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Direct trifluoromethoxylation without OCF₃-carrier via in-situ generation of fluorophosgene

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Abstract: Owing to the high interest into the OCF₃ group for pharmaceutical and agrochemical applications, trifluoromethoxylation received great attention in the last years with several new methods to perform it. Yet, it most often requires the beforehand preparation of specific F₃CO⁻ transfer reagents, which can be toxic, expensive, unstable and/or which generate undesired side-products upon consumption. To circumvent this, the *in-situ* generation of gaseous fluorophosgene from triphosgene, its conversion by fluoride into the OCF₃ anion and the direct use of the latter in nucleophilic substitutions is an appealing strategy, which, although it has been approached recently, has not been fully exploited. We disclose herein our efforts towards this aim.

Introduction

Sometimes called “super-halogen”, the trifluoromethoxy group shows remarkable electronic properties. It is slightly more electron withdrawing than fluorine by induction (OCF₃: $\chi=3.7$, $\sigma_I=+0.50$ to $+0.55$ / F: $\chi=3.98$, $\sigma_I=+0.51$ to $+0.54$) and also less electron-donating by resonance (OCF₃: $\sigma_R=-0.13$ to -0.18 / F: $\sigma_R=-0.32$ to -0.40).^[1–5] One reason for these special properties is the hyperconjugation of the non-bonding p orbitals of the oxygen atom with the antibonding σ^* orbitals of the C-F bonds. As a result, in the case of trifluoromethoxylated aromatics, the trifluoromethoxy group lies in an orthogonal plane with regard to the aromatic ring, unlike its non-fluorinated analogue (OMe).^[5–7] The lipophilicity of this group is also noticeable since it is one of the most hydrophobic moieties (Hansch lipophilicity parameter $\pi = +1.04$).^[8,9] Such original characteristics make understandable its presence in pharmaceutical and agrochemical bioactive ingredients. Among the general strategies to access the C–OCF₃ motif, the direct introduction of the already constructed OCF₃ group onto molecules is arguably the most appealing strategy, as it allows functionalization at any stage of a synthesis. Whereas radical trifluoromethoxylation has been successfully used only on (hetero)arenes so far, anionic trifluoromethoxylation is more general and has been more studied, although it remains challenging.^[8,10–14] One of the reasons is the easy decomposition of the trifluoromethoxy anion into fluorophosgene and fluoride^[15], and the poor nucleophilicity of trifluoromethoxide. Nevertheless, last decades witnessed an increasing number of reports concerning the introduction of trifluoromethanol onto different

structures thanks to trifluoromethoxylating reagents especially designed for this reaction such as trifluoromethyl trifluoromethanesulfonate (TFMT) whose major drawbacks are the low boiling point and high cost,^[16–20] trifluoromethyl arylsulfonates (TFMS) which has to be synthesized from the corresponding sulfonic acids and 1-(trifluoromethyl)-1,2-benziodoxol-3(1*H*)-one (Togni's reagent)^[21,22] or 2,4-dinitrotrifluoromethoxybenzene which afford trifluoromethoxylated products in low yield.^[23] All these reagents release F₃CO⁻ upon activation by fluoride anions. Very recently, trifluoromethyl methyl ether, a gas of comparable price with regard to TFMT, was used as trifluoromethoxide source by treatment with tertiary amine nucleophiles,^[25] and *O*-trifluoromethyl benzaldoximes (TFBO) were shown to liberate F₃CO⁻ in the presence of cesium carbonate as Brønsted base (Figure 1).^[26]

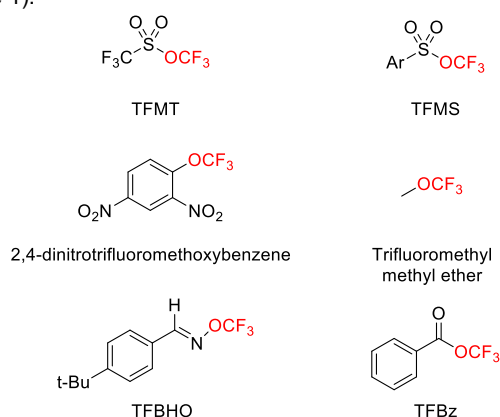


Figure 1: Trifluoromethoxide transfer reagents

However, using a trifluoromethoxylating reagent, besides adding at least one step to the global procedure, leads upon generation of the F₃CO⁻ anion to the presence of a side-product in the reaction mixture (sulfonyl-, aryl- or acyl fluoride for example). An alternate strategy would be to prepare in situ and stabilize the trifluoromethoxide anion and to react it directly with the substrate. Early work on this strategy consisted in forming, from fluorophosgene and a fluoride source, a trifluoromethoxide salt, which could be used in nucleophilic substitution.^[27–29] However, the use of COF₂ gas is quite hazardous and represents a serious limitation. Recently, an interesting approach for the in situ generation and use of trifluoromethoxide was reported by Xiao et

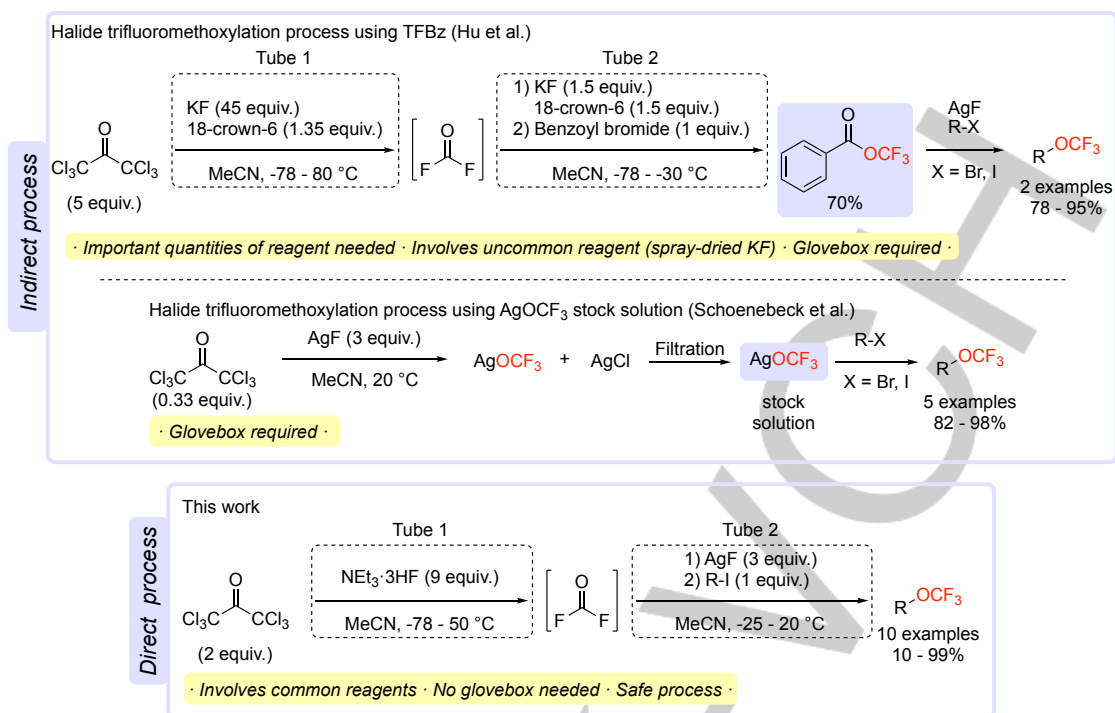


Figure 2 Halide trifluoromethoxylation processes involving fluorophosgene generation from triphosgene

al., where difluorocarbene is oxidized, forming COF_2 , which subsequently reacts with AgF to form the targeted F_3CO^- that can al., where difluorocarbene is oxidized, forming COF_2 , which subsequently reacts with AgF to form the targeted F_3CO^- that can be engaged in nucleophilic substitutions with various $\text{C}(\text{sp}^3)$ halides.^[30] Notably, this approach generates several side-products coming from the carbene source and the oxidant.

Another user-friendly procedure was described by Hu and coworkers in their preparation of trifluoromethyl benzoate (TFBz), a trifluoromethoxylating reagents effective in various kinds of trifluoromethoxylation reactions.^[24] These authors treated triphosgene (5 equiv.) with large amounts of spray-dried potassium fluoride (45 equiv.), leading in situ to the generation of an overpressure of gaseous fluorophosgene. The latter was trapped after its transfer onto a fluoride suspension, affording the trifluoromethoxide anion, which was able to perform a nucleophilic substitution on benzoyl bromide to finally provide TFBz (*vide supra*).^[24] Finally, while our present manuscript was in preparation, Schoenebeck et al. reported, in line with Hu's work, the *ex situ* preparation of AgOCF_3 by mixing triphosgene and silver fluoride. Interestingly, the final stock solution of this salt was shown to be very stable and could be used in trifluoromethoxylation and other reactions; however, a filtration of insoluble silver salts in a glovebox was required.^[31]

Consequently, an efficient process combining the formation of both COF_2 and then F_3CO^- , and the direct use of the latter in trifluoromethoxylation, altogether in situ without the intermediate formation and isolation of a trifluoromethoxylating reagent, would still be highly valuable. We describe herein our efforts towards this aim (Figure 2).

Results and Discussion

The approach described by Hu and co-workers^[24] seemed to us the best starting-point as it should be transposable to a direct process not involving an intermediate trifluoromethoxylation reagent (TFBz) by just replacing benzoyl bromide with a series of substrates. In their paper, the authors described a screening of fluoride sources and conditions in THF for the conversion of fluorophosgene into F_3CO^- , as well as a study of the relative amounts of fluoride sources and 18-C-6 crown ether in both stages —i.e. F_2CO generation and conversion to F_3CO^- .

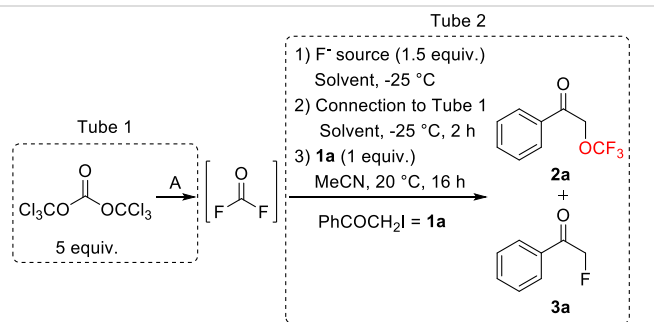
We started our study by choosing α -iodoacetophenone **1a** as a model substrate and using conditions similar to the ones employed by Hu et al. except for the temperature in Tube 1 — where fluorophosgene is generated—, which was maintained at 50 °C instead of 80 °C to prevent condensation of acetonitrile in the second tube, and for temperature in Tube 2 —where the F_3CO^- anion is formed—, which was initially of -25 °C instead of -78 °C for compatibility with more solvents. However, in our case, no desired trifluoromethoxylation product (**2a**) was observed (Table 1, entry 1). As we observed a gas generation in the first tube, we believed the fluorophosgene generation to be effective. Consequently, we first focused on the conditions in the second tube. Therefore, we moved to silver fluoride in the absence of 18-C-6 (entry 2), which provided a mixture of **1a**, **2a** and monofluorinated product **3a** in a 27/37/36 ratio. When the solvent was switched to acetonitrile and using the KF/18-C-6 combination again (entry 3), we were pleased to observe a 42/58 ratio between **1a** and **2a** and no monofluorinated **3a**. Finally, when used in acetonitrile, AgF gave a full conversion of the starting material into the trifluoromethoxylated product (entry 4) and the following studies were conducted using it as fluoride source in Tube 2.

At this point, we noticed that the overpressure of toxic fluorophosgene needed before its transfer onto the fluoride suspension could be a safety issue. To avoid this problem, we used a slightly different method for our following experiments,

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which consists in allowing the transfer of the generated gas onto the fluoride salt (here, AgF) suspension as soon as it is generated. This allows the pressure to be distributed in the whole reaction set-up and gratifyingly gave the same results (Table 1, entry 5). We therefore pursued our study according to this technical modification (Table 1).

Table 1: Modifications of Hu's conditions for the trifluoromethoxylation of α -iodoacetophenone



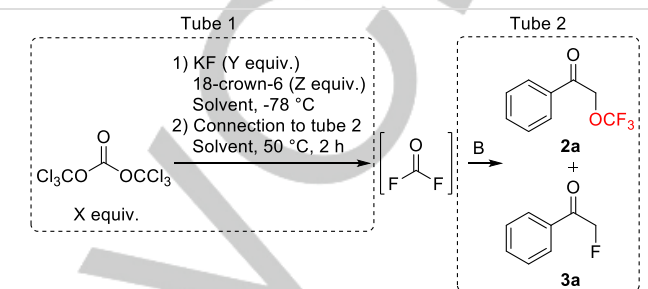
Entry	Solvent	F ⁻ source	1a/2a/3a ratio ^{[a],[b]}
1	THF	KF/18-C-6 1:1	100/nd/nd
2	THF	AgF	27/37/36
3	MeCN	KF/18-C-6 1:1	42/58/0
4	MeCN	AgF	0/100/0
5 ^[c]	MeCN	AgF	0/100/0

Conditions A : 1) KF (45 equiv.), 18-crown-6 (1.35 equiv.), MeCN, -78 °C. 2) MeCN, 50 °C, 1h. 3) Connection to Tube 2, MeCN, 50 °C, 2h [a] ¹H NMR ratio in the crude mixture using the methylene signal of each compound as characteristic signal. [b] nd = not detected. [c] Gas transfer during the whole process

We decided therefore to decrease these amounts to the most atom-economical point without affecting yields. When we reduced the equivalents of triphosgene and KF in Tube 1 to respectively 3 and 32 equivalents with 1.35 equivalents of crown ether, the results remained unchanged (Table 2, entries 1 and 2). We were also interested in decreasing the quantity of crown ether used. Consequently, we carried out an experiment with respectively 3, 32 and 1 equivalents of triphosgene, KF and 18-C-6 (Table 2, entry 3), which gave similar results. Performing the reaction in the absence of crown ether proved detrimental, as a significant amount of monofluorinated product **3a** was formed (Table 2, entry 4). Following this idea, instead of using 18-C-6 as additive to solubilize KF and enhance its reactivity in acetonitrile, we wondered if diglyme as solvent would be suitable for the reaction in Tube 1; unfortunately, the conversion of the starting material was incomplete under these conditions (Table 2, entry 5). Hence, we turned back to the use of acetonitrile as solvent and 18-C-6 as additive. We carried out reactions involving respectively, 3 and 27 equivalents (Table 2, entry 6), 2 and 18 equivalents (entry 7), 2 and 12 equivalents (entry 8) of triphosgene and KF, always with a proportional amount of crown ether with regard to KF. The two first experiments gave an unchanged yield (Table 2, entries 5–6). With the last ratio (triphosgene/KF = 1/6), which is theoretically the lowest possible amount of KF relative to triphosgene to achieve full conversion of the latter into COF₂, unreacted substrate **1a** was observed and the desired product **2a** was formed along undesired **3a** (Table 2,

entries 7 vs. 8), probably indicating an inefficient generation of COF₂. Accordingly, we maintained a constant 1/9/0.27 ratio of triphosgene/KF/18-C-6 and decreased the global number of equivalents, with reactions involving 1.5 and 1 equivalent of triphosgene and the proportional amounts of other reagents in Tube 1 (Table 2, entries 9–10). In these experiments, the monofluorinated product **3a** was formed in significant amounts, highlighting the lower limits for the quantities of reagents for fluorophosgene generation (Table 2).

Table 2: Study of reactions parameters used in Tube 1 for fluorophosgene generation



Entry	X	Y	Z	Solvent	1a/2a/3a ratio ^{[a],[b]}
1	5	45	1.35	MeCN	0/100/0
2	3	32	1.35	MeCN	1/99/0
3	3	32	1	MeCN	3/97/0
4	3	32	0	MeCN	0/76/24
5	3	32	0	Diglyme	29/38/33
6	3	27	0.8	MeCN	5/95/0
7	2	18	0.6	MeCN	0/100/0
8	2	12	0.36	MeCN	11/77/12
9	1.5	13.5	0.4	MeCN	0/78/22
10	1	9	0.26	MeCN	11/12/77

Conditions B : 1) AgF (1.5 equiv.), MeCN, -25 °C. 2) Connection to Tube 1, MeCN, -25 °C, 2h. 3) **1a** (1 equiv.), MeCN, 20 °C, 16h. [a] ¹H NMR ratio in the crude mixture using the methylene signal of each compound as characteristic signal. [b] nd = not detected

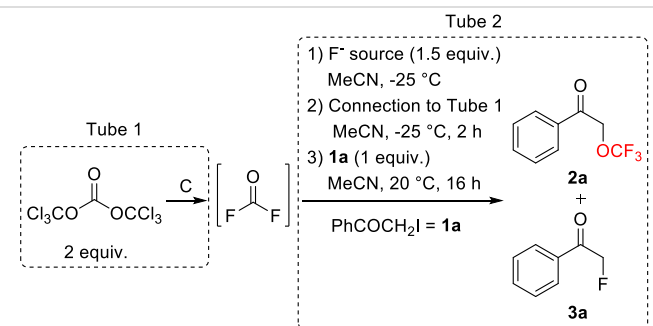
We then considered increasing the fluorophosgene pressure by reducing the free volume of the reaction, i.e. reducing the glassware volume. By this means, we would possibly be able to keep decreasing the amounts of reagents. Unfortunately, despite an important search for the good system, the reproducibility of the obtained results was not satisfying. Finally, the reaction conditions demanding 2 equivalents of triphosgene, 18 equivalents of potassium fluoride and 0.6 equivalent of crown ether were selected for the generation of fluorophosgene (Tube 1).

The next parameter to be examined was the fluoride source in the second tube, for the generation of the trifluoromethoxide anion. Tetrabutylammonium fluoride (TBAF), tetramethylammonium fluoride (TMAF), tetrabutylammonium difluorotriphenylsilicate (TBAT) and cesium fluoride were assessed as potential replacements for AgF; however, they all proved inefficient (Table 3). Lastly, the amount of silver fluoride employed in Tube 2 was investigated. When the reaction was

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carried out with only one equivalent of the metal salt, the amount of trifluoromethoxylated product **2a** in the crude material decreased to 73% (Table 3, entry 7).

Table 3: Screening of fluoride sources in Tube 2 for the generation of F_3CO^-



Entry	F ⁻ sources	1a/2a/3a ratio ^{[a],[b]}
1	AgF	0/100/0
2	TBAF ^[c]	90/0/10
3	TMAF	74/0/26
4	TBAT	94/6/0
5	CsF	100/0/0
6	Flamed CsF	95/4/1
7	AgF ^[d]	22/73/5

Conditions C: 1) KF (18 equiv.), 18-crown-6 (0.6 equiv.), MeCN, -78 °C. 2) Connection to Tube 2, MeCN, 50 °C, 2h. [a] ¹H NMR ratio in the crude mixture using the methylene signal of each compound as characteristic signal. [b] nd = not detected. [c] 1 M in THF. [d] 1 equiv of AgF was used

Unfortunately, while studying the scope of the reaction, we observed some reproducibility issues due to the quality of the commercial spray-dried potassium fluoride which must be further dried and handled very carefully. Additionally, its cost and its low availability pushed us to envision another fluoride source in Tube 1. To this end, a reaction involving $\text{NEt}_3 \bullet 3\text{HF}$ instead of KF/18-C-6 to generate fluorophosgene was carried out. Triethylamine trihydrofluoride being less expensive than potassium fluoride, it could even be used in larger amount to promote more efficiently the generation of fluorophosgene gas. Also, the use of $\text{NEt}_3 \bullet 3\text{HF}$ makes the mixture of Tube 1 homogenous, which would be suitable for an industrial application. After a quick optimization of the reaction conditions to the employment of $\text{NEt}_3 \bullet 3\text{HF}$, the use of 3 equivalents of triphosgene, 9 equivalents of $\text{NEt}_3 \bullet 3\text{HF}$ in Tube 1 and 3 equivalents of AgF in Tube 2 was determined as the best conditions.

Starting with benzyl-2-iodoacetate **1b** as an α -iodoester, the trifluoromethoxylated product was obtained in excellent yield. (Table 4, entry 2) Benzylic iodides 4-(iodomethyl)benzonitrile **1c** and 1-bromo-4-(iodomethyl)benzene **1d** provided good results (Table 4, entries 3–4). An excellent yield was also obtained for the reaction using iodoundecane **1e** as starting material (Table 4, entry 5). When submitted to the reaction conditions, 1-iodoethyl-2-benzene **1f** also provided good results although purification proved difficult (Table 4, entry 6). Unsurprisingly, reactions involving bromides as substrates provided lower yields as shown by the reaction with bromoacetophenone **1g** (Table 4, entry 7).

Trifluoromethoxylation of 3-iodoprop-1-ynylbenzene **1h** indicates that the presence of an alkyne does not perturbate the reaction (Table 4, entry 8). Reactions with secondary iodides **1i-k** were also carried out, however, lower yields were obtained (Table 4, entries 9–11). As often when it comes to trifluoromethoxylated products, isolated yields are in some cases much lower than NMR yields because of the difficult purification from starting materials and monofluorinated side-products (Table 4).

Table 4: Scope of the reaction

Entry	R-X (1)	¹ H NMR ratio ^{[a],[b]}			¹⁹ F NMR yield ^[c] (isolated yield)
		(1)	(2)	(3)	
1		-	100	-	93% (92%)
2		-	100	-	90% (94%)
3		-	100	-	(87%)
4		-	100	-	70% (74%)
5		-	100	-	Quant. (99%)
6		-	90	traces	94% (16%)
7		10	39	51	10%
8		-	98	traces	87% (56%)
9		-	39	61	37% (27%) ^[d]
10		19	81	-	72%
11		-	-	-	72% (19%)

Conditions D: 1) $\text{NEt}_3 \bullet 3\text{HF}$ (9 equiv.), MeCN, -78 °C. 2) MeCN, 50 °C, 2h. Conditions E: 1) AgF (3 equiv.), MeCN, -25 °C. 2) MeCN, -25 °C, 2h. 3) **1** (1 equiv.), MeCN, 20 °C, 16h. [a] ¹H NMR ratio in the crude mixture using the methylene signal of each compound as characteristic signal. [b] nd = not detected. [c] Determined using fluorobenzene as internal standard. [d] isolated as 8:2 mixture with **1j**

Conclusion

In conclusion, the method presented in this article allows the preparation of a range of trifluoromethoxylated structures with no use of an intermediate trifluoromethoxylating reagent, but *in situ* construction and use of the F_3CO^- anion as a salt, avoiding the presence of a useless side-product resulting from activation of an OCF_3 carrier. Product separation is thus facilitated. This method relies on the *in-situ* generation of gaseous fluorophosgene which we believe to be the most atom-economical manner to generate the OCF_3 anion.

Experimental Section

General information: Starting materials, if commercially available, were purchased from standard suppliers (Sigma-Aldrich, Fluorochem, ABCR, Acros, Alfa-Aesar or Apollo Scientific) and used as such, provided that adequate checks by NMR analysis had confirmed the claimed purity. THF was dried by distillation over sodium/benzophenone and used within the day. Acetonitrile was firstly distilled on P_2O_5 and then on CaH_2 and used within the day. Air- and moisture-sensitive materials were stored and handled under an atmosphere of argon. Reactions were carried out under an atmosphere of argon when needed using classic Schlenk-line techniques. Reactions were monitored by using thin-layer chromatography with precoated silica on aluminum foils (0.25 mm, Merck silica-gel (60-F254)). Flash column chromatography was performed on VWR silica gel (40–63 μm) using the indicated solvents, the solvent systems being indicated in v/v. Spectroscopic NMR and MS data were obtained using chromatographically homogeneous samples. 1H NMR (400 or 500 MHz), ^{19}F NMR (376 or 472 MHz) and ^{13}C NMR (101 or 126 MHz) spectra were recorded in $CDCl_3$ on a Bruker Avance III HD 400 MHz or 500 MHz instruments respectively, unless noted otherwise. Chemical shifts are reported in parts per million (ppm) and are referred to partially deuterated chloroform ($\delta[^1H] = 7.26$ ppm and $\delta[^{13}C] = 77.16$ ppm). Multiplicities were abbreviated as br s (broad signal), s (singlet), d (doublet), t (triplet), q (quartet), p (pintuplet) m (multiplet), td (triplet of doublets), dd (doublet of doublets). Coupling constants J were given in Hz. Spectra were processed with the program MestReNova v14.1.0-24037

General procedure for the synthesis of starting alkyl, benzyl or propargyl iodides: All non-commercial iodides used as starting materials were synthesized by a Finkelstein reaction. To a solution of Alkyl, benzyl or propargyl bromide in acetone (1 eq., 0.2M) was added a solution of NaI in acetone (1.1 eq., 0.2M). The reaction was monitored by 1H NMR. If necessary, more of the NaI solution could be added to obtain a full conversion of the starting material. The mixture was then filtered through a pad of Celite® and the solvent removed under reduced pressure. DCM was added to reach a concentration of 0.2M and the mixture was filtered again and the filtrate was concentrated under reduced pressure. The desired iodides obtained were used without further purification.

α -Iodoacetophenone 1a 1H NMR (400 MHz, $CDCl_3$) $\delta = 4.37$ (s, 2H), 7.49 (dd, $^3J = 8.0, 7.5$ Hz, 2H), 7.60 (dd, $^3J = 8.0, 7.5$ Hz, 1H), 7.99 (d, $^3J = 7.5$ Hz, 2H). ^{13}C NMR (400 MHz, $CDCl_3$): $\delta = 2.0, 128.9, 129.1, 133.2, 133.9, 193.0$. In accordance with previous reports.^[32]

Benzyl 2-iodoacetate 1b 1H NMR (400 MHz, $CDCl_3$) $\delta = 3.74$ (s, 2H), 5.18 (s, 2H), 7.30 – 7.45 (m, 5H). ^{13}C NMR (400 MHz, $CDCl_3$): $\delta = -5.4, 67.9, 128.4, 128.6, 128.7, 135.2, 168.7$. In accordance with previous reports.^[33]

4-(Iodomethyl)benzonitrile 1c 1H NMR (400 MHz, $CDCl_3$) $\delta = 4.31$ (s, 2H), 7.34 (d, $^3J = 8.3$ Hz, 2H), 7.43 (d, $^3J = 8.4$ Hz, 2H) ^{13}C NMR (400 MHz,

$CDCl_3$): $\delta = 3.0, 111.7, 118.6, 129.6, 132.7, 144.8$. In accordance with previous reports.^[34]

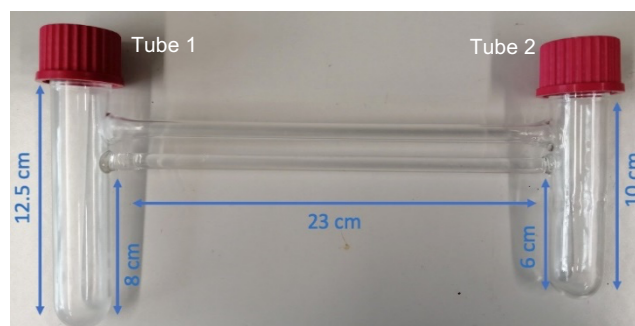
1-Bromo-4-(iodomethyl)benzene 1d 1H NMR (400 MHz, $CDCl_3$) $\delta = 4.40$ (s, 2H), 7.25 (d, $^3J = 8.5$ Hz, 2H), 7.42 (d, $^3J = 8.5$ Hz, 2H). ^{13}C NMR (400 MHz, $CDCl_3$): $\delta = 4.3, 121.9, 130.5, 132.1, 138.5$. In accordance with previous reports.^[35]

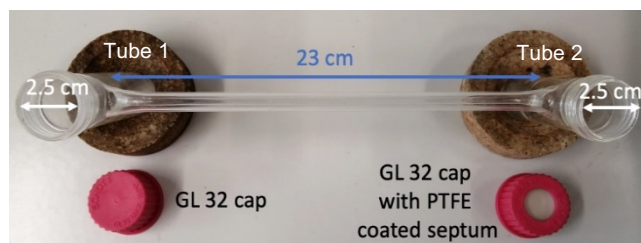
(3-Iodoprop-1-ynyl)benzene 1g 1H NMR (400 MHz, $CDCl_3$) $\delta = 3.97$ (s, 2H), 7.28 – 7.36 (m, 3H), 7.37 – 7.48 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) $\delta = 17.3, 85.4, 86.4, 122.6, 128.4, 128.8, 131.8$. In accordance with previous reports.^[36]

2-Iodo-1-phenyl-1-propanone 1i 1H NMR (400 MHz, $CDCl_3$) $\delta = 2.08$ (d, $^3J = 6.7$ Hz, 3H), 5.50 (q, $^3J = 6.7$ Hz, 1H), 7.43 – 7.52 (m, 2H), 7.54 – 7.62 (m, 1H), 7.98 – 8.05 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) $\delta = 18.2, 22.1, 128.8, 128.8, 133.6, 133.8, 194.9$. In accordance with previous reports.^[37]

3 β -Iodopregn-5-en-20-one 1k 1H NMR (400 MHz, $CDCl_3$) $\delta = 0.63$ (s, 3H), 0.91 – 1.03 (m, 1H), 1.03 – 1.20 (m, 3H), 1.08 – 1.32 (m, 3H), 1.36 – 1.79 (m, 7H), 1.94 – 2.08 (m, 2H), 2.12 (s, 3H), 2.11 – 2.36 (m, 3H), 2.52 (t, $^3J = 8.9$ Hz, 1H), 2.68 (ddd, $^2J = 13.8, ^3J = 4.5, 2.2$ Hz, 1H), 2.93 (m, 1H), 3.81 – 4.21 (m, 1H), 5.34 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) $\delta = 13.3, 19.4, 20.9, 23.0, 24.6, 30.2, 31.7, 31.7, 36.6, 36.7, 38.9, 42.0, 44.1, 46.5, 50.4, 57.0, 63.8, 121.5, 142.9, 209.6$. In accordance with previous reports.^[38]

General procedure for trifluoromethoxylation via in-situ generation of fluorophosgene: A H-shaped tube (see figure below)¹ was used for this reaction. In tube 1 was added $NEt_3 \cdot 3HF$ (6 eq.) and freshly distilled acetonitrile (20 mL) under argon. In tube 2 was added AgF (3 eq) and freshly distilled acetonitrile (3.94 mL) under Ar and the tube was covered with aluminum foil to be protected from light. Tube 2 was sealed and tube 1 was cooled to -78 °C. When the solution in tube 1 was frozen, triphosgene (3 eq.) was added to tube 1, which was then sealed and the cooling bath was removed. Tube 2 was cooled to -30 °C. Tube 1 was allowed to warm gently to room temperature and was then heated to 50 °C for 2 h. The substrate 1 (1 eq., 2 mmol) was syringed (using a minimal amount of solvent to solubilize it when it is a solid) into tube 2 through the PTFE coated septum. The mixtures in tubes 1 and 2 were then stirred overnight at room temperature. The reaction mixture in tube 2 was then filtered through Celite® and the solvent was evaporated under reduced pressure. The crude material was then dissolved in the minimal amount of DCM and washed with brine. The aqueous layer was extracted three times with DCM. The combined organic phases were then dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. The crude mixture was purified by flash column chromatography on silica gel.





¹ Attention must be paid to the distance between the tubes which must allow the easy handle of hot and cold bathes. In our case, a distance of 23 cm was used.

α -Trifluoromethoxyacetophenone 2a

Obtained from the general procedure as a light yellow oil (375 mg, 1.84 mmol, 92%).

¹H NMR (400 MHz, CDCl₃) δ 5.18 (s, 2H), 7.56 – 7.47 (m, 2H), 7.68 – 7.59 (m, 1H), 7.94 – 7.87 (m, 2H). ¹³C NMR (400 MHz, CDCl₃) δ 68.4 (q, ³J_{C-F} = 2.9 Hz), 120.5 (q, ¹J_{C-F} = 256.7 Hz), 128.0, 129.2, 133.9, 134.5, 190.3. ¹⁹F NMR (400 MHz, CDCl₃) δ -61.00 (s, 3F). In accordance with previous reports.^[17]

Benzyl 2-(trifluoromethoxy)acetate 2b

Obtained from the general procedure as a light yellow oil (440 mg, 1.88 mmol, 94%).

¹H NMR (400 MHz, CDCl₃) δ 4.52 (s, 2H), 5.25 (s, 2H), 7.30 – 7.44 (m, 5H). ¹³C NMR (400 MHz, CDCl₃) δ 63.2 (q, ³J_{C-F} = 3.6 Hz), 67.7, 121.6 (d, ¹J_{C-F} = 256.9 Hz), 128.7, 128.9, 128.9, 134.8, 166.0. ¹⁹F NMR (400 MHz, CDCl₃) δ -61.42 (s, 3F). In accordance with previous reports.^[17]

4-((Trifluoromethoxy)methyl)benzotrile 2c

Obtained from the general procedure a yellow oil (350 mg, 1.74 mmol, 87%).

¹H NMR (400 MHz, CDCl₃) δ 5.05 (s, 2H), 7.48 (d, ³J = 8.0 Hz, 2H), 7.70 (d, ³J = 8.4 Hz, 2H). ¹³C NMR (400 MHz, CDCl₃) δ 67.8 (q, ³J_{C-F} = 3.6 Hz), 112.9, 118.4, 121.7 (q, ¹J_{C-F} = 256.3 Hz), 128.1, 132.7, 139.1. ¹⁹F NMR (400 MHz, CDCl₃) δ -60.75 (s, 3F). In accordance with previous reports.^[99]

1-Bromo-4-((trifluoromethoxy)methyl)benzene 2d

Obtained from the general procedure a light yellow oil (377 mg, 1.48 mmol, 74%).

¹H NMR (400 MHz, CDCl₃) δ 4.94 (s, 2H), 7.24 (d, ³J = 8.5 Hz, 2H), 7.53 (d, ³J = 8.8 Hz, 2H). ¹³C NMR (400 MHz, CDCl₃) δ 68.4 (q, ³J_{C-F} = 3.5 Hz), 121.8 (d, ¹J_{C-F} = 255.8 Hz), 123.2, 129.7, 132.1, 133.0. ¹⁹F NMR (400 MHz, CDCl₃) δ -60.45 (s, 3F). In accordance with previous reports.^[39]

1-(Trifluoromethoxy)undecane 2e

Obtained from the general procedure a colorless oil (475.81 mg, 1.98 mmol, 99%).

¹H NMR (400 MHz, CDCl₃) δ 0.80 – 1.01 (m, 2H), 1.20 – 1.44 (m, 16H), 1.68 (p, ³J = 6.7 Hz, 2H), 3.95 (t, ³J = 6.6 Hz, 2H). ¹³C NMR (101 MHz, CDCl₃) δ 14.1, 22.7, 25.4, 28.7, 29.1, 29.3, 29.4, 29.5, 29.7, 31.9, 67.5, 67.5, 67.5, 67.6, 120.4, 123.0. ¹⁹F NMR (377 MHz, CDCl₃) δ -60.64 (s, 3F). GC-MS: [M]⁺ 240.200, [M-OCF₃]⁺ 155.100, [M-CH₂OCF₃]⁺ 141.100, [M-CH₃CH₂]⁺ 211.200, [M-CH₃CH₂CH₂]⁺ 197.100. IR (neat, cm⁻¹) ν 2925, 2856, 1467, 1408, 1263, 1136, 1219, 1045

[2-(Trifluoromethoxy)ethyl]benzene 2f

Obtained from the general procedure as a yellow oil (60.5 mg, 0.32 mmol, 16%).

¹H NMR (400 MHz, CDCl₃) δ 3.01 (t, ³J = 7.2 Hz, 2H), 4.16 (t, ³J = 7.2 Hz, 2H), 7.20 – 7.29 (m, 3H), 7.30 – 7.38 (m, 2H). ¹³C NMR (101 MHz, CDCl₃) δ 35.5, 68.0 (q, ³J_{C-F} = 3.0 Hz), 121.9 (d, ¹J_{C-F} = 254.3 Hz), 127.2, 128.9, 129.1, 136.8. ¹⁹F NMR (377 MHz, CDCl₃) δ -60.69 (s, 3F). In accordance with previous reports.^[40]

(3-Trifluoromethoxyprop-1-ynyl)benzene 2h

Obtained from the general procedure as a yellow oil (226 mg, 1.13 mmol, 56%). Purified by flash column chromatography (heptane).

¹H NMR (400 MHz, CDCl₃) δ 4.83 (s, 2H), 7.28 – 7.43 (m, 4H), 7.43 – 7.52 (m, 2H). ¹³C NMR (101 MHz, CDCl₃) δ 56.1 (q, ³J_{C-F} = 4.5 Hz), 80.9, 88.3, 121.7, 121.8 (q, ¹J_{C-F} = 257.2 Hz), 128.5, 129.3, 132.0. ¹⁹F NMR (377 MHz, CDCl₃) δ -60.69 (s, 3F). In accordance with previous reports.^[26]

2-Trifluoromethoxy-1-phenyl-1-propanone 2i

Obtained from the general procedure as a yellow oil (218.18 mg, 0.54 mmol, 27%). Purified by flash column chromatography (pentane:EtOAc 10:1).

¹H NMR (400 MHz, CDCl₃) δ 1.66 (dd, ³J = 6.9, 0.8 Hz, 3H), 5.49 (q, ³J = 6.9 Hz, 1H), 7.44 – 7.55 (m, 2H), 7.58 – 7.67 (m, 1H), 7.93 – 8.02 (m, 2H). ¹³C NMR (101 MHz, CDCl₃) δ 18.8, 75.5 (q, ³J_{C-F} = 2.5 Hz), 121.6 (q, ¹J_{C-F} = 256.6 Hz), 128.9, 129.1, 133.7, 134.2, 195.1. ¹⁹F NMR (377 MHz, CDCl₃) δ -58.78 (s, 3F). In accordance with previous reports.^[41]

Ethyl 2-(trifluoromethoxy)propanoate 2j

Obtained from the general procedure in mixture with the corresponding iodide (8/2)

¹H NMR (400 MHz, CDCl₃) δ 1.30 (t, ³J = 7.1 Hz, 3H), 1.52 – 1.66 (m, 4H), 4.25 (qd, ³J = 7.1, 0.8 Hz, 2H), 4.68 (q, ³J = 6.9 Hz, 1H). ¹⁹F NMR (377 MHz, CDCl₃) δ -59.65 (s, 3F). In accordance with previous reports.^[42]

3 β -(Trifluoromethoxy)pregn-5-en-20-one 2k

Obtained from the general procedure as a white solid (148 mg, 0.38 mmol, 19%). Purified by flash column chromatography (pentane:EtOAc 10:0.5).

¹H NMR (400 MHz, CDCl₃) δ 0.64 (s, 3H), 0.67 (t, ³J = 7.0 Hz, 1H), 0.86 – 1.01 (m, 1H), 1.02 (s, 3H), 1.06 – 1.31 (m, 3H), 1.39 – 1.81 (m, 7H), 1.87 – 2.09 (m, 4H), 2.13 (s, 3H), 2.14 – 2.27 (m, 1H), 2.38 – 2.57 (m, 3H), 3.88 – 4.26 (m, 1H), 5.41 (m, 1H). ¹³C NMR (101 MHz, CDCl₃) δ 13.3, 19.3, 21.1, 22.9, 24.6, 28.7, 31.6, 31.9, 36.5, 36.9, 38.9, 39.0, 44.1, 50.0, 56.9, 63.8, 78.6 (q, ³J_{C-F} = 1.9 Hz), 121.7 (q, ¹J_{C-F} = 254.2 Hz), 123.1, 139.2, 209.5. ¹⁹F NMR (377 MHz, CDCl₃) δ -57.54 (s, 3F). HR-MS m/z: Calcd for C₂₂H₃₂F₃O₂ [M+H]⁺ 385.2352 found 385.2349. IR (neat, cm⁻¹) ν 2938, 2851, 1701, 1469, 1357, 1274, 1205, 1194, 1128, 1012, 870, 662 mp = 85-90 °C

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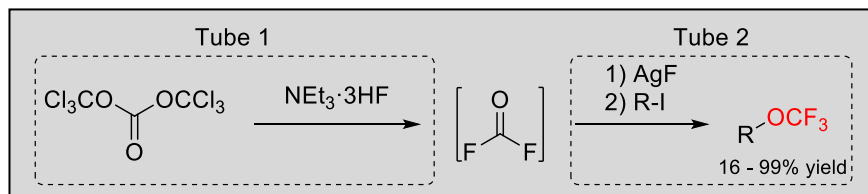
Keywords: Fluorine • Trifluoromethoxylation •

Fluorophosgene • Nucleophilic substitution

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Entry for the Table of Contents



An efficient atom economical trifluoromethoxylation method has been developed with no need for trifluoromethoxylation reagent. This method relies on the in-situ generation of fluorophosgene and its conversion into OCF_3 anion to achieve nucleophilic substitution on a series of alkyl iodides.

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Keywords: Fluorine • Trifluoromethoxylation • Fluorophosgene • Nucleophilic substitution