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Intertwined Processes in the Pummerer-Type Rearrangement Affording α -Trifluoromethoxylated Thioethers and the Corresponding Highly Enantioenriched Sulfoxides

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A method to access racemic or highly stereoenriched α -trifluoromethoxylated sulfoxides through the Pummerer rearrangement of aryl methyl sulfoxides followed by the oxidation of the resulting trifluoromethoxylated sulfides is described. Among the three reagents selected as both rearrangement activators and F_3CO^- anion sources, 2,4-dinitro-1-(trifluoromethoxy)benzene (DNTFB) was found to be the most effective. In each case, the OCF_3 -source was shown to play diverse key roles in the rearrangement. Enantioenriched

trifluoromethoxy-sulfoxides (up to 95% enantiomeric excess) were obtained using an oxaziridinium salt derived from cholesterol. The configurational stability of these sulfoxides was investigated by thermal enantiomerization followed by enantioselective chromatography. Finally, the acidity of the protons in α -position of the sulfinyl group was determined in DMSO (pK_a value 20.3) suggesting the potency of this new scaffold for preparing trifluoromethoxylated trisubstituted $C-sp^3$ centers via a deprotonation/alkylation sequence.

1. Introduction

Organofluorine chemistry has established itself as an important area of research in organic chemistry, with applications notably in medicinal chemistry^[1–16] and agrochemistry.^[7,17–19] The substitution of a proton by a fluorinated group can improve the chemical stability of molecules, tune their lipophilicity and improve their overall biological activity.^[5,11,12,20–22] Among fluorinated groups, the trifluoromethoxy one (OCF_3) remains relatively poorly studied,^[23,24] and is mostly found on aromatic cycles. Moreover, in the case of aliphatic OCF_3 compounds, the absolute configuration of the newly formed C^*-OCF_3 stereocenters was controlled in only few cases. These contributions could be classified in 5 main approaches (Scheme 1):

1) The strain-release enantioselective trifluoromethoxylation of epibromonium ions or epoxides;^[25–27] 2) The metal-catalyzed allylic or propargylic enantioselective trifluoromethoxylation;^[28,29] 3) The enantiospecific or partially enantioselective substitution of an oxygenated leaving group on an alkyl chain;^[30,31] 4) The metal-catalyzed enantioselective trifluoromethoxylation of alkenes under oxidizing conditions;^[32,33] and 5) The enantioselective functionalization of nonstereogenic $C_{sp^2}-OCF_3$ centers or of $C_{sp^3}-OCF_3$ stereocenter-containing racemic substrates.^[34–36] Several of these methods smartly address the challenge of controlling a trifluoromethoxylated stereocenter; many of them afford good yields and enantioselectivities; however, they rely on expensive trifluoromethoxylation methods or reagents, with often overstoichiometric amounts of metals or costly noncommercial reagents in large excess. The present work displays an alternative, metal-free, and cheap commercial OCF_3 -reagent-based approach for the installation of a trifluoromethoxy group on a $C-sp^3$ carbon, with potential for stereocontrol.

The strategy that we devised consisted in the first preparation of highly enantioenriched α -trifluoromethoxylated sulfoxides as a potential chiral trifluoromethoxylated synthetic block. It is based on the trifluoromethoxylation of aryl methyl sulfoxides via a Pummerer-type reaction using several electrophilic OCF_3 sources, able to both produce the trifluoromethoxide anion in situ and activate the starting aryl methyl sulfoxide (Scheme 2). Among the potential electrophilic trifluoromethoxide donors, trifluoromethyl triflate (TFMT),^[37] trifluoromethyl *p*-toluenesulfonate (hereafter designed as TFMS)^[38,39] and 2,4-dinitro-trifluoromethoxybenzene (DNTFB)^[40–47] (Scheme 2) were selected for our study. The resulting trifluoromethoxylated sulfides would then undergo enantioselective sulfoxidation to afford unprecedented α -trifluoromethoxylated sulfoxides, which could be functionalized by a deprotonation/

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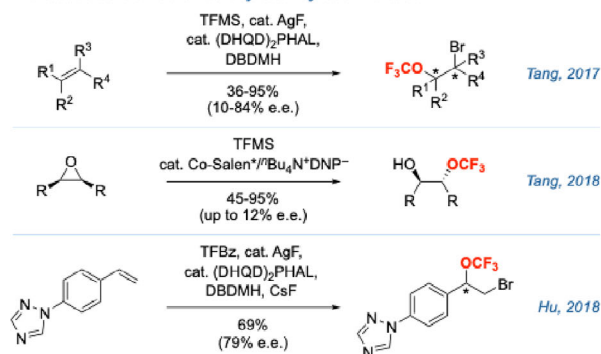
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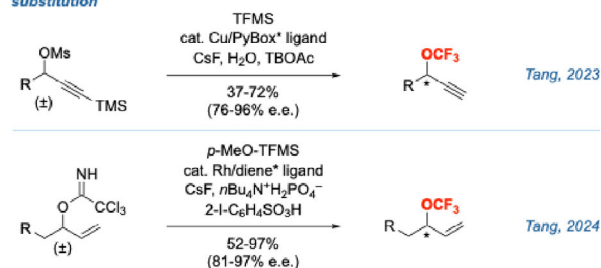
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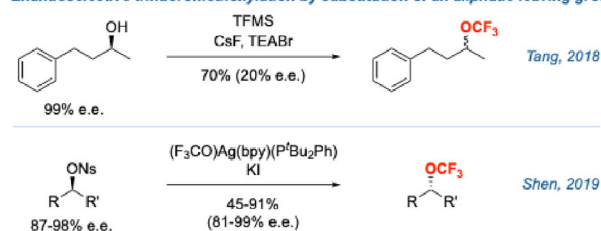
Enantioselective trifluoromethoxylation by strain release



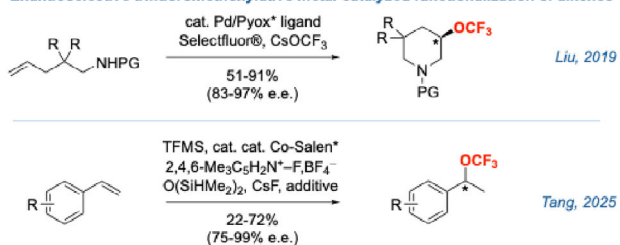
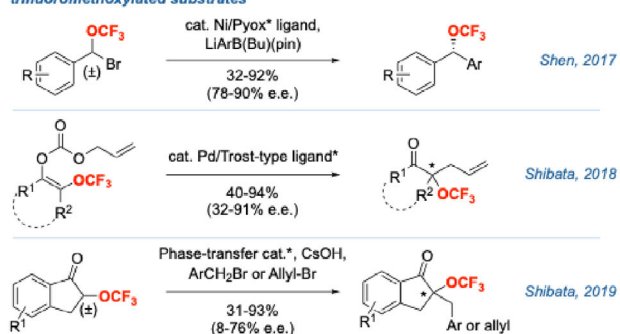
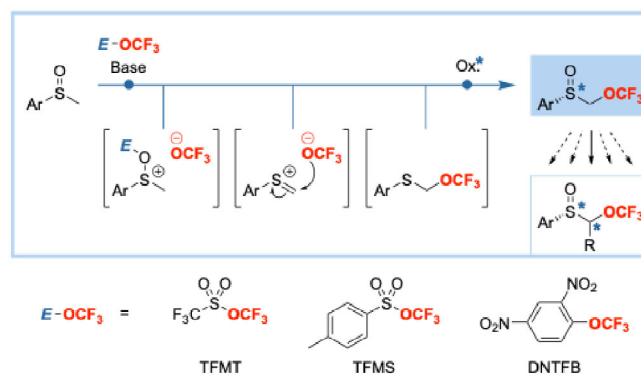
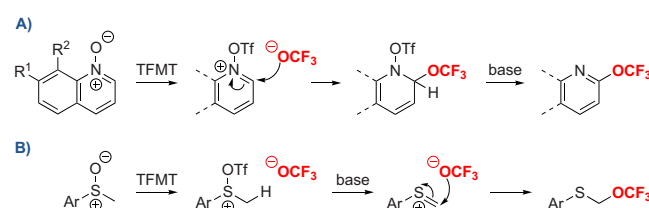
Enantioselective trifluoromethoxylation by metal-catalyzed allylic or propargylic substitution



Enantioselective trifluoromethoxylation by substitution of an aliphatic leaving group



Enantioselective trifluoromethoxylation metal-catalyzed functionalization of alkenes

Access to enantiocontrolled C_{sp3}-OCF₃ centers from achiral or racemic trifluoromethoxylated substratesScheme 1. State of the art of the stereocontrol of C-OCF₃ centers.Scheme 2. Our strategy to access α -trifluoromethoxylated sulfoxides with the structures of the electrophilic trifluoromethoxide donors studied.Scheme 3. A) Trifluoromethoxylation of quinoline *N*-oxide derivatives described by Hartwig et al. B) TFMT-promoted Pummerer rearrangement of sulfoxides.

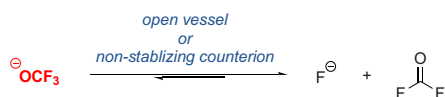
electrophilic trapping sequence. While we were completing this manuscript, the group of Tang reported similar access to α -trifluoromethoxylated sulfides by Pummerer rearrangement, using 4-F-TFMS (trifluoromethyl *p*-fluorobenzenesulfonate) as OCF₃-source.^[48] Interestingly, our study is complementary, since it describes the assessment of 2 additional OCF₃-sources, concurs with the mechanistic proposal by Tang et al., but also establishes the nonasymmetric but also enantioselective oxidations into the desired α -trifluoromethoxylated sulfoxides, with additional physico-chemical investigations of the latter, and proof-of-principle α -functionalization. Hereafter is presented this whole study.

2. Results and Discussion

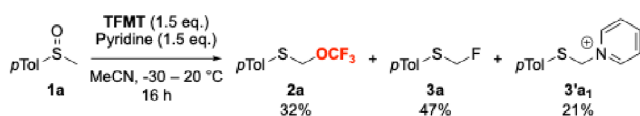
2.1. TFMT as OCF₃-Source for the Pummerer Rearrangement

TFMT, a commercial, but costly and low-boiling-point reagent, had already been successfully used by Hartwig et al. in 2018 for the trifluoromethoxylation of heterocyclic *N*-oxides.^[49] The proposed mechanism, where TFMT plays the dual role of activating the *N*-oxide as well as releasing the trifluoromethoxide anion nucleophile in the medium, is very close to the expected Pummerer-type process that we wished to develop (Scheme 3).

Since the F₃CO⁻ anion is unstable, its addition on the generated electrophilic species must be effective before its degradation into fluoride anion and gaseous fluorophosgene (Scheme 4).^[50] Indeed, competitive addition of the fluoride ion on the thionium intermediate could be expected. According to



Scheme 4. Trifluoromethoxide anion degradation.

Scheme 5. First hit with TFMT (¹H NMR yields, caffeine CAS 58–08–2 as internal standard).

Entry	Solvent	Temp.	Conversion ^[a]	Yields ^[b]		
				2a	3a	3'a ₁
1	MeCN	20 °C	100%	32%	47%	21%
2	NMP	20 °C	83%	36%	13%	34%
3	DMF	20 °C	65%	27%	7%	31%
4	CHCl ₃	20 °C	81%	6%	63%	12%
5	MeCN	50 °C	100%	5%	57%	38%
6	MeCN	−30 °C	70%	16%	30%	24%

[a] With regard to the starting sulfoxide **1a**.
[b] ¹H NMR yield calculated with caffeine (CAS 58–08–2) as internal standard.

the HSAB theory, the F₃CO[−] anion is softer than the fluoride anion, since the charge of the latter is fully localized on the F atom, while the one on the former can be delocalized from oxygen to fluorine thanks to negative hyperconjugation. The thionium cation intermediate is also a soft species because the positive charge is shared between the sulfur and carbon atoms. The thionium should then more favorably be attacked by the F₃CO[−] anion than by fluoride; however, a higher concentration of fluoride with regard to F₃CO[−] can still increase the amount of corresponding side-product.

When the model methyl *p*-tolyl sulfoxide **1a** was submitted to 1.5 equivalents of TFMT and 1.5 equivalents of pyridine in acetonitrile, the corresponding trifluoromethoxylated thioether **2a** was obtained with a 32% ¹H NMR yield, along with two other side products, the monofluorinated thioether **3a** and the pyridinium adduct **3'a₁** resulting, respectively, from the addition of F₃CO[−], F[−], and pyridine on the thionium intermediate (Scheme 5).

After this encouraging first hit, the reaction conditions were optimized by screening several solvents and temperatures (Table 1). Although acetonitrile gave the best conversion at 20 °C (entries 1–4), lower temperatures led to incomplete conversion (entry 6) and a higher one favored the degradation of the trifluoromethoxide anion, increasing the concentration of fluoride in the mixture, thus also favoring the formation of **3a** against **2a** (entry 5).

Table 2. Screening of bases.

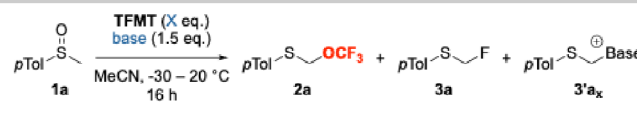
Entry	Base	Conversion ^[a]	Yields ^[b]		
			2a	3a	3'a _x
1	Pyridine	100%	32%	47%	3'a ₁ 21%
2	DIPEA	13%	6%	7%	3'a ₂ 0%
3	2,6-di- <i>tert</i> -butylpyridine	65%	15%	50%	3'a ₃ 0%
4	2,2,6,6-tetramethylpiperidine	71%	13%	58%	3'a ₄ 0%
5	DMAP	6%	6%	0%	3'a ₅ 0%
6	/	0%	0%	0%	3'a ₅ 0%

[a] With regard to the starting sulfoxide **1a**.
[b] ¹H NMR yield calculated with caffeine (CAS 58–08–2) as internal standard.

Different organic bases were screened in acetonitrile at 20 °C (Table 2). In order to decrease the formation of **3'a₁**, less nucleophilic bases than pyridine (entry 1) were tried. With DIPEA (*N,N*-diisopropylethylamine), **3'a₂** was not observed anymore, but the conversion of the starting sulfoxide **1a** fell to 13% (entry 2). 2,6-Di-*tert*-butylpyridine was screened as a bulkier pyridine analog (entry 3) as well as 2,2,6,6-tetramethylpiperidine (entry 4). In any case, the conversion was incomplete and the ¹H NMR yield of **2a** was never higher than 15%, whereas a large amount of adduct **3a** was obtained. However, the formation of the side products **3'a₃** and **3'a₄** were not observed, thus confirming our hypothesis that their formation is disfavored when using less nucleophilic and more hindered bases. In the absence of base, **1a** was not converted (entry 6). Surprisingly, when pyridine was replaced by the more nucleophilic DMAP (4-dimethylaminopyridine), conversion of **1a** dropped to 6% NMR yield but in the meantime, no thionium adducts **3'a₅** nor monofluorinated thioether **3a** were observed (entry 5).

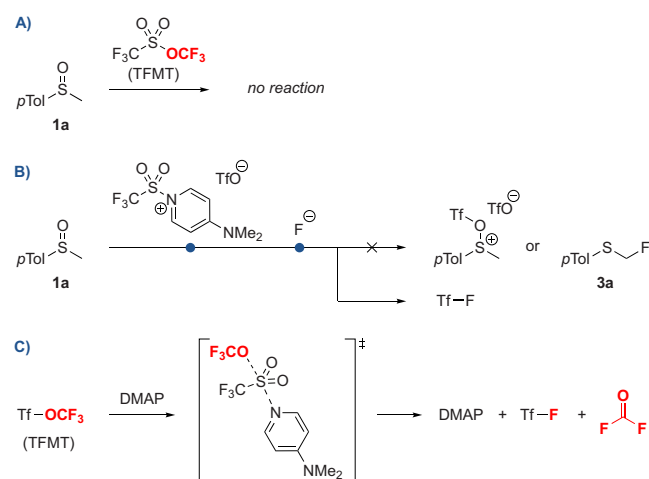
A large excess of TFMT in the presence of 1.5 eq. of pyridine led to an increase of the conversion of **1a** into **2a** (from 32 to 50%) and decreased yields of **3a** (from 47 to 21%) and **3'a₁** (from 21 to 10%) (Table 3, entries 1–2). With DMAP (1.5 eq.) as the base, increasing amounts of TFMT resulted in an increase of sulfoxide conversion from 6 to 89%, and of ¹H NMR yields of **2a** from 6 to 74%, with amounts of side product **3a** lower than 15%, and no formation of the adduct **3'a₅** (entries 3–6). A larger excess of TFMT is indeed expected to favor the activation of the sulfoxide and to increase the excess of F₃CO[−] anion in the mixture. The addition of the latter on the thionium intermediate would thus be favored, pushing the conversion toward the formation of the desired thioether **2a**. Moreover, as the reaction is performed in a sealed microwave vial, an increase of the pressure inside the vial disfavors the degradation of the F₃CO[−] anion into fluoride and gaseous fluorophosgene, enhancing the “lifespan” of the anion in the mixture.

Table 3. Screening of the amount of TFMT with 1.5 eq. of base.



Entry	X eq. of TFMT	Conversion ^[a]	Yields ^[b]		
			2a	3a	3'a
1 ^[c]	1.5	100%	32%	47%	3'a ₁ 21%
2 ^[c]	10	100%	50%	21%	3'a ₁ 10%
3 ^[d]	1.5	6%	6%	0%	3'a ₅ 0%
4 ^[d]	3	25%	18%	7%	3'a ₅ 0%
5 ^[d]	6	56%	41%	15%	3'a ₅ 0%
6 ^[d]	10	89%	74%	15%	3'a ₅ 0%

[a] With regard to the starting sulfoxide **1a**.
 [b] ¹H NMR yield calculated with caffeine (CAS 58–08–2) as internal standard.
 [c] Base = pyridine.
 [d] Base = DMAP.



Scheme 6. Activation of TFMT by DMAP with transient formation of a *N*-sulfonylpyridinium.

Therefore, the optimal conditions for the trifluoromethoxylation of sulfoxides with TFMT were 10 eq. of the OCF₃ donor in the presence of 1.5 eq. of DMAP in acetonitrile at room temperature for 16 hours.

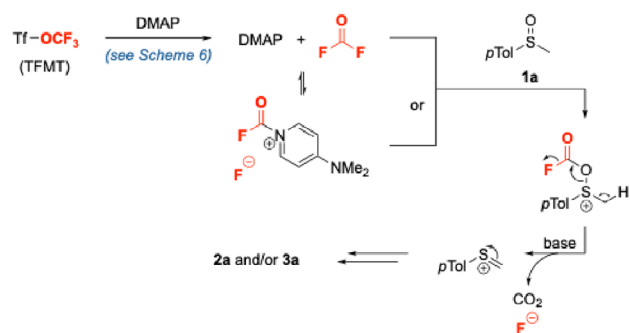
2.2. TFMT as OCF₃-source–Mechanistic Discussion

When only the sulfoxide was put in solution with TFMT, no conversion was observed by NMR (Scheme 6-A). This suggests that the reaction must be initiated by another species than TFMT alone. This led us to think that DMAP played the role of activating agent for TFMT, which would lead to an *N*-triflylpyridinium derived from DMAP that would, instead of TFMT alone, serve as electrophilic activator of the sulfoxide in the Pummerer process. On the one hand, the addition of DMAP on triflic anhydride is described;^[51] on the other hand, F₃CO[−] being a good leaving group, its substitution by DMAP on TFMT is likely to occur. We

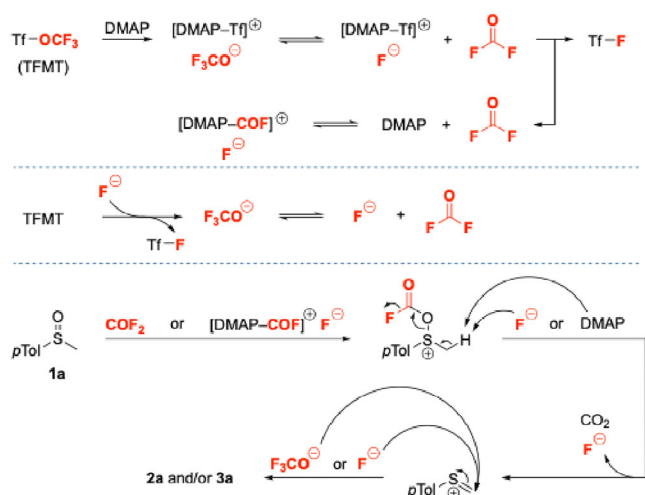
hypothesized that the *N*-sulfonylpyridinium would be reactive enough so that the starting sulfoxide **1** could perform the substitution of DMAP on the electrophilic sulfur atom. However, after mixing triflic anhydride and DMAP to form 4-(dimethylamino)-1-triflylpyridinium triflate, then adding the sulfoxide along with a fluoride source in the solution, no displacement of DMAP by the sulfoxide was observed, as well as no formation of thioether **3a** (Scheme 6-B). In the absence of a fluoride source in the solution, no displacement of DMAP by the sulfoxide was observed either. The only reaction was the formation of triflyl fluoride, which departs the reaction mixture due to its volatility (b.p. = −21.7 °C). Thus, it is reasonable to assume that when the DMAP base approaches TFMT, a rapid stepwise or concerted process takes place where the F₃CO[−] anion is released, (at least partly) degraded into difluorophosgene and fluoride, and that the latter directly adds on the sulfur atom of TFMT or [DMAP-Tf]⁺ to form triflyl fluoride (Scheme 6-C). In fact, a similar conclusion was reached by Zhang *et al.* when using DMAP and TFMT to convert carboxylic acids into the corresponding acyl fluorides.^[74] All in all, the activation of the sulfoxide by TFMT or by the *N*-triflylpyridinium of DMAP cannot be considered as the effective mechanistic scenario.

When a poorly nucleophilic base (2,6-di-*tert*-butylpyridine) was used, the full disappearance of the ¹⁹F NMR signal of TFMT was observed and 65% of **1a** were converted into only 15% of **2a** but 50% of **3a** (¹⁹F NMR yields). This observation has three implications: 1) Under these conditions, fluoride must be present in higher amount than trifluoromethoxide; 2) As the sulfoxide is unable to activate TFMT, a possible explanation for the formation of **2a** and **3a** could be a chain process initiated by the activation of trace moisture by the bulky pyridine, leading to attack of hydroxide onto TFMT, then to the release of F₃CO[−] followed by degradation to F[−] (and COF₂); the fluoride anion would then either act as nucleophile attacking on the thionium intermediate, or trigger the liberation of F₃CO[−] from TFMT, and so on; 3) Consequently, the only way to have a higher amount of fluoride than of trifluoromethoxide in the reaction medium is that fluorophosgene is attacked by a nucleophile to release fluoride too. The presumed culprit for this attack is of course the sulfoxide substrate, since **1a** does not react with TFMT alone and must yet be activated somehow. In fact, Tang *et al.* also separately observed that the sulfoxide did not react with the related TFMS reagent alone, and hence proposed that it was rather activated by fluorophosgene.^[48]

To test this hypothesis, a solution of freshly distilled acetonitrile was saturated with gaseous fluorophosgene; sulfoxide **1a** or a mixture of sulfoxide **1a** and DMAP were then added, and additional fluorophosgene was bubbled through the solution for 5 hours. The aim was to observe the conversion of **1a** into **3a**, proving the role of difluorophosgene as the activator of the sulfoxide. Up to 13% of **3a** and 12% ¹⁹F NMR yield of **2a** were obtained with DMAP and 3% and 10% ¹⁹F NMR yield for **2a** and **3a**, respectively, without DMAP. Despite these modest yields, probably due to the rather low gas pressure in these test experiments, the latter demonstrate that the sulfoxide is activated either by fluorophosgene itself, or by the corresponding *N*-(fluoroformyl)pyridinium generated by addition of DMAP onto COF₂. After deprotonation



Scheme 7. Activation of the sulfoxide by fluorophosgene or by the DMAP-fluorophosgene adduct.

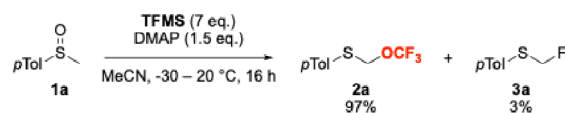


Scheme 8. Activation of the sulfoxide by carbonyl fluoride, deprotonation of the sulfonium and nucleophilic addition of F_3CO^- anion on the thionium intermediate.

of the resulting sulfonium by a base to form the thionium intermediate, a second fluoride as well as CO_2 would be released (Scheme 7). In fact, a Pummerer reaction with a similar activation of a sulfoxide by phosgene was already reported,^[52] as well as a Pummerer reaction with fluorophosgene without base where no trifluoromethoxylated products were reported.^[53]

The last remaining grey area in this mechanism was the nature of the base deprotonating the sulfonium intermediate to lead to the thionium species. The most straightforward candidate was DMAP. Protonated DMAP is indeed visible by NMR spectroscopy at the end of the reaction. However, the reaction still occurs if a substoichiometric amount of DMAP is used. 50 % of HF was observed by NMR when only 0.5 eq. of DMAP was used. The significant amount of fluoride anion present in the mixture could play the role of base^[54] and deprotonate the activated sulfoxide to form the thionium intermediate with formation of HF (rapidly trapped by some free DMAP in the mixture to form $DMAP \cdot HF$ or $[DMAP-H]^+[HF_2]^-$).

Finally, the last step of the mechanism is the addition of the trifluoromethoxide anion on the thionium intermediate to form the desired thioether. This affords now a complete picture for the mechanism of the Pummerer-type trifluoromethoxylation process (Scheme 8).



Scheme 9. Optimized conditions for the Pummerer rearrangement-type trifluoromethoxylation of sulfoxides with TFMS.

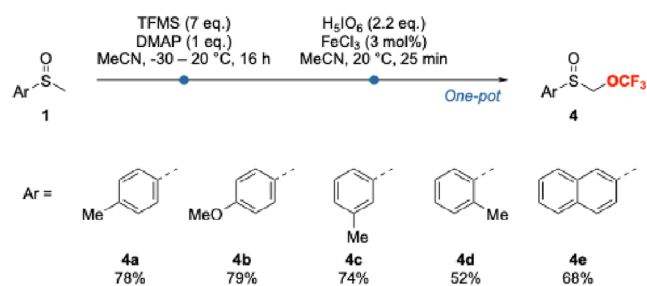
To summarize, in this trifluoromethoxylation Pummerer process, the sulfoxide is most probably activated by fluorophosgene, or by the *N*-(fluoroformyl)-(4-dimethylamino)pyridinium cation to afford the sulfonium intermediate. The whole process does not occur in the absence of a base to activate the trifluoromethoxide —and COF_2 — donor, namely TFMT, and deprotonate the sulfonium intermediate. The best conditions for the trifluoromethoxylation of sulfoxides with TFMT yielded the desired trifluoromethoxylated thioether **2a** in a 74% yield (Table 3, entry 6).

Since this reaction requires a large excess of TFMT to reach an acceptable conversion and a good yield of **2a**, and due to the elevated price of TFMT as well as its difficulty to be synthesized at the bench and to be manipulated, we considered an alternative reagent as OCF_3 source.

2.3. TFMS as OCF_3 -Source for the Pummerer Rearrangement

While TFMT is very volatile (b.p. = 21 °C), expensive and difficult to use, TFMS is simpler to handle, stable over time and easily synthesized by the *O*-trifluoromethylation of PTSA with Togni II reagent with up to 90% isolated yield.^[38] The Pummerer-type trifluoromethoxylation reaction was hence tested with TFMS, and after a short optimization (see Supporting Information for details), the best results were obtained with 7 eq. of TFMS for 1.5 equivalents of DMAP in acetonitrile, at 20 °C for 16 hours, affording 97% 1H NMR yield of **2a** with only traces of **3a** (Scheme 9). In comparison, the group of Tang obtained 78% NMR yield of **2a** when using 5 eq. of TFMS, 2 eq. of KF, 1 eq. of benzo-18-c-6 and 4 Å MS at r.t. for 34 hours.^[48]

Thanks to these high yield and selectivity, the isolation of the desired thioether could be considered. However, in our initial attempts, two difficulties were faced, namely the volatility (high vapor pressure under rotary evaporation) of **2a** and the difficulty to purify it on silica (16% best isolated yield). Indeed, in our hands, silica gel chromatography on the crude material of the Pummerer reaction systematically led to the loss of considerable amounts of **2a**, whichever OCF_3 source was used (TFMT, TFMS or DNTFB). In fact, we could show that after stirring overnight a deuterated chloroform solution of **2a** and **3a** in the presence of a spatula tip of silica, no NMR signals of any fragment of **2a** or **3a** could be observed after filtration, thus pointing at a silica-promoted degradation of **2a** and **3a** into volatile products or their retention on silica-gel. Accordingly, we decided to perform the next step, that is, the oxidation of **2a**, *in situ* by means of periodic acid and catalytic iron(III) chloride,^[55] the corresponding sulfoxides being expected to be less volatile and more tolerant to silica. Pure **4a** was effectively isolated with 78% yield over 2 steps (Pummerer process and oxidation). Several



Scheme 10. Scope of the two-step reaction to access trifluoromethoxylated sulfoxides with TFMS.

thioethers were obtained, with yields ranging from 52% to 79%. The *ortho*-methyl-decorated trifluoromethoxylated sulfoxide **4d** was obtained with a lower yield due to the steric hindrance around the α -position (Scheme 10).

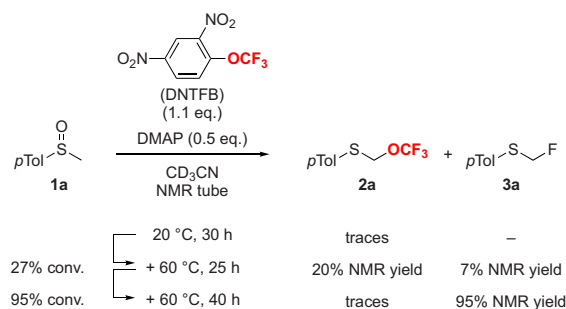
2.4. TFMS as OCF₃-Source–Mechanistic Discussion

TFMT and TFMS have similar structure and reactivity and all the experiments presented on TFMT have been conducted on TFMS as well (see Supporting Information). It appeared that all the observations and corresponding conclusions on the mechanism with TFMT also apply for the mechanism with TFMS.

2.5. DNTFB as OCF₃-Source for the Pummerer Rearrangement

The encouraging results obtained with TFMS were however, shadowed by its synthetic cost. Indeed, the Togni II reagent required for its preparation is expensive (€692 for 10 g of 60% wt. product in June 2025)^[56] and submitted to transportation restrictions. We synthesized it following Togni's procedure^[38] with the Ruppert-Prakash reagent (€344/25 mL in June 2025).^[57] The overall synthesis of the Togni II reagent takes more than 2 days. The TFMS synthesis costs are therefore high in time and money, which is aggravated by the fact that 7 equivalents of it are required for each reaction with a sulfoxide. Consequently, we turned our attention to another source of trifluoromethoxide anion, namely DNTFB (2,4-dinitro-1-(trifluoromethoxy)benzene), that could also serve as an activator of the sulfoxide substrate thanks to the electron-poor dinitrophenyl motif. Indeed, we and others had previously shown that the association of DMAP and DNTFB produces a stable solution of trifluoromethoxide anion in the form of the 1-(2,4-dinitrophenyl)-4-(dimethylamino)pyridinium trifluoromethoxide salt (DDPyOCF₃), for nucleophilic trifluoromethoxylation as well as other applications.^[40–47,58] We thus considered using commercial and inexpensive DNTFB for the Pummerer-type trifluoromethoxylation process.

We started our investigations by mixing, in an NMR tube, 1 equivalent of sulfoxide **1a** in the presence of 1.1 equivalent of DNTFB and 0.5 equivalent of DMAP in deuterated acetonitrile at 20 °C. Traces of **2a** were observed after 30 hours. Heating the tube at 60 °C for 25 hours led to the formation of 20% ¹⁹F NMR



Scheme 11. First experiments in NMR tubes with DNTFB.

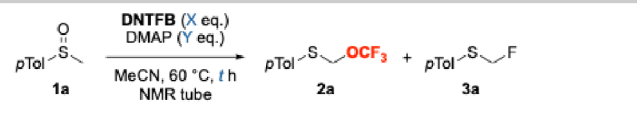
Table 4. Influence of the addition order on the reaction. ^[a]				
Entry	Addition order	Conversion ^[b]	Yields ^[c]	
			2a	3a
1	DMAP added last	27%	20%	7%
2	Sulfoxide 1a added last	35%	31%	4%
3 ^[d]	DMAP + sulfoxide 1a added on DNTFB	30%	27%	3%

[a] Reactions carried out at 0.1 mmol scale in NMR tubes.
 [b] With regard to the starting sulfoxide **1a**.
 [c] ¹⁹F NMR yield calculated with α,α,α -trifluorotoluene (CAS 98–08–8) as internal standard.
 [d] Solution of DMAP and sulfoxide added onto DNTFB to maintain an excess of DNTFB over DMAP during the addition.

yield of **2a** and 7% ¹⁹F NMR yield of **3a** for a 27% conversion of the starting sulfoxide **1a**. After 40 more hours, the conversion reached 95%, with 95% ¹⁹F NMR yield of **3a** without traces left of **2a**. Our hypothesis for this result was that **2a** was degrading over time to form **3a** (Scheme 11).

Variations of the time and order of addition of the reagents were investigated at 0.1 mmol scale in NMR tubes. First, a solution of the sulfoxide and DNTFB in acetonitrile was prepared, but the reaction only started to progress when DMAP was added (Table 4, entry 1). Adding instead sulfoxide **1a** onto a solution of DMAP and DNTFB in acetonitrile afforded 31% ¹⁹F NMR yield of **2a** and 4% ¹⁹F NMR yield of **3a** for a 35% conversion of **1a** after 25 hours (entry 2). When a solution of DMAP and sulfoxide **1a** was added onto DNTFB, a 30% conversion of **1a** after 20 hours was achieved, with 27% ¹⁹F NMR yield of **2a** and 3% ¹⁹F NMR yield of **3a** (entry 3). In any case, the reactivity observed was similar. The reaction is slightly faster when sulfoxide **1a** is added last, but in that case, opening the reaction tube to introduce **1a** decreases the gas pressure in the vessel, favoring the degradation of the F₃CO⁻ anion into fluorophosgene. The reaction between DMAP and DNTFB being exothermic, we chose to mix DNTFB with sulfoxide **1a** in acetonitrile before adding DMAP.

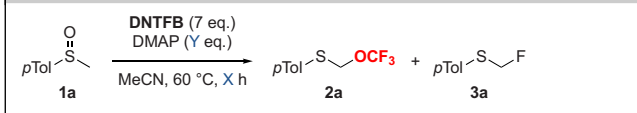
Table 5. Influence of ratios and amounts of DNTFB and DMAP.



Entry	X eq. of DNTFB	DMAP	t [h]	Conv. ^[a]	Yields ^[b]	
					2a	3a
1 ^[c]	1.1	Y eq. of	25	27%	20%	7%
2 ^[c]	1.1	0.95	50	66%	30%	36%
3 ^[c]	2.2	1.95	50	71%	36%	35%
4 ^[c]	7	1.95	25	89%	68%	3%
5 ^[d]	7	2	16	100%	64%	30%

[a] With regard to the starting sulfoxide **1a**.
 [b] ¹⁹F NMR yield calculated with α,α,α -trifluorotoluene (CAS 98–08–8) as internal standard.
 [c] Experiments conducted with 0.1 mmol of **1a** in NMR tubes.
 [d] Experiments conducted with 3 mmol of **1a** in crimp-capped heavy wall reaction tubes.

Table 6. Influence of amounts of DMAP and reaction time.



Entry	X h reaction time	Y eq. of DMAP	Conversion ^[a]	Yields ^[b]	
				2a	3a
1	16 hours	2	100%	64%	30%
2	16 hours	3	100%	79%	18%
3	6 hours	3	86%	77%	9%
4	7 hours	3	91%	80%	9%
5	8 hours	3	95%	76%	17%

[a] With regard to the starting sulfoxide **1a**.
 [b] ¹⁹F NMR yield calculated with α,α,α -trifluorotoluene (CAS 98–08–8) as internal standard.

For this reason and to avoid the release of gaseous difluorophosgene, we decided to pursue our study with the addition of DMAP at the end (conditions of entry 1).

The reaction was then carried out with some poorly nucleophilic bases (2,6-lutidine, 2,6-di-*tert*-butylpyridine) structurally related to DMAP. The degradation of DNTFB, and the release of trifluoromethoxide anion in the presence of these bases is known to be slower and incomplete.^[41] Considering the unavoidable degradation equilibrium of F_3CO^- into fluorophosgene and fluoride, a slower release of F_3CO^- anion could minimize the formation of fluoride that would lead competitively to **3a**, hence improving the **2a/3a** ratio obtained with DMAP. However, with these bulky bases, no conversion of the starting sulfoxide **1a** was observed.

As we already described,^[41] the stability of $DDPyOCF_3$ in solution depends on the ratio between DNTFB and DMAP. With only a slight excess of DMAP, the F_3CO^- anion in solution will degrade rapidly. Three different amounts and ratios of DNTFB and DMAP were investigated in NMR tubes (Table 5). Longer reaction times and higher ratios of DNTFB/DMAP had a positive impact on the conversion, but a negative impact on selectivity (entries 1–2). To enhance the latter, the hypothesis was made that a larger amount of DNTFB and DMAP would push the conversion of sulfoxide **1a** by increasing the concentration of F_3CO^- anions in the reaction mixture and proved correct (entry 3). Finally, inspired by the procedures employed with TFMT and TFMS, we also tested conditions where an excess of DNTFB was used with regard to DMAP, itself in excess regarding the sulfoxide. This would not only allow a large amount of F_3CO^- to be present in solution, but also to trap fluoride with the excess of DNTFB, to minimize the amount of F^- and release another F_3CO^- anion instead.^[40] Satisfyingly, a drastic increase of the amount of DNTFB to 7 equivalents for 1.95 equivalents of DMAP enabled to reach 89% conversion of **1a**, with 68% ¹⁹F NMR yield of **2a** for only 3% ¹⁹F NMR yield of **3a** (entry 4). The presence of a large amount of 1-fluoro-2,4-dinitrobenzene (Sanger's reagent) was observed at

the end of the reaction, resulting from the substitution of fluoride on DNTFB. It appeared that changing from NMR-tube scale (0.1 mmol of starting sulfoxide **1a**) to a larger one (3 mmol of **1a**) in crimp-capped heavy wall reaction tubes increased the reaction rate, thus diminishing the duration from 25 hours to 16 hours (entry 5).

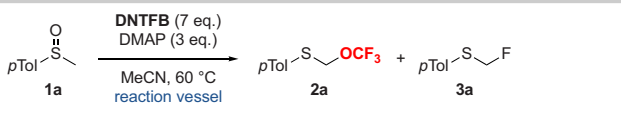
Comforted by the good yield of **2a**, the reaction conditions at the 3 mmol scale in crimp-capped heavy wall reaction tubes were further optimized. It was necessary to have enough liquid phase to diminish the headspace in the vial and limit the decomposition of the trifluoromethoxide anion into fluorophosgene gas. Then, increasing the amount of DMAP to 3 equivalents instead of 2 afforded a higher 79% ¹⁹F NMR yield of **2a** for 18% ¹⁹F NMR yield of **3a** (Table 6, entries 1 vs. 2). With these conditions, the reaction time can be reduced to 7 hours with an 80% ¹⁹F NMR yield of **2a** and 9% ¹⁹F NMR yield of **3a** (entry 4). Longer reaction time increases the conversion of sulfoxide **1a** but does not increase the yield of **2a** (entry 5).

A pressure-resistant vessel from Ace Glass Inc. (see [Supporting Information](#) for details) was used to scale up the reaction further, reaching a 6 mmol scale. With this specific type of glassware, 87% NMR yield of **2a** (corresponding to a mass of 1.46 g of **2a** in the mixture) at the end of the reaction, with full conversion of **1a** and 12% of **3a** were obtained (Table 7, entry 3). Noteworthy, the combined yields of **2a** and **3a** in the NMR tube and in the crimp-capped heavy-walled vial do not match the conversion of **1a** (Tables 5, 6). The result obtained with the Ace pressure tube indicates that the missing mass problem was resulting from the evaporation of **3a** from the NMR tube or crimp-capped vials, which are less efficiently sealed than Ace pressure tubes. In fact, the seal of Ace pressure tubes had to be changed after every reaction due to corrosion and degradation.

Having found the most appropriate reaction setup (Table 7, entries 2–3), a scope of 11 substrates was studied, with ¹H and ¹⁹F yields ranging from 0% to 87%, depending on the nature of the aryl substituent (Figure 1).

Having these interesting NMR yields of the desired α -trifluoromethoxylated thioethers, we tackled their isolation.

Table 7. Scaling up of the reaction.



Entry	Type of vessel ^[c]	mmol of 1a	Time	Conversion ^[a]	Yields ^[b]	
					2a	3a
1 ^[d]	NMR tube	0.1	25 h	89%	68%	3%
2	Vial	3	7 h	91%	80%	9%
3	Ace pressure tube	6	7 h	100%	87%	12%

[a] With regard to the starting sulfoxide **1a**.
 [b] ¹H and ¹⁹F NMR yields calculated with 1-methoxy-4-(trifluoromethyl)benzene (CAS 402–52–8) as internal standard.
 [c] NMR tube (ca. 2.2 mL, 1.6–1.8 mL headspace), crimp-capped heavy walled vial (ca. 9 mL, 4–5 mL headspace), Ace pressure tube (ca. 38 mL, 18–20 mL headspace).
 [d] Performed with 1.95 eq. of DMAP.

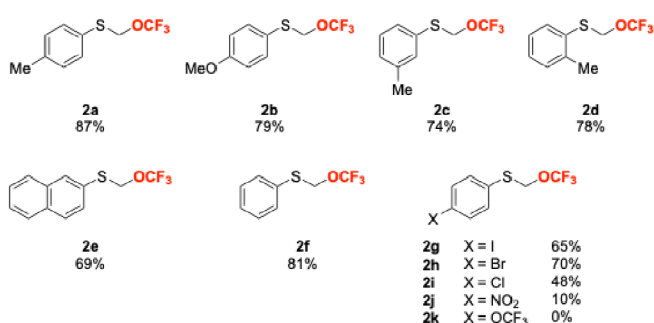
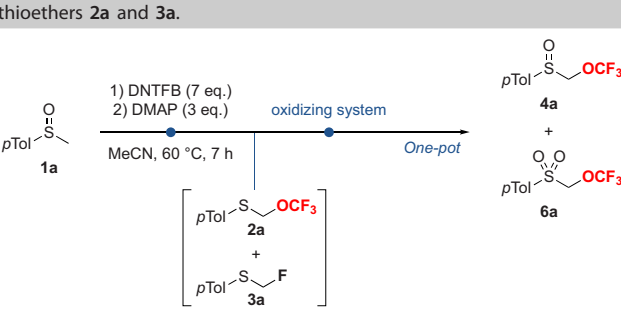


Figure 1. α -Trifluoromethoxylated thioethers accessed with the procedure using DNTFB. ¹H and ¹⁹F NMR yields calculated with 1-methoxy-4-(trifluoromethyl)benzene (CAS 402–52–8) as internal standard.

Disappointingly, the complete loss of trifluoromethoxylated thioethers was observed once again during purification attempts, especially due to their volatility and sensitivity on silica gel (whether neutral or basified), as mentioned earlier. Distillation proved unsuccessful due to the full conversion of **2a** into **3a**. To facilitate the isolation of **2a**, carrying out its in situ oxidation was considered again, as trifluoromethoxylated sulfoxides are the targets of interest and are less volatile than thioethers. A few oxidation systems were investigated (Table 8). First, a system initially developed for the epoxidation of alkenes^[59,60] involving a reactive peroxyimidic acid was tested, the latter being formed by the reaction of hydrogen peroxide with acetonitrile in the presence of a base. The crude material containing the trifluoromethoxylated thioether **2a** was submitted to 2 equivalents of hydrogen peroxide and 2 equivalents of DMAP to play the role of the base. 31% ¹H NMR yield of **4a** were obtained along with 55% of remaining **2a** (Table 8, entry 1). With 2 equivalents of potassium carbonate instead of added DMAP as the base, **4a** was formed in 29% ¹H NMR yield (entry 2). Surprisingly, when 2 equivalents of DMAP and 2 equivalents of H₂O₂ were added to a solution of isolated **2a** in acetonitrile, no conversion was

Table 8. In situ oxidation of the crude reaction mixture containing thioethers **2a** and **3a**.



Entry	Conditions	Conversion ^[a]	Yields ^[b]	
			4a	6a
1	H ₂ O ₂ (2 eq.) / DMAP (2 eq.), MeCN, r.t., 1 hour	45%	31%	Traces
2	H ₂ O ₂ (2 eq.) / K ₂ CO ₃ (2 eq.), MeCN, r.t., 1 hour	64%	29%	Traces
3 ^[c]	H ₂ O ₂ (2 eq.) / DMAP (2 eq.), MeCN, r.t., 1 hour	1%	1%	/
4	H ₅ IO ₆ (1.1 eq.) / FeCl ₃ (3 mol %), MeCN, r.t., 45 min	0%	/	/
5 ^[c]	H ₅ IO ₆ (1.1 eq.) / FeCl ₃ (3 mol %), MeCN, r.t., 45 minutes	100%	58% ^[d]	4%
6	<i>m</i> -CPBA (2.2 eq.), MeCN, r.t., 3 hours	84%	68%(44% ^[d])	15%
7 ^[c]	<i>m</i> -CPBA (1.1 eq.), DCM, r.t., 1 hours	87%	76% ^[d]	13%

[a] With regard to **2a** (average of numbers obtained from ¹H and ¹⁹F NMR analysis).
 [b] ¹H and ¹⁹F NMR yields calculated with 1-methoxy-4-(trifluoromethyl)benzene (CAS 402–52–8) as internal standard.
 [c] Performed on isolated **2a** (see text).
 [d] isolated yields.

observed (entry 3). The absence of conversion when this system was used on isolated thioethers suggests that the active species in the oxidation of the crude mixture is probably not the peroxyimidic acid as expected, but a newly formed oxidant resulting from the oxidation of one of the reactants in the mixture. Experiments were also carried out with other oxidizing systems such as FeCl₃/H₅IO₆—as in the previous trifluoromethoxylation procedure involving TFMS, see Scheme 10—, but with these conditions, no reactivity was recorded (entry 4). Alternately, treating the crude trifluoromethoxylation reaction mixture with *m*CPBA managed to afford a 68% ¹⁹F NMR yield (entry 6) and 44% isolated yield of **4a** but along with the corresponding sulfone **6a**, due to the excess of 2.2 eq. of active oxygen to push forward the oxidation of the electron-depleted sulfide. The formation of the *N*-oxide of DMAP was also consuming some significant amount of oxidant.

Finally, to circumvent the nonoptimal and unselective oxidation, another strategy was devised to isolate the desired sulfides. To improve their separation from remaining amounts of DNTFB

and of Sanger's reagent, the latter species were converted into more polar, hydrosoluble ones. On the one hand, all the remaining DNTFB was converted into DDPyOCF₃ by adding 0.5 to 1 eq. of DMAP at the end of the reaction at 0 °C; on the other hand, the remaining Sanger reagent was also converted by subsequently adding an aqueous saturated solution of Na₂CO₃ and a large excess of glycine, which is known to react with Sanger's reagent by nucleophilic aromatic substitution.^[61] The desired thioether **2a** could then be easily separated by extraction with pentane, with a yield of 66%. This purification method relies on the strong difference of polarity between solvents and produced only good results with pentane as the organic phase. With this isolation method, thioethers **2a** (66% yield), **2c** (47% yield) and **2d** (43% yield) were obtained. The oxidation of **2a** was assessed with either the FeCl₃/periodic acid system or *m*-CPBA (Table 8, entries 5 and 7). When comparing entries 4 and 5, it appears that the use of periodic acid requires a very clean thioether, as any remaining traces of other compounds from the Pummerer step will inhibit the oxidation. Entries 6 and 7 show that the oxidation with *m*CPBA is not complete and that using an excess of oxidant leads to overoxidation of thioether **2a** and sulfoxide **4a** into sulfone **6a**.

Therefore, an organocatalyzed method of sulfoxidation was developed, based on the previous work done by Lusinchi and Hanquet.^[62,63] It consists in the in situ generation of an electrophilic oxidation reagent, namely an oxaziridinium salt, which would therefore be able to oxidize the thioether only, not the sulfoxide, whose sulfur atom is less nucleophilic, thus avoiding sulfone formation. Two procedures were investigated: 1) A solution of thioether **2a** was added on the preformed oxaziridinium salt; or 2) *m*CPBA was added on a mixture of thioether **2a** and iminium salt **A** as catalyst. In both cases, conversions and yields were similar. Gratifyingly, the oxaziridinium salt formed in situ from the reaction of iminium salt **A** and *m*-CPBA proved able to oxidize completely and very rapidly trifluoromethoxylated thioether **2a** into sulfoxide **4a** without any overoxidation into sulfone **6a** (Table 9, entry 2). When the crude mixture of the Pummerer reaction was submitted to these conditions, full conversion was observed, and an almost quantitative yield of **4a** without any overoxidation into **6a** as well, with down to only 0.3 mol% of catalyst **A** and even in the presence of 2.2 equivalents of *m*-CPBA (entries 3–5). With the conditions of entry 5 in hand, a little scope of sulfides was submitted to the 2-step process involving Pummerer-type trifluoromethoxylation/highly selective in situ catalytic oxidation with the oxaziridinium derived from **A**. Good overall yields ranging from 48 to 84% were obtained for **4a–i** (Scheme 12).

DNTFB as OCF₃-source–Mechanistic discussion.

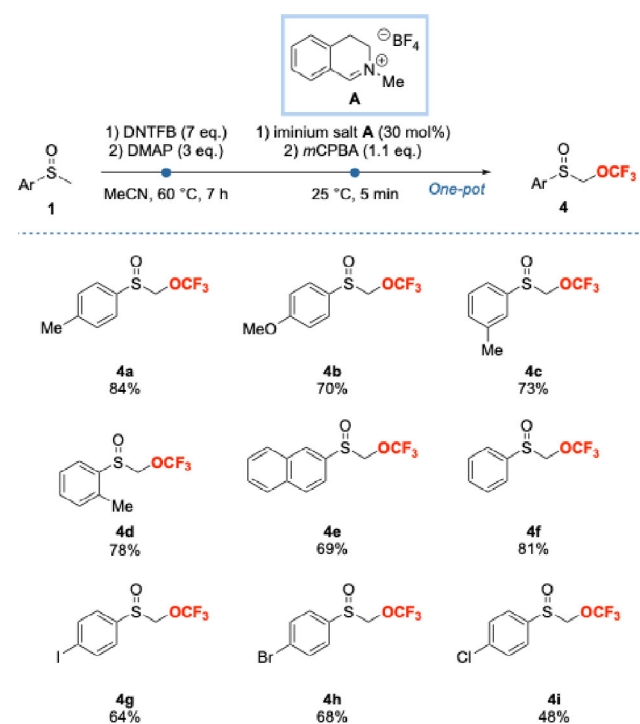
Analogously to the mechanistic investigation conducted for TFMT (Scheme 8), the roles of the activator for the sulfoxide substrate as well as of the base were scrutinized again.

With DNTFB as OCF₃ source, one could expect the sulfoxide to be activated by DNTFB itself, Sanger's reagent (2,4-dinitro-1-fluorobenzene), the DDPy⁺ cation, or, as in the case of TFMT and TFMS, by COF₂ or the COF₂-DMAP adduct (Scheme 13). To decide between these different scenarios, some control experiments were carried out. Mixing DNTFB or Sanger's reagent and

Table 9. Oxidation of thioether **2a** organocatalyzed with an oxaziridinium salt derived from **A**.

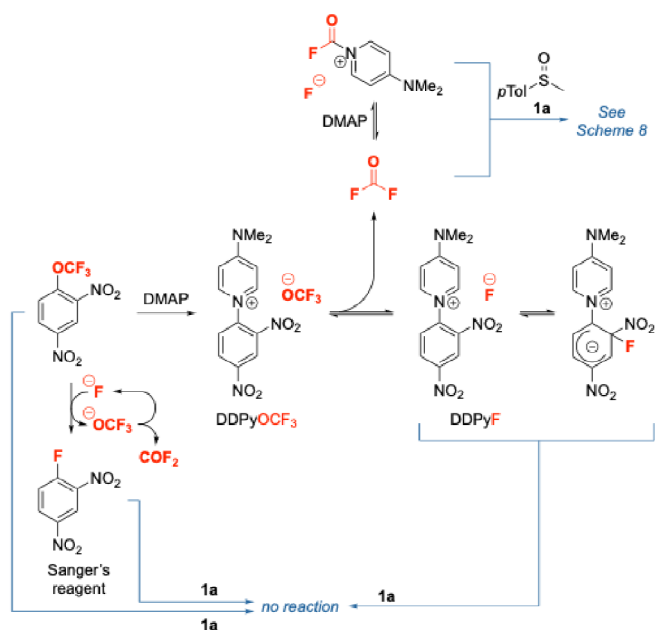
Entry	Scale [mmol]	X mol% of iminium salt	Conversion ^[a]	Isolated yield of 4a
1	0.7	—	87%	76%
2	0.7	0.5	100%	98%
3 ^[b]	1	—	84%	68%
4 ^[b]	1	0.3	97%	92%
5 ^[b]	6.6	0.3	100%	96%

[a] With regard to **2a** (average ¹H and ¹⁹F NMR, 1-methoxy-4-(trifluoromethyl)benzene (CAS 402–52–8) as internal standard).
 [b] Oxidation of the crude mixture obtained from the Pummerer trifluoromethoxylation step, performed with 2.2 eq. of *m*-CPBA.



Scheme 12. Scope of α -trifluoromethoxylated sulfoxides obtained with the 2-step procedure employing DNTFB/DMAP then **A**/*m*-CPBA. Yields calculated over the two steps.

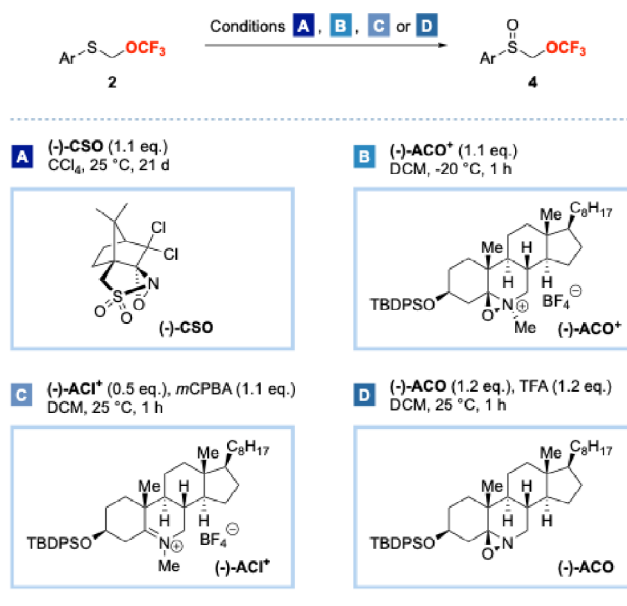
sulfoxide **1a** resulted in no conversion nor observable interaction by NMR. In order to evaluate DDPy⁺ as activator in the absence of any fluorophosgene, DDPyOCF₃ was formed and left in open air while heating at 80 °C and stirring overnight. After verifying the full degradation of the F₃CO⁻ anion by ¹⁹F NMR, argon was bubbled in the solution to get rid of the traces of COF₂, thus leaving a mixture of DDPyF salt and the corresponding zwitterion (resulting from attack of fluoride onto C–NO₂)^[41,47] (Scheme 13). Adding sulfoxide **1a** in the mixture resulted in no conversion

Scheme 13. Mechanism of formation of **2a** with DNTFB.

as well. With these 3 experiments, we confirmed that neither DNTFB, Sanger's reagent, nor DDPy^+ are activators of the sulfoxide in the Pummerer process. Once again, COF_2 or its DMAP adduct are the effective species converting the starting sulfoxide into a sulfonium salt. Then, to confirm that fluoride is a competent base as in the case of TFMT or TFMS discussed earlier, an experiment was conducted with 7 eq. of DNTFB, 1 eq. of CsF salt, 0.5 eq. of 18-crown-6 ether and in the absence of DMAP. Up to 82% conversion of the sulfoxide **1a** with 0% and 78% ^{19}F NMR yields for **2a** and **3a**, respectively, were obtained. Fluoride is, hence, a competent base when DNTFB is employed as OCF_3 source, analogously to the conditions involving TFMT or TFMS.

2.6. Asymmetric Oxidation

Having shown that α -trifluoromethoxylated sulfides could be oxidized into the corresponding racemic sulfoxides, we wondered whether their asymmetric sulfoxidation would be feasible. Different described methods for the asymmetric oxidation of sulfides into sulfoxides were tested. The Kagan and Modena method,^[64,65] based on the use of a Ti(IV) species, a chiral tartrate-derived ligand, *tert*-butylhydroperoxide as the oxidant and water gave no conversion of the trifluoromethoxylated thioether **2a** into the corresponding sulfoxide **4a** after 6 days of reaction. The next conditions tested were derived from those developed by Bolm^[66] with hydrogen peroxide as the oxidant, catalyzed by an iron complex comprising a chiral Schiff base as ligand. After 6 days of reaction, 12% of the desired sulfoxide were isolated but no enantioselectivity was observed. The trifluoromethoxylated thioethers **2a–b,d–e,h** were then oxidized by Davis' *gem*-dichlorinated camphorsulfonyloxaziridine^[67,68] (-)-CSO, an electrophilic oxidant (Scheme 14, conditions A). Modest



	4a	4b	4d	4e	4h
A	22% ^[a] 79% e.e.	51% 25% e.e.	59% 60% e.e.	38% 80% e.e. ^[b]	45% 65% e.e.
B	91% 89% e.e.	83% 90% e.e. ^[c]	90% 92% e.e.		92% 95% e.e. ^[d]
B ^[e]	63% 91.5% e.e.	72% 89% e.e.	58% 91% e.e.		67% 90% e.e.
C	92% 60% e.e.				
D	75% 95% e.e. ^[f]	62% 91% e.e.	63% 92% e.e. ^[g]		61% 93% e.e.

Scheme 14. Asymmetric sulfoxidations using Davis' dichlorocamphorylsulfonyloxaziridine (-)-CSO and cholesterol-derived iminium (-)-ACI⁺, oxaziridine (-)-ACO and oxaziridinium (-)-ACO⁺.

to encouraging e.e.'s were obtained, but the reaction suffered impractical reaction times.

As the oxidation with chiral oxaziridines showed good results, and given the efficient and selective sulfoxidation by in situ generated racemic oxaziridinium salts discussed above, we turned our attention to a chiral oxaziridinium salt (-)-ACO⁺ derived from cholesterol and described by Bohé et al. for the asymmetric oxidation of nonfluorinated sulfides.^[69] With this oxidant (Scheme 14, conditions B), not only the reaction proved much faster than with (-)-CSO, since it was completed within one hour, but it also afforded much higher enantioselectivities, with e.e.'s in the high 89–95% range on the same series of isolated substrates **2a–b,d,h**. In all cases under conditions B, yields were high (83–92%). With these good results in hand, we were interested in performing the enantioselective oxidation on the crude mixture of the DNTFB-based Pummerer reaction-trifluoromethoxylation process, instead of the isolated sulfides. While e.e.'s of products

Table 10. Rate constants, inversion energy barriers and half-life times for sulfoxides **4a–b** and **4 h** at 214 °C (487 K) in 1,2,4-trichlorobenzene.

Entry	Sulfoxide	k_{ent} [s ⁻¹] ^[c]	ΔG^\ddagger [kcal.mol ⁻¹]	$t_{1/2}$ [minutes or hours]
1 ^[a]	PhS(O)Me	$3.84 \cdot 10^{-6}$	41.1	25.1 hours
2 ^[a]	<i>p</i> TolS(O)CF ₂ H	$3.48 \cdot 10^{-5}$	38.7	166 minutes
3 ^[a]	<i>p</i> AnS(O)CF ₂ H	$3.21 \cdot 10^{-5}$	38.9	180 minutes
4 ^[a]	(4-Cl-C ₆ H ₄)S(O)CF ₂ H	$3.49 \cdot 10^{-5}$	39.0	166 minutes
5 ^[b]	4a	$6.58 \cdot 10^{-5}$	38.3	88 minutes
6 ^[b]	4b	$5.87 \cdot 10^{-5}$	38.4	98 minutes
7 ^[b]	4h	$5.84 \cdot 10^{-5}$	38.4	99 minutes

[a] Reference.^[71]

[b] This work.

[c] Enantiomerization rate constant.

4a–b,d,h remained in the same 89–92% range, yields were lower (58–72%). Next, we wondered if, as in the organocatalyzed oxidation with achiral iminium salt **A**, instead of pre-forming the oxaziridinium (-)-**ACO**⁺ and use it as stoichiometric oxidant, the latter could be generated in situ from a catalytic amount of iminium salt (-)-**ACI**⁺ and stoichiometric *m*CPBA (Scheme 14, conditions C). It turned out that, although the reaction provided a high yield of oxidation, the enantiomeric excess of the product dropped significantly. It thus appears that the peracidic oxidation of iminium (-)-**ACI**⁺ is much slower than the one of **A**, leading to competitive direct oxidation of sulfide **2a** by *m*CPBA. Finally, we also assessed the parent oxaziridine (-)-**ACO** as chiral oxidant, activated not by methylation but by protonation of the nitrogen atom with trifluoroacetic acid.^[70] Under these conditions (Scheme 14, conditions D), we were pleased to record even higher enantiomeric excesses of products **4a–b,d,h** (91–95% e.e.), although at the expense of yields (61–75%).

Under all conditions B–D, the major enantiomer of sulfoxides **4a–b,h** was determined to be (+)-(*S*), by polarimetry and/or HPLC and comparison with absolute configuration determined during the configurational stability study (vide infra), which is in accordance with the stereoinduction observed by Bohé et al.^[69]

2.7. Configurational Stability

We had already studied quantitatively the configurational stability of aryl di- or trifluoromethyl sulfoxides by thermal enantiomerization and chiral HPLC analysis.^[71] As an extension of this study, we also investigated the configurational stability of aryl (trifluoromethoxy)methyl sulfoxides **4a** (aryl = *p*Tol), **4b** (aryl = *p*An), and **4 h** (aryl = 4-bromophenyl) with the same procedure. Despite its size, the flexibility of the CH₂OCF₃ group and the strong inductive attractive effect of the OCF₃ group seem to facilitate to some extent the enantiomerization of the sulfoxides when comparing with methyl phenyl sulfoxide and aryl difluoromethyl sulfoxides (with aryl = *para*-anisyl, *para*-tolyl or 4-chlorophenyl), although enantiomerization barriers of HF₂C- and F₃COH₂C- derivatives lie in the same range (Table 10). The

absolute configuration of the (+) enantiomer of **4a–b,h** was determined to be (*S*) (see Supporting Information for details).

2.8. Physico-Chemical Measurements

The pK_a of the trifluoromethoxylated sulfoxide **4a** was measured in order to determine the most appropriate base to perform the deprotonation and functionalization of the methylene between the sulfanyl and OCF₃ moieties. An indirect colorimetric method developed by Bordwell^[72] that was successfully used in our group for the determination of the pK_a of other fluoroalkyl sulfoxides^[72] was followed. This method relies on the titration of the colored anion of an indicator (In⁻) by its proton exchange with the sulfoxide (HA), leading to the conjugate species InH and deprotonated sulfoxide A⁻. The concentration of In⁻, the only absorbing species in the medium, was followed by absorption measurements. With this method and with carbazole as indicator, a pK_a value of 20.33 ± 0.11 for *p*-tolyl (trifluoromethoxy)methyl sulfoxide **4a** was obtained. Since the pK_a of (methylsulfanyl)benzene in DMSO is 33, an increased acidity of neighboring protons with the introduction of the fluorinated group is observed, as anticipated.

To assess its lipophilicity, the logarithm of the partition coefficient *P* of trifluoromethoxylated sulfoxide **4a** between a water and an octanol phase was determined. The log *P* is often used during the structure-activity relationship study of a biological target. A log *P* value of 1.90 ± 0.19 for *p*-tolyl (trifluoromethoxy)methyl sulfoxide **4a** was measured following a shake-flask method with a HPLC-UV detection procedure described by Anselmi, Magnier, Leito, and Billard.^[73] Accordingly, the Hansch-Leo parameter π for the S(O)CH₂OCF₃ substituent, corresponding to the difference in log *P* between **4a** and benzene (log *P* = 2.13), is of ca. -0.23, meaning that S(O)CH₂OCF₃ brings hydrophilicity to the core structure.

2.9. Functionalization

The stability of the deprotonated sulfoxide **4a** in solution was studied. **4a** was submitted to deprotonation with 2 eq. of *t*-BuOK at -78 °C in THF, then left under stirring for 1 h and quenched with methanol. No degradation was observed, and the sulfoxide was fully recovered. Trifluoromethoxylated sulfoxides **4a** and **4d** were then functionalized by deprotonation on the α -position and electrophilic trapping by methyl iodide. Different bases and temperatures were screened in THF (Table 11). LiHMDS, *t*-BuOK and *P*₄-*t*-Bu gave the best ¹⁹F NMR yields of **4'a**, that is, 87%, 85%, and 100%, respectively, (entries 2, 7 and 10) with diastereoselectivities up to 66:34 d.r. (entry 11). Deprotonation with LDA produced an acceptable ¹⁹F NMR yield of **4'a** up to 48% (entry 5). However, using this base showed reproducibility issues depending on the quality of the commercial *n*-BuLi used to prepare LDA. The elevated price of the phosphazene superbase precluded its use in stoichiometric amount on a regular basis. As LiHMDS and *t*-BuOK produced similar yields and as *t*-BuOK is easier to handle than LiHMDS, we decided to employ potassium *tert*-butoxide as

Table 11. Electrophilic methylation under in situ quenching conditions.

Entry	Ar	Base	Y eq.	T °C	Conversion ^[a]	Yield of 4'a/4'd ^[a]	Diastereoisomeric ratio ^[a]
1	<i>p</i> Tol (4a)	LiHMDS	1	−30 °C	78%	(78%)	48:52
2	<i>p</i> Tol (4a)	LiHMDS	1.5	−30 °C	100%	(87%)	43:57
3 ^[b]	<i>p</i> Tol (4a)	LDA	1	−100 °C	100%	(41%)	46:54
4 ^[b]	<i>p</i> Tol (4a)	LDA	1	−78 °C	68%	(3%)	39:61
5 ^[b]	<i>p</i> Tol (4a)	LDA	1	−30 °C	100%	(48%)	40:60
6	<i>p</i> Tol (4a)	<i>t</i> -BuOK	1	−30 °C	35%	(32%)	40:60
7	<i>p</i> Tol (4a)	<i>t</i> -BuOK	1.5	−30 °C	58%	(51%)	38:62
8 ^[c]	<i>p</i> Tol (4a)	<i>t</i> -BuOK	2	−30 °C	89%	(85%)	34:66
9	<i>p</i> Tol (4a)	P ₄ - <i>t</i> -Bu	1	−30 °C	99%	(73%)	44:56
10	<i>p</i> Tol (4a)	P ₄ - <i>t</i> -Bu	1.5	−30 °C	100%	(100%) 69%	39:61
11	<i>o</i> Tol (4d)	P ₄ - <i>t</i> -Bu	1.1	−30 °C	100%	73%	16:84
12 ^[c]	<i>o</i> Tol (4d)	<i>t</i> -BuOK	2	−30 °C	78%	76%	21:79

[a] NMR yields were determined with 1-fluorobenzene as internal standard and are given in parentheses; Isolated yields are given without parentheses.
 [b] Sequential addition (LDA first, then MeI after 5 minutes).
 [c] Performed with 2 eq. of MeI.

our base of choice. Methylation of the *ortho*-tolyl substituted sulfoxide **4d** with P₄-*t*-Bu and *t*-BuOK resulted in similar yields than with the *para*-tolyl substituted sulfoxide **4a**, with, respectively, 73% and 76% isolated yields of **4'd** (entries 11–12). However, the d.r. improved up to 84:16 (entry 11) thanks to the more sterically demanding *o*-tolyl group.

3. Conclusion

We present herein a novel method to introduce a trifluoromethoxy group on a C-sp³ carbon, starting from nonfluorinated sulfoxides and using three different electrophilic OCF₃-donors, by means of a Pummerer-type reaction followed by sulfoxidation. The mechanism of this process, and particularly the multiple roles of the OCF₃-donor, which behaves directly or indirectly as sulfoxide activator, source of F₃CO[−] nucleophile and source of fluoride as base, have been clarified. The configurational stability of 3 α -trifluoromethoxylated aryl methyl sulfoxides resulting from this process has been determined, as well as the pK_a of one of them. The subsequent functionalization of such sulfoxides on the C–OCF₃ center by deprotonation and electrophilic trapping was undertaken, and could be achieved with a high 84:16 diastereomeric ratio. Our method gives also access to the corresponding thioethers, that can then undergo an asymmetric oxidation to give access to unprecedented highly enantioenriched α -trifluoromethoxylated sulfoxides. We will now explore the synthetic potential of these new chiral trifluoromethoxylated synthons.

4. Experimental Section

General procedure for the synthesis of trifluoromethoxylated sulfoxides **4** with trifluoromethyl *p*-toluenesulfonate (TFMS)

To a solution of trifluoromethyl *p*-toluenesulfonate (7 eq.) and the corresponding nonfluorinated sulfoxide (1 eq.) in dry acetonitrile at −30 °C in a crimp-cap heavy-wall tube was added DMAP (1.5 eq.) under a stream of argon. The solution was stirred for 30 min at −30 °C and then overnight at 21 °C. To the crude mixture was added FeCl₃ (3.0 mol%), and then, after 5 minutes of stirring, H₅IO₆ (1.1 eq.). After stirring for 25 minutes, an additional equivalent of H₅IO₆ (1.1 eq.) was added. After another 25 minutes of reaction, the mixture was poured onto a saturated solution of Na₂S₂O₃ at 0 °C. The aqueous layer was extracted with CH₂Cl₂. The combined organic layers were washed with brine and dried over anhydrous MgSO₄. The volume was reduced on the rotary evaporator under ambient pressure. The crude material was purified by flash column chromatography on silica gel (pentane/EtOAc 90/10) to afford the corresponding trifluoromethoxylated sulfoxides **4**.

General procedure for the synthesis of trifluoromethoxylated thioethers **2** with 2,4-dinitro-1-(trifluoromethoxy)benzene (DNTFB)

To a solution of aryl methyl sulfoxide **1** (1 eq.) in acetonitrile (2 mL) was added DNTFB (7 eq.), and the mixture was stirred for 5 minutes before adding DMAP (3 eq.). The reaction tube was flushed with argon, sealed, and left under stirring at 60 °C for 7 hours. The tube was cooled down to room temperature and carefully degassed, and the crude mixture was analyzed by quantitative ¹H and ¹⁹F NMR with 1 eq. of 1-methoxy-4-(trifluoromethyl)benzene as probe. The reaction mixture was then quenched with water at 0 °C. A relatively intense evolution of gas was observed. The aqueous layer was extracted with pentane and an excess of glycine (more than 5 eq.) in a saturated solution of NaHCO₃ in water was added. The mixture was stirred at 40 °C for 1 to 2 hours. The aqueous layer was extracted again twice with pentane. The combined organic layers

were washed with brine, dried over anhydrous Na₂SO₄, filtered and the solvent was evaporated on the rotary evaporator under ambient pressure. Dry air was flushed on the crude to remove traces of pentane, finally affording the corresponding trifluoromethoxylated thioethers **2**.

General procedure for the synthesis of trifluoromethoxylated sulfoxides **4** with 2,4-dinitro-1-(trifluoromethoxy)benzene (DNTFB)

To the crude mixture of the Pummerer reaction were added, at room temperature, NaHCO₃ (0.03 eq.) and iminium salt **A** (0.3 eq.), followed by *m*CPBA (1 eq. of active O₂). After 5 minutes and a negative potassium iodide paper test, the crude mixture was analyzed by quantitative ¹H and ¹⁹F NMR with 4-methoxybenzotrifluoride as probe. An appropriate additional quantity of *m*CPBA was added, that is, 1 eq. regarding the amount of remaining sulfide. After 5 more minutes and a negative potassium iodide paper test, the mixture was quenched with water at 0 °C. The aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine and dried over anhydrous MgSO₄. The crude material was purified by flash column chromatography on silica gel (pentane/EtOAc gradient from 98/2 to 90/10) to afford the trifluoromethoxylated sulfoxides **4**.

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Conflict of Interest

The author declares no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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