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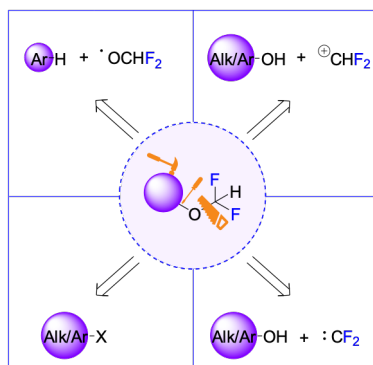
## Graphical Abstract

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### Recent synthetic methods towards the $-\text{OCHF}_2$ moiety

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# Recent synthetic methods towards the $-OCHF_2$ moiety

Anaïs Loison<sup>a</sup>, Fabien Toulgoat<sup>b,c</sup>, Thierry Billard<sup>b,d</sup>, Gilles Hanquet<sup>a,\*</sup>, Armen Panossian<sup>a,\*</sup> and Frédéric R. Leroux<sup>a,\*</sup>

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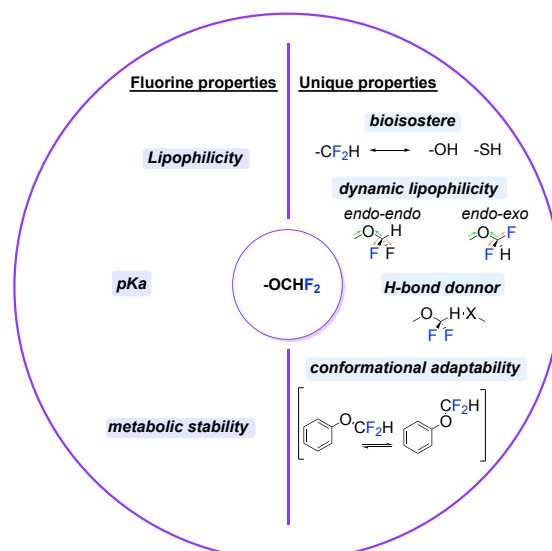
## ABSTRACT

The fluorine atom and fluorinated substituents are currently key motifs in pharmaceutical and agrochemical active ingredients, since they often beneficially modulate the physico-chemical and biological properties of the latter when installed in place of a hydrogen substituent. Among such fluorinated moieties,  $-OCHF_2$  is emerging as an interesting group, which is notably capable of forming a hydrogen bond. These appealing properties have led to a growing need for introduction methods of this group. In this review we summarize all current methods allowing access to the  $-OCHF_2$  moiety. We will hence discuss procedures applicable to either aromatic or aliphatic substrates, and based on different disconnections, including difluoromethylation of alcohols, or radical addition onto arenes.

## Introduction

The use of fluorinated groups in medicinal chemistry or agrochemistry has become common, fluorine atoms being present in more than 18% of the commercial pharmaceuticals and in 53% of the pesticides.[1,2] Fluorine has indeed shown its ability to change the physicochemical and biological properties of molecules compared to their hydrogen-bearing analogues, improving for instance their distribution and metabolic stability.[3,4] Thus, the demand for new fluorinated groups, commonly called emergent fluorinated groups (EFG), and new insertion methods is perpetually increasing.[5]

Among these fluorinated groups, the difluoromethoxy group ( $-OCHF_2$ ) is emerging as an interesting moiety. Indeed, the aryl- $-OCHF_2$  motif is already present in numerous bioactive compounds such as potent enzyme inhibitors[6] like Roflumilast, antimicrobial agents,[7] or anti-HIV agents.[8] The most striking example of a bioactive molecule containing the moiety is the proton pump inhibitor Pantoprazole.[9] As a matter of fact,  $-OCHF_2$  can act as a hydrogen donor through weak hydrogen bonding interactions, lending it an original character compared to other fluorinated moieties. It is noteworthy to remind that  $-CF_2H$  acts as a bioisostere of alcohols and thiols. Besides, the group has the ability to modulate the  $pK_a$  of molecules depending on their environment. This unique dynamic lipophilicity is indeed induced by a simple rotation of the  $O-CHF_2$  bond, which changes the overall dipole moment of the moiety. Furthermore, Ar- $-OCHF_2$ , contrary to Ar- $OCH_3$  or Ar- $OCF_3$ , shows no preferential conformation of the  $-OCHF_2$  bond (in/out of the plane), conferring it thus an adaptability which might increase the binding affinity to active sites.[10–12]

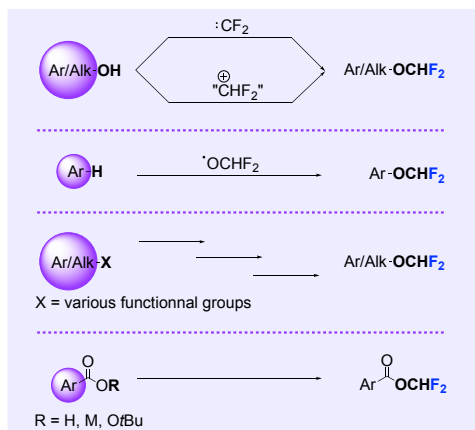


**Figure 1.** Usual beneficial properties of fluorine-containing substituents in active ingredients and unique properties of the  $-OCHF_2$  group.

In view of these interesting properties of the  $-OCHF_2$  moiety (Figure 1), the need for new access methods is high, especially since the main processes developed during the previous century are now inadequate as they were based on ozone-depleting substances or on their derivatives.[13] Nevertheless, various alternatives to these methods were developed in the last decades in order to facilitate the access to the  $-OCHF_2$  motif, by transforming molecules following different disconnections (Scheme 1).

Furthermore, new procedures have proved to be efficient not only for the difluoromethoxylation of aromatics, as the classical methods were, but also on aliphatic substrates.

In this review, all current methods allowing to access the -OCHF<sub>2</sub> moiety will be discussed in terms of the nature of the disconnection leading to the function. First will be described methods consisting in the difluoromethylation of alcohols, based on difluorocarbene or electrophilic -CHF<sub>2</sub> sources, then examples of radical difluoromethoxylation of arenes will be presented, and procedures based on the transformation of other various functional groups will be evoked. Finally, the methods allowing the introduction of the -OCHF<sub>2</sub> as part of a difluoromethyl ester function will be summarized (Scheme 1). Unfortunately, the OCHF<sub>2</sub> anion being highly unstable,[14] turning rapidly into formyl fluoride after elimination of F<sup>-</sup>, none of the developed techniques described below involves this intermediate.



Scheme 1. Access to the -OCHF<sub>2</sub> motif following different disconnections.

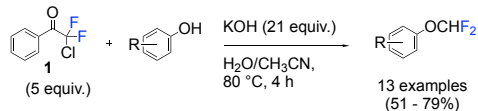
## 1. Difluoromethylation of alcohols

As previously mentioned, the most common methods enabling the introduction of an -OCHF<sub>2</sub> group are based on the difluoromethylation of alkanols and phenols. These approaches, which mostly proceed *via* difluorocarbene as intermediate, will hence be discussed hereafter.

### 1.1. O-Difluoromethylation by means of difluorocarbene.

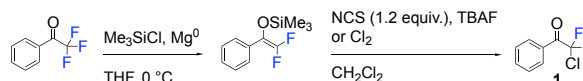
Difluorocarbene sources are versatile and reactive, yet relatively stable reagents. This slightly electrophilic species owes its reactivity to a combination of stabilization and destabilization. Indeed, the carbene is stabilized by  $\pi$ -donation from the fluorine non-bonding orbitals, and destabilized by its attractive inductive effect. Difluorocarbene is mainly used for difluoromethylations (O-, N-, S-, or C-) and for *gem*-difluorocycloalkanations. Fortunately, its electrophilic character confers difluorocarbene a good reactivity towards nucleophilic reagents like alcohols.[15]

Among the first difluorocarbene sources used with satisfying efficiency, CHF<sub>2</sub>Cl, CHF<sub>2</sub>Br, or chlorodifluoroacetates cannot be used anymore. Indeed, all of them were either classified as ozone-depleting substances (ODS) or were prepared from the latter. Besides, some other sources initially explored were toxic, such as Me<sub>3</sub>SnCF<sub>3</sub> and CF<sub>3</sub>HgI. Therefore, new, less toxic, and non-ozone-depleting difluorocarbene sources have been developed in the last decades. For instance, the Hu group developed in 2006 a method using 2-chloro-2,2-difluoroacetophenone **1**,[16] which allows the difluoromethylation of phenols under basic conditions using potassium hydroxide or potassium carbonate (Scheme 2).



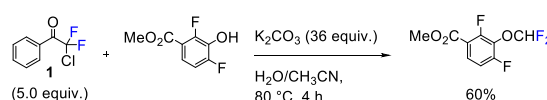
Scheme 2. Difluoromethylation of phenols using 2-chloro-2,2-difluoroacetophenone **1**.

Chlorodifluoroacetophenone **1** was synthesized from  $\alpha,\alpha,\alpha$ -trifluoroacetophenone *via* the corresponding difluorinated silyl enol ether (Scheme 3). The latter was initially chlorinated by *N*-chlorosuccinimide in the presence of TBAF, but this approach only gave moderate yields, which explains why a second method, more easily scalable and reproducible, involving elemental chlorine in dichloromethane, and giving yields up to 87%, was finally selected.



Scheme 3. Synthesis of the 2-chloro-2,2-difluoroacetophenone **1**.

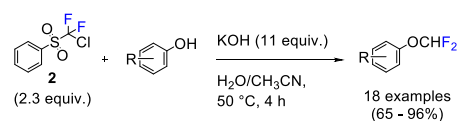
The reaction was compatible with a broad variety of substrates, including chloro-, bromo- and iodo-substituted phenols, with yields up to 79%. An ester group present on the synthetic intermediate towards garenoxacin mesylate (an antimicrobial agent) was even tolerated when potassium carbonate was used as the base instead of potassium hydroxide (Scheme 4).



Scheme 4. Difluoromethylation of an ester-bearing phenol.

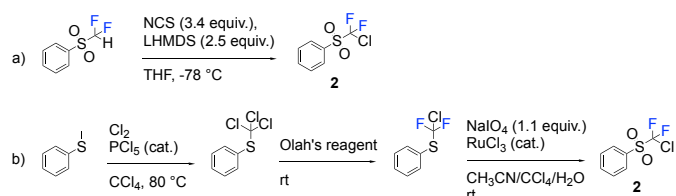
Regarding the mechanism, the formation of a chlorodifluoromethyl anion by the reaction of 2-chloro-2,2-difluoroacetophenone **1** with hydroxide is proposed. The  $\alpha$ -elimination of chloride would thus give difluorocarbene (:CF<sub>2</sub>), which would then react with the phenolate. However, a drawback of the method is the requirement of a somewhat large excess of the difluoromethylation agent (>5 equiv.).

In 2007, a second non-ODS difluorocarbene source was then developed by the same group. Chlorodifluoromethyl phenyl sulfone **2** [17] (PhSO<sub>2</sub>CF<sub>2</sub>Cl) indeed appeared as a more efficient reagent, which is also applicable to *N*-heterocycles. After a screening of various solvent systems and temperatures, they concluded that the yields were optimum when the reaction was carried out at 50 °C in a H<sub>2</sub>O/MeCN (2:7) medium and that the presence of water and the use of KOH were necessary. (Scheme 5).



Scheme 5. Difluoromethylation of phenols using chlorodifluoromethyl phenyl sulfone **2**.

Reagent **2** was prepared either by chlorination of PhSO<sub>2</sub>CF<sub>2</sub>H or by a three-step synthesis starting from non-expensive and commercially available thioanisole (Scheme 6). The chlorination of the latter with Cl<sub>2</sub> was followed by Olah's selective fluorination and then oxidation with NaIO<sub>4</sub> yielding the sulfone **2**.



Scheme 6. Synthetic strategies to access chlorodifluoromethyl phenyl sulfone **2**.

The formation of the active carbene is based on the F<sub>2</sub>CIC-SO<sub>2</sub>Ph bond breaking, which is much slower than the breaking of the CF<sub>2</sub>Cl-CO bond in 2-

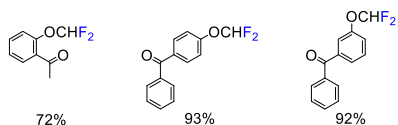
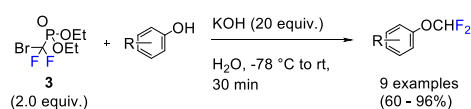
chloro-2,2-difluoroacetophenone **1**. The generation of the difluorocarbene being slower, less parasite reactions can lead to its consumption, and the use of a smaller amount (2.3 equiv.) of reactant is thus sufficient.

Hu *et al.* later performed a comparative study of the efficiency of many chlorodifluoromethylketones and -sulfones,[18] confirming thus the better results of sulfones and giving precisions on the influence of the substituents on the efficiency of this transformation. Indeed, electron-withdrawing substituted sulfones, and especially chlorodifluoromethyl *p*-chlorophenyl sulfone and chlorodifluoromethyl *p*-nitrophenyl sulfone, appeared to be the best difluorocarbene sources. In the case of ketones, the influence of the substitution is neglectable since the formation of the carbene occurs much faster.

Chlorodifluoroacetate can also be used under basic conditions for *O*-difluoromethylation, but only a few examples were reported, including one for the preparation of an inhibitor of PDE4 (phosphodiesterase type 4 inhibitor).[19] Furthermore, the generation of CO<sub>2</sub> caused by the reaction can be a drawback when operating on large scales.

Although all the previously cited methods are efficient non-ODS based difluorocarbene sources, that allow the difluoromethylation of aromatic alcohols, a common disadvantage of these procedures is the need for high temperature conditions. Nevertheless, new difluorocarbene sources addressing the latter issue were developed over the years.

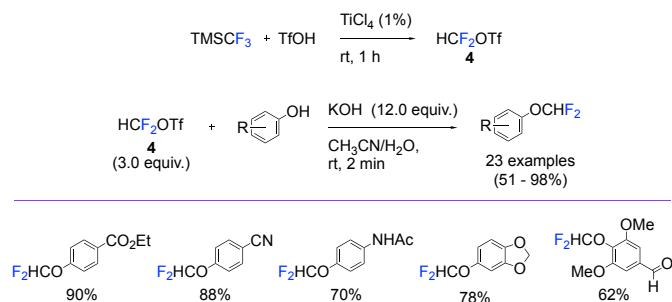
Among these, Zafrani *et al.*[20] reported in 2009 the use of commercially available diethyl bromodifluoromethylphosphonate **3** as a difluorocarbene precursor under milder temperature conditions in quasi stoichiometric quantities (*Scheme 7*). The carbene is easily formed by the cleavage of the P–C bond by hydrolysis under basic conditions (KOH), leading to the unstable bromodifluoromethyl anion, which readily eliminates bromide to give difluorocarbene. This method allowed the difluoromethylation of phenols, but additionally works on thiophenols with excellent yields, sometimes more efficiently than with their alcohol analogues. This might be rationalized by a greater polarizability of the sulfur atom, inducing a better nucleophilicity of the thiols. A partial chemoselectivity of the reaction was also observed as it proved to be tolerant to ketone and enol functions (*Scheme 7*). Furthermore, this procedure also partly meets the goals of green chemistry since its main by-product is an eco-friendly water-soluble phosphate ion.



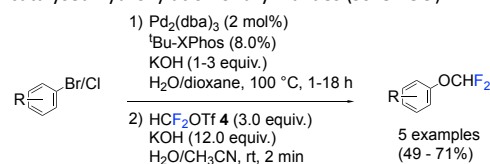
**Scheme 7.** Ketone-tolerant difluoromethylation of (thio)phenols using diethyl bromodifluoromethylphosphonate **3**.

Later Hartwig and Fier[21] explored the use of difluoromethyl triflate **4** as a carbene source. The non ODS substance is readily obtained from the reaction between TMSF<sub>3</sub> (the Ruppert-Prakash reagent) and triflic acid with catalytic TiCl<sub>4</sub> at room temperature. Unlike many previous methods requiring harsh conditions and long reaction times, the reaction between CHF<sub>2</sub>OTf **4** and phenols or thiophenols occurs in a few minutes only at room temperature and was applied to a quite wide variety of substrates. Furthermore, moderate to excellent yields were obtained for sterically hindered, electron-rich as well as electron-deficient aromatic alcohols. Moreover, it proved to be tolerant to numerous functional groups such as esters, amides, ketones, acetals, nitriles, and aldehydes (*Scheme 8*) and allowed the transformation of stable enols.

**Scheme 8.** Functional group-tolerant difluoromethylation of (thio)phenols using difluoromethyl triflate **4**.

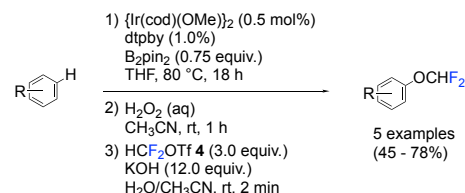


The aryl triflate was observed as the sole byproduct of each reaction. Nevertheless, it was a prevalent product in the case of electron-rich phenols. Fortunately, it could be recycled, and alternately, its formation could be disfavored by using difluoromethyl nonaflate (HCF<sub>2</sub>ONf) bearing a bulkier sulfonyl fragment, instead of HCF<sub>2</sub>OTf **4**. As the *O*-difluoromethylation reaction occurs very fast, it shows a great tolerance towards the byproducts of the previous steps leading to the phenols. This observation led the authors to follow the idea of one-pot procedures. At first, two-step processes were successfully developed, in which the difluoromethylation of phenols followed their *in situ* formation, either from the corresponding boronic acids or *via* a palladium-catalysed hydroxylation of aryl halides (*Scheme 9*).



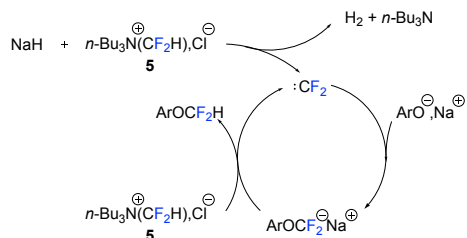
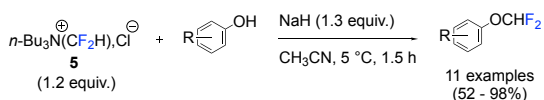
**Scheme 9.** Two-step process to access HF<sub>2</sub>CO-aromatics from aryl halides.

Finally, a metal-catalysed three-step one-pot procedure was developed to convert arenes into *O*-difluoromethylated phenols *via* the boronic acids, only requiring a change of solvent from THF to CH<sub>3</sub>CN (*Scheme 10*).



**Scheme 10.** One-pot synthesis to access HF<sub>2</sub>CO-aromatics from arenes.

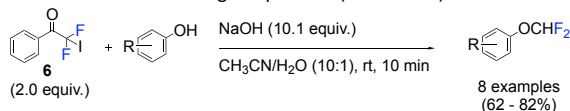
In 2011, difluoromethyltri(*n*-butyl)ammonium chloride **5** was used by Hu *et al.*[22] as a new difluorocarbene source. The reaction has the advantage of requiring only a small excess (1.2 equiv.) of the reactant and occurs rather fast and at low temperature. Nevertheless, the reaction conditions are relatively basic (NaH, 1.3 equiv.). The need for such basic conditions confirms a difluorocarbene pathway, whose formation supposedly implies the deprotonation of the difluoromethyl group of the ammonium, initially by the slight excess of remaining NaH, then by the phenolate itself (*Scheme 11*).



**Scheme 11.** Difluoromethyltri(*n*-butyl)ammonium chloride **5** as a difluorocarbene source for *O*-difluoromethylation.

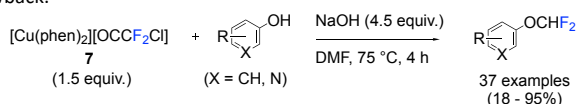
Unfortunately, it appeared that the primary CHF<sub>2</sub> source commonly used to prepare the salt is CHClF<sub>2</sub>, an ozone-depleting substance. Unless new methods are developed for the synthesis of difluoromethyltri(*n*-butyl)ammonium **5**, this reactant cannot actually be considered as a consistent alternative to ODS difluorocarbene sources.

Another example of difluorocarbene source that was developed recently is difluoroiodoacetophenone **6**. Chen *et al.*[23] initially desired to use the reactant for the difluoromethylation of amines, but during this study it also proved to be efficient on a range of phenols (*Scheme 12*).



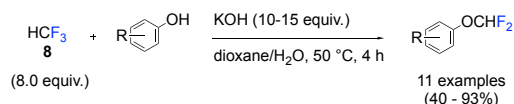
**Scheme 12.** difluoroiodoacetophenone **6** as a difluorocarbene source.

In 2016, Weng *et al.* reported the use of a copper chlorodifluoroacetate complex readily prepared from CuCl and ClCF<sub>2</sub>CO<sub>2</sub>H, as a difluorocarbene source.[24] [Cu(phen)<sub>2</sub>][O<sub>2</sub>CCF<sub>2</sub>Cl] **7** proved to be suitable for the difluoromethylation of various phenols and 3-hydroxypyridines. The optimized conditions involve 4.5 equiv. of sodium hydroxide which enable the difluorocarbene generation and the formation of the phenolate, in DMF at 75 °C (*Scheme 13*). Besides being applied to a large scope of substrates (37 examples with yields up to 95 %), including biologically active ones, the method also tolerated a scale up to 4.0 mmol, proving thus its relative robustness. Nevertheless, the high temperature required could still be a drawback.



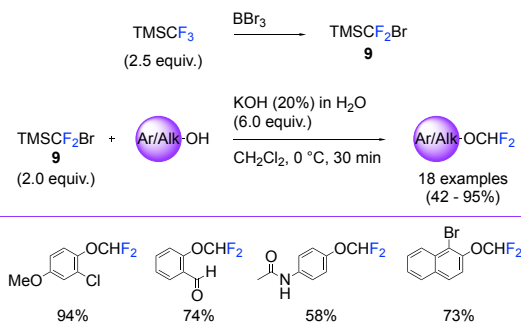
**Scheme 13.** Difluoromethylation of phenols and 3-pyridinols using copper chlorodifluoroacetate complex **7**.

One could also mention fluoroform **8** as a :CF<sub>2</sub> source. Indeed, a method was described by Dolbier *et al.* in 2013 involving this non-ozone-depleting and inexpensive gas,[25] which can be easily accessed since it is a byproduct of Teflon® manufacture. Fluoroform applications in trifluoromethylation were known, but Dolbier described its first use as a difluorocarbene source allowing the difluoromethylation of various aromatic alcohols and thiols (*Scheme 14*). Only the presence of nitro-, amino- or acetamido- functions seemed to inhibit the reaction. Furthermore, this two-phase system was efficient without the need of a phase-transfer catalyst, whose addition did not improve the reaction yields. Unfortunately, due to solubility problems, the reaction requires important amounts of **8** (60 equiv. introduced, among which 52 were re-condensed) and of the base needed to deprotonate the phenols and to form the carbene (10-15 equiv.).



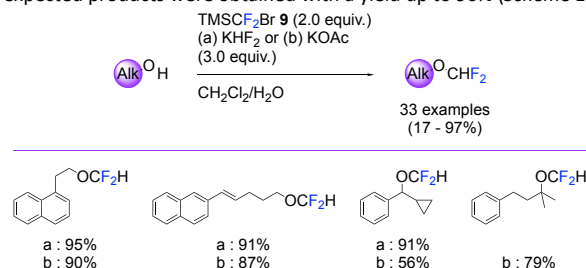
**Scheme 14.** Use of fluoroform **8** as a difluorocarbene source for the difluoromethylation of phenols.

More recently, an *O*-difluoromethylation method involving TMSCF<sub>2</sub>Br **9**, a reagent initially used for the difluoromethylation of alkenes/alkynes initiated by a bromide salt, was reported. The transformation allowing the rapid *O*-difluoromethylation of both aromatic and aliphatic alcohols under quite mild conditions was developed by Hu *et al.*[26] **9** was prepared either from the reaction between the Ruppert-Prakash reagent (TMSCF<sub>3</sub>) and BBr<sub>3</sub> or by bromination of TMSCHF<sub>2</sub> (*Scheme 15*). The authors did not succeed to prepare TMSCF<sub>2</sub>Cl, which is historically a potent difluorocarbene source, by the same methods. Like previous difluoromethylations, this method requires basic conditions (KOH or NaOH), however only 6 equivalents are needed for the reaction to proceed while most methods presented herebefore require larger amounts. In addition, the method could be applied to a rather wide range of aromatics regardless of the electron-rich or electron-deficient character of the substrates, and was tolerant to various functional groups (amides, ketones, halides, aldehydes...). As previously mentioned, the applicability of this method to aliphatic alcohols is an asset. Indeed, the transformation of this class of substrates is still considered a great challenge, even more problematic than the difluoromethylation of phenols.

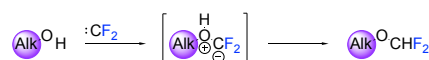


**Scheme 15.** Synthesis and reactivity of TMSCF<sub>2</sub>Br **9**, a difluorocarbene source.

Besides, the group further explored the possibility of using even milder conditions to access aliphatic difluoromethyl ethers.[27] Indeed, it appears that aliphatic alcohols (primary, secondary and even tertiary), unlike phenols, do not require the presence of a base to react with the carbene due to their greater nucleophilic character. In the reported procedure, KOH is thus replaced by KHF<sub>2</sub> or KOAc as activators in CH<sub>2</sub>Cl<sub>2</sub>/H<sub>2</sub>O (1:1) as biphasic solvent. The expected products were obtained with a yield up to 90% (*Scheme 16*).



*Mechanism for aliphatic alcohols*



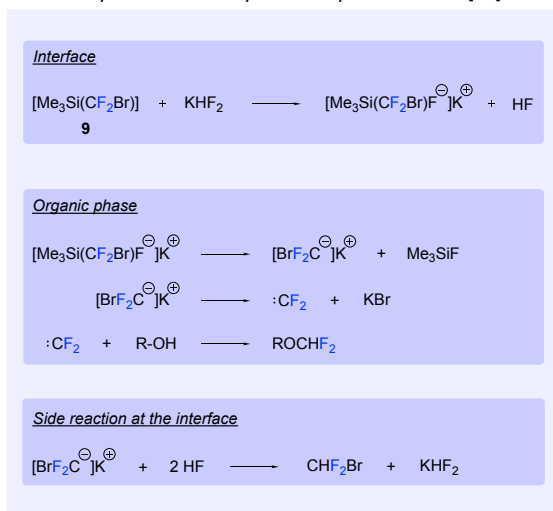
**Scheme 16.** Difluoromethylation of aliphatic alcohols under mild conditions.

TMSCF<sub>2</sub>Br **9** is therefore an interesting difluorocarbene source, that notably allows a certain chemoselectivity. Indeed, the mild activators KOAc

and  $\text{KHF}_2$  thus promoted selective difluoromethylation of alkanols over phenols, and a selectivity was even observed between different classes of aliphatic alcohols, as the primary ones showed a greater reactivity than the secondary and tertiary ones. The transformation of the latter might incidentally require more equivalents of **9** and of the activator. At the same time, the substrate scope was wide, with the conversion of many alkanols, bearing various functional groups, being successful.

Despite the advantages of the method, it yet suffers of a concentration dependence. As a matter of fact, throughout their studies Hu *et al.* observed a correlation between the conversion of aliphatic alcohols and the concentration of the organic phase. Indeed, unlike for phenols, a higher concentration of the organic phase gave enhanced yields. Surprisingly, when the reaction of liquid alcohols was carried out in water only, the rates were even better, as the alcohol itself played the role of the organic phase. Similarly, until a certain point, the decrease of water amount enhanced the reactivity. This observation was later explained by the need for the reaction to proceed at the interface since the activator  $\text{KHF}_2$  is only soluble in the aqueous phase, and the alcohol and  $\text{TMSCF}_2\text{Br}$  in the organic phase. Furthermore, a high amount of water could favour a competitive side reaction between the difluorocarbene precursor intermediate  $\text{BrCF}_2\text{K}^+$  and  $\text{HF}$ , preventing thus the formation of difluorocarbene (Scheme 17). Nevertheless, minimum amounts of water and dichloromethane were required to dissolve respectively  $\text{KHF}_2$  and the starting alcohols when they were found in the solid state. Regarding the latter, an alternative was proposed to perform the reaction in water only and which consisted in heating at  $75^\circ\text{C}$  overnight.

Since then  $\text{TMSCF}_2\text{Br}$  **9** also proved to be an efficient source of carbene for the difluoromethylation of carboxylic acids by Prakash *et al.* [28].

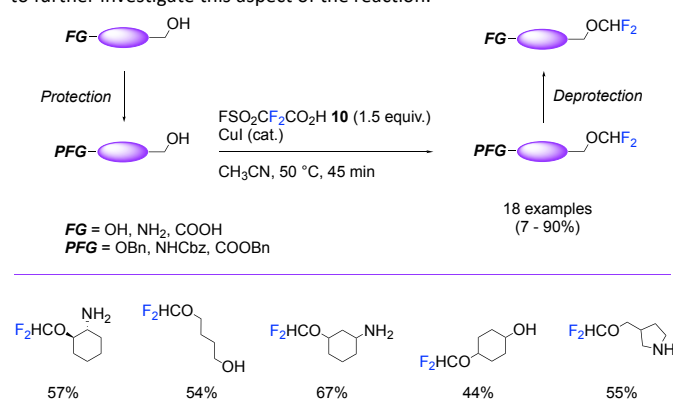


**Scheme 17.** Formation of difluorocarbene from  $\text{TMSCF}_2\text{Br}$  **9** in a two-phase system and potential side-reaction.

Only few difluoromethylation methods involve a catalytic metal source. The first of them was described by Chen *et al.* [29] in 1989, under mild conditions. Indeed, the sodium sulfate- or  $\text{CuI}$ -catalysed reaction requires 0.3 equivalents of  $\text{FSO}_2\text{CF}_2\text{CO}_2\text{H}$  **10** and proceeds through a yet unclear catalytic mechanism in which the carbene is supposedly formed by elimination of  $\text{SO}_2$ ,  $\text{CO}_2$  and  $\text{F}^-$ .

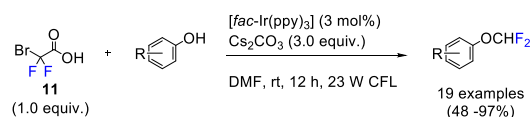
The method was first described on non-functionalized alcohols by Chen *et al.*, then was extended in 2016 by Mykhailiuk *et al.* [30]. The conditions ( $\text{CuI}$  (0.2 equiv.),  $\text{FSO}_2\text{CF}_2\text{CO}_2\text{H}$  **10** (1.5 equiv.),  $\text{CH}_3\text{CN}$ ,  $50^\circ\text{C}$ , 45 min) were selected after a screening of the conditions tested by Chen *et al.* in 1989, and their further optimization. The transformations of primary, secondary, and tertiary alcohols were achieved. The procedure was notably applied to substrates bearing additional protected amines, carboxylic acids, and alcohols (Scheme 18). The good results, along with the relative mildness of the conditions, encouraged the group to investigate the *O*-difluoromethylation of alcohols bearing non-protected amines and acids, but these attempts were not

successful, confirming the necessity to protect these additional functions or to further investigate this aspect of the reaction.



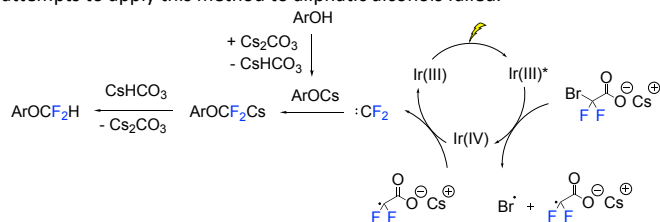
**Scheme 18.** Copper catalyzed difluoromethylation of alcohols in the presence of protected amines and carboxylic acids.

More recently, a photocatalytic route was developed by Fu *et al.* [31]. The reaction was catalyzed by visible light and involves an iridium-based catalyst and inexpensive and readily available difluorobromoacetic acid **11** (1.0 equiv.) as a difluorocarbene source. After the screening of multiple solvents, light sources, catalysts and bases, to enhance the yields, the following conditions were selected: catalytic  $[\text{fac-Ir}(\text{ppy})_3]$ ,  $\text{Cs}_2\text{CO}_3$  (3.0 equiv.) in DMF at room temperature for 12h under a 23W compact fluorescent light (Scheme 19).



**Scheme 19.** Photocatalytic difluoromethylation of phenols.

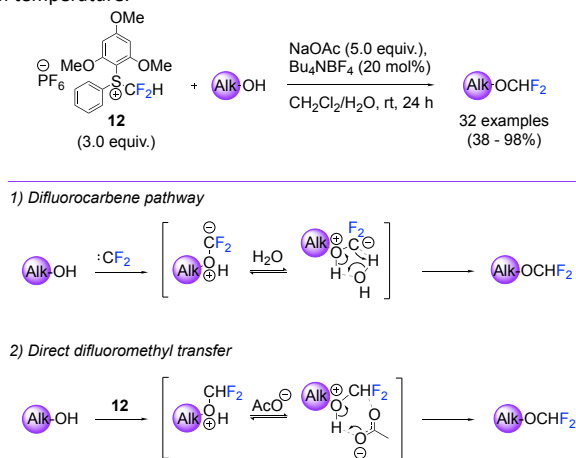
The proposed mechanism is described in Scheme 20. Unlike anionic mechanisms discussed above, the carbene is formed *via* single electron transfer from the difluoroacetate radical to the oxidized catalyst followed by decarboxylation, and allows the difluoromethylation of phenols and thiophenols only. Among them, electron-deficient aromatic rings counter-intuitively afforded higher yields. This phenomenon might be explained by the deprotonation of the phenols being the rate determining step. This method could also be useful for late-stage functionalization as many functional groups are compatible with these mild reaction conditions. Nevertheless, the attempts to apply this method to aliphatic alcohols failed.



**Scheme 20.** Catalytic cycle for the formation of difluorocarbene.

Recently, Liu *et al.* [32] reported a bench stable sulfonium salt **12**, derived from Prakash's unstable previously prepared salts **13** and **14**, which will be evoked in section 1.2. Even though the strategy was applied to both aromatic and aliphatic alcohols, the difluoromethylation was more efficient on the latter, affording good to excellent yields. Chemoselectivity was even observed when *p*-hydroxyphenylethanol was subjected to the reaction conditions, showing only difluoromethylation of the alkanol. Although at first developed as an agent for direct  $\text{CF}_2\text{H}$  transfer (see section 1.2), control experiments implied that the difluorocarbene process is the major pathway involved, even though the direct nucleophilic substitution probably occurs as well; in particular, water and sodium acetate both seem to play crucial roles since,

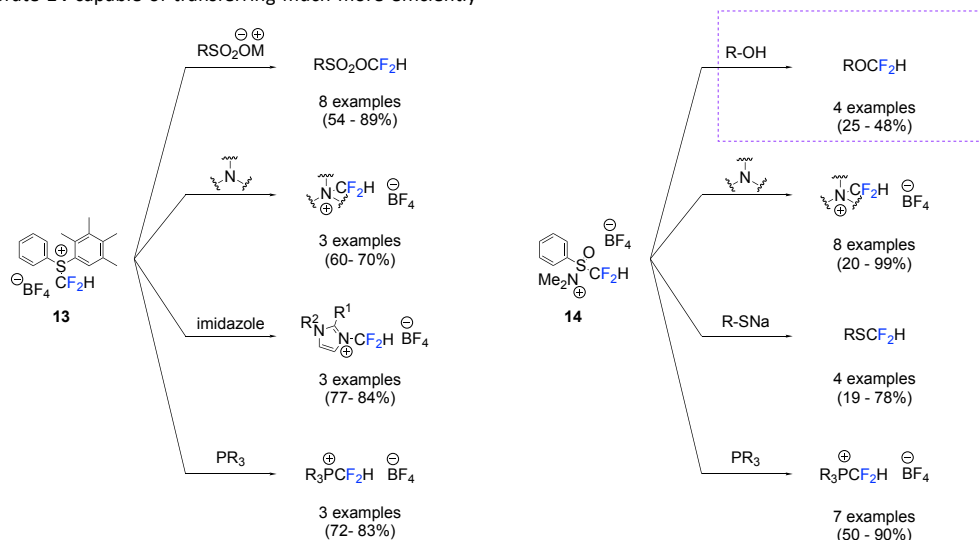
when using one in the absence of the other, there seems to be a complete switch of reaction pathway in favour of either one of the two mechanisms (Scheme 21). Furthermore, despite the need to synthesize the salt and the rather long reaction time, the procedure offers the advantage of operating at room temperature.



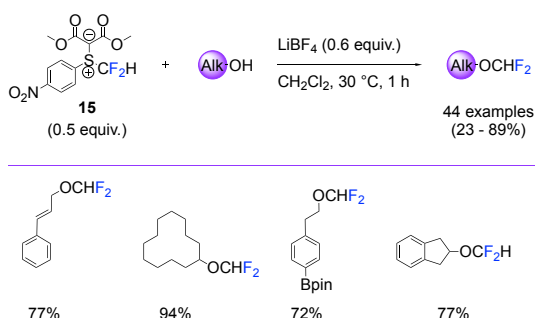
Scheme 21. Difluoromethylation of alkanols with Liu's sulfonium salt **12**.

### 1.2. *O*-Difluoromethylation by electrophilic $\text{CHF}_2$ -sulfonium salts

A difluoromethyl transfer is also possible from an electrophilic  $-\text{CF}_2\text{H}$ , as shown by Prakash *et al.* in 2007, on sulfonic acids, tertiary amines, imidazole derivatives and phosphines, and with low yields on alcohols.[33] In 2011, the same group described *N,N*-dimethyl-*S*-difluoromethyl-*S*-phenylsulfonium tetrafluoroborate **14** capable of transferring much more efficiently



Scheme 22. Prakash's sulfonium salts **13** and **14**.



Scheme 23. Difluoromethylation of various aliphatic alcohols using Shen's sulfonium ylide

an electrophilic  $-\text{CHF}_2$  on an alcohol;[34] the method was applicable to primary, secondary and even tertiary ones (Scheme 22). Nevertheless, this sulfonium salt was unstable (prepared *in situ* from a bench-stable intermediate) and only afforded the desired difluoromethyl ethers in low yields, especially from phenols. Interestingly, Prakash *et al.* ruled out the involvement of difluorocarbene in these reactions by means of deuterium-labelling experiments, thus confirming that such *S*-difluoromethyl sulfoximinium derivatives did indeed behave as electrophilic  $\text{CF}_2\text{H}$ -transfer reagents.

Again with deuterium-labelling experiments, a similar conclusion was reached by Shen *et al.*,[35] who proposed a solution to the stability problem of Prakash's sulfonium by synthesizing a stable sulfonium ylide **15** (Scheme 23).

The sulfonium ylide **15** was easily prepared by reaction of readily available 4-nitrophenyl (difluoromethyl)thioether and dimethyl diazomalonate with 0.1 mol %  $\text{Rh}_2(\text{esp})_2$  as catalyst. In the presence of  $\text{LiBF}_4$ , good yields were obtained in the difluoromethylation of aliphatic alcohols. The authors postulate a chelation of the lithium cation by the two carbonyls of the sulfonium salt, thus enhancing of the electrophilicity of the ylide and allowing mild reaction conditions and rapid transformation (Scheme 23). It is noteworthy to mention that this method was only applied to aliphatic alcohols.

As seen in section 1.1, Liu *et al.* also developed a bench stable sulfonium **12**, whose difluoromethylation mechanism might as well go through a direct  $\text{CHF}_2$  transfer, although the difluorocarbene pathway is the favored one.

In summary, most alcohol difluoromethylation methods are based on difluorocarbene intermediates, even though a few sulfonium salts showed moderate to good difluoromethylation abilities by direct  $\text{CHF}_2^+$  transfer. One should note as particularly relevant the three-step one-pot procedure developed by Hartwig *et al.*, allowing a rapid access to difluoromethyl ethers from either arenes or halides. On the other hand, in view of its generality and practical ease,  $\text{TMSCF}_2\text{Br}$  appears as a very convenient reagent allowing the difluoromethylation of a broad scope of phenols, alkanols, and carboxylic acids (cf. Section 5) under mild conditions and even presenting a potential chemoselectivity depending on the activators used.

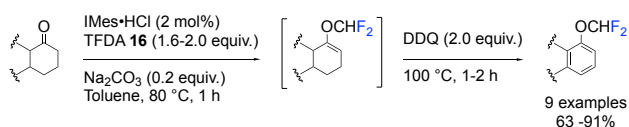
## 2. Difluoromethylation of ketones

Apart from phenols or alkanols, ketones are also suitable substrates for *O*-difluoromethylation, by taking advantage of their enol/enolate form, thus affording difluoromethyl enol ethers.

As for now, all described methods allowing the *O*-difluoromethylation of ketones to give difluoromethyl ethers involve, at least partially, a difluorocarbene pathway.

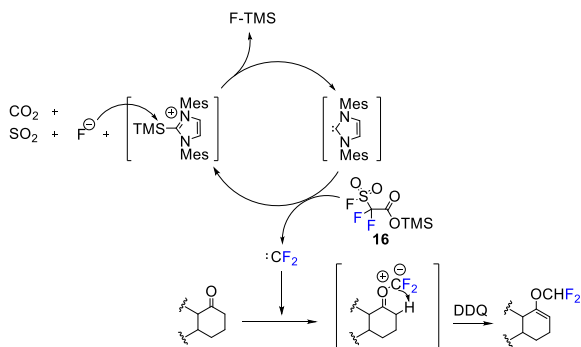
As a matter of fact, the first method was proposed by Ichikawa *et al.* in 2011. The group reported the catalytic generation of difluorocarbene from TFDA **16** (trimethylsilyl 2,2-difluoro-2-(fluorosulfonyl)acetate) using a *N*-heterocyclic carbene (NHC).[36] TFDA **16** was already known by the group as a difluorocarbene source, but usually led to *gem*-difluorocyclopropanation products. After a screening of many activators, the *in situ* formed NHC seemed to enable the selective formation of the *O*-difluoromethylation product. It is noteworthy to mention that the NHC has to be formed *in situ* from IMes•HCl and a base (Na<sub>2</sub>CO<sub>3</sub>), since the direct introduction of the previously isolated NHC, and thus a too rapid generation of difluorocarbene, caused a decrease in the yield of the desired difluoromethyl ether, and an increase of the one of the overreaction product difluorocyclopropane.

After optimization of the conditions, the transformation was applied to a wide range of cyclohexenones and tetralones. A one-pot synthesis was even developed to afford aryl difluoromethyl ethers by a sequential dehydrogenation using DDQ. The products were obtained in moderate to good yields (63% - 91%) (Scheme 24).



Scheme 24. *O*-Difluoromethylation of ketones using TFDA **16**.

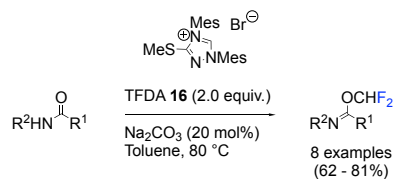
A plausible mechanism for the catalytic generation of :CF<sub>2</sub> would involve the formation of an NHC-trimethylsilylium adduct leading to the decomposition of **16** and release of difluorocarbene, SO<sub>2</sub>, CO<sub>2</sub> and a fluoride ion. The latter will then attack the silylium and thus allow the regeneration of the NHC (Scheme 25).



Scheme 25. Plausible mechanism for the *O*-difluoromethylation of ketones using TFDA **16**.

This procedure was later employed by the same group[37] on other ketones, such as flavanone, or even acyclic acetophenone by using respectively 1 mol% and 3 mol% of the catalyst and yielding 50% and 57% of the corresponding products. The method was also extended to the synthesis of difluoromethyl imidates and 2-difluoromethoxy pyridines, which are interesting moieties for bioactive molecules. In this case, the use of a slightly different NHC catalyst allowed selective *O*-difluoromethylation over *N*-difluoromethylation. The reaction proved to be efficient with aryl and alkyl derived amides yielding 66% to 81% of the expected products (Scheme 26). Furthermore, when aryl amides were submitted to this transformation, no effect of the electron

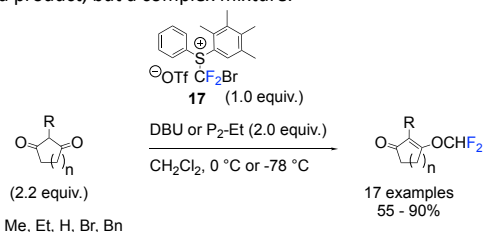
richness/deficiency of the aryl was observed. Nevertheless, for the transformation of both amides and ketones, high temperature conditions are required.



Scheme 26. *O*-Difluoromethylation of amides using TFDA **16**.

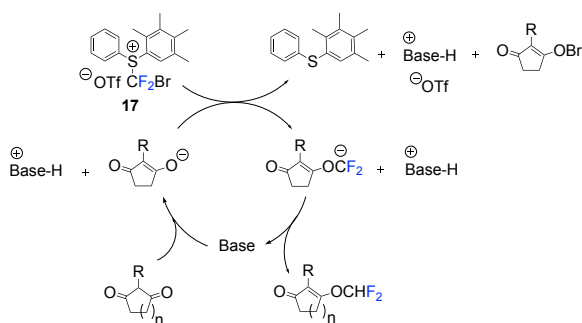
Later, in 2013, Shibata *et al.* reported the difluoromethylation of 1,3-diones using an unsymmetrical *S*-(bromodifluoromethyl)diarylsulfonium salt **17** and an organic base (DBU or P<sub>2</sub>-Et) at low temperature.[38] Surprisingly, these conditions enabled a perfectly selective *O*-difluoromethylation of 1,3-diones, whereas when used on  $\beta$ -ketoesters, they yielded mostly *C*-difluoromethylation products.

After optimization of the equivalents (2 equiv. of the diones are necessary) and the screening of various bases, reaction temperatures and solvents, the selected conditions were used on various cyclopentanediones as well as cyclohexanones (Scheme 27). Substitutions of the C2-positions, and C5-position for the latter, were tolerated. The transformation of indanediones was also possible under these conditions, affording slightly lower yields (55%-66%), whereas the acyclic diones submitted to the conditions did not afford the expected product, but a complex mixture.



Scheme 27. *O*-Difluoromethylation of 1,3-diones using sulfonium salt **17**.

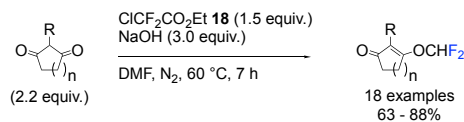
The proposed mechanism is described in Scheme 28. The enolate formed after deprotonation by the base supposedly attacks the bromine atom of **17** allowing thus the release of difluorocarbene, which can then react with an enolate before re-protonation towards the expected product.



Scheme 28. Proposed mechanism for the *O*-difluoromethylation of 1,3-diones using sulfonium salt **17**.

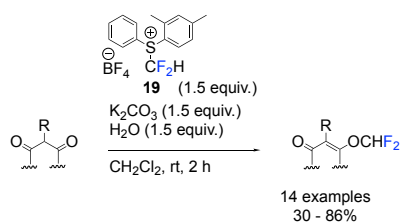
A second method allowing the access to difluoromethyl enol ethers from cyclic 1,3-diones was developed independently by Weng *et al.*[39] Contrary to the previously described method, heating was necessary to perform this transformation using commercially available ethyl chlorodifluoroacetate **18** as a difluorocarbene source. After a screening of various bases, solvents, and optimization of the substrate ratios, sodium hydroxide was finally selected as the most efficient base in DMF and in a 3:1:1.5 ratio towards respectively the starting dione and **18** (Scheme 29). Both cyclohexanediones and

cyclopentanediones substituted at the C2-positions were submitted to these conditions yielding the expected products in good yields. For cyclohexanones, substitution at the C5-position with methyl, dimethyl, iso-propyl and phenyl was tolerated.



**Scheme 29.** *O*-Difluoromethylation of 1,3-diones using chlorodifluoroacetate **18**.

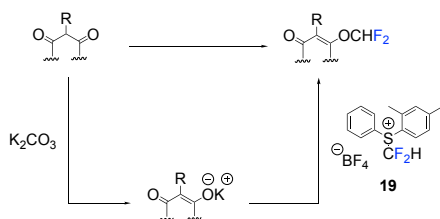
In parallel to these two groups, Xiao *et al.*[40] also reported the difluoromethylation of 1,3-diketones toward difluoromethyl enol ethers using sulfonium salt **19** (Scheme 30). This reaction was performed under mild conditions, using  $K_2CO_3$  as a base in water, in order to maximize the solubility of the latter and thus its efficiency. The transformation apparently does not suffer from steric or electronic effects, since many substituents were tolerated on the C2-position without any significant impact on the reaction yields. As a matter of fact, these conditions allowed the first transformation of acyclic diones. Whereas only the *Z*-isomers of the latter were observed after quenching of the reactions, the products seemed to slowly isomerize during column chromatography or in  $CDCl_3$ .



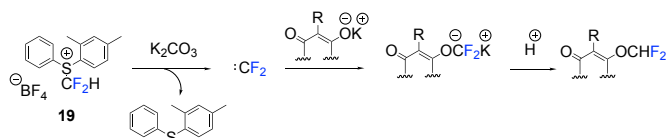
**Scheme 30.** *O*-Difluoromethylation of 1,3-diones using sulfonium salt **19**.

The mechanism of this transformation is also a point worthy of attention. Even though the strongly electrophilic character of the  $CF_2H$  moiety on **19** would suggest a direct electrophilic transfer, which probably occurs, deuterium labelling experiments proved that the difluorocarbene generation also occurs (Scheme 31).

#### 1) Direct difluoromethyl transfer

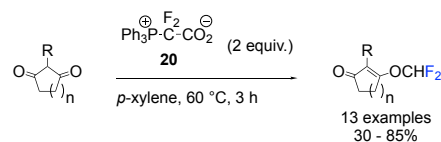


#### 2) Difluorocarbene pathway



**Scheme 31.** Two plausible pathways for the *O*-difluoromethylation of 1,3-diones using sulfonium salt **19**.

In 2016 the same group also proposed the use of PDFA **20** (triphenylphosphoniodifluoroacetate) as a difluorocarbene source for the *O*-difluoromethylation of 1,3-diones in a base-free system.[41] The reaction was performed in *p*-xylene at 60 °C and requires the use of 2.0 equivalents of PDFA (Scheme 32). Pentanediones as well as hexanediones were successfully transformed, unlike acyclic 1,3-diones and heptanediones.

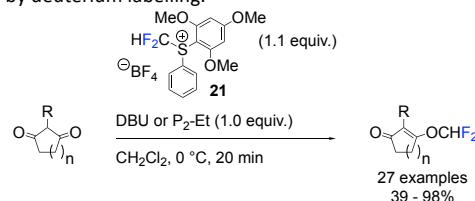


**Scheme 32.** *O*-Difluoromethylation of 1,3-diones using difluoromethylene phosphobetaine **20**.

The proposed mechanism described involves the decarboxylation of **20**, followed by the dissociation of the P- $CF_2$  bond allowing the generation of difluorocarbene, which will then react with the enol form of the substrate.

Moreover, it is worth mentioning that, although not evoked in the first section concerning the difluoromethylation of alcohols, the group also applied PDFA **20** to the difluoromethylation of two phenols as well as 3 benzoic acids affording respectively the  $Ar-OCHF_2$  and  $Ar-CO_2CF_2H$  structures.[42]

More recently, Liu described a novel *S*-(difluoromethyl) sulfonium salt **21** that can be used to perform a selective *O*-difluoromethylation of 1,3-diones under relatively mild conditions.[43] Indeed, after a screening of the reaction conditions, the optimized method only required the presence of 1.0 equiv. of DBU or  $P_2Et$  as bases in  $CH_2Cl_2$  at 0 °C (Scheme 33). Similarly, to the previously reported ones, this method was applicable to various C2-substituted cyclopentanediones and C2- as well as C5-substituted cyclohexanediones. Furthermore, an acyclic 1,3-dione could be *O*-difluoromethylated and the corresponding difluoromethyl enol ether was isolated in 39% yield. As in the case of Xiao *et al.*'s sulfonium salt **19**, the major difluorocarbene pathway was confirmed by deuterium labelling.



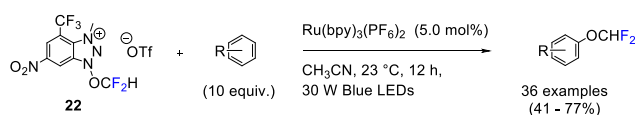
**Scheme 33.** *O*-Difluoromethylation of 1,3-diones using sulfonium salt **21**.

As mentioned before, the *O*-difluoromethylation of enolizable ketones always involves difluorocarbenes as  $CF_2$  sources. Except for Ichikawa's TFDA-based method, the existing procedures are nowadays limited to 1,3-diones, and mainly cyclic ones, highlighting the need for further investigation.

### 3. Difluoromethoxylation by radical coupling with arenes

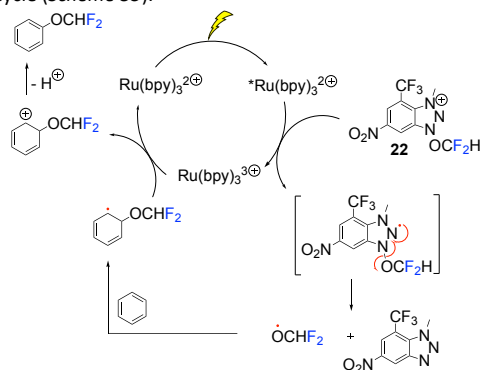
Although being the main employed strategy, the difluoromethylation of alcohols is not the only way to access the  $-OCHF_2$  moiety, especially for aromatics, which can undergo a coupling with the  $\cdot OCHF_2$  radical.

In 2019, Ngai proposed a novel method to access the  $-OCHF_2$  fragment. Unlike the previously mentioned ones, this approach consists in a direct C-H difluoromethoxylation *via* a radical photoredox catalysis.[44] This unique transformation enables the synthesis of difluoromethoxylated (hetero)arenes without previous activation, involving a bench stable *N*-(difluoromethoxy)benzotriazole derivative **22** and  $Ru(bpy)_3(PF_6)_2$  as the catalyst in  $CH_3CN$ . Furthermore, the reaction proceeds at room temperature and under visible light, without the need for an oxygen-free atmosphere (Scheme 34). It is thus a highly practical procedure, which is additionally widely tolerant. It was indeed applied to various substrates bearing functional groups such as unprotected alcohols and phenols, aldehydes, carboxylic acids, esters, amides and carbonates. Moreover, it was efficient on molecules substituted with trifluoromethyl, methoxy, trifluoromethoxy, cyano, nitro, sulfonyl, and pyridinium groups. Biorelevant products were also successfully subjected to this transformation.



**Scheme 34.** Direct C–H difluoromethoxylation *via* radical photoredox catalysis.

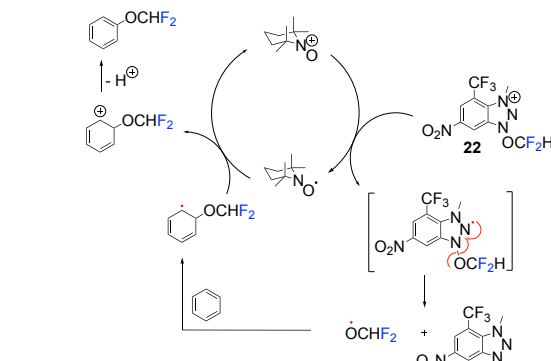
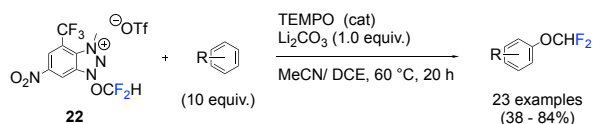
The  $\cdot\text{OCHF}_2$  radical arises from **22** after single electron transfer (SET) from the photoactivated ruthenium-based catalyst, taking advantage of the weak N–O bond. The radical adds to the arene, which is then reduced back by SET to the catalyst and is finally deprotonated to furnish the difluoromethoxylated aromatic cycle (*Scheme 35*).



**Scheme 35.** Mechanism of the radical photoredox difluoromethoxylation of arenes.

Despite this remarkable achievement, some drawbacks of this reaction should be mentioned. Indeed, until now, it could only be applied to (hetero)aromatics, and moreover with a yet not totally controlled regioselectivity. Even though the reaction follows the classical regio-preferences of radical-mediated aromatic substitution reactions, minor regioisomers can also form. It is also worth mentioning that **22** was in fact synthesized from the corresponding benzotriazole-1-ol, whose difluoromethylation, although possible on gram scale, was classically achieved with difluorocarbene formed from diethyl (bromodifluoromethyl)phosphonate.

More recently Ngai developed a second method using readily available, inexpensive, kinetically and thermodynamically stable TEMPO as a redox catalyst.<sup>[45]</sup> The supposed mechanism involves the TEMPO $\cdot$ /TEMPO $^+$  couple. Analogously to their previous publication, benzotriazole-based reagents were the source of the  $\text{OCHF}_2$  radical *via* a single electron transfer from the catalyst (*Scheme 36*). Nevertheless, conversely to the previous paper, TEMPO acts here as a redox catalyst, without the need for photoactivation. Surprisingly, the presence of  $\text{Li}_2\text{CO}_3$  seems to be necessary to the catalytic cycle. It is suggested that the equivalent of acid generated during the reaction could promote the disproportionation of TEMPO $\cdot$  explaining the necessity of a base to disfavor this phenomenon. The carbonate also seems to play the role of a sacrificial reductant by promoting the reduction of TEMPO $^+$  to active TEMPO $\cdot$ , thus preventing the catalyst deactivation. Conditions were optimized and it appeared that, contrary to the first version, heating at 60 °C was unfortunately necessary in order to improve the yields and that the  $\text{CH}_3\text{CN}/\text{DCE}$  (1:1) solvent system gave the best results. However, the reaction was still not affected by the presence of oxygen nor water.



**Scheme 36.** Difluoromethoxylation of arenes *via* redox catalysis using TEMPO.

The method was applied to a wide range of phenols, showing good tolerance towards functional groups, hence potential for use in late-stage functionalization. Furthermore, the same conditions were successful for the trifluoromethoxylation of arenes, simply by modifying **22** into an  $-\text{OCF}_3$  derivative.

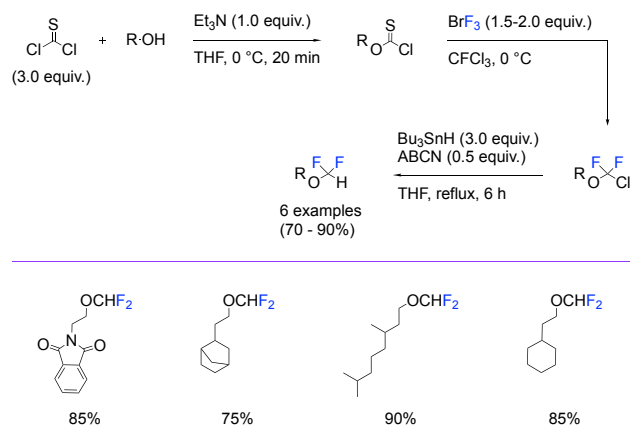
This method is thus competing directly Hartwig's three-step one-pot procedure with  $\text{TfOCF}_2\text{H}$  also starting from arenes (*Scheme 10*).

#### 4. Transformation of C=S or C=O moieties

Although it might be an interesting and promising idea, the direct insertion of the  $-\text{OCHF}_2$  moiety remains limited to aromatic substrates. Some groups have intended to develop general methods to access difluoromethyl ethers, mainly originating from alcohols, but without using a preconstructed  $-\text{CHF}_2$  source. Thereby a few routes were developed, based on the transformation of various functional groups.

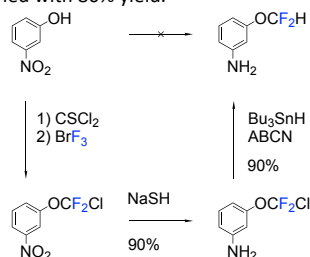
##### 4.1. Transformation of the C=S bond starting from thiophosgene and $\text{BrF}_3$ .

Rozen *et al.*<sup>[46,47]</sup> described a general route using commercially available thiophosgene and  $\text{BrF}_3$  to access the  $-\text{OCHF}_2$  moiety. The process started with the conversion of an alcohol to the corresponding chlorothioformate, whose C=S bond was fluorinated by the uneasy to handle agent  $\text{BrF}_3$ , to give difluorochloromethyl ethers. Even though its practical application remains complicated,  $\text{BrF}_3$  ensures that the reaction will stop at the stage of the previously cited product, and not continue to the  $\text{CF}_3$  moiety, unlike other fluorinating agents such as HF or  $\text{SbF}_3$ , that allow perfluorination from trichloromethyl derivatives. The difluorochloromethyl group is then reduced by radical abstraction with  $\text{Bu}_3\text{SnH}$  to the difluoromethyl ether (*Scheme 37*). The last step must indeed proceed through a radical reduction, because of the strength of the C–Cl bond in the difluorochloromethyl ether. As a matter of fact, DIBAL-H and Raney Ni proved to be completely inefficient, and the use of  $\text{LiAlH}_4$  and Na in MeOH resulted in a complex mixture of products.



**Scheme 37.** Three-step synthesis to access the  $-\text{OCHF}_2$  moiety via C=S bond transformation.

A few functional groups are tolerated by the harsh conditions of the reaction, like ethers, whereas others, like amines, must be protected. Examples of amines protected as phthalimides were for instance described. The transformation of phenols is however limited to electron-deficient aromatics, such as the cyano- or nitro-substituted ones, due to the tendency of  $\text{BrF}_3$  to brominate electron-rich arenes. Thus, to obtain 3-difluoromethoxyaniline, the use of nitrobenzene will be preferred to that of aniline; the reduction of the nitro group with  $\text{NaSH}$  is carried out after the fluorination step, but before the reduction with  $\text{SnBu}_3\text{H}$  as the nitro group would inhibit the radical reaction (Scheme 38). However, an interesting aspect of the difluoromethylation of nitrophenols is that the three regio-isomers could each be obtained with 80% yield.

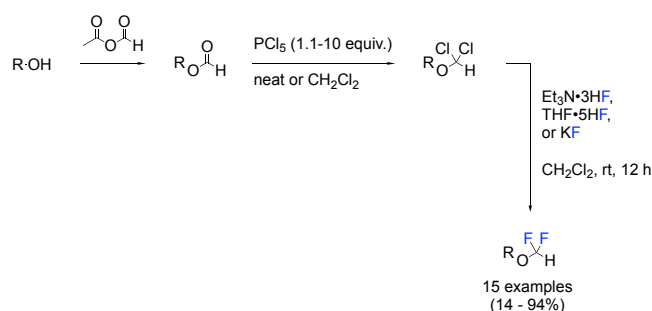


**Scheme 38.** Access to electron-rich substituted difluoromethoxylated aromatics.

#### 4.2. Transformation of the C=O bond starting from an anhydride and $\text{PCl}_5$

Another described alternative is a three-step route starting from an alcohol, based on its formylation, then its dichlorination and finally followed by a Cl/F exchange (Scheme 39).[48] The chlorination occurs by reaction with  $\text{PCl}_5$  and the crude dichloromethoxylated product is directly subjected to the next step, as it is highly unstable. Concerning the fluorine/chlorine exchange, which is a widely used method to convert trichloromethoxyarenes into the corresponding trifluoromethoxy- derivatives, two different methods were explored. On the one hand, dichloromethyl ethers underwent an  $\text{HF}\cdot\text{Lewis base}$ -mediated fluorination, whose mechanism presumably involves the formation of an oxocarbenium; on the other hand, they were subjected to a direct substitution ( $\text{S}_{\text{N}}2$ ) of chlorine by a fluoride ion.  $\text{THF}\cdot 5\text{HF}$  and  $\text{Et}_3\text{N}\cdot 3\text{HF}$  were selected as fluorinating agents at room temperature for the putative oxocarbenium-involving process, whereas  $\text{KF}$  was used as a fluoride anion source proceeding in sulfolane at  $125\text{ }^\circ\text{C}$  for the alternate method. Yields with alkanols were lower than with phenols (up to 56%). In opposition, no conversion was observed with hydroxypyridines, which probably correlates to their high electron-deficiency. Different conditions gave the best results depending on the aromatic or aliphatic character of alcohols. In most but not all cases, the former ones reacted slightly better with the Lewis base $\cdot\text{HF}$  system; in particular, for electron-rich phenols,  $\text{Et}_3\text{N}\cdot 3\text{HF}$  proved superior to  $\text{THF}\cdot 5\text{HF}$ , whereas the latter was more efficient for electron-deficient

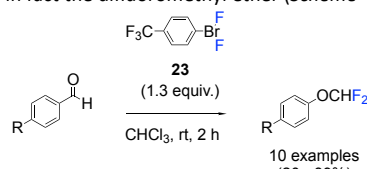
aromatics.  $\text{Et}_3\text{N}\cdot 3\text{HF}$  also happened to be the only agent working for aliphatic alcohols.



**Scheme 39.** Three-step synthesis to access the  $-\text{OCHF}_2$  moiety via C=O bond transformation.

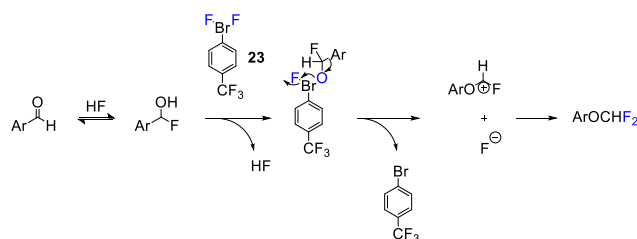
#### 4.3. Transformation of the C=O bond of benzaldehydes

In the course of their investigations of difluoro(aryl)- $\lambda^3$ -bromane **23** as a reactant to obtain acyl fluorides from the corresponding aldehydes, Ochiai *et al.* realized, that when applied to aromatic aldehydes, the major product of the reaction was in fact the difluoromethyl ether (Scheme 40).[49]



**Scheme 40.** Access to  $-\text{OCHF}_2$  from benzaldehydes using difluoro(aryl)- $\lambda^3$ -bromane **23**.

Indeed, the aldehydes react with **23**, which undergoes ligand exchange at the Br(III) center. Then, whereas alkyl groups lead to reductive  $\beta$ -elimination to give the acyl fluoride, aryl groups, due to their great migratory aptitude, rather undergo a Bayer-Villiger-type 1,2-shift yielding the corresponding aryl difluoromethyl ethers (Scheme 41).

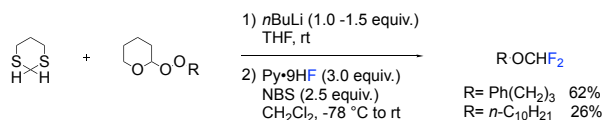


**Scheme 41.** Proposed mechanism to access to  $-\text{OCHF}_2$  from benzaldehydes and difluoro(aryl)- $\lambda^3$ -bromane **22**.

Unfortunately, this procedure was only applied to a small range of aldehydes and gave low yields when used on electron-deficient aromatics, probably due to their low migratory aptitude.

#### 4.4. Synthesis of difluoromethyl ethers from dithianes and peroxides

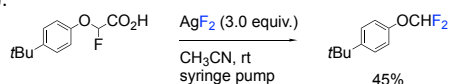
In 2014 Dussault *et al.* developed a method enabling the access to difluoroalkyl ethers.[50] The reaction of lithiated dithianes and peroxides in THF indeed affords *S,S,O*-orthoesters, which can then be transformed into difluoroalkyl ethers by fluorodesulfurization with  $\text{NBS}$  (1.0 equiv.) and pyridine $\cdot 9\text{HF}$  at  $-78\text{ }^\circ\text{C}$  (Scheme 42). By using 1,3-dithiane, it is thus possible to obtain some difluoromethyl ethers. A one-pot synthesis was even developed, allowing to perform the fluorodesulfurization step sequentially. Nevertheless, only two examples were described here, as very particular substrates are required.



**Scheme 42.** Access to OCHF<sub>2</sub>-derivatives from dithianes and peroxides.

#### 4.5. Fluorodecarboxylation for the Synthesis of Difluoromethyl Aryl Ethers

Another method enabling the access to aryl difluoromethyl ethers was developed by Hartwig in parallel to his work on decarboxylative trifluoromethylation.[51] Indeed, by submitting the  $\alpha$ -fluoro aryloxy carboxylic acid derived from 4-(*t*-butyl)phenol to a slow addition of AgF<sub>2</sub> (3.0 equiv.) in CH<sub>3</sub>CN, at room temperature, the fluorodecarboxylation afforded the corresponding 4-(*t*-butyl)phenyl difluoromethyl ether in 45% yield (Scheme 43).



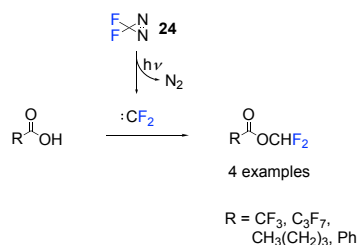
**Scheme 43.** Access to the -OCHF<sub>2</sub> fragment via fluorodecarboxylation of a  $\alpha$ -fluoro aryloxy carboxylic acid.

Although they represent an interesting alternative to difluorocarbene-based difluoromethylation reactions, the above mentioned methods often require many steps and suffer from a lack of generality or from the use of harsh conditions, preventing them from a good functional group tolerance. One should still bring to attention Dolbier's procedure, which allows the transformation of either alkanols, electron-rich or electron-poor phenols depending on the fluorine source used.

### 5. Access to difluoromethyl esters

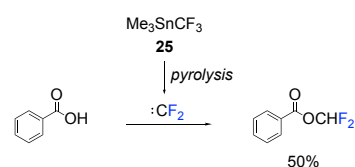
Even though more uncommon than difluoromethyl ethers, difluoromethyl esters are also interesting patterns bearing the -OCHF<sub>2</sub> moiety, especially since their protonated analogues, carboxylic acids, are widely present in nature and bioactive compounds.

The first synthesis of a difluoromethyl ester was reported by Mitsch and Robertson in 1965.[52] The reaction was based on the photolysis of difluorodiazirine **24**, generating thus N<sub>2</sub> and difluorocarbene, which could then react directly with the nucleophilic oxygen of carboxylic acids. The method afforded difluoromethyl trifluoroacetate and difluoromethyl heptafluorobutyrate in respectively 75% and 50% yields and also allowed the transformation of valeric and benzoic acids (Scheme 44). Nevertheless, in addition to only being described on 4 substrates, the required use of difluorodiazirine classifies this method as highly hazardous.



**Scheme 44.** O-Difluoromethylation of carboxylic acids using difluorodiazirine **24**.

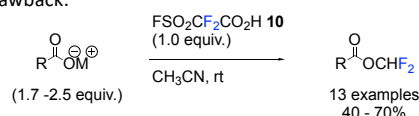
In 1967 Seyferth reported the transfer of difluoromethylene from toxic trimethyl(trifluoromethyl)stannane **25** to benzoic acid in a sealed tube at 155 °C, affording difluoromethyl benzoate in 50% yield (Scheme 45).[53]



**Scheme 45.** O-Difluoromethylation of carboxylic acids using trimethyl(trifluoromethyl)stannane **25**.

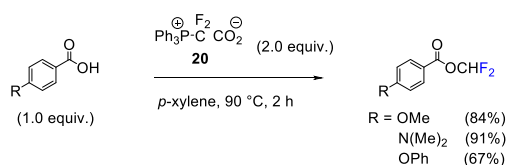
As briefly mentioned before, some difluoromethylation methods involving the generation of difluorocarbene could also be applied to carboxylic acids.

As a matter of fact, Chen *et al.* also applied fluorosulfonyldifluoroacetic acid **10** to the difluoromethylation of various carboxylates.[54] The reaction was carried out in CH<sub>3</sub>CN, starting from the sodium or potassium salts of the acids, at temperatures between 20 °C and 50 °C and afforded the desired difluoromethyl esters in yields from 40% to 70% (Scheme 46). Unfortunately, when employing already fluorinated salts (R = H(CF<sub>2</sub>)<sub>6</sub>, CF<sub>3</sub>, C<sub>3</sub>F<sub>7</sub>OCF(CF<sub>3</sub>)), the reaction did not afford the expected products. In addition to this limitation, one should also mention that the necessity to start from carboxylate salts might be a drawback.



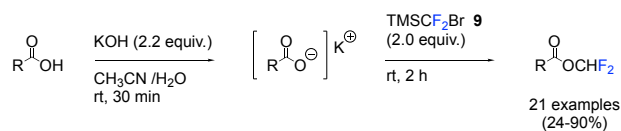
**Scheme 46.** O-Difluoromethylation of carboxylic acid salts using fluorosulfonyldifluoroacetic acid **10**.

As previously mentioned, Xiao *et al.* were able to apply reactive, though highly stable, difluoromethylene phosphobetaine **20** to the difluoromethylation of aromatic carboxylic acids. The reaction was in fact optimized on *p*-methoxybenzoic acid. It appeared that the use of 2.0 equiv. of **20** and heating at 90 °C were necessary to give the best yields (Scheme 47). Although only 3 examples were reported, the results for carboxylic acids were even slightly better (67–91%) than for phenols (56–92%). Unfortunately, the transformation could not be applied to aliphatic acids and alcohols.

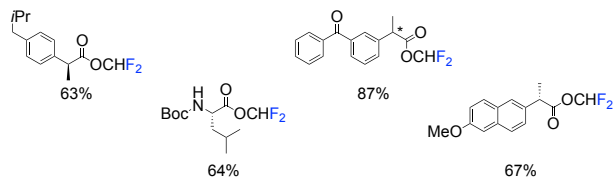


**Scheme 47.** O-Difluoromethylation of carboxylic acids using PDFA **20**.

More recently, in 2019, Prakash reported the use of TMSCF<sub>2</sub>Br **9** as difluorocarbene source for the direct transformation of carboxylic acids into the corresponding difluoromethyl esters.[28] As for phenols, KOH is required to activate the substrates. The reaction thus takes place in CH<sub>3</sub>CN but required the presence of water in order to dissolve the aqueous base. After addition of 2.0 equiv. of **9**, difluoromethylation occurred readily at r.t. within 2h (Scheme 48). Just as for alcohols, the procedure proved to be efficient on both aromatic and aliphatic carboxylic acids. For aryl-bearing acids, the electron density of the ring seems to have an impact on the reactivity, as the presence of electron-withdrawing groups led to decreased yields. Furthermore, the reaction showed a perfect selectivity towards O-difluoromethylation, since no *gem*-difluorocyclopropanation was observed on substrates bearing alkene or alkyne moieties. The authors also showed the late-stage functionalization aptitude of this procedure by performing the transformation of various complex biologically relevant carboxylic acids.

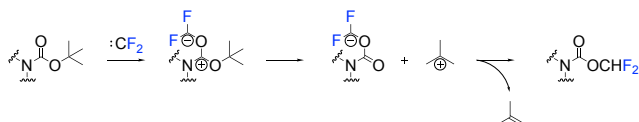
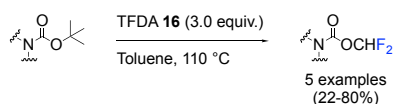


*Transformation of biologically active carboxylic acids*



**Scheme 48.** *O*-Difluoromethylation of carboxylic acids using TMSCF<sub>2</sub>Br **9**.

Also in 2019, Shivaniuk described a procedure allowing the transformation of Boc-protected amines into difluoromethylcarbamates *via* difluorocarbene generated by TFDA **16**, a reagent that allowed the transformation of enolizable ketones at 110 °C in toluene.[55] Examples were reported with yields between 22% and 80 %. It is noteworthy mentioning that the reaction only allowed the transformation of CO<sub>2</sub>tBu since the CO<sub>2</sub>Me moiety present on some substrates remained untouched. Contrariwise, some difluorocyclopropanation was observed on alkene-bearing substrates. The replacement of *t*-Bu supposedly occurs through the addition of difluorocarbene to the C=O bond of the Boc group, followed by the elimination of isobutene (*Scheme 49*). This procedure is nevertheless only reported on 5 examples and requires harsh temperature conditions.



**Scheme 49.** *O*-Difluoromethylation of *N*-Boc-protected amines using TFDA **16**.

To summarize, the access to difluoromethyl esters exclusively proceeds thanks to difluorocarbene sources known for their difluoromethylating abilities on alcohols or enolizable ketones. It is nevertheless a bit unfortunate that, apart from TMSCF<sub>2</sub>Br, whose substrate scope is rather wide, the activity of other reagents has only been described on few substrates so far.






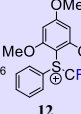






## Conclusion

Since the banning of processes depending on ozone-depleting substances, great advances have been made in order to ensure an easy access to the –OCHF<sub>2</sub> moiety. Plenty of new sources of difluorocarbene were developed, among them chlorodifluoroketones and –sulfones requiring harsh temperature conditions. Nevertheless, reagents requiring milder reaction conditions such as Hartwig's difluoromethyl triflate, or the environmentally friendly diethyl bromodifluoromethylphosphonate afforded good results in the *O*-difluoromethylation of phenols. Moreover, a few methods proved to be efficient on aliphatic alcohols, like for example the use of FSO<sub>2</sub>CF<sub>2</sub>CO<sub>2</sub>H **10** with catalytic CuI or TMSCF<sub>2</sub>Br **9**. The latter emerged as particularly interesting since it showed its ability to convert phenols, alkanols and carboxylic acids. Furthermore, the last decades have seen the development of non-difluorocarbene-based methods, like the direct substitution of *S*-difluoromethyl sulfonium ylides, which proved suitable for aliphatic alcohols, or Ngai's radical difluoromethoxylation of arenes. Besides, many processes have a high functional group compatibility and could thus be used for late-stage functionalization.

The choice of the more convenient method for a transformation obviously depends on several parameters such as the reactant accessibility and cost, the practical ease, the possibility of scale-up, or the substrate scope.... For now, the latter probably remains the main criteria as testified by Table 1, which summarizes the applicability of each reactant with the various types of substrates.

As a matter of fact, many procedures have been developed to access aryl difluoromethyl ethers or esters, but the demand for OCHF<sub>2</sub>-functionalized structures is still growing and the development of methods is necessary, especially regarding aliphatic alcohols, for which efficient procedures are still rather scarce. Subsequently, new procedures with industrial applicability potential will be needed.

Table 1. Reactivity of the various fluorine sources towards the several substrate types in order to access difluoromethyl ethers and esters.

Fluorine source	EWG-Ph-OH	EGD-Ph-OH	Alk-OH	Ar-COOH	Alk-COOH	Aldehyde	Amide	Aldehyde	Acetal	Difluoromethyl ether/ester
	+	+	/	/	/	/	/	/	/	/
	+	+	/	/	/	/	/	/	/	/
$\text{ClCF}_2\text{CO}_2\text{Na}$	/	+	/	/	/	/	/	/	/	/
	±	+	/	/	/	-	/	/	/	/
$\text{HCF}_2\text{OTf}$ <sup>4</sup>	±	+	/	/	/	+	/	/	/	/
$n\text{-Bu}_3\text{N}^+(\text{CF}_2\text{H})\text{Cl}^-$	±	+	/	/	/	/	/	/	/	/
	+	+	/	/	/	-	/	/	/	/
$[\text{Cu}(\text{phen})_2][\text{OCCF}_2\text{Cl}]$	±	+	/	/	/	-	/	/	/	/
$\text{HCF}_3$	±	+	/	/	/	/	/	/	/	/
$\text{TMSCF}_2\text{Br}$ <sup>9</sup>	+	+	+	+	+	-	/	/	/	/
$\text{FSO}_2\text{CF}_2\text{CO}_2\text{H}$ <b>10</b>	±	±	+	±	+	/	/	/	/	/
	±	+	-	/	/	-	/	/	/	/
	-	-	+	/	/	/	/	/	/	/
	/	/	/	/	/	+	+	/	/	/
	/	/	/	/	/	+	/	/	/	/
$\text{ClCF}_2\text{CO}_2\text{Et}$ <b>18</b>	/	/	/	/	/	+	/	/	/	/
	/	/	/	/	/	+	/	/	/	/
$\text{Ph}_3\text{P}^+\text{C}^-\text{F}_2\text{CO}_2^-$ <b>20</b>	±	±	-	+	-	+	/	/	/	/
	/	/	/	/	/	+	/	/	/	/
	/	/	/	+	+	/	/	/	/	/
$\text{Me}_3\text{SnCF}_3$ <b>25</b>	/	/	/	+	/	/	/	/	/	/
$\text{BrF}_3$	-	+	+	/	/	/	/	/	/	/
$\text{Et}_3\text{N}\cdot 3\text{HF}$ , $\text{THF}\cdot 5\text{HF}$ , or $\text{KF}$ <sup>b</sup>	+	+	+	/	/	/	/	/	/	/
	/	/	/	/	/	/	/	+	/	/
$\text{S}(\text{H})_2$ , $n\text{BuLi}$ , $\text{Py}\cdot 9\text{HF}$	/	/	/	/	/	/	/	/	+	/
$\text{AgF}_2$	/	/	/	/	/	/	/	/	/	+

<sup>a</sup> For the transformation of electron-rich phenols, the use of  $\text{HCF}_2\text{ONF}$  is required. <sup>b</sup> The use of particular conditions allows a selectivity between the various functions

+: transformation of the substrate - : no transformation of the substrate ± : moderate transformation of the substrate / : the transformation was not investigated

## Acknowledgments

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