both CF_3O^- stabilization and Finkelstein exchange are required due to an unfavorable kinetic balance between substitution and decomposition of CF_3O^- , as well as with moderate heating to accelerate the reaction without overly promoting degradation of the intermediate iodinated substrate. With these streamlined conditions in hand, the extent of this metal-free nucleophilic trifluoromethoxylation was evaluated (Scheme 2).

The reaction gave good results in benzyl (**2a-h**) or allyl (**2i**) series with bromine or chlorine as leaving groups. Benzyl or allyl mesylates were also successfully trifluoromethoxylated for the first time (**2a, j**). Steric hindrance did not appear to interfere with the reaction (**2f-h**). With the benzyl bromides, the substituents on the aromatic ring did not play a significant role, as similar yields were obtained regardless of the electronic character of the substituents (**2a, c, d**). On the other hand, with benzyl chlorides, while similar results were observed with an electron donating group (**2a-b**), an electron withdrawing group (**2c**) contributed to decrease the yield. A bromoacetate derivative also provided the expected product in good yield (**2m**). With propargyl substrates, a good result was obtained with bromide (**2k**) while propargyl chloride led to a moderate yield (**2l**).

With non-activated compounds, alkyl bromides or iodides gave satisfactory to excellent results (**2n-s**). In contrast to the benzyl series, steric hindrance seemed to have more influence with a lower yield observed with the secondary product **2s** compared to the primary product **2o**. It should be noted that mesylate and tosylate were also trifluoromethoxylated in similar or slightly lower yields than the brominated substrates (**2n**), respectively.

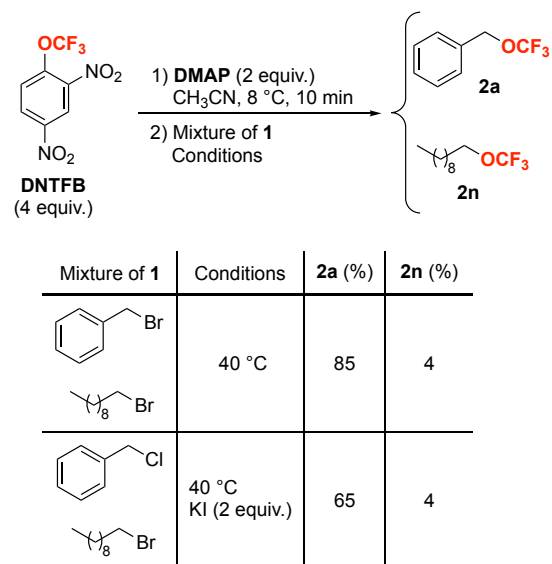
The reaction was successfully carried to 5 mmol under conditions 1 (**2d**) and 3 (**2n**) in similar yields.

Highly reactive and sensitive substrates required specific conditions to promote reaction rather than degradation. In these specific cases, room temperature, without KI, was preferred to achieve optimal but average yields (**2t-v**).

Nevertheless, highly hindered compounds failed to react under all conditions (Scheme 2B).

Finally, having a variety of conditions, depending on the electrophile, is an advantage to promote the chemoselectivity of the reaction. To demonstrate this, competitive trifluoromethoxylations between bromodecane and benzyl bromide or benzyl chloride, using respectively conditions 1 or 2

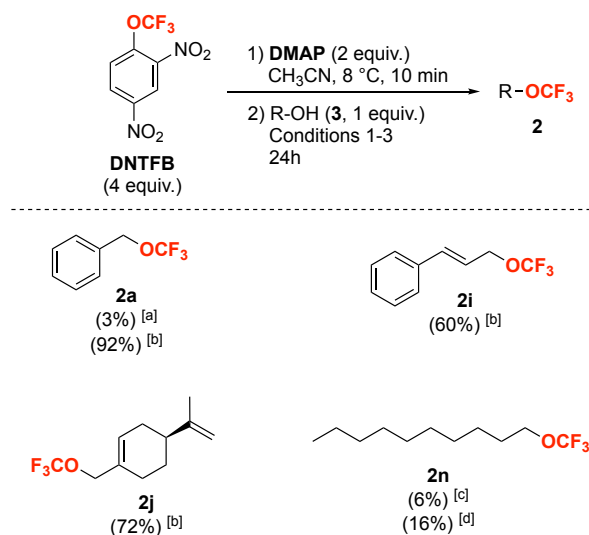
(see Scheme 2) have been performed (Scheme 3). The trifluoromethoxylation of benzyl halides (**2a**) was found to be largely favoured, with only a small amount of trifluoromethoxydecane (**2n**) formed.



Scheme 3. Competitive trifluoromethoxylations. Yields determined by ^{19}F NMR with PhCF_3 as internal standard.

Mesylates and tosylates were successfully trifluoromethoxylated (Scheme 2, **2a, j, n**) but these substrates must be previously synthesized from the corresponding alcohols. A direct trifluoromethoxylation of the alcohol would be an interesting alternative to save time and steps. Only four examples of direct dehydroxytrifluoromethoxylation have been described in the literature.^[21a, 22, 25] Lin and Xiao described the $\text{CF}_3\text{OAg}/\text{PPh}_3/\text{I}\text{CH}_2\text{CH}_2\text{I}$ system (through an in situ formation of iodide derivatives),^[25a] also used later by Schoenebeck,^[21a] to perform this reaction. Tang used a **TFMS** reagent to perform direct dehydroxytrifluoromethoxylations of alcohols. From the mechanistic point of view, **TFMS** generates the CF_3O^- anion which, in part, degrades to difluorophosgene to convert the alcohols to fluoroformates. The latter can then be substituted with the remaining CF_3O^- anion, in DMF/HMPA as solvent.^[25b] Qing applied the same approach with **Phth-OCF₃** on a single example.^[22]

As we had previously demonstrated the ability of **DDPyOCF₃** to generate difluorophosgene,^[26] we considered the possibility of performing a direct dehydroxytrifluoromethoxylation, similar to Tang but in a simpler solvent and with a cheaper reagent, to extend the study of the reactivity of our **DNTFB/DMAP** system (Scheme 4).



Scheme 4. Direct dehydroxytrifluoromethoxylation. Isolated yields (in parentheses, yields determined by ^{19}F NMR with PhCF_3 as internal standard). [a] Conditions 1: 40 °C, [b] Conditions 2: 40 °C, KI (2 equiv.), [c] Conditions 3: 80 °C, KI (2 equiv.), [d] Conditions 3, but stirred at 20 °C for 20 min before heating to 80 °C.

With the benzyl alcohol as activated substrates (leading to **2a**), conditions 2 (40 °C, KI) were required, certainly due to a nucleofugality of the fluoroformate group close to that of Cl. Under these conditions, good results were obtained with other activated substrates leading to **2i**, **j**. However, in the case of non-activated decanol, only low yields were obtained (**2n**), confirming the low nucleofugality of the fluoroformate group. The best yield, although still low, was obtained by stirring the reaction medium at 20 °C to preform the fluoroformate (confirmed by ^{19}F NMR) before heating to 80 °C. This method is complementary to the prior formation of a leaving group for the reactive substrates, with similar yields obtained (**2a**, **j**).

Conclusion

In conclusion, this work confirms that the DDPyOCF_3 salt, formed in situ from the cheap **DNTFB** / **DMAP** system, is a valuable reagent to synthesize trifluoromethoxylated compounds by nucleophilic substitution of halides or sulfonates under mild metal-free conditions. The precise study of the reaction allowed to propose a rational approach with only three well established conditions depending on the reactivity of the starting substrates. In particular, an interesting specific role of the potassium cation was demonstrated and the synthetic interest of the CF_3OK species was introduced. Interestingly, the direct dehydroxytrifluoromethoxylation of alcohols with the **DNTFB** / **DMAP** system also proved feasible. This study will contribute to reinforce the important role of **DNTFB** in the fluorine chemistry toolbox.

Experimental Section

Trifluoromethoxylation reaction – Typical procedures:

Conditions 1: In a 10 mL vial, **DNTFB** (310 μL , 2 mmol, 4 equiv.) was added in one portion into a stirred solution of **DMAP** (120 mg, 1 mmol, 2 equiv.) in 1.5 mL of anhydrous CH_3CN . The vial is closed and the reaction mixture is stirred in an ice bath (ca 8 °C) during 5 min (of note, the reaction mixture becomes orange immediately after **DNTFB** addition and quickly turns into yellow). Then, the tube is opened to add the substrate **1** (0.5 mmol, 1 equiv.) and closed immediately after. The reaction mixture is stirred 24 h at 40 °C. Then, the reaction is cooled down. Conversion was determined by ^{19}F NMR with PhCF_3 as an internal standard. The reaction mixture was partitioned in between pentane and water. The aqueous layer was extracted with pentane and the combined organic layers were washed with H_2O , dried over MgSO_4 , filtered and concentrated to dryness. The crude residue was purified by flash chromatography to produce the desired product.

Conditions 2: In a 10 mL vial, **DNTFB** (310 μL , 2 mmol, 4 equiv.) was added in one portion into a stirred solution of **DMAP** (120 mg, 1 mmol, 2 equiv.) in 1.5 mL of anhydrous CH_3CN . The vial is closed and the reaction mixture is stirred in an ice bath (ca 8 °C) during 5 min (of note, the reaction mixture becomes orange immediately after **DNTFB** addition and quickly turns into yellow). Then, the tube is opened to add KI (1 mmol, 2 equiv.) and the substrate **1** (0.5 mmol, 1 equiv.) and closed immediately after. The reaction mixture is stirred 24 h at 40 °C. Then, the reaction is cooled down. Conversion was determined by ^{19}F NMR with PhCF_3 as an internal standard. The reaction mixture was partitioned in between pentane and water. The aqueous layer was extracted with pentane and the combined organic layers were washed with H_2O , dried over MgSO_4 , filtered and concentrated to dryness. The crude residue was purified by flash chromatography to produce the desired product.

Conditions 3: In a 10 mL vial, **DNTFB** (310 μL , 2 mmol, 4 equiv.) was added in one portion into a stirred solution of **DMAP** (120 mg, 1 mmol, 2 equiv.) in 1.5 mL of anhydrous CH_3CN . The vial is closed and the reaction mixture is stirred in an ice bath (ca 8 °C) during 5 min (of note, the reaction mixture becomes orange immediately after **DNTFB** addition and quickly turns into yellow). Then, the tube is opened to add KI (160 mg, 1 mmol, 2 equiv.) and the substrate **1** (0.5 mmol, 1 equiv.) and closed immediately after. The reaction mixture is stirred 24 h at 80 °C. Then, the reaction is cooled down. Conversion was determined by ^{19}F NMR with PhCF_3 as an internal standard. The reaction mixture was partitioned in between pentane and water. The aqueous layer was extracted with pentane and the combined organic layers were washed with H_2O , dried over MgSO_4 , filtered and concentrated to dryness. The crude residue was purified by flash chromatography to produce the desired product.

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Keywords: 2,4-dinitro-trifluoromethoxybenzene • Fluorine • Nucleophilic substitution • Trifluoromethoxylation • Trifluoromethoxide anion

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