

3.6. Extension to the SCF₂H, SCH₂F, and SCF₂R motifs (R = PO(OEt)₂, CO₂R, Rf)

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3.6.1 Introduction

Nowadays, organofluorine chemistry can be considered as a strategic research area in organic chemistry. Indeed, the importance of fluorinated molecules for the discovery of biologically active molecules cannot be denied in view of the marketed fluorine-containing drugs [1]. All refs must be under brackets before the punctuation. Apply all along the text. Therefore, to broaden the portfolio of available fluorinated groups, the community devoted lot of efforts. As part of them, sulfur-containing fluorinated motifs are of high interest and already found applications in agrochemistry, for instance (*eg.* Fipronil and Toltrazuril). As the most popular sulfur-containing fluorinated group, the SCF₃ attracted lot of attention and plethora of methodologies were developed over the last decades [2]. Complementary, the quest for other sulfur-containing fluorinated groups is important, as their introduction can afford new and interesting physicochemical properties, as well as promising biological activities. In that purpose, considerable efforts were dedicated over the last ten years. As a result, the community has seen the development of practical methodologies to build up molecules having SCF₂H, SCH₂F and SCF₂Rf motifs. In addition, recent efforts culminated in the development of new motifs bearing a functional group that can either be modulated or directly used in drug discovery program. As examples, one can mention the SCF₂CO₂R, SCF₂PO(OEt)₂ and SCF₂SO₂Ph [3] groups.

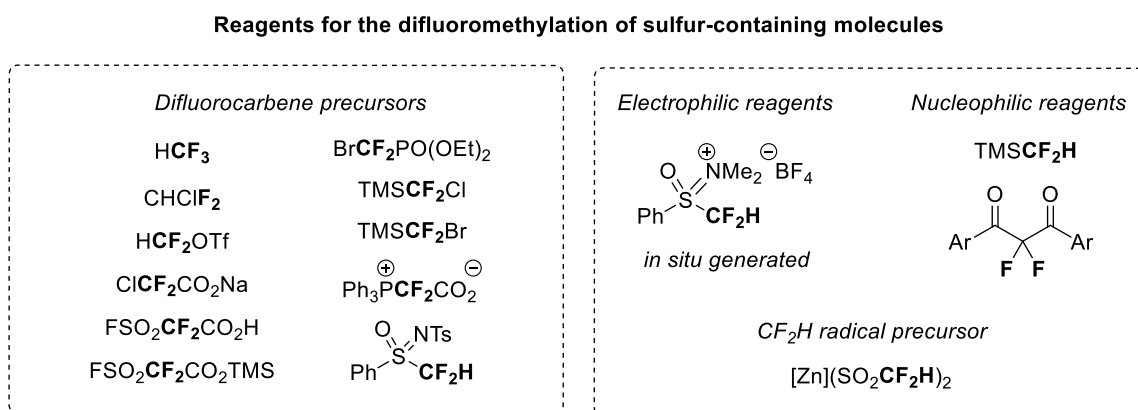
In this chapter, the recent and most significant progress made for the access to SCF₂H, SCH₂F, SCF₂PO(OEt)₂, SCF₂COR, and SRf will be highlighted.

3.6.2 The SCF₂H Motif

Over the last years, a strong interest was paid to the SCF₂H group. Indeed, due to its unique properties such as its lipophilicity, its H-bonding ability [4] and due to the presence of a more acidic proton compared with the one in the CF₂H group, the development of new approaches for its introduction onto various classes of compounds was reported. Two main strategies were depicted, namely 1) the difluoromethylation of sulfur-containing molecules and 2) the direct C-SCF₂H bond construction. In this section will be reported the most relevant advances made since 2016 [5].

3.6.2.1 Construction of the SCF₂H Moiety

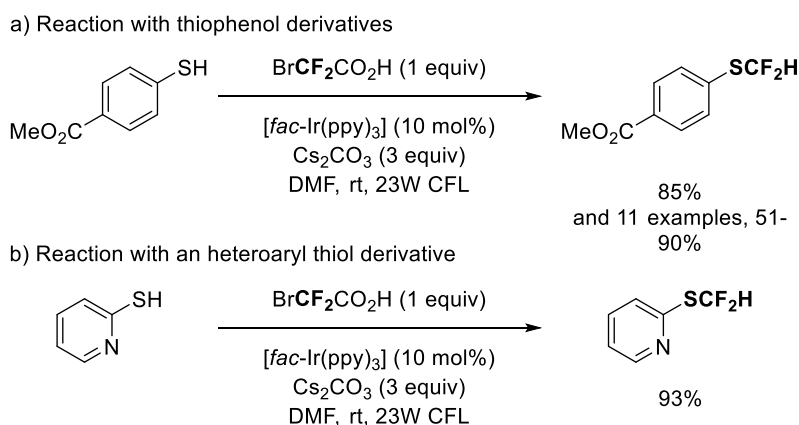
Due to the importance of the SCF₂H group, various strategies were elaborated to build up a S-CF₂H bond. Until 2016, the use of difluorocarbene precursors was the main approach. Alternatives based on electrophilic and nucleophilic reagents or CF₂H radical precursors were promising, although still in their infancy. A summary of the main reagents used in these transformations is depicted in the Scheme 3.6-1 [5].



Scheme 3.6-1 State of the art: reagents used for the difluoromethylation of sulfur-containing molecules until 2016.

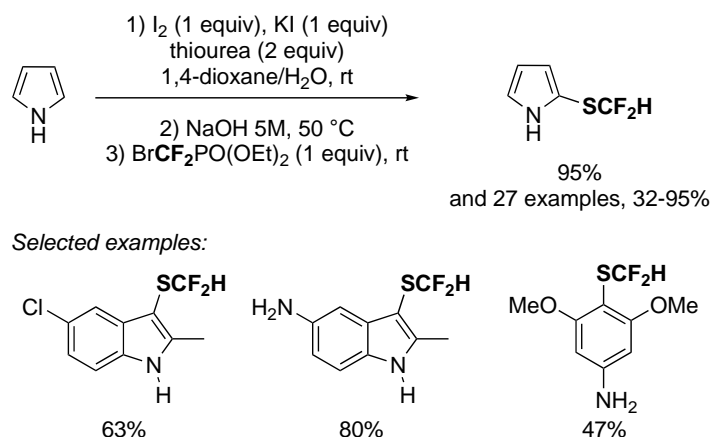
In this section, will be described the recent advances made since 2016 to construct a S-CF₂H bond.

In 2017, the group of Fu developed a methodology for the difluoromethylation of thiophenols under visible light photocatalysis [6]. Using the readily available difluorobromoacetic acid as a difluorocarbene precursor and an iridium complex as photocatalyst, a panel of thiophenols bearing halogens, ester, nitro as functional groups was functionalized in moderate to high yields (Scheme 3.6-2a). Note that even the difluoromethylation of 2-pyridinethiol was smoothly achieved (Scheme 3.6-2b).



Scheme 3.6-2 Difluoromethylation of thiophenols under visible light photocatalysis.

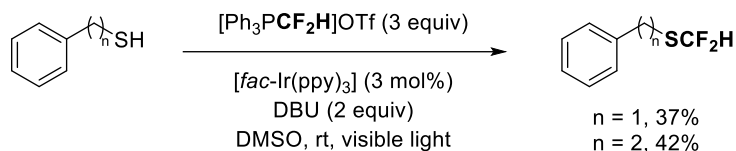
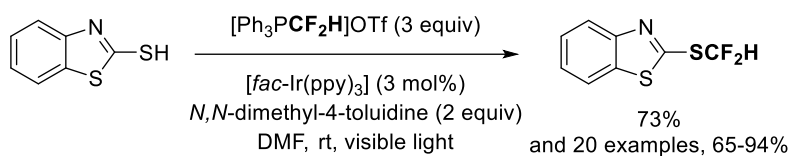
Another difluorocarbene precursor, namely the diethyl bromodifluoromethylphosphonate, was also used in combination with thiourea as the sulfur source [7]. With this system, Yi and coworkers successfully functionalized in a one-pot three-step sequence, a panel of heteroaromatic compounds (indoles, pyrroles) and electron-rich arenes (Scheme 3.6-3).



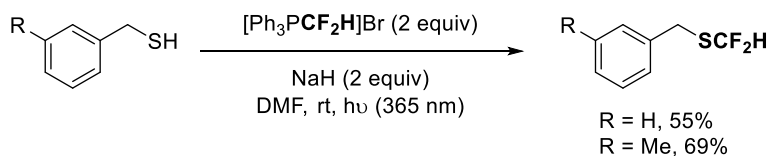
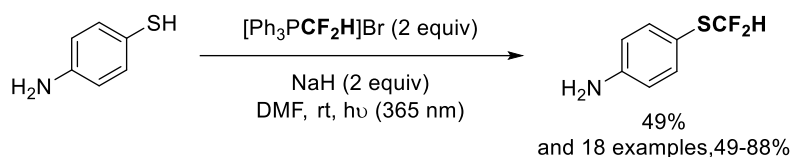
Scheme 3.6-3 Difluoromethylation of heteroaromatic compounds and electron-rich arenes using diethyl bromodifluoromethylphosphonate and thiourea.

In 2017, the groups of Qing and Studer independently developed a method for the difluoromethylation of thiols using a difluoromethyltriphenylphosphonium salt, via a radical process. Indeed, Qing and co-workers reported a Ir-catalyzed difluoromethylation reaction under visible light irradiation [8]. A panel of (hetero)aryl- and alkyl-thiols was functionalized (Scheme 3.6-4a). In the case of Studer's group, a transition metal free process was developed and not only (hetero)arylthiols, benzylic ones but also a benzeneselenol were difluoromethylated, leading to the corresponding products in moderate to high yields (Scheme 3.6-4b) [9].

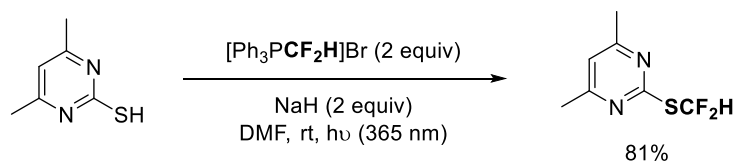
a) Qing *et al.*



b) Studer *et al.*

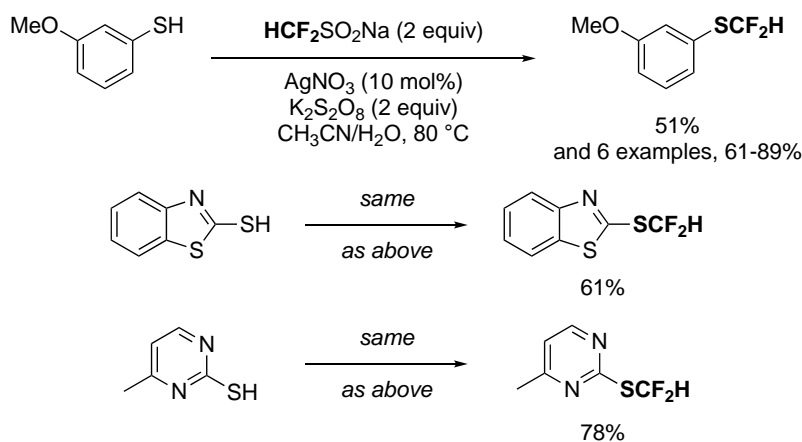


Selected example of an heteroaryl thiol:



Scheme 3.6-4 Difluoromethylation of thiol derivatives with a difluoromethyltriphenylphosphonium salt.

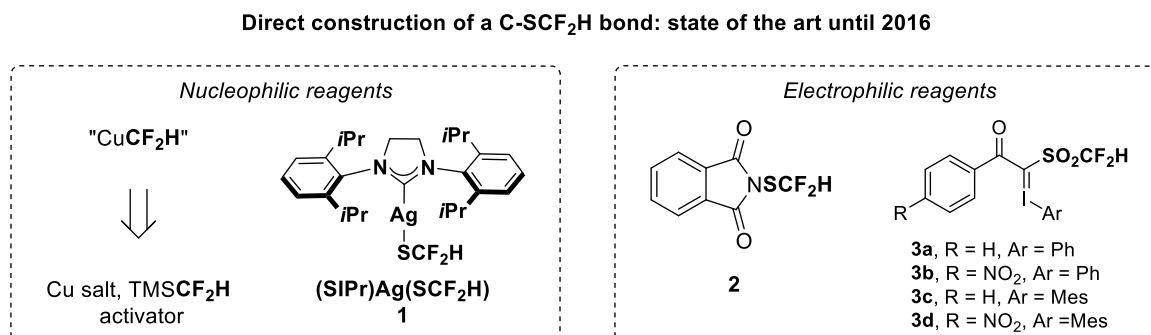
An alternative was suggested by the group of Yi for the difluoromethylation of thiols (Scheme 3.6-5) [10]. Aiming at developing a general method for the construction of S-Rf bond (Rf = CF₃, CF₂H, C_nF_{2n+1}), the authors reported a silver catalyzed difluoromethylation of various (hetero)aromatic thiols using sodium difluoromethanesulfinate (HCF₂SO₂Na).



Scheme 3.6-5 A silver-catalyzed difluoromethylation of thiol derivatives.

3.6.1.2 Direct formation of a C–SCF₂H bond

Major advances were made for the direct construction of a C-SCF₂H bond, as demonstrated by the contributions from several research groups. Novel methods and original reagents (nucleophilic and electrophilic ones) were developed to construct C-SCF₂H bonds [5], as summarized in Scheme 3.6-6.

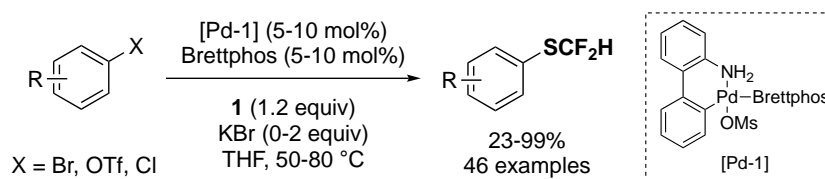


Since then, further developments were realized for the difluoromethylthiolation reaction using nucleophilic reagents, newly designed electrophilic sources and by means of radical precursors.

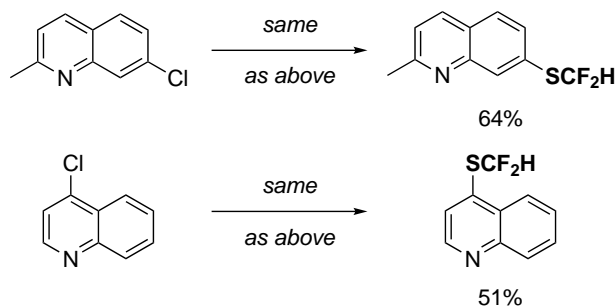
3.6.2.2.1 Difluoromethylthiolation Reaction by a Nucleophilic Pathway

A pioneer work was reported by the group of Goossen. They developed the *in situ* generation of a nucleophilic CuCF₂H reagent from TMSCF₂H, an activator (CsF or Cs₂CO₃) and a suitable copper salt. This reagent was used for the functionalization of organothiocyanate derivatives, themselves prepared from various classes of precursors (alkyl bromides and mesylates, aryl diazonium salts and electron rich arenes)[11]. As another milestone, the first nucleophilic difluoromethylthiolation reagent ([SIPrAg(SCF₂H)], **1**), developed by Shen and co-workers, was applied as a nucleophilic SCF₂H source in a copper-mediated difluoromethylthiolation of aryl diazonium salts and for the Pd-catalyzed functionalization of (Het)ArX (X = I, Br and OTf) [12]. In 2018, the same group showed that a slightly modified catalytic system allowed the functionalization of aryl bromides, triflates and chloride as well as two examples of (hetero)aryl chloride [13]. Indeed, in the presence of the [Pd-1] and BrettPhos, in a catalytic fashion, the difluoromethylthiolation of various aromatic derivatives was achieved (46 examples, up to 98% yield). With this tool in hand, the functionalization of natural, medicinal and material molecules was possible, demonstrating the potential of such approach for the late-stage functionalization (Scheme 3.6-7).

a) Reaction with aryl bromide, triflate and chlorides:



b) Reaction with heteroaryl chlorides:

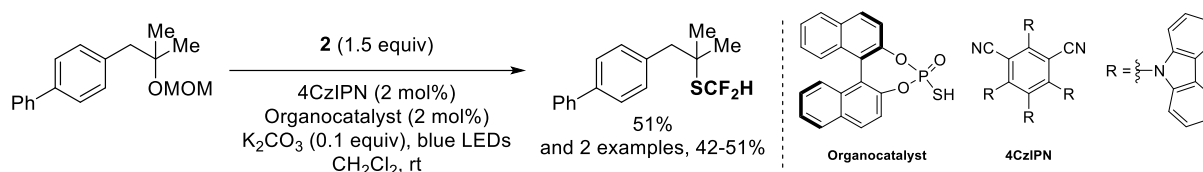


Scheme 3.6-7 Pd-catalyzed difluoromethylthiolation of (Het)ArX (X = Br, OTf and Cl) with the nucleophilic SCF₂H source **1**.

3.6.2.2.1 Difluoromethylthiolation Reaction using Electrophilic Reagents

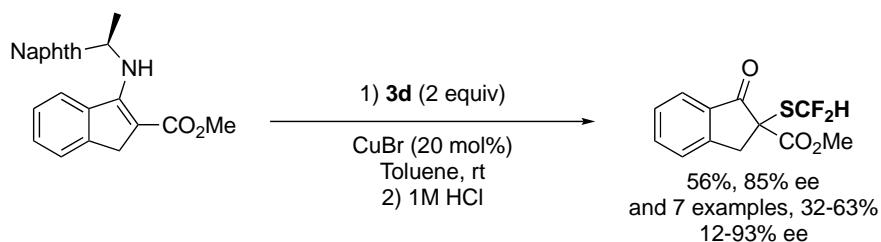
From the key contributions made by the group of Shen and Shibata in the design of electrophilic SCF₂H sources, **2** [14] and **3a-d** (Scheme 3.6-6) [15], several advances were made using either these well-known electrophilic SCF₂H sources or based on original approaches.

In 2018, Xie, Zhu and coworkers reported a transition metal free, unpolluting difluoromethylthiolation of tertiary alkyl ethers using **2** [16]. Although restricted to only three examples, the selective difluoromethylthiolation of a C–O bond was successfully achieved using a synergistic organophotoredox catalysis and organocatalysis (Scheme 3.6- 8).



Scheme 3.6-8 Difluoromethylthiolation of tertiary alkyl ethers using **2**.

Note that Shibata and co-workers recently used these two classes of reagents (**2** and **3a-d**) as SCF₂H sources in the synthesis of racemic α -SCF₂H-containing- β -ketoallylesters. The latter were then converted into the corresponding enantioenriched ketones through a Pd-catalyzed asymmetric Tsuji decarboxylative allylic alkylation with up to 94% ee [17]. More recently, the same group developed a diastereoselective difluoromethylthiolation of indanone-based β -ketoesters thanks to the use of the ylide **3d** by means of a chiral auxiliary (Scheme 3.6-9) [18]. One acyclic enamino ester was also functionalized albeit in a poor 12% ee [19].

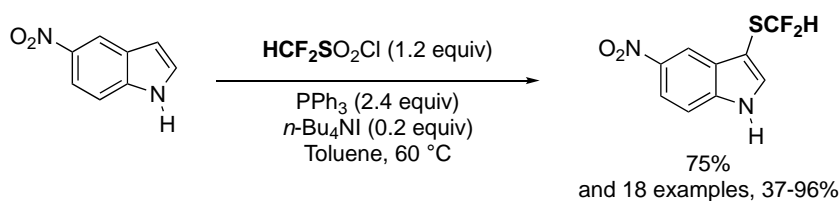


Scheme 3.6-9 Diastereoselective difluoromethylthiolation of indanone-based β -keto esters using **3d**.

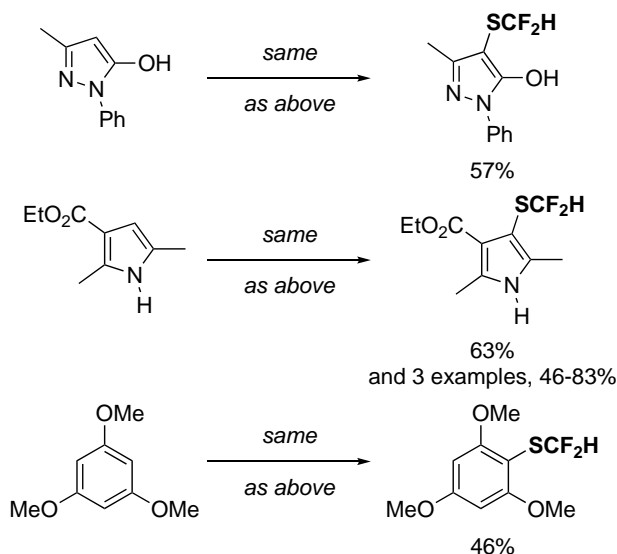
Besides, the quest for new electrophilic SCF_2H sources emerged over the last years and original sources were developed, especially starting from the $\text{HCF}_2\text{SO}_2\text{Cl}$, $\text{HCF}_2\text{SO}_2\text{Na}$ and HCF_2SOCl reagents.

In 2016, Zhao, Lu and coworkers reported the *in situ* generation of the electrophilic difluoromethylsulfenyl chloride (HCF_2SCl) after reduction of the difluoromethanesulfonyl chloride ($\text{HCF}_2\text{SO}_2\text{Cl}$) by PPh_3 [20]. With this tool in hand, the difluoromethylthiolation of a panel of indoles was achieved, leading to the corresponding products in good to high yields. Note that other heteroaromatic derivatives (pyrrole, indolizine, pyrazole derivatives...) and electron-rich arenes were functionalized under these reaction conditions. The presence of *n*- Bu_4NI as an additive was mandatory, presumably for the generation of iodine in the course of the reaction, which might facilitate the transformation (Scheme 3.6-10).

a) Reaction with indole derivatives:



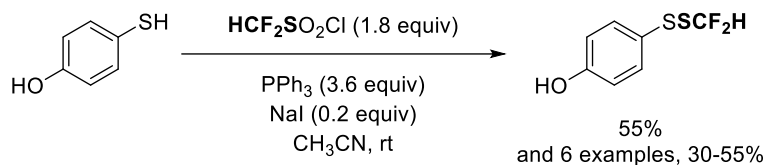
b) Selected examples with other heteroarenes and electron-rich arenes:



Scheme 3.6-10 Difluoromethylthiolation of heteroaromatic derivatives and electron-rich arenes using PPh_3 as the reducing agent and $\text{HCF}_2\text{SO}_2\text{Cl}$.

The combination of $\text{HCF}_2\text{SO}_2\text{Cl}$ and PPh_3 was then applied to the functionalization of other classes of compounds. Zhao, Lu and co-workers studied the difluoromethylthiolation of thiol derivatives using $\text{HCF}_2\text{SO}_2\text{Cl}$ combined with PPh_3 in the presence of NaI as the iodine source (Scheme 3.6-11) [21].

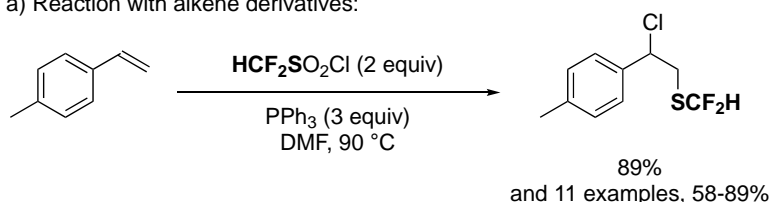
Reaction with thiol derivatives:



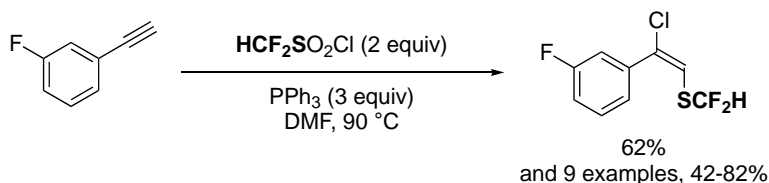
Scheme 3.6-11 Difluoromethylthiolation of thiol derivatives using PPh_3 as the reducing agent and $\text{HCF}_2\text{SO}_2\text{Cl}$.

In the same vein, in 2018, Yi, Zhang and co-workers investigated the difunctionalization of unsaturated compounds. Indeed, using the difluoromethanesulfonyl chloride ($\text{HCF}_2\text{SO}_2\text{Cl}$) in the presence of PPh_3 , the chloro-difluoromethylthiolation of alkenes (styrene derivatives and other classes of alkenes) and terminal alkynes was achieved leading to the corresponding products in moderate to high yields with a high atom economy [22]. Note that when styrene derivatives were used, the Markovnikov products were regioselectively obtained, while the other alkenes provided the *anti*-Markovnikov adducts preferentially (Scheme 3.6-12).

a) Reaction with alkene derivatives:



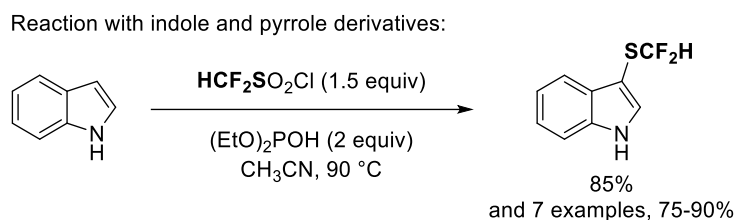
b) Reaction with alkyne derivatives:



Scheme 3.6-12 Chloro-difluoromethylthiolation of alkenes and alkynes using the $\text{HCF}_2\text{SO}_2\text{Cl}/\text{PPh}_3$ system.

In 2016, in the course of their investigations towards the development of a general methodology for the fluoroalkylthiolation of electron rich arenes and thiol derivatives using fluoroalkylsulfonyl chloride, the group of Yi depicted few examples of

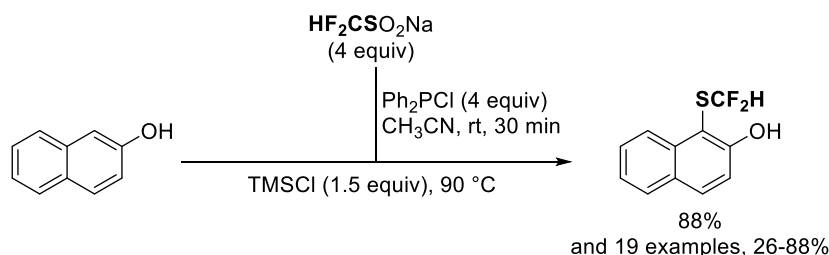
difluoromethylthiolation of indole and pyrrole derivatives using $\text{HCF}_2\text{SO}_2\text{Cl}$ and $(\text{EtO})_2\text{POH}$ as the reducing agent (Scheme 3.6-13) [23].



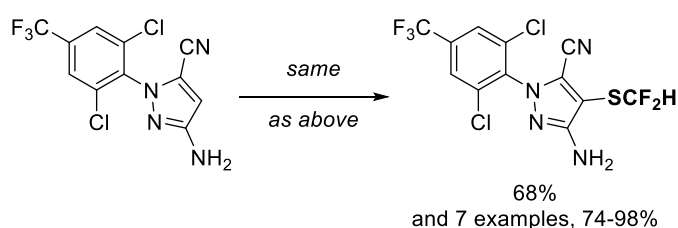
Scheme 3.6-13 Difluoromethylthiolation of indole and pyrrole derivatives using $(\text{EtO})_2\text{POH}$ as the reducing agent and $\text{HCF}_2\text{SO}_2\text{Cl}$.

In 2017, Shibata and co-workers depicted the astute combination of $\text{HF}_2\text{CSO}_2\text{Na}/\text{Ph}_2\text{PCI}/\text{TMSCl}$ for the electrophilic difluoromethylthiolation of $\text{C}(\text{sp}^2)$ and $\text{C}(\text{sp}^3)$ centers [24]. Indeed, with this mild, metal- and base-free system, a large panel of nucleophiles was functionalized including a wide range of phenol and naphthol derivatives. In addition, the scope of the transformation was broad and the difluoromethylthiolation of other heterocyclic compounds (pyrroles, indoles, ...), electron-rich arenes as well as enamines, ketones and β -ketoesters was efficiently carried out (Scheme 3.6-14).

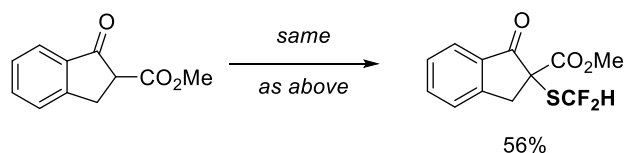
a) Reaction with naphthol and phenols derivatives



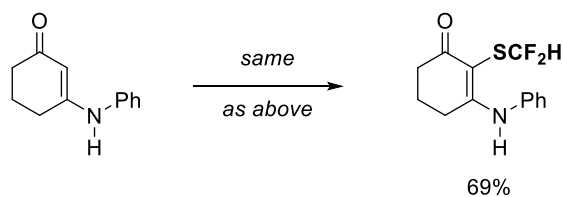
b) Reaction with N-heterocycles



c) Reaction with β -keto-ester



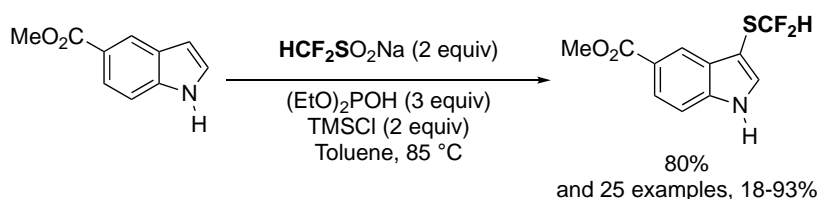
d) Reaction with enamide



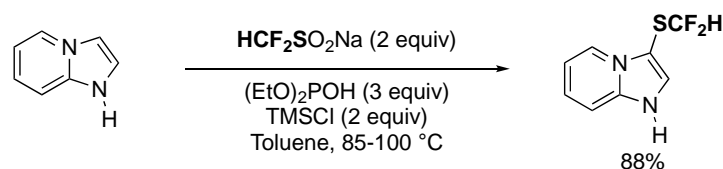
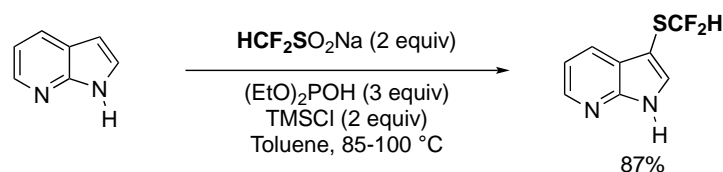
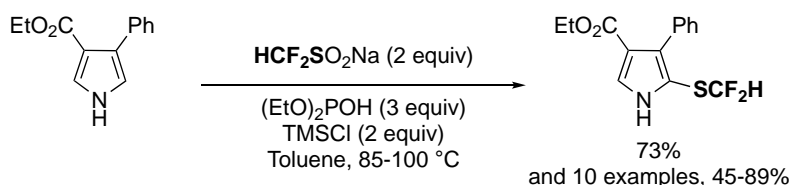
Scheme 3.6-14 Electrophilic difluoromethylthiolation of C(sp²) and C(sp³) nucleophiles with the HF₂CSO₂Na/Ph₂PCI/TMSCl system.

The same year, the group of Yi and Zhang reported an alternative approach. Indeed, in their case, the HCF₂SO₂Na was reduced with (EtO)₂POH in the presence of TMSCl to generate *in situ* an electrophilic SCF₂H source [25]. With this metal free process, various heterocycles such as indoles (26 examples), pyrroles (10 examples) and other heteroarenes (eg. 7-azaindole, imidazo[1,2-*a*]pyridine,...) were difluoromethylthiolated. In addition, electron-rich arenes were also suitable substrates (8 examples, Scheme 3.6-15).

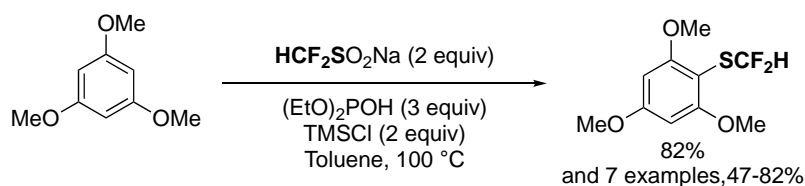
a) Reaction with indole derivatives:



b) Reaction with pyrroles and other heteroarenes:

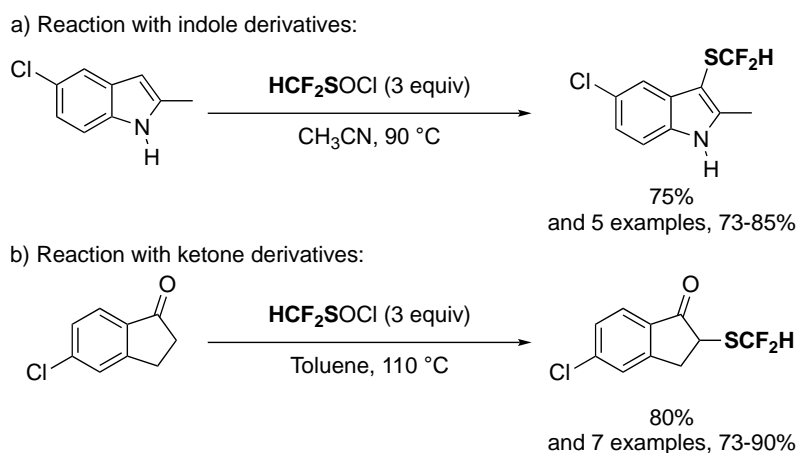


c) Reaction with electron rich arenes:



Scheme 3.6-15 Electrophilic difluoromethylthiolation of C(sp²) nucleophiles with the HF₂CSO₂Na/(EtO)₂POH/TMSCl system

Finally, in 2018, Yi, Zhang and co-workers demonstrated that trifluoromethanesulfinyl chloride and difluoromethanesulfinyl chloride reacted as CF₃SCI and HCF₂SCI precursors [26]. Indeed, without additional reductant, the HCF₂SOCl was prone to react with several indoles and ketones such as indanone derivatives, 1-tetralone and 1-acenaphthenone (Scheme 3.6-16).



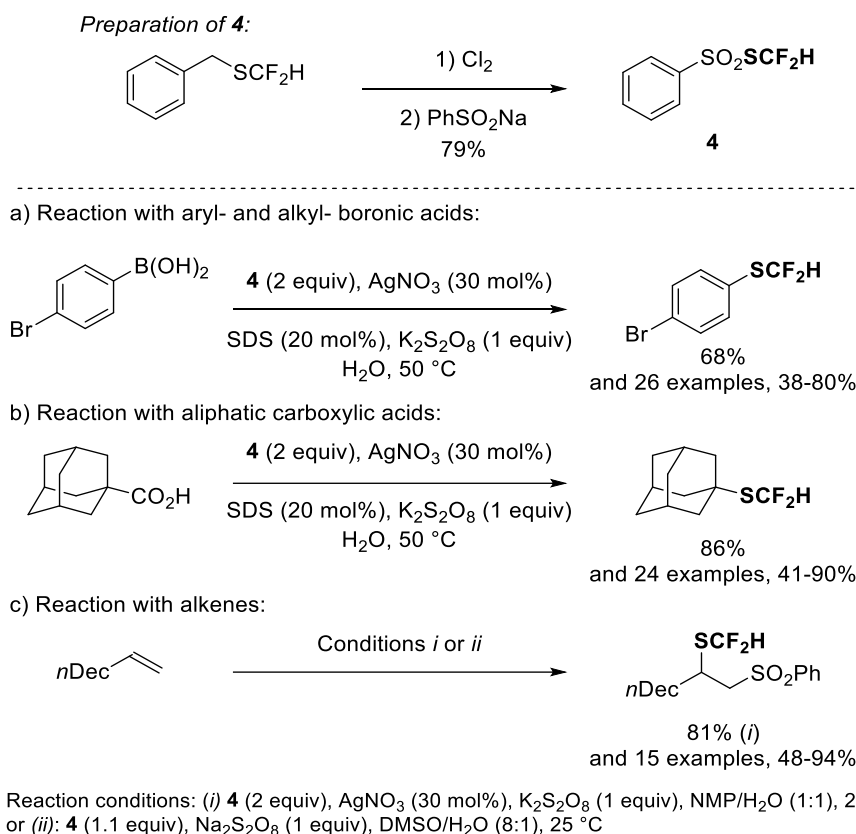
Scheme 3.6-16 Difluoromethylthiolation of indole derivatives and ketones with HCF_2SOCl . Note that in case of indoles the reaction was carried out in CH_3CN , $90\text{ }^\circ\text{C}$.

3.6.2.2.3. $\text{PhSO}_2\text{SCF}_2\text{H}$ (**4**) as an efficient reagent for the radical difluoromethylthiolation

Recently a strong interest was paid to thiosulfonate derivatives (ArSO_2SRf) as emerging reagents for the introduction of sulfur-containing fluorinated moieties and in particular the SCF_2H residue [27]. Therefore, in the following section, the major breakthroughs that have been recently developed using the $\text{PhSO}_2\text{SCF}_2\text{H}$ as a SCF_2H source for the direct introduction of the SCF_2H moiety onto molecules will be summarized.

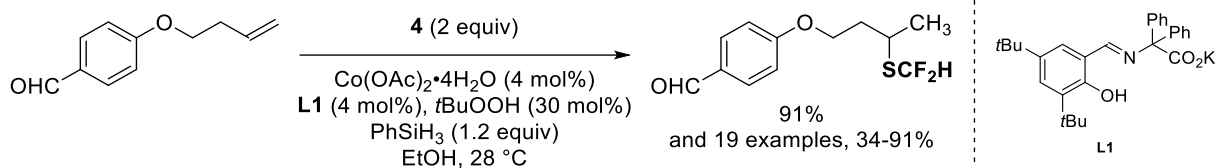
In 2016, the group of Lu and Shen investigated the synthesis and the application of the *S*-(difluoromethyl)benzenesulfonothioate (**4**, $\text{PhSO}_2\text{SCF}_2\text{H}$) [28]. This latter was synthesized via a one-pot two-step sequence from benzyldifluoromethylsulfide (Scheme 3.6-17). It was then applied for the difluoromethylthiolation of different classes of compounds.

The silver catalyzed difluoromethylthiolation of both aryl and alkyl boronic acids was described (Scheme 3.6-17a). The reaction turned out to be functional group tolerant (halides, ester, ketone, nitro...). In addition, to further demonstrate the synthetic utility of the reagent, the functionalization of aliphatic carboxylic acids was investigated under silver catalysis. Under these reaction conditions, the decarboxylative difluoromethylthiolation of cyclic and acyclic carboxylic acids (primary, secondary and tertiary ones) was achieved (Scheme 3.6-17b). Finally, the 1,2-difunctionalization of terminal aliphatic alkenes was studied leading to the corresponding phenylsulfonyl-difluoromethylthio derivatives in the presence or not of the silver catalyst. Note that styrenes and α,β -unsaturated esters were reluctant substrates (Scheme 3.6-17c).



Scheme 3.6-17 Synthesis and application of the *S*-(difluoromethyl)benzenesulfonylthioate **4**. SDS: Sodium dodecyl sulfate.

In 2019, the same group reported a Co(III)-catalyzed hydro-difluoromethylthiolation reaction of unactivated alkenes as a complementary approach (Scheme 3.6-18). With this method, the functionalization of terminal alkenes and 1,1-disubstituted alkenes was achieved providing the expected products with a good Markovnikov selectivity [29]. The reaction demonstrated a large functional group tolerance (halides, aldehyde, sulfonate, cyano....).

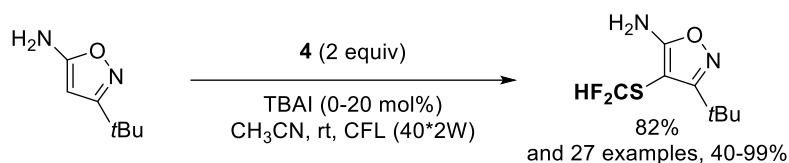


Scheme 3.6-18 Co-catalyzed hydro-difluoromethylthiolation of unactivated terminal alkenes.

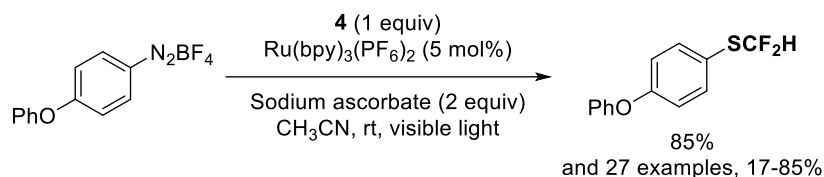
The difluoromethylthiolation of aromatic derivatives was also studied by several research groups. The group of Li demonstrated that the reagent **4** was efficiently used as SCF_2H source under visible light irradiation for the radical difluoromethylthiolation. Various (hetero)aromatic compounds (such as indoles, pyrroles, azaindoles, pyrazoles, isoxazole, chromones, thiophene) and electron-rich arenes were functionalized at innate positions via a metal-free process at room temperature (Scheme 3.6-19a) [30]. In the same vein, Wang, Wang

and co-workers studied the functionalization of aryldiazonium salts with **4** under photocatalytic conditions (Scheme 3.6-19b) [31].

a) Reaction with (het)ArH (indoles, pyrroles, electron rich arenes....):

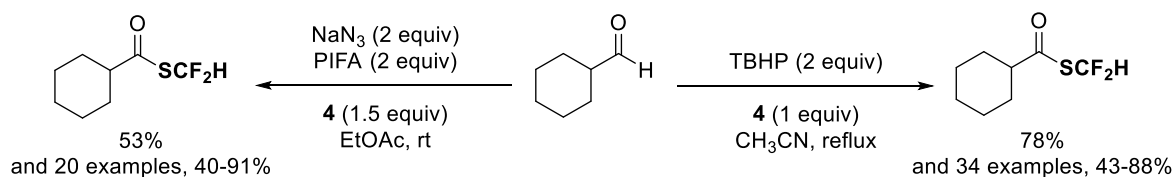


b) Reaction with aryldiazonium salts:



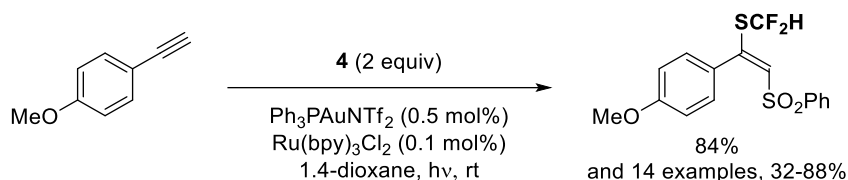
Scheme 3.6-19 Photocatalyzed difluoromethylthiolation of (Het)ArH and (Het)ArN₂BF₄ derivatives with **4**.

In 2018, the synthesis of difluoromethylthioester derivatives with the aid of reagent **4** was independently studied by the groups of Wang[32] as well as Wang, Hu and Shen[33] via a radical process (Scheme 3.6-20). In the first case, the difluoromethylthiolation of (hetero)aromatic aldehydes was conducted in the presence of TBHP as the radical initiator. The transformation was not restricted to aromatic aldehydes as aliphatic ones and even α,β -unsaturated aldehydes were successfully difluoromethylthiolated. A complementary approach was depicted by Wang, Hu and Shen. In the presence of **4**, the combination of NaN₃ and PIFA permitted the functionalization of a panel of (hetero)aromatic and aliphatic aldehydes in ethyl acetate as a green solvent.



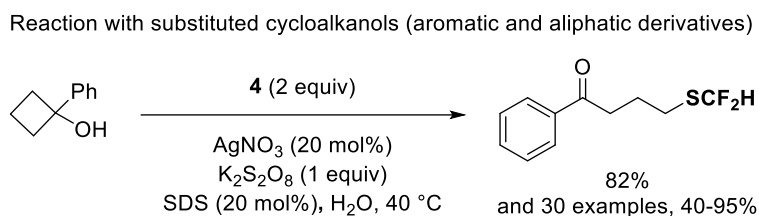
Scheme 3.6-20 Difluoromethylthiolation of aldehydes by means of **4**.

In 2018, in the course of their study regarding the trifluoromethylthiosulfonylation of alkynes via a process merging visible light photocatalysis and gold catalysis, the group of Xu also investigated the difluoromethylthiosulfonylation reaction of terminal alkynes, leading to the corresponding trisubstituted alkenes as *E* isomers (Scheme 3.6-21) [34]. Various functional groups were tolerated such as ester, halogens, free phenol and the reaction was not restricted to (hetero)aromatic alkynes as one example of an aliphatic one was depicted. Besides, in the case of 1-methoxy-4-(1-propyn-1-yl)-benzene as an internal alkyne, the expected product was obtained in 77% yield as a *E/Z* mixture of 3:1 (Scheme 3.6-21).



Scheme 3.6-21 Difluoromethylthiosulfonylation of alkynes.

A methodology allowing the synthesis of aliphatic ketones substituted by a SCF_2H group at a remote position was developed by Hu, Shen and co-workers [35]. In the presence of AgNO_3 , SDS as a surfactant (sodium dodecyl sulfate) and $\text{K}_2\text{S}_2\text{O}_8$, a silver-catalyzed difluoromethylthiolation reaction of a variety of cycloalkanols as precursors of the functionalized alkyl ketones was carried out, offering an access to the corresponding difluoromethylthioethers. Various cycloalkanols were compatible such as cyclobutanols, cyclopropanols, cyclopentanols, cyclohexanols and cycloheptanol (Scheme 3.6-22).



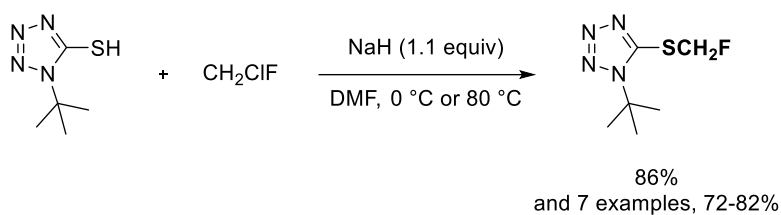
Scheme 3.6-22 Synthesis of aliphatic ketones substituted by a SCF_2H group at a remote position.

3.6.3 The SCH_2F Motif

As part of the sulfur-containing fluorinated groups, the SCH_2F one is underexplored compared to the SCF_2H and the SCF_3 residues. Indeed, prior the twenty first century only a handful of methods were available to access this class of compounds, which could suffer from a lack of stability in some cases. One should mention, the different variants of the fluoro-Pummerer rearrangement, which allowed the conversion of sulfoxides into α -fluoromethyl thioethers [36]. Fuchigami and co-workers extensively studied the anodic oxidation of thioethers into the corresponding α -fluoromethyl thioethers, although it was restricted to few specific substrates [37]. Finally, the use of electrophilic fluorine source to promote the oxidation of thioethers into α -fluoromethyl thioethers was also reported using N-fluoropyridinium salt [38] or F-TEDA- BF_4 [39].

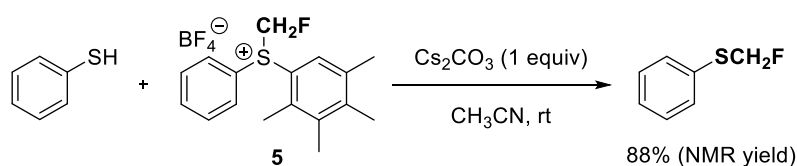
From 2000, more convenient and general methods were described and are highlighted in this section.

In 2007, Hu and co-workers described the use of chlorofluoromethane as an electrophilic source of the fluoromethyl moiety [40]. Under basic conditions in DMF, aryl, heteroaryl and benzyl thiols were readily converted into the corresponding SCH_2F -containing derivatives in good to excellent yields (Scheme 3.6-23).



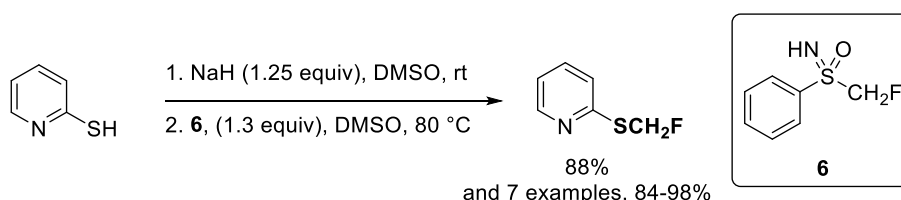
Scheme 3.6-23 Monofluoromethylation of thiols.

In 2008, Prakash, Olah and co-workers described the synthesis of the sulfonium salt **5**, as an electrophilic source of CH_2F [41]. Although a single example was described, the reaction of this salt with thiophenol yielded the corresponding and poorly stable α -fluoromethylthioether in 88% NMR yield (Scheme 3.6-24).



Scheme 3.6-24 Electrophilic monofluoromethylation of thiophenol using **5**.

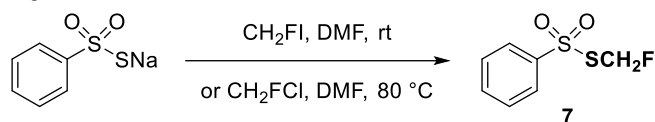
Complementary to these methods, the group of Hu reported the use of the sulfoximine **6** as a CH_2F source [42]. The reaction of **6** with thiols, proceeding presumably according to a $\text{S}_{\text{RN}}1$ mechanism, provided a straightforward access to the corresponding SCH_2F -containing molecules in good yields. The reaction was applied to aryl, heteroaryl and benzyl thiol derivatives (Scheme 3.6-25).



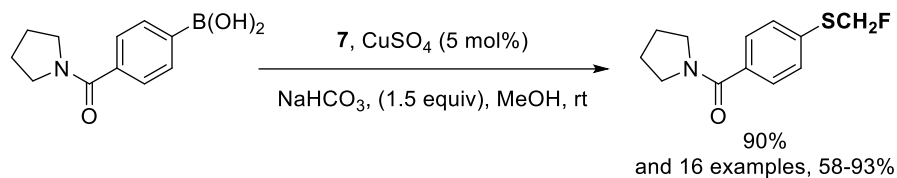
Scheme 3.6-25 Monofluoromethylation of thiols using sulfoximine **6**.

In 2017, the group of Shen described the synthesis of a new reagent to introduce the SCH_2F moiety: the *S*-(fluoromethyl)benzenesulfonylthioate **7** [43]. This bench-stable reagent **7**, easily prepared from sodium benzenesulfonylthioate, was used to convert boronic acids into the desired aryl- SCH_2F -containing molecules in good to excellent yields with an outstanding functional group tolerance. In the same report, the authors described the radical addition of the reagent **7** onto terminal alkenes according to an ATRA reaction. The reaction proceeded nicely with a complete and predictable control of the selectivity of the addition. The products were obtained in good yields and the functional group tolerance of the process was excellent (Scheme 3.6-26).

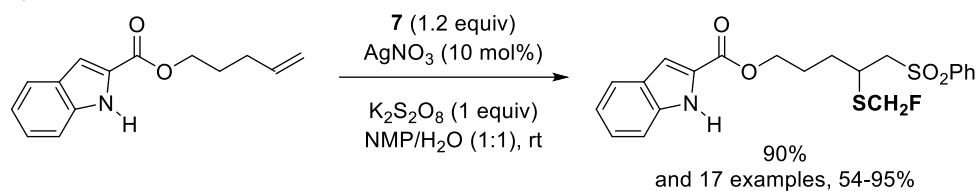
Preparation of reagent **7**:



a) Reaction with aryl boronic acids

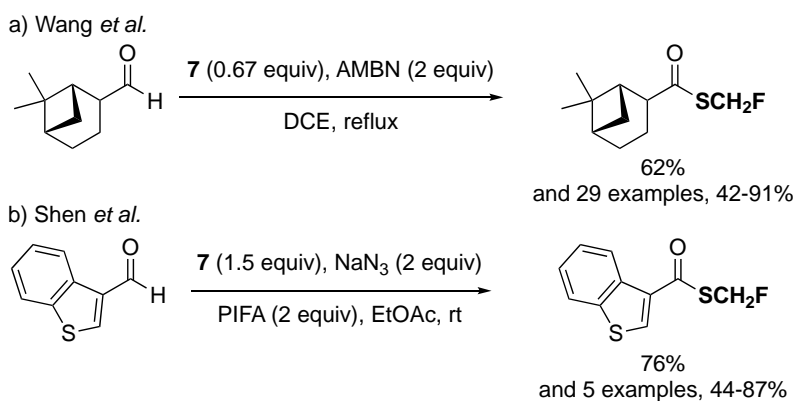


b) Addition reaction on alkenes



Scheme 3.6-26 Monofluoromethylthiolation of aryl boronic acid and alkenes using **7**.

In 2018, Wang[44] and Shen [33], concomitantly reported the use of the above-mentioned reagent **7** to get access to monofluoromethylthioesters, starting from aldehydes. While Wang was using AMBN (2,2'-Azobis(2-methylbutyronitrile)) to promote the acyl radical formation followed by its recombination with SCH₂F moiety onto a broad range of aldehydes, Shen used the combination of NaN₃ and PIFA to carry out the same transformation. In both cases, yields were moderate to excellent and the reaction proved to be functional group tolerant (Scheme 3.6-27).

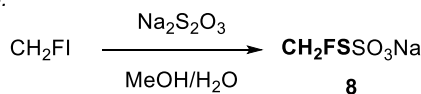


Scheme 3.6-27 Synthesis of monofluoromethylthioesters using **7**.

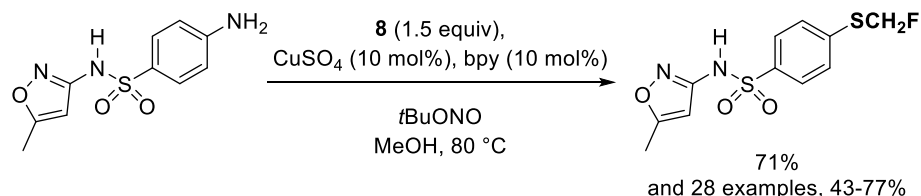
Finally, in 2018 the group of Yi described the synthesis of the Bunte salt FCH₂SSO₃Na **8** for the installation of the SCH₂F residue (Scheme 3.6-28). This motif was introduced onto anilines through the *in situ* formation of the corresponding diazonium salts [45]. This transformation demonstrated an excellent scope, various functionalities were tolerated and heteroaromatic derivatives were compatible. The products were isolated in good to excellent yields. Note that

the reaction was extended to the functionalization of thiophenol derivatives and the corresponding unsymmetrical disulfides were isolated in good to excellent yields.

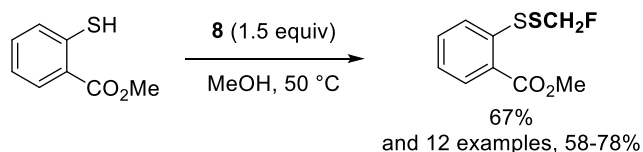
Preparation of reagent **8**:



a) Reaction with aniline derivatives:



b) Reaction with thiols:



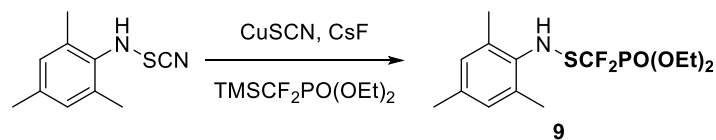
Scheme 3.6-28 Monofluoromethylthiolation of anilines and thiols using Bunte salt **8**.

3.6.4 The SCF₂PO(OEt)₂ Motif

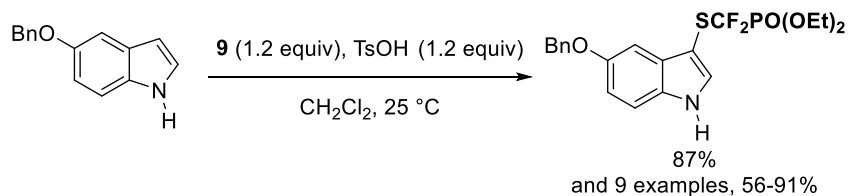
As another interesting motif that allowed modifications of the physicochemical properties of a molecule, the SCF₂PO(OEt)₂ group was underexplored till 2016. Indeed, most of the previous methodologies were restricted to very few examples and/or focused on the synthesis of reagents to introduce the CF₂PO(OEt)₂ group [46], a phosphate bioisoster [47]. Thus, after 2016, new methods for its introduction or construction have been developed to broaden the scope of available SCF₂PO(OEt)₂-containing molecules.

In 2016, Besset and co-workers described the synthesis of the reagent **9**, an electrophilic source of the SCF₂PO(OEt)₂ group, from a simple aniline derivative and TMSCF₂PO(OEt)₂ in 2 steps (Scheme 3.6-29) [48]. This reagent **9** allowed the introduction of this sulfur-containing fluorinated group on various scaffolds. Indeed, **9** was reacted with indoles or electron rich aromatic derivatives in a SEAr type transformation to form the C-SCF₂PO(OEt)₂ bond. In addition, this reagent was efficient for the introduction of this group onto anilines and thiols. Finally, the authors demonstrated the possibility to build up a C-SCF₂PO(OEt)₂ when **9** was reacted with ketones and a β-ketoester.

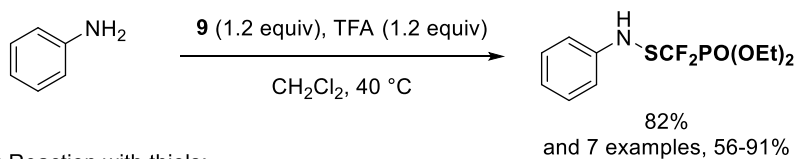
Preparation of **9**:



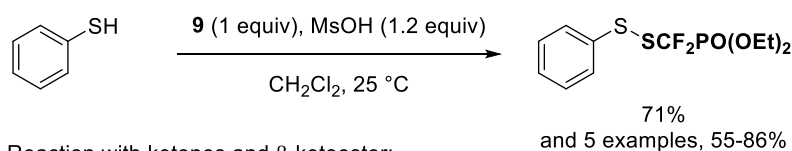
a) Reaction with electron rich arenes (indoles, aryles and pyrrole):



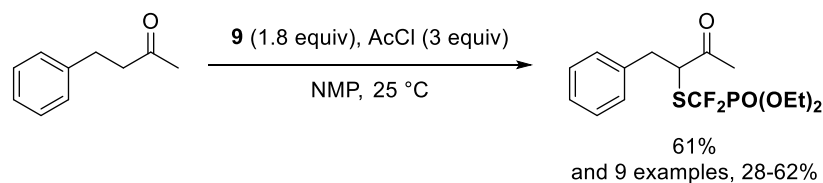
b) Reaction with anilines:



c) Reaction with thiols:



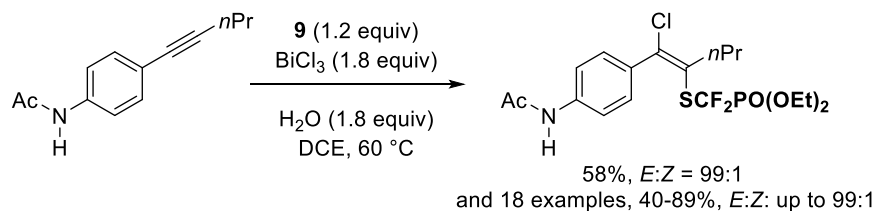
d) Reaction with ketones and β -ketoester:



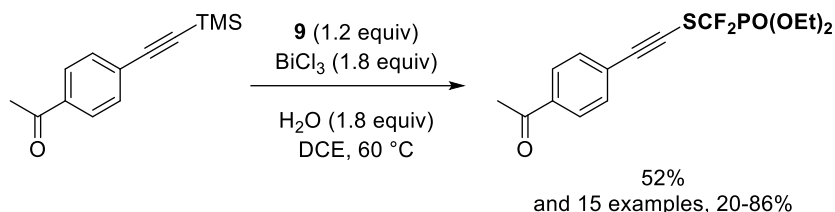
Scheme 3.6-29 Introduction of the $\text{SCF}_2\text{PO}(\text{OEt})_2$ motif using the electrophilic reagent **9**.

Later in 2019, the same group reported the use of this reagent **9** for the BiCl_3 -mediated difunctionalization of alkynes and alkenes, as well as for the synthesis of $\text{SCF}_2\text{PO}(\text{OEt})_2$ -containing alkynes (Scheme 3.6-30) [49]. These transformations afforded the first access to aliphatic and vinylic $\text{SCF}_2\text{PO}(\text{OEt})_2$ -containing molecules and $\text{SCF}_2\text{PO}(\text{OEt})_2$ -containing alkynes.

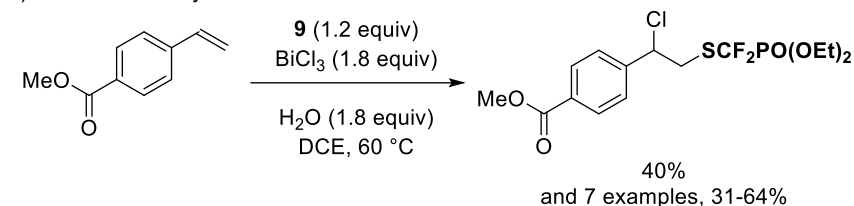
a) Reaction with internal alkynes:



b) Reaction with trimethylsilyl acetylene derivatives:



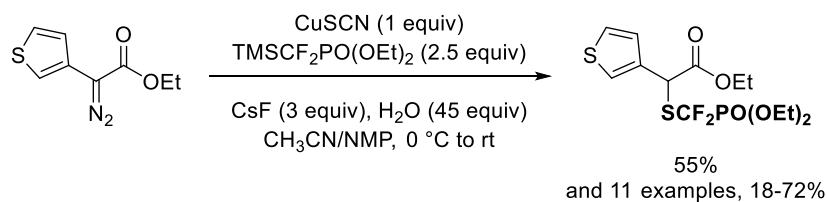
c) Reaction with styrene derivatives:



Scheme 3.6-30 Addition of the $\text{SCF}_2\text{PO}(\text{OEt})_2$ motif onto alkynes and alkenes using **9**.

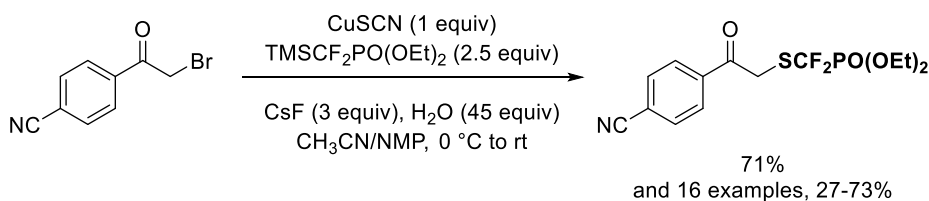
Another complementary strategy to access the $\text{SCF}_2\text{PO}(\text{OEt})_2$ containing molecules relied on the construction of this motif.

In 2016, Poisson and co-workers described the reaction of α -diazocarbonyl derivatives with the $\text{CuCF}_2\text{PO}(\text{OEt})_2$ reagent prepared from CuSCN and $\text{TMSCF}_2\text{PO}(\text{OEt})_2$ (Scheme 3.6-31) [50]. This process allowed the formation of the corresponding α - $\text{SCF}_2\text{PO}(\text{OEt})_2$ arylacetates in moderate to good yields. The reaction was also extended to the α -phenyl diazoketone and α -alkyl diazoacetates, albeit with low yields in the last case.



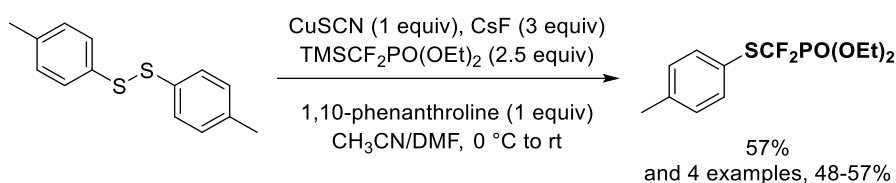
Scheme 3.6-31 Synthesis of α - $\text{SCF}_2\text{PO}(\text{OEt})_2$ esters and ketone from α -diazocarbonyl derivatives.

In 2017, the same authors described the access to α - $\text{SCF}_2\text{PO}(\text{OEt})_2$ ketones starting from α -bromoketones (Scheme 3.6-32) [51]. Although restricted to secondary α -bromoketones, the corresponding products were obtained in good yields and the functional group tolerance was good.



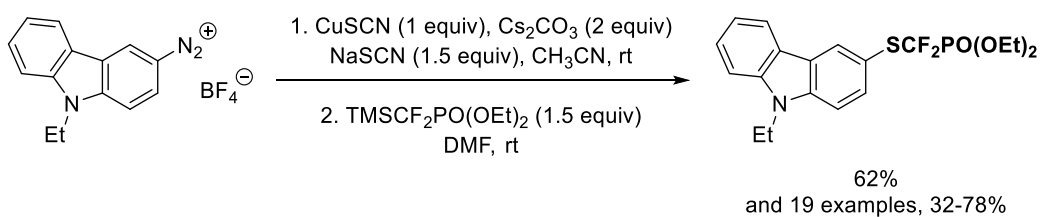
Scheme 3.6-32 Reaction of α -bromoketones with $\text{TMSCF}_2\text{PO}(\text{OEt})_2$ and CuSCN to access α - $\text{SCF}_2\text{PO}(\text{OEt})_2$ ketones.

The same year, these authors reported the construction of arenes substituted with a $\text{SCF}_2\text{PO}(\text{OEt})_2$ moiety starting from bis-aryldisulfides (Scheme 3.6-33) [52]. The reaction with the *in situ* generated $\text{CuCF}_2\text{PO}(\text{OEt})_2$ reagent gave an access to the targeted molecules in moderate to good yields.



Scheme 3.6-33 Reaction of disulfides with the *in situ* generated $\text{CuCF}_2\text{PO}(\text{OEt})_2$.

Finally, in 2019 Goossen and Ou reported the one-pot two-step synthesis of aryl- $\text{SCF}_2\text{PO}(\text{OEt})_2$ derivatives starting from aryl diazonium salts (Scheme 3.6-34) [53]. The *in situ* generation of the aryl thiocyanate followed in a second step by the introduction of the $\text{CF}_2\text{PO}(\text{OEt})_2$ motif on the latter, according to a Langlois type substitution, yielded the corresponding aryl- $\text{SCF}_2\text{PO}(\text{OEt})_2$ derivatives in moderate to good yields.



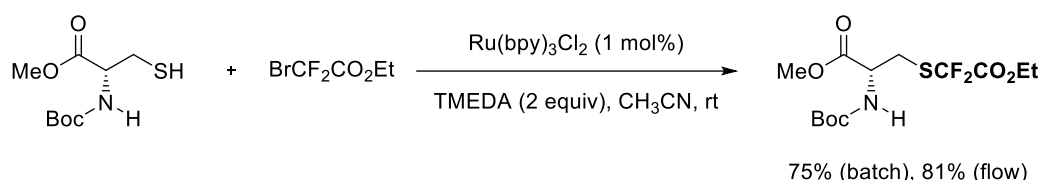
Scheme 3.6-34 Synthesis of $\text{SCF}_2\text{PO}(\text{OEt})_2$ -containing arenes from diazonium salts.

3.6.5 The $\text{SCF}_2\text{CO}_2\text{R}$ group (R = Ar, OR)

The adjunction of a α,α -difluoromethylcarbonyl motif to the sulfur atom offers new fluorinated motifs of particular interest. In addition to offer specific physicochemical properties, it allows easy and various transformations into others functional groups (ketones, alcohols...). Initially, this motifs was usually build up through classical $\text{S}_{\text{RN}}1$ reactions [54],

electro- or chemical oxidation[55] and halox process [56]. From 2016, original and milder reaction manifolds were developed to construct or install this motif onto molecules.

Noël and co-workers reported a photocatalyzed addition of the $\text{CF}_2\text{CO}_2\text{Et}$ radical on a cysteine derivative (Scheme 3.6-35) [57]. The developed process was applied in batch and in continuous flow conditions. The targeted compound was obtained in good yield in batch (75%) and 81% yield under continuous flow conditions (residence time = 5 min). Note that the methodology was extended to the construction of SRf residues (7 examples).



Scheme 3.6-35 Synthesis of $\text{SCF}_2\text{CO}_2\text{Et}$ cysteine analog.

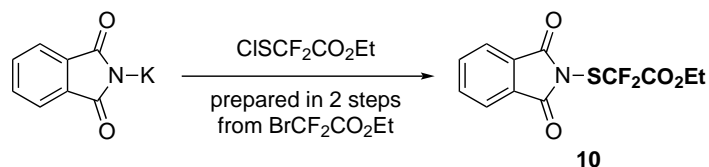
In 2017, Shen and co-workers reported the first electrophilic reagent to introduce the $\text{SCF}_2\text{CO}_2\text{Et}$ motif: the [[(ethoxycarbonyl)difluoromethyl]thio]phthalimide **10** (Scheme 3.6-36) [58]. This reagent, conveniently prepared from phthalimide and $\text{BrCF}_2\text{CO}_2\text{Et}$ or $\text{TMSCF}_2\text{CO}_2\text{Et}$ in a three-step sequence, was reacted with various nucleophiles. Reagent **10** was reacted with indoles, pyrroles, thiophene and electron rich arenes according to a SEAr pathway to build up $\text{SCF}_2\text{CO}_2\text{Et}$ -containing arenes and heteroarenes. In addition, this reagent proved to be reactive with thiol nucleophiles, giving an access to non-symmetrical disulfides. Finally, the formation of the C- $\text{SCF}_2\text{CO}_2\text{Et}$ bond was possible starting from β -ketoesters, 3-aryloxindoles or 3-arylbenzofuranones.

Preparation of reagent **10**:

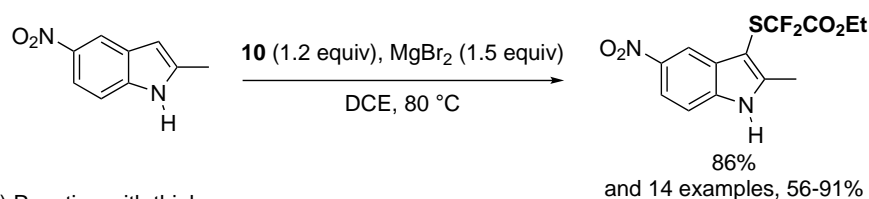
Pathway A:



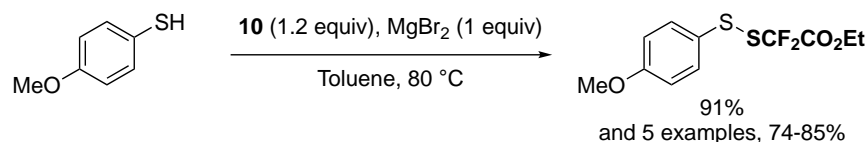
Pathway B:



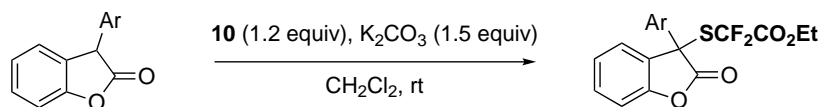
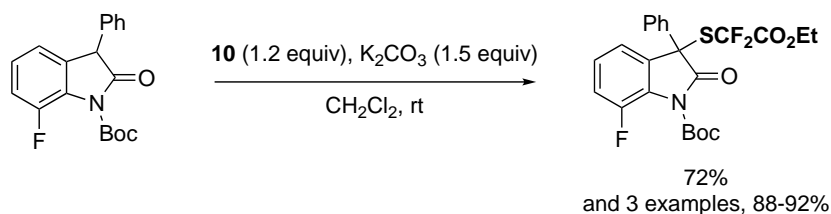
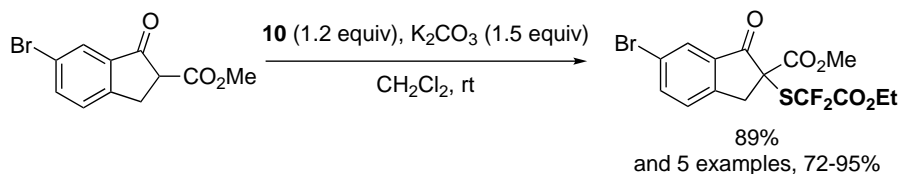
a) Reaction with electron rich arenes and heteroarenes:



b) Reaction with thiols:



c) Reaction with β -ketoesters, oxindoles and benzofuranones:



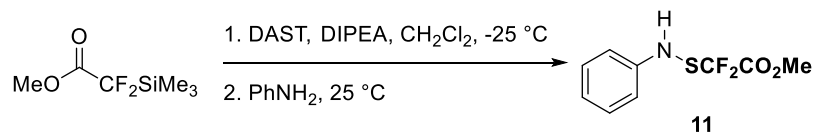
Ar = 4-Cl-C₆H₄, 91%
Ar = 3,4-OCH₂O-C₆H₃, 91%

Scheme 3.6-36 Introduction of the SCF_2CO_2Et group onto electron rich arenes, heteroarenes, thiols, β -ketoesters, oxindoles and benzofuranones using the electrophilic reagent **10**.

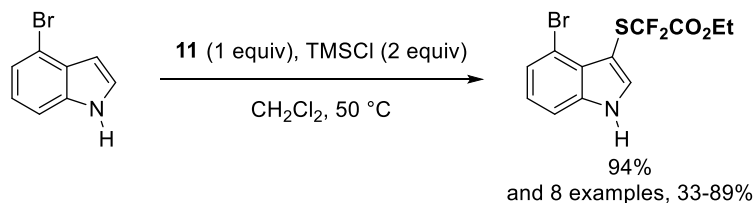
In the same vein, Billard and co-workers reported the synthesis and the application of the (methoxycarbonyl)difluoromethanesulfonamide **11** as a practical reagent to introduce the SCF_2CO_2Me motif (Scheme 3.6-37) [59]. Similarly to the reagent **10**, developed by Shen, this reagent was reacted with electron rich arenes and heteroarenes giving the corresponding

products in high yields. Complementary, this reagent allowed the α -functionalization of ketones, as well as cyclization reactions to access polysubstituted benzofuran, benzothiophene and isochromenone bearing the $\text{SCF}_2\text{CO}_2\text{Me}$ motif, starting from the appropriate alkyne.

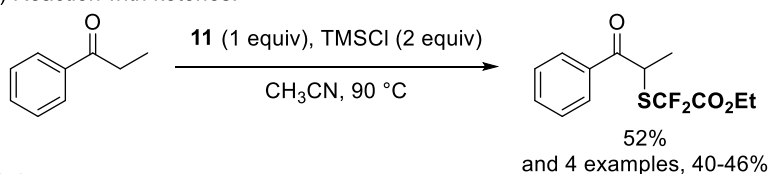
Preparation of reagent **11**:



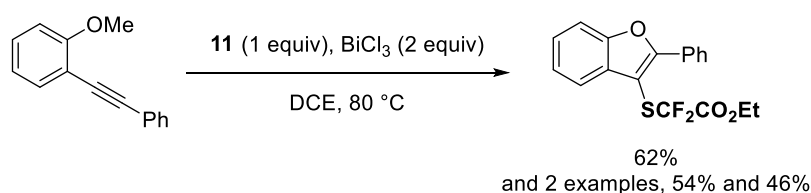
a) Reaction with electron rich arenes and heteroarenes:



b) Reaction with ketones:



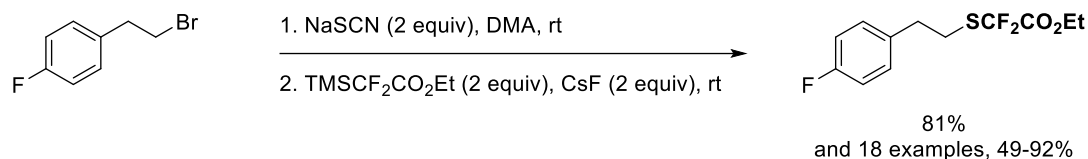
c) Cyclisation reactions:



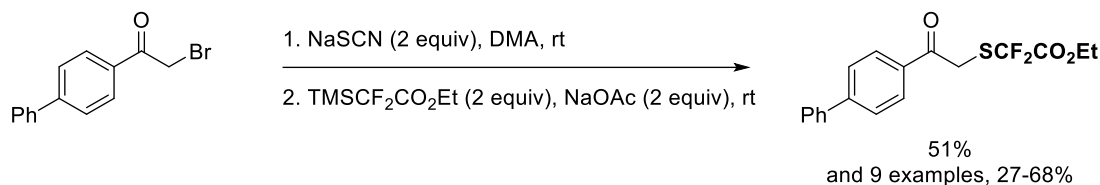
Scheme 3.6-37 Synthesis of $\text{SCF}_2\text{CO}_2\text{Et}$ -containing electron rich (hetero)arenes and ketones.

Later, Zheng and Zhao described the construction of the $\text{SCF}_2\text{CO}_2\text{Et}$ motifs starting from alkyl bromides, α -bromoketones and aryl diazonium salts (Scheme 3.6-38) [60]. This reaction proceeded through the initial formation of the thiocyanate derivatives, followed by a Langlois type substitution using $\text{TMSCF}_2\text{CO}_2\text{Et}$ and CsF as an activator, a concept already described by Goossen [61]. Regarding the reaction with alkyl halides, the reaction proceeded well with benzyl bromides and various alkyl bromides along with a good functional group tolerance. α -Bromo ketones gave the α - $\text{SCF}_2\text{CO}_2\text{Et}$ ketones in low to moderate yields, while aryl diazonium salts gave the aryl- $\text{SCF}_2\text{CO}_2\text{Et}$ derivatives in moderate to excellent yields.

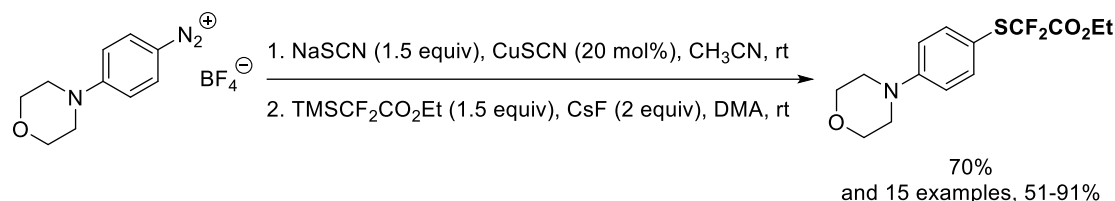
a) Reaction with benzyl bromides and alkyl bromides:



b) Reaction with α -bromoketones:

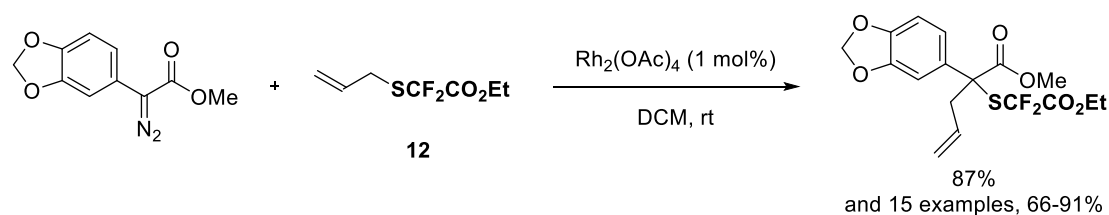


c) Reaction with aryl diazonium salts:



Scheme 3.6-38 Construction of the SCF₂CO₂Et motif on alkyl bromides, benzyl bromides and aryl diazonium salts.

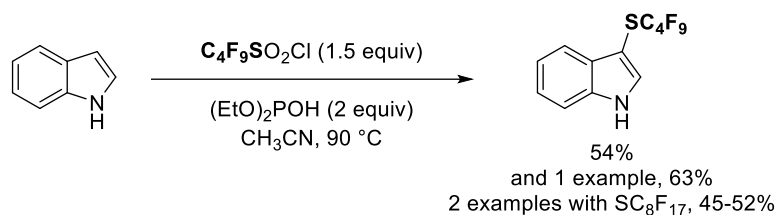
Finally, in 2019, Koenigs and Jana described an elegant Doyle-Kirmse rearrangement using the reagent **12** to access quaternary center bearing the SCF₂CO₂Et motif (Scheme 3.6-39) [62]. Although, the reaction was restricted to α -aryl diazoacetates, the reaction of **12** in the presence of Rh₂(OAc)₄ furnished the desired compounds in good to excellent yields and a large panel of α -aryl diazoacetates was successfully reacted. In addition, the authors demonstrated the possible formation of the product under metal free conditions, using blue light to promote the formation of the carbene involved in the Doyle-Kirmse rearrangement.



Scheme 3.6-39 Doyle-Kirmse rearrangement toward the formation of quaternary carbon centers bearing the SCF₂CO₂Et motif.

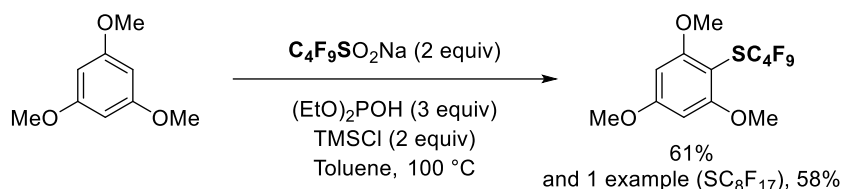
3.6.6 The SCF₂Rf Motif

Since the pioneer work from Goossen, who used Me₄NSC₂F₅ as a SRf source [63] and the design by the group of Billard of an electrophilic source (ArNMeSRf) [64], few reports dealt with the direct introduction of SRf residue. In 2016, using the combination of RfSO₂Cl with (EtO)₂POH, the group of Yi reported few examples of the direct introduction of SC₄F₉ and SC₈F₁₇ residues on indoles derivatives (4 examples) as part of a more general study regarding the fluoroalkylthiolation with fluoroalkylsulfonyl chlorides (Scheme 3.6-40) [23].



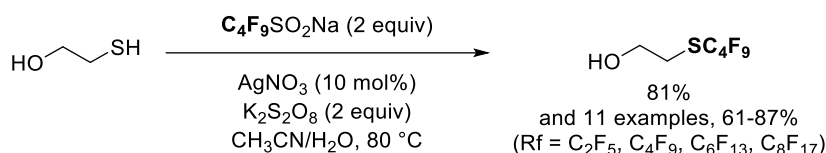
Scheme 3.6-40 Perfluoroalkylthiolation of electron rich arenes with an electrophilic source *in situ* generated from RfSO_2Na

One year later, in the course of their study to generate *in situ* an electrophilic SCF_2H source from $\text{HCF}_2\text{SO}_2\text{Na}$ with $(\text{EtO})_2\text{POH}$ and TMSCl , Yi, Zhang and co-workers extended their methodology to the introduction of other SRf groups ($\text{SRf} = \text{SC}_4\text{F}_9$ and SC_8F_{17}) on 1,3,5-trimethoxybenzene (2 examples, Scheme 3.6-41) [25].



Scheme 3.6-41 Perfluoroalkylthiolation of 1,3,5-trimethoxybenzene with an electrophilic source *in situ* generated from RfSO_2Na

In 2017, the group of Yi developed a methodology to build up a S-Rf bond using the corresponding RfSO_2Na as they depicted a silver catalyzed perfluoroalkylation of thiols [10]. With this approach, a panel of (hetero)aromatic and aliphatic thiols was functionalized. The reaction turned out to be tolerant to several functional groups such as carboxylic acids, free alcohol and halogens (Scheme 3.6-42).



Scheme 3.6-42 Perfluoroalkylthiolation of thiol derivatives with RfSO_2Na .

3.6.7 Conclusions and Perspectives

The last decade, tremendous advances have been witnessed regarding the development of new sulfur-containing fluorinated groups. Indeed, complementary to the SCF_3 motif, the SCF_2H and more recently the SCH_2F , $\text{SCF}_2\text{CO}_2\text{Et}$, $\text{SCF}_2\text{PO}(\text{OEt})_2$, SRf have been implemented to the medicinal chemist toolbox. In this chapter, we summarized the recent progress made in that field. In addition to these pioneer works, we believe that important milestones to introduce or build up these motifs as well as newly designed sulfur-containing fluorinated motifs will appear in the forthcoming years.

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