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Ermal Ismalaj

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New Reagents For Fluoroalkylchalcogenations. Applications To Hot Chemistry

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Abbreviations

Å : Angström
πr : Hansch parameter
χ : Pauling’s scale
Ar : aryl
Ac : acetyl
binap : (2,2'-bis(diphenylphosphino)-1,1'-binaphthyl)
BuLi : butyl lithium
Boc : tert-butoxycarboxyle
bpy : 2,2’-bipyridine
Bu : butyl
Ci : Curie
CN : cyanide
CT : computerized imaging
d : doublet
DABCO : 1,4-Diazabicyclo[2.2.2]octane
DAST : Diethylaminosulfur trifluoride
DIEA : N,N-Diisopropylethylamine
DFMS : zinc difluoromethanesulfinate
DMA : dimethylacetamide
DMF : dimethylformamide
DMSO : dimethylsulfoxide
dppf : 1,1’-Ferrocenediy-l-bis(diphenylphosphine), dppf
dtbp : 4,4’-di-tert-butyl-2,2’bipyridyl
Et : ethyl
FDA : Food and Drug Administration
[18F]FDG : [18F]fluodeoxyglucose
g : gram
h : hour
het : heterocycles
HMPA : hexamethylphosphoramide
HPLC : high-performance liquid chromatography
Hz : hertz
i-Pr : iso-propyl
KHMD : Potassium bis(trimethylsilyl)amide
Abbreviations

LDA : Lithium diisopropylamide
IUPAC : International union of pure and applied chemistry
Liq. : liquid
M : Molarity
m : multiplet
Me : methyl
min : minutes
mL : millilitres
mol : mole
Morph : morpholine
MRI : magnetic resonance imaging
NBS : N-Bromosuccinimide
NSI : N-Iodosuccinimide
NMR : nuclear magnetic resonance
OLED : organic light-emitting diode
OTf : triflate
PDFA : difluoromethylene phosphobetaine
PET : positron emission tomography
Ph : phenyl
Phen : 1,10-phenantroline
pKa : logarithm of the acid dissociation constant
ppm : parts per million
pyr : pyridine
q: quadruplet
RCY: radiochemical yield
r. t : room temperature
SDS : sodium dodecyl sulphate
SPECT : single photon emission computed tomography
s : singlet
SCDA : Sodium chlorodifluoroacetate
S_E,Ar : electrophilic aromatic substitution
S_N,Ar : nucleophilic aromatic substitution
S-Phos : 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl
t : triplet
Abbreviations

T : temperature
TASF : Tris(dimethylamino)sulfonium difluorotrimethylsilicate
TBAT : Tetrabutylammonium difluorotriphenylsilicate
TBHP : tert-butylhydroperoxide
TCCA : Trichloroisocyanuric acid
TDA : 4,4'-Thiodianiline
TDAE : Tetrakis(dimethylamino)ethylene
TDFA : trimethylsilyl 2,2-difluoro-2-fluorosulfonylacetate
THF : Tetrahydrofuran
TfOH : triflic acid
TMG : Tetramethylguanidine
TMS : Trimethylsilyl
US : ultrasound
UV : ultraviolet
General Introduction

Fluorine is the 13th most abundant element of earth’s crust and ranks 24th in universal abundance. Despite its high presence, only a dozen of fluorine-containing natural compounds are known deriving from a few plants and bacteria. Elemental fluorine was first isolated by Henry Moissan (Noble Prize in 1906), and Ferdinand Swarts reported the first synthesis of an organofluorine compound, methyl fluoroacetate.

Since then, the interest towards fluorine increased due to the fascinating intrinsic properties that it owes. The presence of fluorine in organic compounds highly modifies the electronic properties of the molecule, being the most electronegative element (χ = 4 in Pauling’s scale), and on the other hand does not affect too much the steric properties considering its small size (Van Der Waals radii = 1.47 Å). Its presence, also increases the metabolic stability of the molecules considering that the C-F bond is very strong (bond dissociation energy is 105 kJ mol⁻¹).

Nowadays fluorinated compounds find several applications in different fields of chemistry as electro-materials, coatings (Teflon®), textiles (Gore-tex®), agrochemicals and pharmaceuticals. Although the presence fluorinated molecules at the early beginnings was mostly limited to agrochemicals, during recent years the presence of fluorine in pharmaceuticals increased and approximately 20-25 % of pharmaceuticals contain fluorine.

In 1954 Fried and Sabo reported the first introduction of fluorine atom into a pharmaceutical compound (figure 1), fludrocortisone, demonstrating that the presence of fluorine improved the anti-inflammatory activity.

![Fludrocortisone](image)

Figure 1 First fluorinated pharmaceutical to be developed

The presence of fluorine and fluorinated moieties has a key role in determining ADMET (absorption, distribution, metabolism, excretion and toxicity) properties of the small molecules. By increasing the lipophilicity of the molecules they could bring drastic changes exploited in agrochemicals and pharmaceuticals. Furthermore, the high electronegative character of fluorine...
has a strong effect on the acidity or basicity of functional groups adjacent to it, thus modifying the pKa of the molecules, thus the bioavailability of the drugs.\[^6\]

According to the US sales in 2015, four of the first ten most sold drugs contain fluorine or a trifluoromethyl group (figure 2). Fluticasone propionate sold under the name of Advair Diskus is the second most prescribed drug in the US in 2015.

![Figure 2 Structures of fluorine containing market leading pharmaceuticals](image)

In literature is reported that the association of fluorine with a heteroatom increases the Hansch – Leo\[^7\] parameter of the compounds (table 1), thus leading to the expected modulations of these scaffolds.\(^1\)

In recent years, there has been a growing interest in exploring various fluorinated groups, as OCF$_3$ and SCF$_3$ as well as SeCF$_3$. As shown in Table 1 and Table 2, these functional groups have similar electronic properties to CF$_3$, and a higher lipophilic parameter. Often the SCF$_3$ group has been described as an enhanced version of the CF$_3$ especially due to the higher lipophilicity value, and the number of methods to access SCF$_3$ containing compounds has been continuously increasing.

Based on the reported data in literature, we suppose that fluorinated functional groups bound to chalcogens (especially, S and Se) can modulate the physico-chemical properties of the molecules. Despite the fact that compounds containing such moieties still do not find use in therapeutics, the interests towards their use as potential candidates has been growing.

Various trifluoromethylthiolating molecules as the adenosine analogue and the losartan analogue, an antihypertensive drug, are already accessible to medicinal chemists. Toltrazuril, a coccidiostatic drug for veterinary use, contains a SCF$_3$ moiety (Figure 3).\[8\] Also compounds containing a difluoromethylthio group are already known and some of them are defined as biologically active compounds. The benzoxazole derivative reported in Figure 3 has shown to be active against HIV-1 meanwhile its OCF$_2$ analogue showed no activity. Flomofex sodium, a molecule

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containing a SCF$_3$H moiety distinguished for its antibacterial activity showed to be resistant to β-lactamase enzymes (Figure 3).

Although the similitudes between sulfur and selenium, the chemistry of selenium has been less developed. The malodorous smell as well as the unknown toxicity data of selenium compounds limited the advancement of this field towards the development synthetic methodologies. Nevertheless compounds containing selenium gave promising results in several fields. Selenolated derivatives have been tested as sensitizers in photodynamic therapy as well as potential anti-tumor agents. Ebselen, a synthetic organoselenium compound, has shown anti-inflammatory, anti-oxidant was well as cytoprotective activity. It has shown a remarkable activity in the treatment of different pathologies as bipolar disorders as well as hear loss and tinnitus. Moreover Ebselen has shown a good bactericidal activity towards multi-drug resistant clinical isolates of staphylococcus aureus.$^{[9]}$

Figure 3 Biologically active compounds containing chalcogens

Figure 4 Se-containing active molecules
Despite the promising preliminary results obtained by the SCF$_2$R containing compounds or Se containing compounds, accessing to such compounds is far away than trivial. With the recent advances made in the field and the interest of medicinal chemists towards these molecules there is still need for the development of new synthetic methodologies that easily conducts to such scaffolds.

The work reported on this dissertation is based on the synthesis of fluoroalkylchalcogens that acts as ‘SCF$_2$R and ‘SeCF$_2$R donors. All the synthesized reagents were used to perform electrophilic reactions leading to different scaffolds bearing SCF$_2$R as well as SeCF$_2$R.
References:


CHAPTER I

SYNTHESIS OF SCF$_2$R DERIVATIVES AND THEIR APPLICATION IN ELECTROPHILIC REACTIONS
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Chapter I. Synthesis of SCF₂R derivatives and their application in electrophilic reactions

In this chapter, we report the syntheses of two new shelf-stable, functionalized difluoromethanesulfenamides reagents, which were successfully used in reactions as SCF₂R donors. Both reagents showed a good reactivity in electrophilic reactions. Moreover, taking advantage of the good ability of the functional groups to be displaced, post-functionalization reactions were performed leading to newly synthesized compounds.

I. Bibliography SCF₃ and SCF₂R

In the first part of the chapter a detailed bibliographic summary of different synthetic methodologies capable to lead to SCF₃ and SCF₂R containing compounds will be reported. Such methodologies were divided in two classes, direct and indirect SeCF₃ and SeCF₂R bond formation. In both cases the methodologies were reported by classifying them in radical, nucleophilic or electrophilic pathway. The below reported bibliography includes works published prior October 2016.

I.1 Indirect insertion of SCF₃ group:

Herein is reported a short summary of radical, electrophilic and nucleophilic trifluoromethylation of aliphatic and aromatic thiols, thiolates, disulfides based on the use of different sources of CF₃.

I.1.1 Radical trifluoromethylation of thiols, thiolates and disulfides.

Radical trifluoromethylation has been widely applied to different compounds, such as aliphatic and aromatic thiols, thiolates, and disulfides. One of the most used reagents for the syntheses of these compounds is the non-ozone depleting, environmentally-acceptable trifluoroiodomethane, CF₃I.

In the early 70's Haszeldine et al. reported the synthesis of alkyl-trifluoromethylthiolates by irradiation of the reaction media. The reaction proceeds slowly (Scheme 1, eq. a) and in the case of the higher homolog, as diethyl disulfide, the formation of CF₃H is observed. Such phenomenon may depend partly due to a larger number of available H and partly by the fact that diethyl disulfide contains four secondary C-H bonds. [1] Aromatic disulfides were trifluoromethylated in liq. NH₃ (Scheme 1, eq. b). [2] Soloshonok and coll. reported the direct trifluoromethylation of homocystine in liq. NH₃ under ultraviolet irradiation. [3] Yagupolskii and coll. accessed to various p-substituted thiols by replacing liq. NH₃ with a biphasic system in presence of a phase transfer catalyst (Scheme 1 eq. d). [4] Another route to access Ar-SCF₃ adducts is using methylviologen as radical generator. [5] Recently
Shibata and coll., reported the trifluoromethylation of homocystine by adapting the Birch reduction conditions, Na/NH$_3$ liq. in presence of CF$_3$I as trifluoromethylating agent (Scheme 1, eq. c) in order to avoid the inconvieniencies of ultraviolet irradiation.[6]

In situ preformed thiolates in presence of NaH gave Het-SCF$_3$ compounds in good yields (Scheme 1, eq. e). The authors avoided the use of ultra-violet irradiation, leading to simpler synthetic procedures.[7] Recently a ruthenium-based photocatalyst activated by visible light has been used in the trifluoromethylation of thiols, in batch as well as in flow chemistry (Scheme 1, eq. f).[8] Ritter and coll., by using the halogen bonding ability, accessed to an easy-to-handle, liquid and stable CF$_3$I-TMG reagent used in trifluoromethylation of arenes and thiophenols (Scheme 1, eq. g).[9]

Despite its toxicity and its environmentally-known hazards, CF$_3$Br has been used in, trifluoromethylation reactions. Wakselman and coll. accessed to aryl-SCF$_3$ compounds starting from the potassium thiolates in presence of CF$_3$Br.[10] They also reported the trifluoromethylation of aliphatic and aromatic thiols and disulfides, using sodium hydroxymethane sulfinate as a
source of radical SO$_2$•- under pressurized atmosphere (Scheme 1, eq. h).\cite{11} Some years ago in our group has been studied the generation of the trifluoromethyl radical under oxidative conditions, from sodium trifluoromethanesulfinate, which in presence of disulfides gave the excepted compounds (Scheme 1, eq. i).\cite{12} Also trifluorothioacetates and trifluoromethanethiosulfinates have been used in the trifluoromethylation of sulphur-containing compounds (Scheme 1, eq. j).\cite{13} Two different N-trifluoromethyl-N-nitroso sulfenamides have been prepared and used in the trifluoromethylation of thiols and disulfides.\cite{14} Another possibility to access to Ar-SCF$_3$ compounds is the trifluoromethylation of tetrabutylammonium phenylthiolate using Bi(CF$_3$)$_3$, as a source of CF$_3$ radicals in presence of a Cu salt (Scheme 1, eq. l).

I.1.2 Electrophilic trifluoromethylation of thiols and thiolates.

Although electrophilic trifluoromethylation reactions have been widely used for the synthesis of trifluoromethylated adducts, in the case of S-containing compounds still remains limited to a few number of papers.

The first reagent involved in electrophilic trifluoromethylation of thiolates has been developed by Yagupolskii and coll., a diaryl(trifluoromethyl)sulfonium salt used in the trifluoromethylation of S-containing starting materials (Scheme 2, eq. a).\cite{15}

![Scheme 2 Electrophilic trifluoromethylation of thiols, thiolates and disulfides](image)

Later, Umemoto and coll. described the trifluoromethylation of thiolates, among other substrates, using trifluoromethyl dibenzochalcogenophenonium salts. Their efficiency as trifluoromethylating agents depends on the chalcogen itself and the reaction system in which is applied (Scheme 2, eq.
b. Nevertheless, the formation of the product is accompanied by the formation of a considerable amount of disulfide as a by-product.[17]

A huge step forward in these reactions has been made by Togni and coll., by designing the synthesis of a relatively cheap and readily accessible hypervalent iodine(III)-CF₃ reagent. Their methodology does not require the use of a base or thioclates as starting materials. Moreover, the formation of disulfides is avoided. With their work, they showed also the synthetic convenience of this reagent, as well as its high functional group tolerance and solvent independence. Aromatic, heteroaromatic, aliphatic compounds, as well as unprotected or protected esters of cysteine and protected carbohydrates were trifluoromethylated leading to SCF₃ containing compounds (Scheme 2, eq. c).[18]

I.1.3 Nucleophilic trifluoromethylation of thiols, thiolates and disulfides.

Unlike electrophilic reactions, different ways and reagents already exist for nucleophilic trifluoromethylation reactions. The generated CF₃ anion is very unstable and can easily collapse into difluorocarbene and fluoride.[19]

One of the ways to generate CF₃ anion is the use of CF₃Br in presence of zinc and pyridine (Scheme 3, eq. a).[20] Yagupolskii and coll. described the formation of Ar-SCF₃ by using TMSCF₃ as a source of trifluoromethyl anion in presence of TASF, starting from the ArS-Cl derivatives (Scheme 3, eq. b).[21] In our group was performed the trifluoromethylation of thiocyanates and disulfides by using TMSCF₃ as a trifluoromethylating reagent in presence of TBAF. Thus, by using easy-to-handle starting materials in a simple process an improvement in terms of yield was also obtained (Scheme 3, eq. c and n).[22] By adapting the same strategy the synthesis of trifluoromethylthiolated amphiphilic cyclodextrins, important carriers in encapsulation and drug delivery, has been reported.[23]

Since the use of CF₃Br has been restricted by the Montreal protocol due to its ozone-depleting character, its use is becoming limited and expensive. Also TMSCF₃, a well-known trifluoromethylating agent, was obtained by using CF₃Br as a starting material in the early beginnings. More recently, huge efforts has been made to substitute ozone depleting substances, and the use of fluoroform (CF₃H), a large-volume by-product in manufacture and a stable greenhouse gas, seems a breakthrough considering the economical advantage and the easy accessibility.[24] Fluoroform has been used in nucleophilic trifluoromethylation of C-, Si- (leading to the synthesis of TMSCF₃ itself) and S-centers. By deprotonating CF₃H with t-BuOK, the generated CF₃ anion is able to substitute aryl disulfides, aryl sulfonyl chlorides as well as aryl thiosulfonates leading to the formation of Ar-SCF₃ (Scheme 3, eq. d).[25]
As shown in Scheme 3, most of the procedures involve the trifluoromethylation of disulfides, despite the fact that lacks of high yields (substrate dependence). Moreover only one part of the molecule is trifluoromethylated in general, causing the loss of the second part as thiolate. Nevertheless, by adapting this synthetic procedure is easy to access to a wide number of different classes of compounds.
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Also in our group the trifluoromethylating capacity CF₃H has been exploited. Deprotonation with a strong base and subsequent trapping of the CF₃ anion by DMF produces a reservoir-like adduct directly implied in the trifluoromethylation of disulfides[26] (Scheme 3, eq. e). In the case of disulfides the reaction is not DMF-dependent, working also in THF.

Shibata and coll. employed an organo-superbase to form the CF₃ anion which was trapped by the disulfide (Scheme 3, eq. e).[27] Also the thermal decomposition of potassium trifluoroacetate, in presence of disulfides led to the formation Ar-SCF₃ (Scheme 3, eq. f).[28] Trifluoromethyl sulfoxide also has been employed to generate CF₃ anion, after activation with t-BuOK and gave PhSCF₃ with only 26 % yield (Scheme 3, eq. h).[29] In our group has been reported the trifluoromethylation of disulfides, among other substrates, by using two novel reagents, the fluoral hemiaminal derivatives in presence of TBAT[30] (Scheme 3, eq. j), and the trifluoromethanesulfonic acid derivatives in presence of t-BuOK[31] (Scheme 3, eq. k). However, in the case of disulfides, the hemiaminal derivatives are more efficient than the trifluoromethanesulfonic acid derivatives in trifluoromethylation reactions. Recently, Colby and coll. reported the synthesis of an aminidate salt of hexafluoroacetone hydrate as an alternative for the generation of –CF₃ species in situ (Scheme 3, eq. l).[32] Beier and coll. explored the trifluoromethylation of disulfides by using diethyl trifluoromethylphosphonate as reagent in presence of t-BuOK (Scheme 3, eq m).[33] Dolbier and coll. demonstrated that the system CF₃I/TDAE is effective in both nucleophilic and radical trifluoromethylation of disulfides.[34]

I.2 Direct insertion of SCF₃ group

Late-stage trifluoromethylthiolation of organic adducts is an important issue in SCF₃ chemistry. The direct insertion of the motif could circumvent the use of thiols or pre-functionalized thiolates as starting materials, thus permitting to access to a wider range of CF₃S-containing compounds. Recently, the interest for developing such strategies and reagents involved in C-SCF₃ bond formation has been growing.

I.2.1 Radical trifluoromethylthiolation reactions

I.2.1.1 Trifluoromethanethiol and trifluoromethanesulfonyl chloride

The free radical addition of trifluoromethanethiol (CF₃SH) and trifluoromethanesulfonyl chloride (CF₃SOCl) to olefins, described by Harris and coll. resulted in the formation of various alkyl trifluoromethyl sulfides. Using CF₃SH the reaction gave the regioselective compound with 62 % yield. Also minor products have been formed due to radical propagation in lower yields (Scheme 4, eq a). On the other hand, the use of CF₃SOCl (Scheme 4, eq. b) led to a mixture of isomers
where the one formed in eq. (a) is the minor one in this case. The direction of the attack could be attributed to the stability of the intermediate.\[35\]

![Scheme 4 Radical trifluoroethylation of olefins](image)

A few years later the same authors described the preparation of trifluoromethylthiolated alkanes, olefins and acetylenes with a various number of SCF$_3$ substituents.\[36\]

The trifluoromethylthiolation of alkanes has been explored by Harris using CF$_3$SCl under irradiation. As reported in Scheme 5 a mixture of compounds has been obtained. Nevertheless, the trifluoromethylthiolated compound has been obtained as the major product in terms of yield.\[37\]

![Scheme 5 Radical trifluoroethylation of alkanes](image)

In the early 2000’s Munavalli and coll., reported several works describing the radical trifluoromethylthiolation using CF$_3$SCl.\[38\]

![Scheme 6](image)

Unfortunately, the above reported reagents are known to be gaseous and highly toxic, thus the need for designing less toxic synthetic approaches and reagents has been a primary importance in direct trifluoromethylthiolation.

**I.2.1.2 Trifluoromethylthiosilver (I)**

As reported in Scheme 7 the most used reagent in these reactions is trifluoromethylthiosilver (I) Wang and coll. accessed to trifluoromethylthiolated oxindoles starting from activated alkenes in presence of K$_2$S$_2$O$_8$ and HMPA as a base (Scheme 7, eq. a).\[39\] Qing and coll. described the Cu-
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mediated oxidative trifluoromethylthiolation of unactivated terminal alkenes in presence of K₃S₂O₈ and K₃PO₄ (Scheme 7, eq. b).\[^{[40]}\] The same group reported the first Cu-catalyzed direct trifluoromethylthiolation of benzylic Csp³ bonds using t-BuOOBz(3-CF₃) as the oxidant and AgSCF₃ as the SCF₃ active source.\[^{[41]}\] Nevado and coll. reported the synthesis of trifluoromethylthiolated highly functionalized heterocycles, via a chemoselective addition of an in-situ generated radical able to activate double bonds, which triggered a multi-step reaction cascade and led to the desired compounds.\[^{[42]}\]

Scheme 7 Radical trifluoromethylthiolation using AgSCF₃

Wang and coll. disclosed the synthesis of 3-trifluoromethylthiolated coumarins, in presence of AgSCF₃/K₃S₂O₈ in DMSO, by a radical cyclization reaction of aryl alkynoate esters.\[^{[43]}\] Liang and coll. first reported a radical cascade trifluoromethylthiolation/cyclization of 1,6-enynes to synthesize various SCF₃ containing adducts, in presence of K₃S₂O₈/HMPA and a 2,2′:6′,2″-terpyridine ligand, which in association with HMPA seems to coordinate AgSCF₃ in order to reduce the potential redox of the high valent silver species, thus blocking the further oxidative decomposition of substrates and products (Scheme 7, eq d).\[^{[44]}\] Later the same group reported the synthesis of 3-trifluoromethylthiospiro trienones, starting from alkynes, through a radical
oxidative trifluoromethylthiolation/dearomatization process, in presence of a dual system such as K$_2$S$_2$O$_8$/TBHP (Scheme 7, eq. e).

### I.2.1.3 N- and O- trifluoromethylthiolating reagents

Very recently, 2 electrophilic reagents have been implied in radical trifluoromethylthiolation reactions (Scheme 8). Shen and coll. reported a silver-catalyzed decarboxylative trifluoromethylthiolation of secondary and tertiary aliphatic carboxylic acids in an aqueous emulsion, formed by the addition of SDS to water. Although the reaction tolerates various functional groups, decarboxylation of primary as well as aromatic carboxylic acids does not work (Scheme 8, eq. a). Later Glorius and coll. implied a phthalimide reagent for the decarboxylative trifluoromethylthiolation of primary, secondary and tertiary carboxylic acids as well as heteroarenes, activated by visible light in presence of an iridium catalyst. The method demonstrated to be efficient also when the iridium catalyst has been substituted by an oxidizing organic dye (Scheme 8, eq. d).

![Scheme 8 Radical trifluoromethylthiolation using two electrophilic reagents](image)

The same group developed a new, efficient trifluoromethylthiolation method of styrenes; based on the combination of a dual photoredox/halide catalytic system. Moreover, the synthesis of SCF$_3$-oxindoles and cyclic ketones employing a radical-polar crossover process involving ring expansion or cyclization has been reported (Scheme 8, eq. c). The two reagents reported above have been also used in an iron-mediated Markovnikov hydro-trifluoromethylthiolation reaction of unactivated olefins (Scheme 8, eq. b).
I.2.2 Nucleophilic trifluoromethylthiolation reactions

Nucleophilic trifluoromethylthiolation reactions have been widely used in organic chemistry although synthetic problems such as the instability of the SCF$_3$ anion have been reported 50 years ago.\textsuperscript{50} Thus potassium trifluoromethylthiolate forms a right-side-favoured equilibrium leading to the formation of difluorothiophosgene and potassium fluoride (Scheme 9).\textsuperscript{51}

\[
\text{F}_2\text{S}^- + \text{K}^+ \rightleftharpoons \text{S} \text{F}_2 + \text{KF}
\]

Scheme 9 Dissociation of potassium trifluoromethylthiolate into difluorothiophosgene and KF

Herein, the nucleophilic trifluoromethylthiolation of substrates will be reported and the methodologies are ordered based on the use of the various reagents.

I.2.2.1 Difluorothiophosgene

The above reported equilibrium (See Scheme 9) has been successfully implied for the generation of trifluoromethylthiolate anion in situ and applied to the nucleophilic aromatic substitution and also extended to the addition of different fluoride sources to other difluorothiophosgene analogs.

\[
\begin{align*}
\text{MeCN} & \\
\text{Y} & = \text{CH, N} \\
\text{EWG} & \\
\text{X} & = \text{F, Cl, SCF}_3 \\
\text{MF} & \\
\text{SCF}_3 & \\
\text{Y} & = \text{CH, N}
\end{align*}
\]

Scheme 10 Trifluoromethylthiolation reactions based on thiophosgene derivatives

Such strategy finds application only in reactions involving electron-deficient molecules (Scheme 10).\textsuperscript{51}

I.2.2.2 Mercury (II) trifluoromethylthiolate

One of the first ever employed sources of SCF$_3$ anion is the bis(trifluoromethylthio)mercury generated by reacting carbon disulfide (CS$_2$) and mercuric fluoride (HgF$_2$)\textsuperscript{52} or reducing CF$_3$SSCF$_3$ by employing metallic Hg.\textsuperscript{53} Muetterties and coll. reported the synthesis of alkyl and acyl trifluoromethylthiolates starting from the chlorininated derivatives (Scheme 11, eq. b).\textsuperscript{52} Alkyl as well as bis halogenates gave corresponding trifluoromethylthio containing compounds as well (Scheme 11, eq. a).\textsuperscript{56}
Chapter I. Synthesis of SCF₂R derivatives and their application in electrophilic reactions

Scheme 11 Trifluoromethylthiolation reactions using bis(trifluoromethylthio)mercury

1.2.2.3 Trifluoromethylthiosilver (I)

The first synthesis of AgSCF₃ has been reported by Muetterties and coll. reacting aqueous silver nitrate with bis(trifluoromethylthio)mercury.[52] Later on, MacDuffie and coll. synthesized AgSCF₃ from silver fluoride (AgF) and carbon disulfide in autoclave at 140 °C and yielded 70 – 80 %.[54] Since then, it has been used in several nucleophilic reactions with the aim to access CF₃S- containing motifs. It allows to convert propargylic halides,[55] tropylium bromide,[56] α-haloketones,[57] electron-poor benzyl halides,[58] and aromatic halides[59] to the corresponding CF₃S- containing analogs. However, the addition of an inorganic iodide salt seems to be crucial for the reaction in some cases, as it leads to the in-situ formation of active species, such as [Ag(SCF₃)I].[58-59] Sambur and coll. described the synthesis of aryl-SCF₃ compounds starting from aryl diazonium salts.[60]

Scheme 12 AgSCF₃-based trifluoromethylthiolation of arenes

In the recent years, with the breakthrough of organometallics into fluorine chemistry, several methodologies able to form aryl-SCF₃ compounds have been reported (Scheme 12). Buchwald and coll. described the Pd-catalyzed synthesis of Ar-SCF₃ compounds, in presence of a bulky phosphine ligand and an iodide salt that generates an anionic “ate” complex, starting from the
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Br-derivatives. The mild reaction conditions tolerated a wide range of functional groups and the methodology has been successfully extended to heterocyclic moieties (Scheme 12, eq. a).[^61] Cu-catalyzed trifluoromethylthiolation of aryl halides in presence of a directing group does not require the use of iodine-containing additives to access Ar-SCF₃ compounds. A wide range of coordinating groups have been employed and demonstrated to be efficient. In the case of strong directing groups such as pyridine the reaction gave satisfying results even at room temperature (Scheme 12, eq. b).[^62]

Cu-catalyzed trifluoromethylthiolation has been reported in absence of a ligand[^63] as well as in presence of S-Phos[^64] as a ligand starting from aryliodonium salts (Scheme 12, eq. c). After a detailed mechanistic study Anbarasan *and coll.* concluded that the in-situ trifluoromethylthiocopper formed complex is responsible for the trifluoromethylthiolation of di(hetero)aryl-λ³-iodines. Nevertheless, in the presence of a coordinating counterion such as TfO⁻, the presence of the silver is crucial for promoting the oxidative addition of the iodonium salts onto the S-PhosCuSCF₃ complex. On the other hand, the presence of a non-coordinating counterion such as SbF₆⁻, increases the electron deficiency of the iodonium center, thus promoting the oxidative addition step without the need of the silver salt. Huang *and coll.* reported a palladium-catalyzed ortho-selective trifluoromethylthiolation of arenes (Scheme 12, eq. d). Several functional groups were tolerated and different directing groups showed a good efficiency in directing the C-H activation. Selectfluor was found to be the best F⁺ source for the formation of Ar-Pd(IV)-F intermediate, which might be involved in the CF₃S-F ligand exchange leading to Ar-SCF₃ compounds. The use of acetic acid seems to be crucial to suppress the oxidative dimerization of the starting material.[^65]

Recently Qing *and coll.* reported the trifluoromethylthiolation of primary and secondary aliphatic alcohols passing through a carbonofluoridothioate intermediate, generated in situ by the reaction of the alcohol and the difluorothiophosgene (Scheme 13). During this reaction formation of alkyl fluorides is also observed. Nevertheless, such drawback has been fine-tuned by changing the amount of equivalents of AgSCF₃ and nBu₄NI, leading to the formation of the desired compound.[^66]
Contrary to known methods that require aromatic precursors, Lee and coll. reported the synthesis of aryl-SCF₃ compounds starting from non-aromatic building blocks such as triynes, which underwent a thermal hexadehydro-Diels-Alder reaction leading to the silver-coordinated aryne. The formed intermediate was trapped by a nucleophile such as $\tilde{\text{SCF}}_3$ to form the final compound (Scheme 14, eq. a). Both ring formation and subsequent trifluoromethylthiolation of the intermediate occur in a single step and in most of the cases the reaction presents an excellent regioselectivity. 2-Alkynylbenzaldoximes have been activated in presence of p-methoxybenzenesulfonyl chloride and AgOTf as a catalyst, trifluoromethylthiolated by using AgSCF₃ as a source, to access CF₃S-containing isoquinolines. Also a thiophene-containing substrate led to the formation of the desired compound in good yield (Scheme 14, eq. b).
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1.2.2.4 Trifluoromethylthiocopper (I)

The first Cu-based nucleophilic reagent involved in trifluoromethylthiolations was CuSCF₃. Several procedures concerning its preparation have been already reported involving the reaction between Hg(SCF₃)₂ with Cu powder in autoclave, or in dimethylformamide solution. It has been also prepared by reacting AgSCF₃ with CuBr, CuCl, or bis(trifluoromethyl) disulfide with Cu powder.

Aryl-SCF₃ compounds were obtained starting from iodo-derivatives whether isolating CuSCF₃, or preparing it in situ following by addition of the starting materials to the reaction media. It has been demonstrated the compatibility of such reaction in presence of carboxylic and ester functionalities. The reaction worked well also in the presence of adjacent fluoride atoms. Metzler-Nolte and coll. described the synthesis of trifluoromethylthioferrocene, through an in situ formation of the copper salt, using the Br-analog as a starting material. Clark and coll. reported the synthesis and the use of an Alumina-supported CuSCF₃ reagent. Contrary to the unsupported copper salt, this reagent was found to decompose with time, and therefore should be used immediately after preparation. On the other hand, the reagent was found to undergo reactions with iodoaromatics and activated bromoaromatics leading to higher isolated yields than the previous methodologies (Scheme 15, eq. a, for all above-reported reactions).

The synthesis of CF₃S-containing aromatic compounds has been achieved also using diazonium salts as starting materials (Scheme 15, eq. b). Despite drawbacks such as explosive-related as well as the restriction to electron-poor moieties, the reaction involving diazonium salts gave high-yielded reactions and the final compounds were obtained after a simple work-up procedure. Rueping and coll. reported the synthesis of different alkyl and aryl di-, tri- and tetra-substituted vinyl trifluoromethyl thioethers, starting from the corresponding vinyl iodides, with high yields.
The reaction showed also full stereochemical retention (Scheme 15, eq.). The same group described the synthesis of aryl and allylic trifluoromethylthioethers starting from the corresponding alcohols, using CuSCF₃ and BF₃·Et₂O as a Lewis acid.

The group of Weng has extensively studied copper trifluoromethylthiolate complexes in trifluoromethylthiolation reactions. They reported the synthesis of different copper trifluoromethylthiolate complexes. By reacting CuF₂ with TMSCF₃ and S₈ in presence of diimine ligands or a phosphine ligand, they accessed to monomeric or dimeric N-coordinated CuSCF₃ complexes and monomeric bis(PPh₃)-CuSCF₃ chelating complexes.

Aryl and heteroaryl, alkyl, allyl and benzyl CF₃S-containing substrates have been prepared starting from their corresponding halide analogs (Scheme 16, eq. a). Allylic trifluoromethylthioethers have been prepared also by using the phosphine complex as an anionic donor. Different complexes capable to chelate copper were prepared, thus enhancing the stability even in presence of air, differently from the unchelated copper trifluoromethylthiolate previously used. The use of such N-containing ligands improved the trifluoromethylthiolation of aryl and heteroaryl moieties especially, increasing the yields in comparison to previous methods.

The best ligand seems to be bipyridine, probably due to its preference to maintain the monomeric form, more active towards cross-coupling reactions as observed by the authors.

Scheme 16 bpy-CuSCF₃ mediated trifluoromethylthiolation

The same group reported also the synthesis of vinyl-SCF₃, α- and β-trifluoromethylthio-α,β-unsaturated carbonyl compounds (Scheme 16, eq. b and d), and α-trifluoromethylthio substituted ketones starting from their halide analogs. The reaction seems to go through an oxidative addition/reductive elimination mechanism in most of the cases.

AgSCF₃ reacted with CuCl to prepare in situ CuSCF₃, which is the active donor species of SCF₃ anion. Different (hetero)aryl diazo compounds have been trifluoromethylthiolated (Scheme 17,
eq. b and c).\[71\] (bpy)CuSCF$_3$ showed less efficacy in trifluoromethylthiolating diazo compounds yielding only 13 % of the desired compound (Scheme 17, eq. a).\[71\] Wang and coll. described the trifluoromethylthiolation of diazo compounds after an in situ formation of CuSCF$_3$ reacting AgSCF$_3$ and CuI (Scheme 17, eq. c).\[87\] Rueping and coll. reported the synthesis of α-SCF$_3$ substituted esters starting from the diazo compounds using CuSCF$_3$. N-trifluoromethylthiophtalimide was used, in absence of H$_2$O, for the insertion of a second SCF$_3$ motif in α position (Scheme 17, eq. d).\[88\]

Scheme 17 Trifluorothiomethylation of α-diazo compounds

1.2.2.5 **Trifluoromethylthio ammonium/cesium**

As shown above, the association of SCF$_3$ with a metal stabilizes the anion making possible its involvement in nucleophilic trifluoromethylthiolation reactions. Ag (I), Cu (I) and Hg (II) –SCF$_3$ found a wide use in nucleophilic trifluoromethylthiolations, as shown above. Several other MSCF$_3$ derivatives (where M = K, Cs, NMe$_4$, TDAE)\[89\] have been reported to literature. Difficult synthetic steps and employment of highly toxic materials are required and most of these complexes are reported as unstable at ambient temperature. The in situ formation of such complexes has been exploited to access aryl-SCF$_3$ moieties from aryl halogens.\[51\] A stable (SCF$_3$)$_2$TDAE complex has been synthesized and characterized, with a yield of 98 %, starting from (SCF$_3$)$_2$ and TDAE, and has been used as a SCF$_3$ source in nucleophilic trifluoromethylthiolation of aryl halogenated compounds. (NMe$_4$)SCF$_3$ and CsSCF$_3$ have been used in nucleophilic substitution reactions over a few allylic, benzylic and (hetero)aromatic substrates.\[90\] (NMe$_4$)SCF$_3$ has been used also in the synthesis of S-trifluoromethyl esters of the
corresponding carboxylic acids in a halogen substitution reaction. The same complexes have been used in inorganic and organometallic chemistry for the synthesis of Hg(SCF₃)₂, CuSCF₃, and AgSCF₃, which have also been quantitatively prepared (Scheme 18).

(NMe₄)SCF₃ has been described as thermally unstable at high temperatures, and later its thermal stability has been related to the preparation procedures. Vicic and coll. found that (NMe₄)SCF₃ is thermally stable in THF up to 60 °C. They described the synthesis of aryl-SCF₃ compounds starting from the iodo- and bromo- derivatives in mild conditions, using a Ni/bpy catalytic system. Chloro derivatives showed to be unreactive toward Ni-catalyzed system in such conditions (Scheme 19, eq. a).

Schoenebeck and coll. explored the importance of the ligands chelating Ni and showed that the use of a Ni/wide-bite-angle phosphine ligand (xantphos, dppf or binap) system allowed the synthesis of aryl-SCF₃ starting from the chloro derivatives (Scheme 19, eq. a). Although small bite-angle ligands render the metal center more nucleophilic, wide bite-angle ligands contribute
on lowering the energy barriers during the transition states, making the oxidative addition step easier. Moreover, addition of CH₃CN led to the in situ formation of a more reactive version of catalyst that undergoes easily oxidative addition easily. Meanwhile, the same group reported the trifluoromethylthiolation of different aryl bromo and iodo derivatives in a cross-coupling reaction, by using a S-bridged dinuclear Pd(I) catalyst (Scheme 19, eq. a). Vicic and coll. reported the Cu-mediated cross-coupling reaction under air, between (NMe₄)SCF₃ and aryl/vinyl boronics, in presence of dtbpy as a ligand and Cs₂CO₃ as a base. (Scheme 19, b) Goossen and coll. reported the trifluoromethylthiolation of diazonium salts in a Cu-mediated Sandmeyer-type reaction (Scheme 19, eq. c). Also vinyl iodides have been successfully trifluoromethylthiolated in presence of catalytic amounts of CuI (Scheme 19, eq. d). You and coll. extended the use of (NMe₄)SCF₃ and CsSCF₃ by developing an efficient Ru-catalyzed, regioselective trifluoromethylthiolation reaction involving allelic carbonates as starting materials (Scheme 19, eq. e). Their mechanistic studies revealed that the reaction proceeded through a double allelic trifluoromethylthiolation reaction leading only to linear allylic compounds.

1.2.2.6 S₈ and CF₃ anion

Another way to access trifluoromethylthiolated compounds is the in situ formation of C-S-CF₃ bonds using elemental sulfur, and a source of trifluoromethyl anion. Duan and coll. reported the first example using sulfur (S₈), fluorosulfonyldifluoroacetate (FSO₂CF₂CO₂Me) as a generator of difluorocarbene and F⁻, which in presence of a source of copper forms CuSCF₃ in situ, a well-known trifluoromethylthiolating agent. They transformed aryl- and alkyl- halides into CF₃S-bearing compounds. From a cost effectiveness point of view, the best way to access trifluoromethylthiolated molecules could be the use of the Ruppert-Prakash reagent (TMSCF₃) and S₈ in presence of copper salts. Qing and coll. fine-tuned a synthetic strategy to access aryl-SCF₃ compounds starting from boronic acids, by mixing TMSCF₃, S₈ and CuSCN, under mild reaction conditions (Scheme 20, eq. a). The proposed reaction mechanisms report the in-situ formation of a thiolate firstly, followed by a subsequent trifluoromethylation to give aryl-SCF₃ compounds. Such evidence has been proven by GC/MS data observing the presence of the thiolate. The same group studied the metal-free oxidative trifluoromethylthiolation of terminal alkynes, in DMF. They found evidence that the SCF₃ anionic species might be involved in the reaction pathway and DMF acts as a reservoir for the S²⁻ species generated in situ (Scheme 20, eq. b). Copper-mediated trifluoromethylthiolation of allylic halides, by using TMSCF₃, S₈ and KF, has been achieved (Scheme 20, eq. c). Mechanistic studies report the formation of a bis(trifluoromethylthio)-Cu(SCN)
complex which involves a Cu$^{1-III}$ cycle, with oxidative addition and successive reductive elimination leading to the generation of CuSCN and the desired compound.$^{[101]}$

Weng and coll. reported a catalytic copper-mediated trifluoromethylthiolation of allylic halogens in presence of catalytic amounts of phenantroline, in dioxane (Scheme 20, eq. c). Trifluoromethylthiolation of propargylic chlorides has been reported successfully reported. Their mechanistic studies are consistent with the $C^{1-III}$ catalytic cycle, thus oxidative addition of the allyl halide to form a Cu$^{III}$ complex and reductive elimination that leads to the formation of the allylic-SCF$_3$ and generation of a the BrCu-complex (Scheme 20, eq. c and d).$^{[102]}$ The same group reported the trifluoromethylthiolation of $\alpha$-bromo ketones reacting S$_8$, TMSCF$_3$ and KF in presence of catalytic amounts of Cu and ligand (Scheme 20, eq. e). They concluded that a radical CF$_3$ species might be involved in the reaction, due to the formation of TEMPO-CF$_3$ when the radical scavenger was added to the reaction media.$^{[103]}$ $\alpha$-trifluoromethylthio ketones have been obtained in absence of a ligand to chelate the copper salt (Scheme 20, eq. e).$^{[104]}$ Also the trifluoromethylthiolation of Morita-Baylis-Hillman carbonates has been achieved leading to primary allylic-SCF$_3$ compounds (Scheme 20, eq. f).$^{[105]}$

1.2.2.7 O-Octadecyl-S-trifluorothiolcarbonate

O-Octadecyl-S-trifluorothiolcarbonate has been prepared and used as a donor of SCF$_3$ anion by Zard and coll. They reported the trifluoromethylthiolation of gramine and $\alpha$-bromoketones in presence of KF and pyrrolidine to access high-yielded trifluoromethylthiolated compounds (Scheme 21, eq. a).$^{[106]}$ The trifluoromethylthiolation of Morita-Baylis-Hillman carbonates to lead
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to primary SCF₃ allylic products has been obtained in good yields, in presence of catalytic quantities of DABCO (Scheme 21, eq. c).[105]

Scheme 21 Trifluoromethylthiolation using Zard’s reagent

I.2.2.8 Trifluoromethanesulfenamides used in nucleophilic reaction

In the late 2000’s trifluoromethanesulfenamides has been synthesized in our labs. Since then they found a wide use in electrophilic trifluoromethylthiolation reactions developed by both our group and others (For more details see Trifluoromethanesulfenamides). Recently, trifluoromethanesulfenamides has been involved also in nucleophilic trifluoromethylthiolations in presence of n-BuNI, through a change in polarization of SCF₃ group induced by iodine after the formation of CF₃SI. Aliphatic alcohols as well as halogen, mesyl and tosyl derivatives have been trifluoromethylthiolated using these conditions.[107]

Scheme 22 Trifluoromethanesulfenamides used as trifluoromethylthiolating reagents
I.2.3 Electrophilic trifluoromethylthiolation reactions

Synthetic methodologies for the development of electrophilic trifluoromethylthiolation reactions has been growing in number these last years due to the synthesis of several reagents that act as $^+$SCF$_3$ donors to circumvent the use of CF$_3$SCl, a highly volatile and toxic gas.

I.2.3.1 Trifluoromethanesulfenyl chloride and bis-trifluoromethyl disulfide

The first reagent used in electrophilic trifluoromethylthiolation is CF$_3$SCl, despite its volatility and toxicity. Nevertheless, CF$_3$SCl showed good reactivity in trifluoromethylthiolating various molecules. Electrophilic addition to olefins$^{[108]}$ and aromatic electrophilic substitution to arenes$^{[109]}$ and heteroarenes$^{[109b, 110]}$ were successfully obtained. It showed good reactivity also towards Grignard reagents,$^{[110a, 111]}$ enolates$^{[112]}$ and enamines$^{[113]}$ (Scheme 23, eq. a – d). Recently, Glorius and coll. formed in situ CF$_3$SCl, starting from Munavalli reagent and catalytic amounts of Lewis base. They reported the trifluoromethylthiolation of N-heteroarenes without the need of a transition metal (Scheme 23, eq. e).$^{[114]}$

\[
\begin{align*}
\text{CF}_3\text{SCl} & \quad \text{CF}_3\text{CO}_2\text{H} \quad 6 \text{ mol \%} \\
& \quad \text{NaCl} \\
& \quad \text{R} - \text{SCF}_3 \quad 8 - 54 \% \\
& \quad \text{R} - \text{SCF}_3 \\
& \quad \text{RMgXR} \quad \text{41 - 68 \%} \\
& \quad \text{R} - \text{SCF}_3 \\
\end{align*}
\]

Another trifluoromethylthiolating reagent is the CF$_3$SSCF$_3$. Despite its toxicity and volatility, CF$_3$SSCF$_3$ has been used in trifluoromethylthiolations. Daugulis and coll. reported the Cu-mediated trifluoromethylthiolation of $\beta$-sp$^2$ C-H bond of benzoic acid derivatives in presence of a directing group (Scheme 24, eq. a).$^{[115]}$ Zhang and coll. described the in situ preparation of CF$_3$SSCF$_3$ from the stable sodium sulfinate (CF$_3$SO$_2$Na) and the trifluoromethylthiolation of $\beta$-Csp$^3$ bonds in indoles (Scheme 24, eq. b).$^{[116]}$
1.2.3.2 Trifluoromethanesulfenamides

Trifluoromethanesulfenamide reagents have been developed in our laboratory as powerful tools in direct electrophilic trifluoromethylthiolations. In 2008 was reported the synthesis of trifluoromethanesulfenamide reagents as potential interesting compounds for use in medicinal or agrochemistry. The reaction between DAST and Ruppert-Prakash reagent in presence of a tertiary amine needed to activate DAST, and followed by the addition of a primary amine led to trifluoromethanesulfenamides (Scheme 25).[117] However, in the early beginnings those compounds were prepared as potential biologically active compounds.

Surprisingly, was found that trifluoromethanesulfenamides could behave as SCF₃ donors. The reaction between alkenes/alkynes and trifluoromethanesulfenamides in presence of Lewis or Bronsted acid gave the expected SCF₃-containing compounds (Scheme 26, eq. g).[118] Both first and second generation of sulfenamides reacted with double bonds.[119] Acidic actitavation-mediated trifluoromethylthiolation of (hetero)aromatic compounds has been reported by our group and others as well.[119-120] Organometallic species underwent trifluoromethylthiolation in presence of a base or in base-free conditions. Aromatic, heteroaromatic compounds as well as terminal alkynes,[119, 120c, 121] reacted well in presence of catalytic amounts of base and acid[122] as
well (Scheme 26, eq. a-d and o). Also primary and secondary amines were trifluoromethylthiolated in basic conditions (Scheme 26, eq. e).[123]

Electrophilic trifluoromethylthiolation of thiols through acidic activation has been reported by Jereb et al (Scheme 26, eq. f).[124] Qing and coll. reported the transformation of allyl silanes into secondary allyl trifluoromethylthiolated adducts (Scheme 26, eq. h).[125] A sequential and selective trifluoromethylthiolation-cyclization of tryptamines led to pyrrolidinoindolinic alkaloid motifs, and their cytotoxic activity was tested against three cell lines (Scheme 26, eq. i).[126] Diverse alkynyl or propargylic derivatives underwent trifluoromethylthiolation and subsequent cyclization leading to trifluoromethylthio- dihydrofurans,[127] benzofurans and benzothiophenes,[128] indoles,[129]...
isocoumarin derivatives\textsuperscript{130} benzofulvenes,\textsuperscript{131} and benzothiazine dioxides \textsuperscript{132} (Scheme 26, eq. j). In most of the cases the presence of BiCl\textsubscript{3} seems to be crucial for the reaction. Electrophilic trifluoromethylthiolation of $\alpha$-ketones and aldehydes has been described with both stoichiometric\textsuperscript{133} and catalytic\textsuperscript{134} amounts of acid (Scheme 26, eq. k). Cu-catalyzed cross-coupling of boronic acids led to the formation of CF\textsubscript{3}S-containing moieties (Scheme 26, eq. l).\textsuperscript{135} A selective palladium-catalyzed C(sp\textsuperscript{3})-SCF\textsubscript{3} bond formation, in presence of a directing group, in $\beta$ position respect to the carbonyl has been described (Scheme 26, eq. m).\textsuperscript{136} Liu and coll. reported Pd(II)-catalyzed C-H activation trifluoromethylthiolation of arenes by using pyridines as directing groups.\textsuperscript{137} Recently it was reported the catalytic Cu-mediated trifluoromethylthiolation of alkynes, in presence of 1,10-phenanthroline as a ligand to access alkynyl trifluoromethylthiolated compounds. By changing the amounts of Cu and using 2,2'-bipyridine they obtained the bis(trifluoromethylthiolated) alkene compounds (Scheme 26, eq. p).\textsuperscript{138} Considering the importance of the reagent and the wide use of the reagent, their synthesis has been optimized and scaled-up without any decrease in yield efficiency.\textsuperscript{139}
I.2.3.3 N-Trifluoromethylthiophthalimide and N-trifluoromethylthiosuccinimide

The first synthesis of N-trifluoromethylthiophthalimide has been described by Munavalli and coll. in 2000, reacting the phthalimide salt with CF₃SCl (Scheme 27, eq. a). Despite the synthesis of the reagent they reported only an example of trifluoromethylthiolation of a carbonyl compound in α position, starting from enamines.[140]

![Scheme 27 N-trifluoromethylthiophthalimide; Synthesis and reactivity](image)

Considering the high toxicity and the corrosive character of the CF₃SCl, two other methods for the preparation of N-trifluoromethylthiophthalimide has been reported. The use of Cu[141] and Ag[142] trifluoromethylthiolate as less-toxic source of SCF₃ led to the formation of the expected compound (Scheme 27, eq. a). Since then, the reagent found a wide use as SCF₃ source. Rueping and coll. accessed to highly enantiopure β-trifluoromethylthiolated ketoesters employing quinidine as a catalyst (Scheme 27, eq. b).[143] Catalytic Cu-mediated trifluoromethylthiolation of aryl and vinyl boronic acids as well as terminal alkynes gave the expected compounds (Scheme 27, eq. c-d).[141-142] Enantioselective cinchona alkaloid-catalyzed trifluoromethylthiolation of relevant moieties such as oxindoles has been reported. The authors established by X-ray crystal structure analysis that the (S) configuration has been obtained, as expected (Scheme 27, eq. g).[144] N-SCF₃ bond formation starting from primary and secondary amines, as well as S-SCF₃ bond formation that led to aliphatic and aromatic disulfides has been reported (Scheme 27, eq. e and f).[145]

Another trifluoromethylthiolating reagent is N-trifluoromethylthiosuccinimide, prepared for the first time in 1996, reacting silver succinimide with CF₃SCl.[146] Nevertheless, its first use in
electrophilic trifluoromethylthiolation reactions dates 2014. The synthesis has been later improved in order to avoid the use of CF₃SCl (Scheme 28, eq. a). Shen and coll. described a C-H bond trifluoromethylthiolation catalyzed by palladium and proposed a mechanism, which follows a Pd³⁺ or Pd⁴⁺ complex formation pathway (Scheme 28, eq. b).

Zhou and coll. reported the synthesis of trifluoromethylthiolated dithioketals in presence of catalytic amounts of dihydroquinine (Scheme 28, eq. c). N-trifluoromethylsuccinimide has been also prepared in situ and used as a trifluoromethylthiolating agent in presence of silver (Scheme 28, eq. d).
I.2.3.4 Trifluoromethylsulfenate reagents

Among the various reagents reported by Shen’s group, trifluoromethylsulfenates occupy an important position as electrophilic SCF$_3$ donors. The reagent has been obtained by reacting the chlorobenziodoxole with trifluoromethylthiosilver (Scheme 29, eq. a).\cite{150} The first reported structural formula describing the formation of an iodine-sulfur bond has been corrected latter. Buchwald and coll. reported evidences of the formation of a stable open thioperoxide based on spectroscopic and crystallographic studies (Scheme 29, eq. b).\cite{151}

Trifluoromethylsulfenates has been already used in different reactions as electrophilic trifluoromethylthiolating sources. β-ketoesters underwent trifluoromethylthiolation giving the corresponding α-trifluoromethylthiolated compounds (Scheme 30, eq. a).\cite{150,152} Cu-catalyzed trifluoromethylthiolation of alkyl as well as (hetero)arylboronic acids and alkynes led to the corresponding trifluoromethylthiolated products (Scheme 30, eq. b and c).\cite{150,152-153} The same group reported the acid-catalyzed synthesis of trifluoromethylthiolated indoles (Scheme 30, eq. d).\cite{152,154} Trifluoromethylthiolated arenes have been obtained also by starting from Grignard reagents (Scheme 30, eq. e).\cite{152} Racemic\cite{152} and enantioselective\cite{155} β-trifluoromethylthiolation of oxindoles has been obtained in the presence of DMAP or a chincona alcaloid (Scheme 30, eq. f and g). The same group reported the base-catalyzed enantioselective trifluoromethylthiolation of β-ketoesters (Scheme 30, eq h).\cite{156} Even when the base has been substituted by an enantioselective copper-boxmi complex the method led to the formation of highly entantioselective final compounds (Scheme 30, eq. h).\cite{157} Dai and coll. described the synthesis of β-SCF$_3$ carbonyl compounds after Cu-mediated ring opening of propanols (Scheme 30, eq. i). A Cu$^{II}$ or a Cu$^{III}$ mechanism for the ring opening and coupling has been proposed by the authors.\cite{158}
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Another reagent developed by Shen’s group is the N-trifluoromethylthiosaccarin, obtained reacting N-chlorosaccarin and AgSCF₃\(^{[159]}\). Different functional groups such as alcohols, thiols and amines underwent trifluoromethylthiolation in presence of N-trifluoromethylthiosaccarin (Scheme 31, eq. g). Also trifluoromethylthiolation of alkynes has been obtained in the presence of a copper salt (Scheme 31, eq. f). CF₃S-containing β-ketoesters, α-ketones and aldehydes has also been obtained starting from the corresponding starting materials (Scheme 31, eq. e).\(^{[159]}\) Trifluoromethylthiolation of electron-rich (hetero) arenes in presence of catalytic or equimolar amounts of Lewis or protic acid, has also been reported (Scheme 31, eq. b).\(^{[159-160]}\) Trifluoromethylthiolation of pyrroles and indoles in presence of a directing group led to the formation of the desired products through a Rh-catalyzed C-H activation (Scheme 31, eq. a).\(^{[161]}\) Zhao and coll. reported the vicinal SCF₃-amination and SCF₃-esterification of double bonds in a multicomponent reaction mediated by selenium disulfide as a catalyst (Scheme 31, eq. d).\(^{[162]}\) Also the trifluoromethylthio lactonization/lactamization of olefins catalyzed by a Lewis acid has been described (Scheme 31, eq. c).\(^{[163]}\)
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Scheme 31 Reactivity of N-Trifluoromethylthiosuccinimide

Y = NHCOR, OCOR
YR₃
R SCF₃
R₁

Y = O, S, NH
R - SCF₃
R₁

42-94 %

50-99 %

57-86 %

66-95 %

50-99 %

35-98 %

42-94 %

61-91 %

50-97 %

35-98 %
I.2.3.6 Trifluoromethanesulfenyl hypervalent iodonium ylide

Shibata and coll. reported the synthesis of a novel trifluoromethanesulfonate hypervalent Iodonium ylide, which showed good reactivity in presence of various nucleophiles. The CF$_3$SO$_2$ moiety is reduced into a reactive CF$_3$S species by an intramolecular rearrangement. When an amine is added to the reaction media the authors reported the formation of an ammonium salt, which might be responsible of the trifluoromethylthiolation (Scheme 32, eq. a and b).$^{[164]}$ Also trifluoromethylthiolation of pyrroles in presence of copper has been achieved (Scheme 32, eq. c).$^{[165]}$ Aryl and vinyl boronic acids have been trifluoromethylthiolated in a Cu-mediated coupling reaction leading to the SCF$_3$-containing compounds (Scheme 32, eq. f).$^{[166]}$ Shibata and coll. reported also the trifluoromethylthiolation of primary and secondary aromatic amines, this could be an alternative way to access to the trifluoromethanesulfenamide reagents (Billard reagents) (Scheme 32, eq. e).$^{[167]}$ Copper-catalyzed trifluoromethylthiolation of allyl silanes and silyl enol ethers under the same reaction conditions gave the corresponding compounds (Scheme 32, eq. d).$^{[168]}$

![Scheme 32 Trifluoromethanesulfenyl hypervalent Iodonium reagent and its reactivity](image)

I.2.3.7 Trifluoromethylthiosilver (I) as an electrophilic reagent

AgSCF$_3$ has been used also an electrophilic CF$_3$S$^+$ reagent in presence of TCCA (trichloroisocyanuric acid). Tan and coll. reported the entantioselective synthesis of CF$_3$S-
oxindoles in presence of a chinona-base organocatalyst (Scheme 32, eq. a).\textsuperscript{[169]} Although CF$_3$SSCF$_3$ has been identified as the trifluoromethylthiolating species; the authors reported also the involvement of other unidentified SCF$_3$ species in the electrophilic trifluoromethylthiolation.

![Scheme 33 AgSCF$_3$ used as an electrophilic SCF$_3$ donor](image)

Also the synthesis of chromenones bearing an SCF$_3$ unit has been obtained in presence of the dual system AgSCF$_3$/TCCA methodology (Scheme 32, eq. b).\textsuperscript{[170]}
I.3 S-CF$_2$H and S-CF$_2$FG bond formation; indirect approach

As shown in the SCF$_1$ chemistry, the most common approach for the synthesis of SCF$_2$H or SCF$_2$FG (FG= SO$_2$Ph, COR, halogen except F, SAr) molecules is the difluoromethylation of thiols, thiolates or disulfides. When we started the project the direct introduction of SCF$_2$H and SCF$_2$FG into molecules lacked of reagents and synthetic strategies. During the last two years there have been reported various methods and two shelf-stable reagents to access difluoromethylthiolated molecules.$^{[171]}$

I.3.1 Difluoromethylation with difluorocarbene sources

There already exist several difluorocarbene sources in literature involved in difluoromethylation of C-, O-, S-, Se-, N- and P- nucleophiles. Difluorocarbene precursors such as ClCF$_2$H, TMSCF$_2$X (X= Cl, Br, F), CF$_2$H, HCF$_2$OTf, BrCF$_2$PO(OEt)$_2$, ClCF$_2$CO$_2$Na and many others has been extensively used throughout the years (For a more detailed review concerning difluorocarbene sources see reference $^{[172]}$). Herein, we will report the difluoromethylation of S-centers.

I.3.1.1 ClCF$_2$H as a difluorocarbene source

One of the first compounds that have been employed as a difluorocarbene precursor is the chlorodifluoromethane, a gas, which is concerned by the Montreal Protocol restrictions due to its ozone depletion and global warming potentials.$^{1}$ In the late 50's, Porter and coll.$^{[173]}$ reported evidences of the formation of a difluorocarbene species in a α-dehydrohalogenation reaction catalyzed by sodium methoxide, with concerted loss of proton and chloride ion. They also noticed that such a reactive species, in presence of thiophenoxide gave the corresponding difluoromethylthiol (Scheme 34, eq. a). Furthermore, based on their kinetic calculations,$^{[173]}$ evidences were found that such reaction could not pass through an S$_2$N$_2$ mechanism.$^{[173]}$ More than 20 years later such considerations has been proven unambiguously by deuterium exchange studies.$^{[174]}$ Schots and coll.$^{[175]}$ reported the difluoromethylation of thiols, through the formation of a difluorocarbene in presence of a strong base in dioxane/H$_2$O media (Scheme 34, eq. b).$^{[175]}$ Nevertheless, such methodologies suffer a main drawback, the consumption of difluorocarbene in presence of high concentrations of base.$^{[176]}$ Langlois described an improved synthetic strategy to tackle down such a inconvenience, using a biphasic solid-liquid system: NaOH being the solid

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phase and TDA-1 used to transport anionic salts thus making easier their solubility (Scheme 34, eq. c).[177]

Difluoromethylation of heteroaromatic moieties like mercaptazoles has been also investigated. In the case of the mercaptazole shown in Scheme 34 eq. e, difluoromethylation of thiol is reported as a major product. N- and S- bis(difluoromethylation) has also been observed in a 5 % yield. On the other hand, the presence of electron-donating groups on the benzene ring highly influences the reaction pathway. Enhancement of the nucleophilicity over the N-center led to the formation of N- and S- bis(difluoromethylated) compounds.[178] Later on, Yagupolskii and coll. found out, in the difluoromethylation of 5-sulfonyltetrazoles, that at low temperatures the kinetic product is the S-CF$_2$ whereas N-SCF$_2$ product formation is favoured at high temperatures.[179] Also the difluoromethylation of acetophenone has been reported in a scale-up reaction (700 mmol) confirming the robustness of such method (Scheme 34, eq. d).[180]

I.3.1.2 CF$_2$Br$_2$ and ClCF$_2$Br as difluorocarbene sources

Bromochlorodifluoromethane, a restricted-use gas nowadays from the Montreal Protocol, has been used as a difluorocarbene generator.

Wakselman and coll.[181] used both ClCF$_2$Br and the more benign CF$_2$Br$_2$ as carbene precursors, in this case leading to the formation of SCF$_2$Br an interesting moiety especially for post-functionalization. Although the formation of SCF$_2$Br derivatives had been obtained using both
reagents, CF$_2$Br$_2$ gave a slightly higher yield. The presence of functional groups in para position influences the overall yield of the reaction. Meanwhile the electron-withdrawing power decreases the total yield, with an increase in the formation of SCF$_2$H derivative at the expense of SCF$_2$Br. An ionic mechanism through a carbenic pathway has been proposed totally in accordance with the obtained results.

### 1.3.1.3 SCDA, PDFA and TFDA as difluorocarbene sources

Sodium chlorodifluoroacetate (SCDA) has been one of the first difluorocarbene precursors used in carbene chemistry by Haszeldine. Moreover, it does not face any environmental or restrictive issues. Nevertheless, his role in difluorocarbene chemistry is quite modest.

**Scheme 36 SCDA as a difluorocarbene precursor**

Greaney and coll. used SCDA as a source to difluoromethylate aromatic and heteroaromatic thiols compounds in relatively mild conditions. Also in this case, at high temperatures the N-SCF$_2$H formation increases (Scheme 36).[182]

Difluoromethylene phosphobetaine (PDFA) has also been used as a difluorocarbene precursor in the difluoromethylation of activated S-H bonds as well as primary and secondary benzylic thiols under mild conditions and in absence of a base (Scheme 37).[183]

**Scheme 37 PDFA as a difluorocarbene precursor**

Trimethylsilyl 2,2-difluoro-2-fluorosulfonylacetate (TDFA) has been used as a difluoromethylating agent. S-difluoromethyl thioimidates have been obtained starting from thioamides in a reaction catalyzed by tetramethyldiaminonaphtalene (Proton Sponge) (Scheme 38).[184]
Chapter I. Synthesis of SCF₂R derivatives and their application in electrophilic reactions

1.3.1.4 Diethyl bromodifluoromethylphosphonate and Difluoromethyltri(6-butyl)ammonium chloride

Segall and coll. reported the difluoromethylation of thiophenols using BrCF₂PO(Et)₂ as a difluorocarbene generator, via a hydrolysis-based P-C bond cleavage, and subsequent trapping of the carbene species formed (Scheme 39, eq. a).[185]

The reaction proceeds as follows:

\[
\begin{align*}
\text{BrCF}_2\text{PO(Et)}_2 &\rightarrow \text{BrCF}_2\text{PO(Et)} \rightarrow \text{BrCF}_2\text{PO} \rightarrow \text{BrCF}_2\text{H} \rightarrow \text{SCF}_2\text{H} \\
\end{align*}
\]

Scheme 39 Phosphonate-CF₂Br and TBA-CF₂Cl complexes as difluorocarbene sources

Hu and coll. disclosed the use of n-Bu₃(CF₂H)Cl as a difluorocarbene source to easily access S-CF₂H moieties, obtaining good yields (Scheme 39, eq. b).[186]

1.3.1.5 HCF₃, TMSCF₂Br and HCF₂OTf as difluorocarbene sources

As reported above in this dissertation, fluoroform (HCF₃) is formed as a waste by-product in a large volume during the manufacture of refrigerants, Teflon, foams, and many other materials. Its non-toxic, environmentally-benign, ozone-non-depleting features combined with the low price make it an interesting trifluoromethylating reagent. It has been also used as a starting material in the synthesis of Ruppert-Prakash reagent TMSCF₃. With the aim to avoid the use of ozone-depleting difluorocarbene generators and on the same time consume a waste formed from the manufacturing industry, Dolbier and coll. used fluoroform as a difluorocarbene precursor for the difluoromethylation of thiophenols (Scheme 40, eq. a).[187]

Hartwig and coll. reported the synthesis of the non-ozone-depleting and liquid difluoromethyltriflate (HCF₂OTf), starting from triflic acid and TMSCF₃. HCF₂OTf has been used in the synthesis of difluoromethylating aromatic thiols Scheme 40, eq. b).[188] The Rupert-
Prakash reagent has been involved also in the synthesis of TMSCF₂Br, another reagent belonging to the silane family used in difluoromethylation.

![Scheme 40 Fluoroform, HCF₂OTf and TMSCF₂Br as difluorocarbene sources](image)

Hu and coll. described the difluoromethylation of aryl, alkyl and heteroaryl thiols using bromodifluoromethane. In the case of heteroaryl compounds regioselective difluoromethylation at the S atom has been obtained.[189]

### 1.3.1.6 N-Tosyl-S-difluoromethyl-S-phenylsulfoximine as a difluorocarbene source

A novel shelf-stable difluoromethylating α-difluoromethylsulfoximine compound has been prepared starting from difluoromethylsulfoxide and PhINTs in presence of copper triflate. Efficient difluoromethylation of benzylic and heteroaromatic thiols has been performed in presence of NaH.

![Scheme 41 Synthesis of a sulfoximine derivative and its use as a difluorocarbene source](image)

Despite the fact the reagent lacks in efficiency concerning regioselective difluoromethylation over S atom it still remains a valuable tool in difluoromethylation reactions.[190]

### 1.3.2 Radical Difluoromethylation

Less attention has been given to the insertion of CF₂H or CF₂FG groups into molecules through radical difluoromethylation reactions with the aim to obtain S-CF₂H(FG) bonds. Herein are
disclosed the most used reagents and synthetic pathways involved to obtain S-containing compounds.

I.3.2.1 DFMS, ICF₂COOEt; new reagents for radical difluoromethylation

Important breakthrough in radical difluoromethylation of heteroarenes especially, is the work of Baran and coll., where the preparation of Zn(SO₂CF₂H)₂ has been reported. Although most of the work concerns difluoromethylation of N-heteroarenes, three valid examples of regioselective difluoromethylation over the S-atom of thiols has been reported (Scheme 42).¹⁹¹

A visible light-induced Ru-mediated photocatalytic example of ethoxycarbonyldifluorometylation of a cysteine moiety has been performed using both batch and flow processes. Continuous-flow microreactors show a slight increase in the yield of the final products (Scheme 43).¹⁹²

I.3.3 Nucleophilic difluoromethylation of disulfides

I.3.3.1 Difluoromethyl trimethylsilane, difluoromethyl phenyl sulfone and α-fluorodiaroylmethanes

Difluoromethyl phenyl sulfone occupies an important position as a difluoromethylating agent in nucleophilic substitution reactions. Its peculiar ability to behave as difluoromethylene dianion (CF₂⁺) has been exploited by Prakash et al. As reported in Scheme 44, by increasing the amount of equivalents of t-BuOK and disulphide, they could obtain the PhS-subsituted sulfone or PhS-disubstituted compound as a major product.¹⁹³
Chapter I. Synthesis of SCF₂R derivatives and their application in electrophilic reactions

Difluoromethyl trimethylsilane (TMSCF₂H) has been used in the difluoromethylation of disulfides giving rise to aromatic, heteroaromatic and alkyl difluoromethylthioethers employing CsF desilylating agent (Scheme 45, eq. a).[194] On the other hand, using t-BuOK as a base only formation of difluorobis(arylthio)methanes has been reported as the only product obtained (Scheme 45, eq. a and b).[194b] Also α,α-difluorodiarylomethanes in presence of a nucleophile and a base can lead to the formation of aryl and heteroaryl α-thioaryl-α-α-difluoroacetophenones. However, increasing the temperature of the reaction the authors could obtain the aryl and heteroaryl difluoromethylated thiols in good yields (Scheme 45, eq c and d).[195]

Hu and coll. reported the use of sodium bromodifluoroacetate as a perfluoroalkylating reagent with differently substituted aromatic thiols (Scheme 46).[196]

I.3.3.2 (NHC)Ag(CF₂H) in nucleophilic difluoromethylations

N-heterocyclic carbene difluoromethylated silver complex has been prepared by Shen and coll. It has been employed in the preparation of N-difluoromethylthioptalimide, the first electrophilic reagent used in difluoromethylthiolations. The authors scaled the synthesis up to 175 mmol obtaining a yield of 66 %. Moreover, the chlorinated silver complex has been recycled to give the
NHC-ligated difluoromethylated silver complex yielding 83 %, in presence of TMSCF₂H as a difluoromethyllating agent (Scheme 47).[197].

Electrophilic difluoromethylthiolations using N-difluoromethylthiophtalimide will be reported on the appropriate section

### I.3.4 Electrophilic difluoromethylation of thiols and thiolates

A few reagents and methodologies concerning electrophilic difluoromethylation of thiols and thiolates have been reported. Herein, three different reagents involved in electrophilic difluoromethylthiation of molecules over the S-atom have been reported.

#### I.3.4.1 Rupert-Prakash reagent and a sulfoximine derivative used in electrophilic difluoromethylation

Recently, the use of Ruppert-Prakash reagent as a difluoromethylating source has been reported. Electrophilic difluoromethylation of aromatic and aliphatic thiols, after desilylation of the in situ formed (trimethylsilyl)difluoromethylthiol compounds, using a F⁻ source has been successfully obtained (Scheme 48).[198]

\[
\text{R} \text{-} \text{SH} \xrightarrow{\text{LiH, LiBF}_4, \text{DMF}} \text{R} \text{-} \text{SCF}_2\text{TMS} \xrightarrow{\text{KF or TBAF}} \text{R} \text{-} \text{SCF}_2\text{H} \quad 24-86 \%
\]

**Scheme 48 Prakash-Ruppert as a difluoromethylating electrophilic reagent**

\(N,N\text{-dimethyl}-S\text{-difluoromethyl}-S\text{-phenylsulfoximinium tetrafluoroborate, Johnson’s trifluoromethylating agent analogue, is one of the few difluoromethylating reagents involved in S-C bond formation through electrophilic difluoromethylation reactions. Prakash et al. reported the synthesis of the before-mentioned reagent in 3 steps starting from difluoromethyl phenyl sulfoxide. However, the difluoromethylation of thiolates has been obtained after a second methylation of the reagent in situ and subsequent addition of the proper thiolate in a second time**
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(Scheme 49). Authors referred that deuterium studies led to the conclusion that an electrophilic pathway takes place.\(^{199}\)

![Scheme 49](image)

1.3.4.2 Hypervalent iodine(III)-CF₂SO₂Ph reagent

A Togni-analog reagent has been developed for electrophilic (phenylsulfonyl)difluoromethylation of aromatic, heteroaromatic and benzyl S-nucleophiles under mild conditions (Scheme 50). The reagent itself has been obtained after an acetoxylation of the hypervalent iodine(III)-Cl derivative and (phenylsulfonyl)difluoromethylation of the intermediate in situ with a 71 % yield.\(^{200}\)

![Scheme 50](image)

1.3.5 C-S-CF₂H(FG) in situ bonds formation

Another practical way to access SCF₂R compounds is the consecutive C-S-CF₂H(FG) bond formation. Two works embracing such strategy have been recently reported to literature.

1.3.5.1 Copper thiocyanide and N-thiocyanatosuccinimide

Copper thiocyanide has been employed as a SCN donor contributing in the C-SCN bond formation in situ and a further difluoromethylation of the intermediates in a Langlois-type nucleophilic substitution gave the desired SCF₂H compounds. Goossen \(\textit{and coll.}\) reported the synthesis of HCF₂S-molecules in a one-pot methodology accessing to aryl, heteroaryl and alkyl HCF₂S containing compounds.\(^{201}\) Thiocyanates, bromo-derivatives, tosylates and diazonium salts used as starting materials underwent in a first moment thiocyanation and Cu-mediated difluoromethylation to give rise to HCF₂S containing molecules (Scheme 51, eq. a, b and d).
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Poisson and coll. accessed to α-difluoromethylthiolated phosphonates in a reaction involving α-diazocarbonyl compounds, CuSCN and a difluoromethylsilyl derivative containing a phosphonate group (Scheme 51, eq. c). [202]

Goossen and coll. reported the difluoromethylthiolation of arenes in a one-pot two-step process, starting from AlCl₃-mediated thiocyanation of arenes followed by Cu-mediated difluoromethylation of the thiocyanide formed in situ (Scheme 52). [203]
I.4 C-SCF₂H and C-SCF₂FG bond formation; direct approach

Direct insertion of SCF₂H or SCF₂FG into molecules is more appealing than indirect difluoromethylation of thiols because it could pave the way to access to a plethora of different compounds bearing SCF₂H or SCF₂FG group, thus not only limiting the choice to S-containing adducts. Since we have been working on this project, also other groups contributed on the progress of such chemistry by the development of new reagents or new methodologies for direct SCF₂H or SCF₂FG insertion. Based on our bibliography research only 6 very recently published papers concerning difluoromethylthiolation have been reported, all of them during the period 2015-2016.

I.4.1 Radical difluoromethylthiolation reactions

I.4.1.1 N-difluoromethylthiophtalimide

N-difluoromethylthiophalimide, as its SCF₃-analogue has been used in the radical difluoromethylthiolation of alkyl carboxylic acids. A visible light-promoted reaction, in presence of an Ir catalyst led to the difluoromethylation of primary, secondary and tertiary alkyl carboxylic acids. Mechanistic elucidations given by the authors suggest a hole-catalyst chain process as a possible mechanistic pathway.

The group of Shen reported the synthesis of a N-heterocyclic carbene difluoromethylthiolated silver complex starting from the previously synthesized compound[204] ((NHC)Ag(CF₂H)) and metallic sulfur (Sₐ) in THF at room temperature (Scheme 54, eq. a). Shen and coll. reported the difluoromethylthiolation of aryl and heteroaryl diazonium salts in a Cu-mediated Sandmeyer-type reaction (Scheme 54, eq. b and c). Moreover, in order to circumvent the pre-syntheses of diazonium salts a one-pot procedure for their synthesis followed by difluoromethylthiolation has been reported (Scheme 54, eq. d).[205] Cu¹⁻¹¹ species are involved in the reaction leading through a single electron transfer (SET) mechanism.
I.4.2 Nucleophilic difluoromethylthiolation reactions

Up to now only one reagent has been used in nucleophilic difluoromethylthiolation reactions.

I.4.2.1 (NHC)Ag(SCF₂H) complex in difluoromethylthiolation

As reported above, direct difluoromethylthiolation of aromatic and heteroaromatic compounds is limited to the use of aryl and heteroaryl diazonium salts. Even though such methodology showed wide applicability in terms of group tolerance the explosive nature of diazonium salts could limit its practical applications.

In order to circumvent the use of diazonium salts Shen and coll. reported the difluoromethylthiolation of heteroaryl bromides, iodides, triflates and aryl iodides through a Pd-mediated cross-coupling reaction.[206]

I.4.3 Electrophilic difluoromethylthiolation reactions

Recently, two reagents involved in direct difluoromethylthiolation and one reagent able to generate °SCF₂PO(OEt)₂ has been reported to literature up to now.
I.4.3.1 N-difluoromethylthiophthalimide

The synthesis of N-difluoromethylthiophthalimide reported by Shen and coll. has already been described in the previous sections. It has been used in electrophilic difluoromethylthiolations of a variety of molecules (Scheme 56). Copper-catalyzed difluoromethylthiolation of alkynes, using copper(II)-thiophen-2-carboxylate had been successfully applied (Scheme 56, eq. a). The reagent showed a good reactivity also in difluoromethylthiolation of primary and secondary amines as well as aniline derivatives (Scheme 56, eq. b).

Difluoromethyl substituted disulfides have been obtained by reacting the reagent with thiolated adducts (Scheme 56, eq. c). β-ketoesters and 2-oxindoles have been difluoromethylthiolated in presence of potassium carbonate as a base (Scheme 56, eq. d and e). Difluoromethylthiolation of electron-poor arenes has been achieved in a Cu-mediated coupling reaction of aryl boronic acids. Also vinyl boronic acids gave the difluoromethylthiolated products in good yields (Scheme 56, eq. f). Electron-rich heteroarenes has been difluoromethylthiolated in a Friedel-Craft reaction in presence of a Lewis acid (Scheme 56, eq. g).[197]

I.4.3.2 Difluoromethanesulfenyl hypervalent iodonium ylides reagents

Shibata and coll. reported the synthesis of a new hypervalent iodonium ylide difluoromethylthiolating reagent, the analog of the trifluoromethylthiolating iodonium ylide. A series of different ylides has been prepared and two of them successfully engaged in difluoromethylthiolations of different classes of compounds. α-bromoketones reacted with sodium difluoromethanesulfinate to give the corresponding sulfonylacetophenones, which in
presence of KOH and hypervalent iodonium compounds led to the formation of iodonium ylides (Scheme 57).

\[ 
\text{Scheme 57 Syntheses of hypervalent iodonium ylides} 
\]

\[ 
\beta\text{-enamino esters had been difluoromethylthiolated in presence of Cu-catalyzed reaction leading to the formation of } \alpha\text{-SCF}_2\text{H-}\beta\text{-enaminoesters (Scheme 58, eq. a). Adopting the above conditions, difluoromethylthiolation of heteroaromatic compounds as pyrroles and indoles has been performed (Scheme 58, eq. b and c).} 
\]

\[ 
\text{Scheme 58 Difluoromethylsulfonyl hypervalent iodonium ylide reagents for difluoromethylthiolations} 
\]

\[ 
\beta\text{-ketoesters gave the corresponding difluoromethylthiolated products in presence of a base and Cu salt ( Scheme 58, eq. c). } \alpha\text{-SCF}_2\text{H-}\beta\text{-esters and ketoesters has been obtained in a one-pot procedure starting from } \beta\text{-enamino esters followed by a hydrolysis (Scheme 58, eq. f). A similar} 
\]

54
one-pot procedure based on the difluoromethylthiolation of N-protected β-enamino ester and subsequent cyclohydration gave compounds having a pyrazole and a pyrimidine structure (Scheme 58, eq. d). Mechanistically the reaction proceeds through a Cu-catalyzed carbone formation, leading to the formation of oxathiirine-2-oxide, itself involved in a further rearrangement to sulfoxide which collapses to a thioperoxoate that might be responsible for difluoromethylthiolation as authors claimed.\textsuperscript{[207]}

### 1.4.3.3 MesNHSCF\(_2\)PO(OEt)\(_2\) reagent

Very recently, inspired by our works, Besset and coll., prepared a (phosphonate)difluoromethanesulfenamide reagent, through a (phosphonate)difluoromethylation of corresponding thiocyanate.

[Diagram of Scheme 59: (Phosphonate)difluoromethanesulfenamide reagent used as a source of (phosphonate)difluoromethyliations]

SCF\(_2\)PO(OEt)\(_2\) group has been transferred to aromatic and heteroaromatic compounds as well as in α position of ketones in acidic conditions (Scheme 59, eq. b, c, d). Also primary and secondary aromatic amines as well as thiols gave the compounds bearing the difluoromethylphosphonate (Scheme 59, eq. f and e).\textsuperscript{[208]}
Chapter I. Synthesis of SCF₂R derivatives and their application in electrophilic reactions

II. Results and Discussion- C-SCF₂FG bond Formation

Several methodologies and reagents used in electrophilic trifluoromethylthiolation were already known at the beginning of 2014. On the other hand, direct insertion of SCF₂FG/H into molecules was totally unexplored. Thus, an urgent need for the development of reagents and/or methodologies in order to access moieties bearing SCF₂FG could be a main interest especially in agrochemicals and pharmaceuticals.

In this chapter, we describe the syntheses of new reagents that act as SCF₂FG donors and their use in electrophilic aromatic substitution and addition reactions.

II.1 Syntheses of novel sulfenamides bearing a SCF₂FG group

II.1.1 State of the art: Syntheses of sulfenamides

As reported above, trifluoromethanesulfenamides were the first electrophilic trifluoromethylthiolating reagents that found a wide use in methodology thus becoming a real alternative to the highly volatile and toxic ClSCF₃.

Since 2009, trifluoromethanesulfenamides has been used as donors of SCF₃ activated by both electrophilic and nucleophilic ways (See Electrophilic Trifluoromethylthiolations). Trifluoromethanesulfenamides are prepared by reacting DAST with Ruppert-Prakash in presence of a base and later the reaction is quenched with a proper primary amine. Also a mechanism has been proposed by our group (Scheme 60).[117]

Scheme 60 Reaction mechanism for the syntheses of sulfenamides
II.1.2 Syntheses of (PhSO₂)CF₂TMS

Based on literature data shown above and our expertise in the synthesis of sulfenamides, we planned the syntheses of four different sulfenamide reagents.

As reported in Scheme 60 to access sulfenamides, the reaction involves the use of DAST and a corresponding silane. Silanes Si₂, Si₃ and Si₄ are commercially available and do not need to be prepared.

On the other hand, silane Si₁ needs to be synthesized. Several synthetic pathways were tested to obtain Si₁. Firstly the reaction between difluoromethylphenylsulfone and BuLi as a strong base followed by the addition of a silane source to obtain the desired compound was explored.

When TMSCl was used as a silane source two peaks were detected at ¹⁹F NMR after 2 hours. A peak at -112.81 ppm corresponds to our desired compound and has been obtained with a 10 % dosed yield, and a doublet between -122.21 and -122.40 ppm corresponding to the starting material which is not entirely consumed (only 20 % found). In the case of trimethylsilylimidazol only difluoromethylphenyl sulfone was observed. Considering the low yield obtained we changes
synthetic strategy. In a first moment we planned the synthesis of bromodifluoromethyl phenylsulfone, which would lead to the silylated derivative after a transmetallation reaction. Based on literature procedures,[209] we tried to access $S_2$ by using NaOBr formed in situ from aqueous NaOH and Br$_2$. Bromine was added to the aqueous solution of NaOH at low temperatures (around 5 °C) dropwise, following the reported procedure. Unfortunately, as shown in the table below the reaction is not reproducible, neither on a small scale. At this point a new pathway for the synthesis of $S_1$ was explored.

Table 2 Synthesis of bromodifluoromethyl phenylsulfone

<table>
<thead>
<tr>
<th>Entry</th>
<th>Br source eq</th>
<th>Yield %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3 eq</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>5</td>
<td>75 %</td>
</tr>
<tr>
<td>3a</td>
<td>5</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>5</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>5</td>
<td>70 %</td>
</tr>
<tr>
<td>6</td>
<td>5</td>
<td>70 %</td>
</tr>
<tr>
<td>7</td>
<td>5</td>
<td>-</td>
</tr>
<tr>
<td>8b</td>
<td>3</td>
<td>45 %</td>
</tr>
<tr>
<td>9a</td>
<td>3</td>
<td>40%</td>
</tr>
<tr>
<td>10</td>
<td>3</td>
<td>-</td>
</tr>
</tbody>
</table>

Crude yields were determined by $^{19}$F NMR spectroscopic analysis using PhOCF$_3$ as an internal standard. Reactions were run over 1 mmol scale. * Reactions was run over 10 mmol scale. ** Reaction was run over 5 mmol.

$S_1$ was prepared from thiophenol and dibromodifluoromethane in DMF with a 60 % yield based on literature procedures.[210] Thiophenol is converted to the corresponding thiolate after addition of sodium hydride. Addition of CF$_2$Br$_2$ gave the desired compound, passing through the formation of a difluorocarbene. Three equivalents of m-CPBA gave the oxidized analog in a good yield in 24 h. Compound $S_2$ underwent transmetallation in presence of BuLi and TMSCl following a slightly modified procedure[211] yielding 80 %. Using 1.1 equiv. of BuLi and 1.3 equiv. of TMSCl the reaction gave only 40 % of yield.
We started exploring reaction conditions for the synthesis of sulfenamide reagents with the commercially available silanes \textbf{Si2} and \textbf{Si3} at the beginning. After the activation of DAST in CH\textsubscript{2}Cl\textsubscript{2} with DIEA we added (difluoromethyl)trimethylsilane, followed by the addition of aniline after one hour. However, at the end of the reaction TMSCF\textsubscript{2}H was found to be quantitative in the reaction mixture (Table 3, entry 1). TMSCF\textsubscript{2}H is known to be more stable than TMSCF\textsubscript{3} with a bond order value (0.432) of almost the double respect to Ruppert-Prakash reagent (0.220). Therefore, harsher reaction conditions are needed in order to cleave the Si-CF\textsubscript{2} bond.\cite{212} When THF was used as a solvent, a slight consumption of the silane was observed, but the only compound formed seems to be CH\textsubscript{2}F\textsubscript{2}, observed by \textsuperscript{19}F NMR. Even by increasing the temperature up to 70 °C (Table 3, entry 2-4), we did not observe the formation of the desired product. However, it seems that the fluoride generated from the DAST is not strong enough to cleave the Si-C bond, thus we thought that the addition of a supplementary fluoride source could be beneficent for the reaction. Nevertheless, no changes were observed in the reaction media when CsF was used, probably due to its insolubility in THF (Table 3, entry 5). On the other hand, using a soluble fluoride source as TBAT only 25 % of TMSCF\textsubscript{2}H was found in the reaction media after \textsuperscript{19}F NMR spectroscopy analysis. But still we were far from solving our problems, because only the formation of CF\textsubscript{2}H\textsubscript{2} was detected by \textsuperscript{19}F NMR spectroscopy (Table 3, entry 6).

Among various fluorinated moieties bromodifluoromethylthio (SCF\textsubscript{2}Br) could be a valuable group especially in post-functionalization reactions. Its direct introduction into molecules would supply very interesting building blocks that could find use in \textsuperscript{18}F radiolabeling. In order to
prepare SCF₂Br donating sulfenamide reagent we first reacted TMSCF₂Br with DAST, followed the addition of aniline after 1 hour. Unfortunately, no product was formed although only 10% of the starting silane was found intact in the reaction mixture (Table 3, entry 7). Even running the reaction at lower temperatures, no formation of compound 1c was observed (Table 3, entries 8-10). Using THF instead of CH₂Cl₂ no traces of silane were found in the reaction media (Table 3, entries 11-13). Also when 3 eq of TMSCF₂Br were used in THF or CH₃CN/DIEA the silane went to complete degradation (Table 3, entries 14-16).

Table 3 Tentatives for the synthesis of sulfenamides

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Base</th>
<th>Solvent</th>
<th>T (°C)</th>
<th>1 (%)</th>
<th>Remaining Silane (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H</td>
<td>DIEA</td>
<td>CH₂Cl₂</td>
<td>-25 °C</td>
<td>-</td>
<td>100 %</td>
</tr>
<tr>
<td>2</td>
<td>H</td>
<td>-</td>
<td>THF</td>
<td>-25 °C</td>
<td>-</td>
<td>85 %</td>
</tr>
<tr>
<td>3</td>
<td>H</td>
<td>-</td>
<td>THF</td>
<td>25 °C</td>
<td>-</td>
<td>85 %</td>
</tr>
<tr>
<td>4</td>
<td>H</td>
<td>-</td>
<td>THF</td>
<td>50 °C</td>
<td>-</td>
<td>70 %</td>
</tr>
<tr>
<td>5a</td>
<td>H</td>
<td>-</td>
<td>THF</td>
<td>70 °C</td>
<td>-</td>
<td>70 %</td>
</tr>
<tr>
<td>6a</td>
<td>H</td>
<td>-</td>
<td>THF</td>
<td>-45 °C</td>
<td>-</td>
<td>25 %</td>
</tr>
<tr>
<td>7</td>
<td>Br</td>
<td>DIEA</td>
<td>CH₂Cl₂</td>
<td>25 °C</td>
<td>-</td>
<td>10 %</td>
</tr>
<tr>
<td>8</td>
<td>Br</td>
<td>DIEA</td>
<td>CH₂Cl₂</td>
<td>-25 °C</td>
<td>-</td>
<td>45 %</td>
</tr>
<tr>
<td>9</td>
<td>Br</td>
<td>DIEA</td>
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<td>-45 °C</td>
<td>-</td>
<td>60 %</td>
</tr>
<tr>
<td>10</td>
<td>Br</td>
<td>DIEA</td>
<td>CH₂Cl₂</td>
<td>-80 °C</td>
<td>-</td>
<td>100 %</td>
</tr>
<tr>
<td>11</td>
<td>Br</td>
<td>-</td>
<td>THF</td>
<td>25 °C</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>12</td>
<td>Br</td>
<td>-</td>
<td>THF</td>
<td>-45 °C</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>13</td>
<td>Br</td>
<td>-</td>
<td>THF</td>
<td>-80 °C</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>14c</td>
<td>Br</td>
<td>-</td>
<td>THF</td>
<td>25 °C</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>15c</td>
<td>Br</td>
<td>DIEA</td>
<td>CH₃CN</td>
<td>25 °C</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>16c</td>
<td>Br</td>
<td>DIEA</td>
<td>CH₃CN</td>
<td>-25 °C</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Crude yields were determined by ¹⁹F NMR spectroscopic analysis using PhOCF₃ as an internal standard. Reactions were run for 1 hour before addition of aniline. a 1 eq of CsF were used. b 1 eq of TBAT were used. c 3 eq of TMSCF₂Br were used.

Such results confirmed once more the instability of TMSCF₂Br and its capacity to decompose into difluorocarbene. The addition of a silaphilic Lewis base (like F⁻ source) to fluorinated silanes leads to the formation of a pentacoordinated intermediate, which reacts with a suitable electrophile. In the case of TMSCFBr, the generated pentacoordinate intermediate is unstable
and decomposes into a difluorocarbene. Such findings are consistent with data found in literature.\[189\]

For the synthesis of sulfenamide 1a we first used the optimized conditions employed in the synthesis of the trifluoromethanesulfenamides. As shown in Table 4 entry 1, no formation of compound 1a was observed by 19F NMR. When the reaction was run at 25 °C the formation of an intermediate was detected by 19F NMR represented by an AB system between -104.5 and -107.5 ppm. Quenching the reaction with aniline, we observed a new peak at -89.84 ppm in 19F NMR that corresponds to compound 1a, obtained with a 25 % dosed yield in 16 h (Table 4, entry 2). A further increase in temperature or the use of 2 equiv. of DIEA did not improve the yield significantly (Table 4, entries 3-7).

Table 4 Synthesis of (phenylsulfonyl)difluoromethylsulfenamide

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>R</th>
<th>Solvent</th>
<th>T (°C)</th>
<th>Time h</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>DIEA</td>
<td>N(Et)₂</td>
<td>CH₂Cl₂</td>
<td>-25</td>
<td>1 h</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>DIEA</td>
<td>N(Et)₂</td>
<td>CH₂Cl₂</td>
<td>25</td>
<td>1 h</td>
<td>25 %</td>
</tr>
<tr>
<td>3b</td>
<td>DIEA</td>
<td>N(Et)₂</td>
<td>CH₂Cl₂</td>
<td>40</td>
<td>24 h</td>
<td>35 %</td>
</tr>
<tr>
<td>4</td>
<td>DIEA</td>
<td>N(Et)₂</td>
<td>CH₂Cl₂</td>
<td>60</td>
<td>1 h</td>
<td>10 %</td>
</tr>
<tr>
<td>5d</td>
<td>DIEA</td>
<td>N(Et)₂</td>
<td>CH₂Cl₂</td>
<td>60</td>
<td>18 h</td>
<td>25 %</td>
</tr>
<tr>
<td>6b</td>
<td>DIEA</td>
<td>N(Et)₂</td>
<td>CH₂Cl₂</td>
<td>40</td>
<td>2 h</td>
<td>40 %</td>
</tr>
<tr>
<td>7b</td>
<td>DIEA</td>
<td>N(Et)₂</td>
<td>CH₂Cl₂</td>
<td>40</td>
<td>2 h</td>
<td>45 %</td>
</tr>
<tr>
<td>8</td>
<td>DIEA</td>
<td>Morpholine</td>
<td>CH₂Cl₂</td>
<td>25</td>
<td>2 h</td>
<td>-</td>
</tr>
<tr>
<td>9c</td>
<td>DIEA</td>
<td>Morpholine</td>
<td>CH₂Cl₂</td>
<td>60</td>
<td>2 h</td>
<td>-</td>
</tr>
<tr>
<td>10</td>
<td>-</td>
<td>N(Et)₂</td>
<td>THF</td>
<td>25</td>
<td>2 h</td>
<td>60 %</td>
</tr>
</tbody>
</table>

Crude yields were determined by 19F NMR spectroscopic analysis using PhOCF₃ as an internal standard. a Reactions were run for 48 h after the addition of aniline. b Reactions were run at 40 °C after the addition of aniline. c Reactions were run at 60 °C after the addition of aniline. d 2 eq of DIEA were used.

Using Morph-DAST instead of DAST we did not observe any formation of intermediate or final product (Table 4, entries 8-9). After various efforts we discovered that the solvent play an important role in the reaction mechanism. Thus, by substituting CH₂Cl₂ with THF compound 1a was obtained with 60 % yield without adding any base. In the synthesis of trifluoromethanesulfenamides in CH₂Cl₂ the use of a base to activate DAST remains crucial, but
when THF was used as a solvent the electron pair belonging to the oxygen atom in the THF might play the role of the base activating the DAST.

With the aim to access more sulfenamides reagents, difluoromethyl(trimethylsilyl)acetate, Si4, was involved in a reaction with DAST in presence of DIEA. Quenching the reaction with a proper amine would give the desired product. Based on the previous results obtained during the synthesis of 1a, we first tried the reaction in THF, and CH₂Cl₂/DIEA at 25 °C (Table 5, entries 1-2). In both cases the formation of the intermediate was observed in 19F NMR with a 20 % dosed yield, represented by an AB system signal between -110.35 and -112.62 ppm. After 1.5 h, aniline was added to the reaction media leading to the formation of a peak at -93.05 observed in 19F NMR. The peak corresponds to the compound 1d, which was obtained with a 20 % yield (total conversion of the in situ formed intermediate). Decreasing the temperature at -25 °C the yield was doubled up to 40 % when the reaction was run in CH₂Cl₂, 32 % by using CH₃CN as a solvent and 35 % by using THF as a solvent (Table 5, entry 3-4 and 6). A further decrease of the reaction temperature up to -50 °C did not improve the overall yield of the reaction (Table 5, entry 5). The addition of the amine after only 30 minutes, did not lead to the formation of compound 1d (Table 5, entry 7).

Table 5 Synthesis of 1d

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>Solvent</th>
<th>T (°C) Time h</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>DIEA</td>
<td>CH₂Cl₂</td>
<td>25 °C (1.5 h)</td>
<td>20 %</td>
</tr>
<tr>
<td>2</td>
<td>-</td>
<td>THF</td>
<td>25 °C (1.5 h)</td>
<td>20 %</td>
</tr>
<tr>
<td>3</td>
<td>DIEA</td>
<td>CH₃CN</td>
<td>-25 °C (1.5 h)</td>
<td>32 %</td>
</tr>
<tr>
<td>4</td>
<td>DIEA</td>
<td>CH₂Cl₂</td>
<td>-25 °C (1.5 h)</td>
<td>40 %</td>
</tr>
<tr>
<td>5</td>
<td>DIEA</td>
<td>CH₂Cl₂</td>
<td>-50 °C (1.5 h)</td>
<td>32 %</td>
</tr>
<tr>
<td>6</td>
<td>-</td>
<td>THF</td>
<td>-25 °C (1.5 h)</td>
<td>35 %</td>
</tr>
<tr>
<td>7</td>
<td>DIEA</td>
<td>CH₂Cl₂</td>
<td>-25 °C (0.5 h)</td>
<td>-</td>
</tr>
</tbody>
</table>

Crude yields were determined by 19F NMR spectroscopic analysis using PhOCF₃ as an internal standard.

As shown above, the synthesis of two novel reagents has been successfully achieved and both reactions were scaled-up to 100 mmol without affecting the yield. Both compound 1a and 1d were successfully used as difluoromethylthioalkylating reagents in electrophilic reactions.
II.1.3.1 N-methylation of sulfenamides

Based on the previous studies concerning the use of sulfenamides as trifluoromethylthiolating reagents, we observed that a N-methylation leads to a fully-exploitation potential of those reagents. This is due to the acidic character of the hydrogen bounded to nitrogen. Thus, the N-methylated analogues have been used for the trifluoromethylthiolation of Grignard compounds, base-catalyzed trifluoromethylthiolation of \( \alpha \)-ketones and alkynes, Cu-mediated trifluoromethylthiolation of boronic acids and alkynes, and trifluoromethylthiolation of alcohols in basic conditions. Keeping in mind the urge of pharmaceutical and agrochemical companies to access to different classes of adducts bearing \( \text{SCF}_2\text{R} \) groups, capable to modulate their physico-chemical properties we planned the methylation of our two reactants.

Table 6 N-methylation reactions of reagents 1a and 1d

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Base</th>
<th>Me-R1</th>
<th>Solvent</th>
<th>T (°C)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>SO₂Ph</td>
<td>NaH</td>
<td>MeI</td>
<td>DMF</td>
<td>0 - 25 °C</td>
<td>-</td>
</tr>
<tr>
<td>2a</td>
<td>SO₂Ph</td>
<td>DIEA</td>
<td>MeOTf</td>
<td>CH₂Cl₂</td>
<td>25 °C</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>SO₂Ph</td>
<td>NaH</td>
<td>MeOTf</td>
<td>DMF</td>
<td>0 - 25 °C</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>CO₂Me</td>
<td>NaH</td>
<td>MeI</td>
<td>DMF</td>
<td>0 - 25 °C</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>CO₂Me</td>
<td>DIEA</td>
<td>MeOTf</td>
<td>DMF</td>
<td>25 °C</td>
<td>-</td>
</tr>
<tr>
<td>6b</td>
<td>CO₂Me</td>
<td>LDA</td>
<td>MeOTf</td>
<td>THF</td>
<td>0 - 25 °C</td>
<td>-</td>
</tr>
<tr>
<td>7b</td>
<td>CO₂Me</td>
<td>KHMDS</td>
<td>MeOTf</td>
<td>THF</td>
<td>0 - 25 °C</td>
<td>-</td>
</tr>
<tr>
<td>8c</td>
<td>CO₂Me</td>
<td>-</td>
<td>TMSCH₂N₂</td>
<td>MeOH</td>
<td>25 °C</td>
<td>-</td>
</tr>
<tr>
<td>9d</td>
<td>CO₂Me</td>
<td>DIEA</td>
<td>Me₂SO₄</td>
<td>CH₂Cl₂</td>
<td>-20 °C</td>
<td>-</td>
</tr>
<tr>
<td>10d</td>
<td>CO₂Me</td>
<td>n-BuLi</td>
<td>Me₂SO₄</td>
<td>THF</td>
<td>-20 °C</td>
<td>-</td>
</tr>
<tr>
<td>11</td>
<td>CO₂Me</td>
<td>n-BuLi</td>
<td>MeOTf</td>
<td>THF</td>
<td>-20 °C</td>
<td>-</td>
</tr>
<tr>
<td>12e</td>
<td>CO₂Me</td>
<td>DIEA</td>
<td>BF₄(OEt)₃</td>
<td>CH₂Cl₂</td>
<td>-20 °C</td>
<td>-</td>
</tr>
</tbody>
</table>

Crude yields were determined by \(^{19}\text{F}\) NMR spectroscopic analysis using PhOCF₃ as an internal standard. * 2 eq of MeOTf were used. b 1.5 eq of both MeOTf and base were used. d 4 eq of TMSCH₂N₂ were used. e 1.3 eq of Me₂SO₄ were used. f 2.5 eq of BF₄(OEt)₃ were used.

Unfortunately, the N-methylation of 1a and 1b did not lead to the desired compounds 1aa and 1dd. Different methylating sources (MeI, MeOTf, Me₂SO₄, TMSCH₂N₂, BF₄(OEt)₃), in presence of various bases (NaH, DIEA, LDA, KHMDS, n-BuLi) and changing reaction conditions as...
solvents and temperature has been unsuccessfully tested (Table 6, entries 1-12). In most of the cases only remaining starting material could be detected by $^{19}$F NMR.

II.2 Electrophilic (phenylsulfonyl)difluoromethylthiolation using a shelf-stable reagent

II.2.1.1 State of the art: interest of phenylsulfonyl part.

Sulfones were denominated “chemical chameleons” by Prof. Trost due to their ability to behave as nucleophiles in basic media and electrophiles in Lewis acid media.[213] Thus, molecules bearing a phenylsulfonyl group could represent a valuable choice to access new adducts through post-functionalization reactions by displacing the PhSO$_2$ group. Moreover, its high electronic parameters ($\sigma_m = 0.62$ and $\sigma_p = 0.68$) and low Hansch parameter ($\pi_R = 0.27$) could be exploited to modulate the physico-chemical properties of the molecules.

Figure 3 Presence of phenylsulfonyl-containing molecules in material and life science

Over the years, phenylsulfonyl group has demonstrated to be a valuable tool in both material and life science. PSPC (3-(phenylsulfonyl)-pyrazinecarbonitrile) showed a remarkable antibacterial activity against both gram-negative and gram-positive bacteria, meanwhile its sulfide analog showed no activity at all.[214] Phenylsulfonyl-furoxan based hydroxamates showed histone deacetylase inhibitory and NO donating activities in a multifunctional drug approach strategy.[215] Phenylsulfonyl group is found also in Rilmakalim, a molecule that exhibits vasodilatation by
opening ATP-sensitive K⁺ channels. Phenyl sulfonyl group has been also incorporated into molecules used in materials as dyes or OLEDs. Consequently, the synthesis of molecules bearing a SCF₂SO₂Ph substituents could lead to valuable compounds for further applications.

II.2.1.2 S₂Ar reactions using (phenylsulfonyl)difluoromethanesulfenamide

In order to test the efficiency of 1a as an electrophilic (phenylsulfonyl)difluoromethylthiolating reagent and based on previous results obtained with electrophilic SCF₃ reagents, we planned the acid-mediated insertion of PhSO₂CF₂S moiety into aromatic and heteroaromatic compounds.

Indole was chosen as the compound of choice with the aim to fine-tune the reaction conditions. Reagent 1a showed good reactivity in presence of excess, stoichiometric as well as catalytic amounts of p-toluensulfonic acid leading to compound 3a with 89 %, 69 % and 48 % respectively (Table 7, entries 1-3).

Table 7 Acid-mediated activation of reagent 1a

<table>
<thead>
<tr>
<th>Entry</th>
<th>Acid (eq)</th>
<th>Solvent</th>
<th>T (°C)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>p-TsOH 2.5 equiv.</td>
<td>CH₂Cl₂</td>
<td>50 °C</td>
<td>89 %</td>
</tr>
<tr>
<td>2</td>
<td>p-TsOH 1 equiv.</td>
<td>CH₂Cl₂</td>
<td>50 °C</td>
<td>69 %</td>
</tr>
<tr>
<td>3</td>
<td>p-TsOH 20 mol %</td>
<td>DCE</td>
<td>80 °C</td>
<td>48 %</td>
</tr>
<tr>
<td>4</td>
<td>TMSCl 1 equiv.</td>
<td>CH₃CN</td>
<td>80 °C</td>
<td>83 %</td>
</tr>
<tr>
<td>5</td>
<td>TMSCl 1 equiv.</td>
<td>CH₃CN</td>
<td>25 °C</td>
<td>75 %</td>
</tr>
<tr>
<td>6</td>
<td>TMSCl 20 mol %</td>
<td>CH₃CN</td>
<td>80 °C</td>
<td>48 %</td>
</tr>
<tr>
<td>7</td>
<td>TfOH 2.5 equiv.</td>
<td>CH₂Cl₂</td>
<td>50 °C</td>
<td>-</td>
</tr>
<tr>
<td>8</td>
<td>TfOH 1 equiv.</td>
<td>CH₂Cl₂</td>
<td>50 °C</td>
<td>80 %</td>
</tr>
<tr>
<td>9</td>
<td>TfOH 20 mol %</td>
<td>DCE</td>
<td>80 °C</td>
<td>61 %</td>
</tr>
</tbody>
</table>

Also the use of a stronger protic acid as triflic acid (TfOH) was found efficient in catalysing the reaction in stoichiometric or catalytic amounts with 80 % and 61 % yield respectively. (Table 7, entries 8-9). On the other hand, when 2.5 equiv. of TfOH were used neither product formation
was observed, nor traces of 1a were found in the reaction media after checking with $^{19}$F NMR (Table 7, entry 7).

Activation of 1a was obtained also using stoichiometric amounts of a soft Lewis acid as trimethylsilyl chloride (TMSCl) at 80 °C and 25 °C in acetonitrile, with a yield of 83 % and 75 % (Table 7, entries 4-5). Addition of catalytic amounts of TMSCl led to compound 3a in a 48 % yield (Table 7, entry 6). With the optimized conditions in hand (Table 7, entry 1) we extended the reaction scope to other electron-rich aromatic and heteroaromatic substrates.

Heteroaromatic scaffolds as indoles and pyrroles, known for their use in pharmaceuticals and/or agrochemicals were successfully (phenylsulfonyl)difluoromethylthiolated. Compounds 3a-e were obtained with good to excellent yields except the β-methylated indole 3b which was obtained...
Chapter I. Synthesis of SCF₂R derivatives and their application in electrophilic reactions

with 57 % yield. Various functional groups as –Br, -OMe, -COOH, -NH₂ were tolerated and in the case of the tryptophan 2d there was no need to protect the amino group and the carboxyl function. Compound 3f was obtained using 1 equiv. of TMSCl at room temperature. An increase in temperature did not lead to the formation of any product. On the other hand, 3g was obtained with a better yield at 80 °C. The use of a milder acid as TMSCl in the case of pyrroles come from the high sensitivity of pyrroles to acidic condition’s, leading easily to polymerisation. Pyrrole 2t did not lead to the formation of the compound 3t, whatever the conditions. Also electron-rich aromatics, 3i and 3j were obtained with 80 % and 89 % yield respectively. Phenols as 2k and 2l needed a stronger acid to be activated, therefore leading to compounds 3k and 3l in presence of 1 equiv. of TfOH. Less electron-rich compounds as 2m and 2n gave their corresponding PhSO₂CF₂S derivatives with lower yields, 30 % and 45 % respectively. Also in this case the use of a stronger acid as TfOH was necessary. When N-dimethylaniline reacted with 1a in presence of p-TsOH a peak at ~81.56 ppm was detected in ¹⁹F NMR, which presumably corresponds to compound 3o. Unfortunately, we were not able to isolate compound 3o in order to have further evidences concerning its formation. Heteroaromatic compounds as benzothiophene 3p, benzodioxole 3q and dihydroimidazopyridines 3r-s did not give any formation of desired compounds, certainly due to their lower reactivity.
II.2.1.3 Electrophilic addition reactions on alkenes and alkynes

Protic or Lewis acid-mediated reaction between reagent 1a and alkenes were performed. In the case of trifluoromethanesulfenamides the best results were obtained in presence of a Lewis acid and a tosylate salt.[118] In the case of reagent 1a, the addition of SCF₂SO₂Ph to cyclohexene after activation of 1a by TsOH gave 5a in 77% dosed yield whereas only 70% was obtained in Lewis acid conditions (Table 8, entries 1-2). An AB system was observed in ¹⁹F NMR corresponding to compound 5a, which was isolated with 61% yield. An increase in temperature resulted in lower yields, 60% when a protic acid was used and no product formation when a Lewis acid was used (Table 8, entries 3-4).

Table 8 Electrophilic addition on alkenes using 1a

<table>
<thead>
<tr>
<th>Entry</th>
<th>Acid / Nu (eq)</th>
<th>Solvent</th>
<th>T (°C)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>p-TsOH 2.5 equiv.</td>
<td>CH₂Cl₂</td>
<td>50 °C</td>
<td>77 %</td>
</tr>
<tr>
<td>2</td>
<td>BF₃·Et₂O / p-TsONa 5 / 1.5 equiv.</td>
<td>CH₂Cl₂</td>
<td>50 °C</td>
<td>70 %</td>
</tr>
<tr>
<td>3</td>
<td>p-TsOH 2.5 equiv.</td>
<td>DCE</td>
<td>80 °C</td>
<td>60 %</td>
</tr>
<tr>
<td>4</td>
<td>BF₃·Et₂O / p-TsONa 5 / 1.5 equiv.</td>
<td>DCE</td>
<td>80 °C</td>
<td>-</td>
</tr>
</tbody>
</table>

Crude yields were determined by ¹⁹F NMR spectroscopic analysis using PhOCF₃ as an internal standard.

Whatever the conditions, only the *trans* product is formed, demonstrating the stereoselectivity of the reaction.

With our best conditions in hand, we extended the scope to other alkenes. Addition to 1-dodecene gave compound 5b in a modest yield but as the only product based on ¹⁹F NMR analysis. As in the case of 5a the signal in ¹⁹F NMR is represented by an AB system and is the only signal we could observe. This demonstrates the high regioselectivity of this reaction, because only the Markovnikov product is observed.
Electrophilic addition to (Z)-oct-4-ene led to the formation of 5c, and the trans conformation was obtained in a 54 % yield, confirming the stereoselectivity of the reaction. Only a single peak was observed in $^{19}$F NMR at -77.53 ppm as the sole formed peak after 15 h.

Performing the same reaction using (E)-oct-4-ene, as a starting material only 30 % compound 5d was isolated, half respect to the Z enantiomer. However, only one diastereomer has been formed (the other one compare to Z-isomer) demonstrating the stereospecificity of the reaction.

Furthermore, during the reaction, the allylic product 6d was also formed. It seems that the tosylate attack to the intermediate sulfenium is disfavoured due to steric hindrance and deprotonation in $\alpha$-position is favoured, thus leading to the formation of the allylic compound 6d (Scheme 62, eq. a). Using an acid that has a less nucleophilic conjugate base as triflic acid, leads to the exclusive formation of the allylic compound with 58 % yield (Scheme 62, eq. b).

Based on the obtained results, we presume a mechanism involving the formation of a transient episulfonium center. Protonation of 1a leads to the transfer of $^{19}$SCF$_2$SO$_2$Ph to form an episulfonium cation, which opens after the conjugated base (TsO$^-$ anion) approaches from back, to give the compound 5a with a trans configuration.
Considering the low nucleophilicity of weak conjugate bases as TfO\(^-\), the TfOH-mediated activation of 1a leads to the formation of compound 5e through an intramolecular cyclization reaction. Once the sulfonium intermediate is formed, the triflate anion is not enough nucleophilic to open it, thus the available electron pair of the aromatic ring attacks in \(\alpha\)-position of the sulfenium intermediate, causing ring opening and giving compound 5e with a 71 % isolated yield (Scheme 64).

After the encouraging results obtained in the acid-mediated addition of SCF\(_2\)SO\(_2\)Ph to alkenes, we performed the addition to alkynes using the same strategy. Contrary to alkenes, the use of a protic acid was less effective than a Lewis acid and the tosylate salt as a nucleophile. Adding 2.5 equiv. of \(p\)-TsOH to a mixture of 1a and alkyne at room temperature did not lead to the formation of the expected compound. Only the presence of starting material (1a) was observed after 48 h in \(^{19}\)F NMR spectroscopy (Table 9, entry 1). Increasing the temperature at 50 °C, a peak at -81.50 ppm was observed in \(^{19}\)F NMR, which corresponds to the desired compound, with
a dosed yield of 35 % (Table 9, entry 2). However, a further increase in temperature resulted deleterious for the reaction, giving the desired compound with only 15 % dosed yield (Table 9, entry 6). Fortunately, using boron trifluoride as a Lewis acid the reaction gave a yield of 26 % already at room temperature. Further increasing in temperature led to an improvement in yields, 44 % at 50 °C and 63 % at 80 °C (Table 9, entry 4-5).

Table 9 Addition to alkynes

<table>
<thead>
<tr>
<th>Entry</th>
<th>Acid / Nu (eq)</th>
<th>Solvent</th>
<th>T (°C)</th>
<th>Time h</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>p-TsOH 2.5 equiv.</td>
<td>CH₂Cl₂</td>
<td>25 °C</td>
<td>48 h</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>p-TsOH 2.5 equiv.</td>
<td>CH₂Cl₂</td>
<td>50 °C</td>
<td>48 h</td>
<td>35 %</td>
</tr>
<tr>
<td>3</td>
<td>BF₃·Et₂O / p-TsONa 5 / 1.5 equiv.</td>
<td>CH₂Cl₂</td>
<td>25 °C</td>
<td>48 h</td>
<td>26 %</td>
</tr>
<tr>
<td>4</td>
<td>BF₃·Et₂O / p-TsONa 5 / 1.5 equiv.</td>
<td>CH₂Cl₂</td>
<td>50 °C</td>
<td>48 h</td>
<td>44 %</td>
</tr>
<tr>
<td>5</td>
<td>BF₃·Et₂O / p-TsONa 5 / 1.5 equiv.</td>
<td>DCE</td>
<td>80 °C</td>
<td>24 h</td>
<td>63 %</td>
</tr>
<tr>
<td>6</td>
<td>p-TsOH 2.5 equiv.</td>
<td>DCE</td>
<td>80 °C</td>
<td>24 h</td>
<td>15 %</td>
</tr>
</tbody>
</table>

Crude yields were determined by ¹⁹F NMR spectroscopic analysis using PhOCF₃ as an internal standard.

The following reaction conditions were successfully applied to three different alkynes, 7a-c, obtaining single stereo- and regio-isomers 8a-c in modest to good yields

Figure 6 Electrophilic addition to alkynes. Yields shown are of isolated products; values in parentheses are the yields as determined by ¹⁹F NMR

As in the case of alkenes, a transient episulfenium species is supposed as an intermediate leading to the final compounds by means of a nucleophilic attack mediated by the tosylate anion, which causes the opening of the sulfenium species.

II.2.1.4 Reductive desulfonylation: Access to SCF₂H compounds

Difluoromethylthio (SCF₂H) is an emerging group in fluorine chemistry, and there is still a lot of need for reagents and different ways to access difluoromethylthiolated molecules. As shown in
the bibliographic part, very recently there have been reported two shelf-stable reagents and other synthetic methodologies to access difluoromethylthiolated molecules. Thus, we thought of accessing difluoromethylthiolated compounds through a reductive desulfonfonylation reaction by taking advantage of the good capacity of phenylsulfone as a leaving group. Reductive desulfonymlations are typically accomplished with metal amalgams. However, considering the difficulties in the preparation and use of the amalgams and the environmental hazards they do present there was a need to substitute such reductants with safer ones. Hu and coll. accessed to difluoromethylated carbonyl compounds by a magnesium metal-mediated desulfonfonylation reaction using AcOH/NaOAc as a proton source. Based on already reported procedures we first tried a LiAlH₄-mediated desulfonfonylation in THF. A typical doublet corresponding to the SCF₂H group appeared in the ¹⁹F NMR spectra between -93.54 ppm and -93.75 ppm. Substituting the reductive system with Mg/I₂ using MeOH as a proton donor and as a solvent the dosed yield improved to 89 %.

Taking for granted the above reaction conditions as the best ones, we applied it to the different classes of compounds previously synthesized in order to access to various difluoromethylthiolated molecules. Compound 9a was isolated with a yield of 88 %. Also the indole and the pyrrole derivatives gave excellent isolated yields, 95 % and 82 % respectively. The intramolecular cyclization product 5e was also successfully reduced to 9e. In the case of compound 5a simultaneous desulfonfonylation and tosylate hydrolysis were obtained, leading to the compound 9d, in excellent yield. A further advantage of this methodology is that the final compounds were directly obtained after a simple work-up process, thus no need to use other purification techniques.
II.2.1.5 Reductive desulfonylation: Access to SCF₂D compounds

Deuterium is the stable isotope of the hydrogen, discovered by Harold Urey in 1932. Since its discovery, deuterium has been reported in a myriad of scientific publications. Nevertheless, the most common way to access deuterated compounds remains the isotope exchange methodology. Thus, the development of novel methods to access to such compounds is demanding considering also the recent interest of pharmaceutical companies towards deuterium. Being the stable isotope of hydrogen makes deuterium its best bioisostere without bringing any change on steric grounds. C-D bond is reported to be 6-10 times stronger than the C-H bond, thus an increase in stability towards oxidative processes has to be expected. As a consequence incorporation of deuterium into drugs could lead to drastic modifications to ADMET properties.\textsuperscript{[221]} On late 2016 FDA approved the use of the first deuterated drug for the treatment of Huntington Disease, SD-809 (deutetrabenazine). Although head-to-head trials between deutetrabenazine and tetrabenazine has never been run, clinical data comparison suggested that SD-809 has a better safety profile respect to tetrabenazine.\textsuperscript{[222]} Recently a deuterated version of the \textsuperscript{18}F rolipram analogue has been reported in order to avoid the defluorination in vivo, thus limiting the bone uptake of free \textsuperscript{18}F-fluoride.\textsuperscript{[223]} With in mind the interest of deuterium we accessed to deuterated compounds by reductive desulfonylation using simply CD₃OD as a source of deuterium.
As shown in Figure 8, desulfonylation of different classes of products was obtained with good to excellent yields and in $^{19}$F NMR and $^1$H NMR spectroscopy only the formation of deuterated compounds has been observed. Desulfonylation of 5a led to [D]9d and only deuteration of difluoromethylthio moiety was observed based on GC-MS analysis. It should be noticed that these results constitute the first synthesis of DCF$_2$S-molecules.

**II.2.1.6 Post-functionalization of phenylsulfonyl moiety**

Several efforts have been made with the aim to fully exploit the post-functionalization capacity and the “chameleon like” character of the phenylsulfonyl moiety. Compound 3i was used as a starting material in post-functionalization reactions. In a Mg-mediated reductive desulfonylation followed by silylation in presence of TMSCl we obtained compound 11a with a 93 % yield. TMSCl is used both as a silylating reagent and as an Mg$^0$ activator.

Considering the recent interest toward SCF$_2$ moiety and the lack of methodologies in forming C-CF$_2$S bonds, we decided to put our efforts in exploring such demanding chemistry. Starting from the results obtained by Olah and coll. in the t-BuOK-induced trifluoromethylation of carbonyl compounds and disulfides using PhSO$_2$CF$_3$ as a trifluoromethylating source,$^{[29]}$ we planned to extrapolate the above-mentioned conditions in order to access new difluoromethylthiolated compounds.
Table 10 Post-functionalization reactions

<table>
<thead>
<tr>
<th>Entry</th>
<th>Starting Material (equiv.)</th>
<th>T (°C) Time (h)</th>
<th>Additive (equiv.)</th>
<th>Yield (%)</th>
<th>S.M (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1 equiv. Acetophenone</td>
<td>-50 °C – 25 °C 16 h</td>
<td>t-BuOK 2.5 equiv.</td>
<td>n.r</td>
<td>100 %</td>
</tr>
<tr>
<td>2</td>
<td>3 equiv. Benzaldehyde</td>
<td>-50 °C – 25 °C 16 h</td>
<td>t-BuOK 2 equiv.</td>
<td>n.r</td>
<td>100 %</td>
</tr>
<tr>
<td>3</td>
<td>1 equiv. Benzophenone</td>
<td>0 °C 4 h</td>
<td>t-BuOK 3 equiv.</td>
<td>n.r</td>
<td>50 %</td>
</tr>
<tr>
<td>4</td>
<td>1 equiv. Benzoic acid</td>
<td>25 °C 4 h</td>
<td>t-BuOK 3 equiv.</td>
<td>n.r</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>1 equiv. Benzyl chloride</td>
<td>25 °C 2 h</td>
<td>Mg 2 equiv.</td>
<td>n.r</td>
<td>50 %1</td>
</tr>
<tr>
<td>6</td>
<td>1 equiv. Benzyl chloride</td>
<td>25 °C 1.5 h</td>
<td>Mg/I2 5/0.3 equiv.</td>
<td>n.r</td>
<td>100 %1</td>
</tr>
<tr>
<td>7</td>
<td>PhSSPh</td>
<td>25 °C 2 h</td>
<td>Mg/I2 5/0.3 equiv.</td>
<td>n.r</td>
<td>100 %1</td>
</tr>
</tbody>
</table>

*Crude yields were determined by 19F NMR spectroscopic analysis using PhOCF\(_3\) as an internal standard. 1 No starting material was found when the reaction was run for 16 h.*

Addition of a solution of t-BuOK in DMF to a mixture of acetophenone or benzaldehyde and compound 3i under stirring for 1 h at -50 °C and 15 h more hours at 25 °C did not result in the formation of any compound (Table 10, entries 1-2). Moreover, compound 3i was fully recovered after 15 h.

When benzophenone was used as a starting material in DMF at 0 °C and 25 °C the formation of two new peaks was observed. First, an unknown compound corresponding to a peak at -50.48 ppm was observed by 19F NMR (Table 10, entries 3-4), but all the attempts to isolate this product failed. Second, a peak corresponding to the HCF\(_2\)S-adduct, arising from a reductive...
desulfonylation reaction was observed at $^{19}$F NMR spectroscopy. Neither reacting phenyldisulfide with 3i under Mg/I system conditions, led to the formation of the desired compound (Table 10, entry 7). As in the case of benzaldehydes and ketones only starting material was recovered. In the reaction between phenylselenyl chloride and 3i at DMF in presence of Mg a peak at -47 ppm, corresponding to an unknown compound, was observed in $^{19}$F NMR. Unfortunately, we could not isolate the preformed compounds by flash chromatography. When iodine was added to the reaction mixture such peak was not observed in $^{19}$F NMR (Table 10, entries 5-6).

Another way to access C-CF$_2$S bond formation could be the substitution of phenylsulfonyl with an alkyl group. Using methyl iodide as a methylating agent in a Mg-mediated reaction in DMF no reaction was observed and after 16 h 3i was fully recovered (Table 11, entry 1). Methyl triflate was used as a methylating source in THF or as both reagent and solvent without success (Table 11, entries 2 and 5). Neither the use of other alkylating reagents as Me$_2$SO$_4$ and BF$_4$OEt$_3$ led to the formation of the desired product (Table 11, entries 3-4).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Alkyl-R (equiv.)</th>
<th>Additive (equiv.)</th>
<th>Solvent</th>
<th>Yield (%)</th>
<th>Starting material %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MeI 3 equiv.</td>
<td>Mg/I$_2$ 30/0.3 equiv.</td>
<td>DMF</td>
<td>-</td>
<td>100 %</td>
</tr>
<tr>
<td>2</td>
<td>MeOTf 3 equiv.</td>
<td>Mg/I$_2$ 10/0.3 equiv.</td>
<td>THF</td>
<td>-</td>
<td>65 %</td>
</tr>
<tr>
<td>3</td>
<td>Me$_2$SO$_4$ 3 equiv</td>
<td>Mg/I$_2$ 10/0.3 equiv.</td>
<td>CH$_2$Cl$_2$</td>
<td>-</td>
<td>75 %</td>
</tr>
<tr>
<td>4</td>
<td>BF$_4$OEt$_3$</td>
<td>Mg/I$_2$ 10/0.3 equiv.</td>
<td>CH$_3$CN</td>
<td>-</td>
<td>85 %</td>
</tr>
<tr>
<td>5</td>
<td>MeOTf 10/0.3 equiv</td>
<td>Mg/I$_2$ 10/0.3 equiv.</td>
<td>MeOTf</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Crude yields were determined by $^{19}$F NMR spectroscopic analysis using PhOCF$_3$ as an internal standard.

Compounds bearing a SCF$_2$X group (X= Br, I) are interesting building blocks, especially for further use as starting materials in cross-coupling reactions. Thus, recently the demand for the synthesis of halogenated compounds has been increasing. The use of NBS as a halogenating agent in presence of Mg or t-BuOK did lead to the formation of the desired compound. Even after 16 h compound 3i was found to be quantitatively present in the reaction media (Table 12, entries 1-4). Dibromotetrachloroethane (Br$_2$Cl$_4$C$_2$), diiodoethene (I$_2$C$_2$H$_2$) and iodine (I$_2$) were implied in halogenation reactions in presence of Mg in DMF at 25 °C and 80 °C without leading
to the formation of the desired compound even though consummation of starting material was observed (Table 12, entries 5-9). We explored also the replacement of the phenylsulfonyl group by fluorine; an interesting reaction especially for the development of novel methodologies for the synthesis $^{18}$F radiolabeled compounds. The use of Selectfluor as a fluorine source in presence of AgNO$_3$ or Mg did not lead to the formation of any compound (Table 12, entries 10-13).

Table 12 Desulfonative halogenation reactions

<table>
<thead>
<tr>
<th>Entry</th>
<th>R-X (equiv.)</th>
<th>Additive (equiv.)</th>
<th>Solvent</th>
<th>Temp °C</th>
<th>Yield (%)</th>
<th>S. M %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NBS 5 equiv.</td>
<td>Mg 2 equiv.</td>
<td>DMF</td>
<td>25 °C</td>
<td>-</td>
<td>100 %</td>
</tr>
<tr>
<td>2</td>
<td>NBS 2 equiv.</td>
<td>Mg/I$_2$ 10/0.3</td>
<td>DMF</td>
<td>25 °C</td>
<td>-</td>
<td>100 %</td>
</tr>
<tr>
<td>3</td>
<td>NBS 5 equiv.</td>
<td>t-BuOK 3 equiv.</td>
<td>DMF</td>
<td>25 °C</td>
<td>-</td>
<td>100 %</td>
</tr>
<tr>
<td>4</td>
<td>NBS 5 equiv.</td>
<td>Mg/I$_2$ 30/0.3 equiv.</td>
<td>CH$_3$CN</td>
<td>25 °C</td>
<td>-</td>
<td>100 %</td>
</tr>
<tr>
<td>5</td>
<td>I$_2$ 5 equiv.</td>
<td>Mg/I$_2$ 10/0.3 equiv.</td>
<td>DMF</td>
<td>25 °C</td>
<td>-</td>
<td>100 %</td>
</tr>
<tr>
<td>6</td>
<td>Br$_2$Cl$_2$ 10 equiv.</td>
<td>Mg/I$_2$ 30/0.3 equiv.</td>
<td>DMF</td>
<td>25 °C</td>
<td>-</td>
<td>65 %</td>
</tr>
<tr>
<td>7</td>
<td>Br$_2$Cl$_2$ 10 equiv.</td>
<td>Mg/I$_2$ 30/0.3 equiv.</td>
<td>DMF</td>
<td>80 °C</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>8</td>
<td>I$_2$C$_2$H$_2$ 10 equiv.</td>
<td>Mg/I$_2$ 30/0.3 equiv.</td>
<td>DMF</td>
<td>25 °C</td>
<td>-</td>
<td>90 %</td>
</tr>
<tr>
<td>9</td>
<td>I$_2$C$_2$H$_2$ 10 equiv.</td>
<td>Mg/I$_2$ 30/0.3 equiv.</td>
<td>DMF</td>
<td>80 °C</td>
<td>-</td>
<td>95 %</td>
</tr>
<tr>
<td>10</td>
<td>Selectfluor 5 equiv.</td>
<td>AgNO$_3$ 1 equiv.</td>
<td>Acetone/H$_2$O</td>
<td>55 °C</td>
<td>-</td>
<td>40 %</td>
</tr>
<tr>
<td>11</td>
<td>Selectfluor 10 equiv.</td>
<td>Mg/I$_2$ 20/0.3 equiv.</td>
<td>DMF</td>
<td>25 °C</td>
<td>-</td>
<td>35 %</td>
</tr>
<tr>
<td>12</td>
<td>Selectfluor 10 equiv.</td>
<td>Mg/I$_2$ 20/0.3 equiv.</td>
<td>DMF</td>
<td>25 °C</td>
<td>-</td>
<td>75 %</td>
</tr>
</tbody>
</table>

Crude yields were determined by $^{19}$F NMR spectroscopic analysis using PhOCF$_3$ as an internal standard.
II.3 (Methoxycarbonyl)difluoromethanesulfenamide: A new shelf-stable reagent

As reported above compound 1d also was prepared starting from the corresponding silane and DAST and the synthesis was scaled-up to 100 mmol of starting material without any change in the isolated yield. Herein, we disclose the last obtained results using reagent 1d as donor of \(^{+}\text{SCF}_2\text{CO}_2\text{Me}\) in presence of various classes of compounds. The presence of \(\text{CO}_2\text{Me}\) group could be exploited to access various compounds through a series of interesting post-functionalization reactions.

II.3.1.1 SEAr using compound 1d

As in the case of 1a, reagent 1d was involved in electrophilic aromatic substitution reactions, in order to test its reactivity and access to compounds bearing an \(\text{SCF}_2\text{CO}_2\text{Me}\) group.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Acid (equiv.)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>TMSCl 1 equiv.</td>
<td>83 %</td>
</tr>
<tr>
<td>2</td>
<td>TMSCl 2 equiv.</td>
<td>100 %</td>
</tr>
<tr>
<td>3</td>
<td>TMSCl 30 mol %</td>
<td>50 %</td>
</tr>
<tr>
<td>4</td>
<td>(p)-TsOH 1 equiv.</td>
<td>40 %</td>
</tr>
<tr>
<td>5</td>
<td>(p)-TsOH 2.5 equiv.</td>
<td>65 %</td>
</tr>
<tr>
<td>6</td>
<td>(p)-TsOH 30 mol %</td>
<td>40 %</td>
</tr>
<tr>
<td>7</td>
<td>TfOH 1 equiv.</td>
<td>93 %</td>
</tr>
</tbody>
</table>

Crude yields were determined by \(^{19}\text{F}\) NMR spectroscopic analysis using PhOCF₃ as an internal standard.

As shown in Table 13 both Lewis and protic acid can be activate reagent 1d. The use of \(p\)-toluenesulfonic acid in excess (2.5 eq.) led to the formation of the compound 20a with a yield of 65 % (Table 13, entry 5). Stoichiometric and catalytic quantities of \(p\)-toluenesulfonic acid gave the desired indole with a yield of 40 % in both cases (Table 13, entries 4 and 6). Using a stronger acid as TfOH increased the yield at 93 % (Table 13, entry 7). Nevertheless, the use of milder reaction conditions as activation of 1d by a Lewis acid results more advantageous and less complicated from a procedural point of view. Thus, employing TMSCl as an activator we observed the formation of compound 20a by both using excess, stoichiometric and catalytic
Chapter I. Synthesis of SCF₂R derivatives and their application in electrophilic reactions

amounts of acid (Table 13, entries 1-3). However, the best result was obtained using 2 equiv. of TMSCl, which led to the formation of compound 20a with a 100 % dosed yield corresponding to a peak at -84.47 ppm observed by ¹⁹F NMR spectroscopy. Thus with the optimized reaction conditions in hand we extended the substrate scope to a wider number of electron-rich aromatic and heteroaromatic compounds. Compound 20a and 20c were isolated with good yields after activation of 1d by TMSCl.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Yield</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>20a</td>
<td>80% (quant.)</td>
<td></td>
</tr>
<tr>
<td>20b</td>
<td>63% (70%)</td>
<td></td>
</tr>
<tr>
<td>20c</td>
<td>94% (100%)</td>
<td></td>
</tr>
<tr>
<td>20d</td>
<td>(36%)</td>
<td></td>
</tr>
<tr>
<td>20e</td>
<td>(13 %)</td>
<td></td>
</tr>
<tr>
<td>20f</td>
<td>99% (89 %)</td>
<td></td>
</tr>
<tr>
<td>20g</td>
<td>(0%)</td>
<td></td>
</tr>
<tr>
<td>20h</td>
<td>(20 %)</td>
<td></td>
</tr>
<tr>
<td>20i</td>
<td>(0 %)</td>
<td></td>
</tr>
<tr>
<td>20j</td>
<td>25% (33 %)</td>
<td></td>
</tr>
<tr>
<td>20k</td>
<td>80% (83%)</td>
<td></td>
</tr>
<tr>
<td>20l</td>
<td>81% (87%)</td>
<td></td>
</tr>
<tr>
<td>20m</td>
<td>66% (67%)</td>
<td></td>
</tr>
<tr>
<td>20n</td>
<td>83% (84%)</td>
<td></td>
</tr>
<tr>
<td>20o</td>
<td>(13%)</td>
<td></td>
</tr>
<tr>
<td>20p</td>
<td>(12%)</td>
<td></td>
</tr>
<tr>
<td>20q</td>
<td>(9%)</td>
<td></td>
</tr>
<tr>
<td>20r</td>
<td>(0%)</td>
<td></td>
</tr>
</tbody>
</table>

Figure 9 Sear reactions of electron rich arenes and heteroarenes with reagent 1d. Yields shown are of isolated products; values in parentheses are the yields as determined by ¹⁹F NMR. * TfOH 1 equiv., 50 °C, CH₂Cl₂ 15 h; b p-TsOH 2.5 equiv., 50 °C, CH₂Cl₂ 15 h.

On the other hand, to obtain compound 20b stronger conditions were needed as the use of p-TsOH. Using L-tryptophan as a starting material we could not access to compound 20d in a satisfactory yield, therefore the isolation of such compound was not possible. N-protected
indoles were also used in S$_8$Ar reactions. N-Tosyl indole gave compound 20e with only 13 %
dosed yield, making vain the tentative for isolating the compound. This might be due to the
electron-withdrawing properties of the tosyl group, which should deactivate the indole ring.
Reacting N-methyl indole with 1d we could obtain compound 20f with 89 % yield. Compound
20g and 20h were not obtained when we reacted the proper azaindoles with reagent 1d.
However, when compound 3-iodo-azaindole was used as a starting material, a peak at -84.79 ppm
was observed in 19F NMR, which could correspond to compound 20h. Neither the reaction of
an imidazolo-pyridine with the reagent 1d did lead to the formation of 20i. Compound 20j was
obtained in a modest yield, enabling the access to an interesting class of compounds as
substituted pyrroles. Also, electron-rich aromatics reacted with the reagent 1d, leading the desired
compounds in a good yield. However, the best results in this case were obtained when the
reaction was run in presence of a protic acid. Compounds 20k and 20l and 20m were obtained
after reacting dimethoxybenzene, resorcinol and phenol with 1d in presence of p-TsOH with 80
%, 81 % and 66 % yield respectively. In the case of naphthol a stronger acid as triflic acid was
needed to access compound 20n. Reacting less electron-rich adducts with the reagent 1d we
could not isolate the compounds 20p and 20q due to the low dosed yields observed in 19F NMR.
Neither the Boc-protected derivative of L-Dopa was able to give compound 20r.

II.3.1.2 Acid activation of α-ketones

Ketones are known as valuable building blocks and are also found in several natural products and
biomolecules. Moreover, ketones have important physiological properties and are found in
naturally occurring and synthetic steroid hormones. Cortisone, an anti-inflammatory agent has
three ketone groups on its core. Thus, the association of fluorinated motifs to a ketone group
into molecules could be of particular interest. Inspired by the previous works developed by us on
the trifluoromethylthiolation of ketones in α-position using the trifluoromethanesulfenamide
reagents$^{[134]}$ we planned the insertion of SCF$_2$CO$_2$Me moiety through an acid-catalyzed reaction
using 1d as a donor. Catalytic amounts of TMSCl in CH$_3$CN already led to the formation of
traces of the compound 21a, observed in $^{19}$F NMR (Table 14, entry 1). Using stoichiometric
amounts of TMSCl the dosed yield increased to 20 % (Table 14, entry 2). An excess of the Lewis
acid gave the desired compound with a 45 % yield in CH$_3$CN (Table 14, entry 3). Increasing the
amounts of 1d to 2.5 equiv. did not lead to any improvement in terms of yield (Table 14, entry 8).
Changing the solvent to dichloroethane 21a gave rise to 25 % yield (Table 14, entry 4). Even
when 2 equiv. of TMSCl were used at 50 °C in CH$_2$Cl$_2$ no formation of the compound was
observed (Table 14, entry 5). However, replacing CH$_2$Cl$_2$ with CH$_3$CN compound 21a the peak at
-83.45 ppm corresponding to compound 21a was observed in $^{19}$F NMR (Table 14, entry 6).
Substituting TMSCl with acetyl chloride (CH₃COCl) and running the reaction in NMP at 25 °C in presence of 2.5 equiv. of 1d, compound 21a was formed with a 35% yield (Table 14, entry 7).

Table 14 Acidic activation of ketones

<table>
<thead>
<tr>
<th>Entry</th>
<th>Acid (equiv.)</th>
<th>Solvent</th>
<th>T (°C)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>TMSCl (0.3 equiv.)</td>
<td>CH₃CN</td>
<td>90 °C</td>
<td>5</td>
</tr>
<tr>
<td>2</td>
<td>TMSCl (1 equiv.)</td>
<td>CH₃CN</td>
<td>90 °C</td>
<td>20</td>
</tr>
<tr>
<td>3</td>
<td>TMSCl (2 equiv.)</td>
<td>CH₃CN</td>
<td>90 °C</td>
<td>45</td>
</tr>
<tr>
<td>4</td>
<td>TMSCl (2 equiv.)</td>
<td>DCE</td>
<td>90 °C</td>
<td>25</td>
</tr>
<tr>
<td>5</td>
<td>TMSCl (2 equiv.)</td>
<td>CH₂Cl₂</td>
<td>50 °C</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>TMSCl (2 equiv.)</td>
<td>CH₃CN</td>
<td>50 °C</td>
<td>30</td>
</tr>
<tr>
<td>7</td>
<td>CH₃COCl (3 equiv.)</td>
<td>NMP</td>
<td>25 °C</td>
<td>35%²</td>
</tr>
<tr>
<td>8</td>
<td>TMSCl (2 equiv.)</td>
<td>CH₃CN</td>
<td>90 °C</td>
<td>45%²</td>
</tr>
</tbody>
</table>

Crude yields were determined by ¹⁹F NMR spectroscopic analysis using PhOCF₃ as an internal standard. 2.5 equiv. of 1d were used.

Taking for granted as best reaction conditions in entry 3, we extended the scope to a wider number of compounds. Acetophenone and 2-chloroacetophenone gave compound 21a and 21b in reasonable yields of 42% and 40% respectively. Surprisingly, the more hindered propiophenone gave 21d in a better yield of 52%. The benzofuran derivative 21c was obtained with a yield of 46%. Insertion of SCF₂CO₂Me in α-position of tetralone was successfully achieved with a dosed yield of 43%. The new compound 21e was observed in ¹⁹F NMR represented by an AB system between -80.36 and -82.46 ppm. The synthesis of the chromanone derivative was less efficient and a lower yield was obtained. The formation of both compounds was confirmed by GC-MS but still not isolated. More complex structures as cholestenone did not lead to the formation of 21g although all the starting material has been consumed after 16 h. Several peaks were observed in ¹⁹F NMR nevertheless it was not possible to isolate any compound in order to get more insight on the reaction. Also β-ketoester 15g did not give compound 21g. As in the case of cholestenone several peaks were observed in ¹⁹F NMR and simultaneous consumption of 1d also. Reacting ketone 15h with the reagent 1d under the same reaction conditions did not lead to the desired product. An aldehyde also was tested, but unfortunately did not lead to the formation of compound 21j.
II.3.1.3 Post-functionalization reactions

Several efforts were made in order to fully-exploit post-functionalization possibilities of SCF₂CO₂Me and the SCF₂COOH moieties in order to access interesting compounds. We decided to choose compound 20a and 20k as examples in post-functionalization reactions.

II.3.1.3.1 Post-Functionalization of the SCF₂CO₂Me moiety

The first post-functionalization reactions were run with the aim to transform the ester moiety and 20a and 20k were chosen as starting materials. Hydroxyl (OH) is an important functional group in organic. Alcohol compounds find a wide use in science, medicine and industry as antifreeze, antiseptics, preservatives etc. Accessing compounds bearing a SCF₂ group adjacent to the alcohol functionality could be of particular interest in modulating the properties of the molecules. Moreover, it could present a valuable synthetic procedure to access such compounds considering the lack of synthetic strategies. The use of lithium aluminium hydride (2 or 5 equiv.) to reduce the ester moiety into alcohol did not lead to the expected product (Table 15, entries 1 and 2). On the other hand, employing sodium borohydride as a reducing agent the desired product 22a was obtained in a quantitative yield (Table 15, entry 3).
Performing an aminolysis reaction between benzylamine and compound 20k in MeOH in an aminolysis reaction gave the desired product 22b in a quantitative yield. Such reactions could be interesting as a starting point in the peptide-like coupling reactions employing aminoacids instead of the benzylamine (Table 15, entry 22b). Saponification of the ester using a 1M solution of K₂CO₃ at room temperature led to the carboxylic acid derivative 22c with 87 % yield. Carboxylic acids are important motifs in organic chemistry and undergo facile post-functionalization.

Table 15 Post-functionalization reactions using 20k as a starting material

<table>
<thead>
<tr>
<th>Entry</th>
<th>R₁ (equiv.)</th>
<th>Additive (equiv.)</th>
<th>Solvent</th>
<th>Time h</th>
<th>Temp °C</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-</td>
<td>LiAlH₄ 5 equiv.</td>
<td>THF</td>
<td>2 h</td>
<td>0 °C – 25 °C</td>
<td>n.r</td>
</tr>
<tr>
<td>2</td>
<td>-</td>
<td>LiAlH₄ 5 equiv.</td>
<td>THF</td>
<td>2 h</td>
<td>0 °C – 25 °C</td>
<td>n.r</td>
</tr>
<tr>
<td>3</td>
<td>-</td>
<td>NaBH₄ 2 equiv.</td>
<td>MeOH</td>
<td>2 h</td>
<td>0 °C – 25 °C</td>
<td>99 %</td>
</tr>
<tr>
<td>4</td>
<td>NH₂</td>
<td>-</td>
<td>MeOH</td>
<td>3 h</td>
<td>25 °C</td>
<td>100 %</td>
</tr>
<tr>
<td>5</td>
<td>-</td>
<td>K₂CO₃ 3 equiv.</td>
<td>MeOH</td>
<td>3 h</td>
<td>25 °C</td>
<td>87 % (90 %)</td>
</tr>
</tbody>
</table>

Crude yields were determined by ¹⁹F NMR spectroscopic analysis using PhOCF₃ as an internal standard.

The indole core bearing the SCF₂CO₂Me group was also subject to post-functionalization reactions. With the aim to demonstrate that the above-shown post-functionalization reactions are not substrate dependent and to access to new substrates we extended the scope to the indole family, choosing compound 20a as model substrate. NaBH₄-mediated reduction to alcohol gave the expected compound 23a in a good yield (Table 16, entry 1). Also, the aminolysis reaction between benzylamine and the indole 20a led to the formation of the amide 23b with a 95 % isolated yield (Table 16, entry 2). Encouraged by the optimistic results obtained we tried to extend the scope to other primary amines. For instance, tryptophan was reacted with compound 20a without leading to the formation of the desired compound (Table 16, entry 3). As mentioned
before, the use of aminoacid derivatives in peptide-like coupling reactions could open the way to the synthesis of biologically active compounds that might find use in several fields. Unfortunately, neither reacting tert-butyl glycinate with 20a in MeOH the formation of the expected compound was observed. Neither performing the addition of an additive as AlMe₃ we did not observe any formation of the expected compound (Table 16, entry 5). As in the case of the compound 22c, by means of a saponification reaction mediated by a 1M aqueous solution of K₂CO₃, acid compound 23c was obtained.

Table 16 Post-functionalization reactions using 20a as a starting material

<table>
<thead>
<tr>
<th>Entry</th>
<th>R₁</th>
<th>Additive (equiv.)</th>
<th>Solvent</th>
<th>Temp (°C)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-</td>
<td>NaBH₄ 2 equiv.</td>
<td>MeOH</td>
<td>0 °C – 25 °C</td>
<td>74 % (79 %)</td>
</tr>
<tr>
<td>2</td>
<td>-</td>
<td>2 equiv.</td>
<td>MeOH</td>
<td>25 °C</td>
<td>n.r</td>
</tr>
<tr>
<td>3</td>
<td>-</td>
<td>Tryptophane 2 equiv.</td>
<td>MeOH</td>
<td>25 °C</td>
<td>n.r</td>
</tr>
<tr>
<td>4</td>
<td>-</td>
<td>2 equiv.</td>
<td>MeOH</td>
<td>25 °C</td>
<td>n.r</td>
</tr>
<tr>
<td>5</td>
<td>-</td>
<td>AlMe₃ 3 equiv.</td>
<td>MeOH</td>
<td>0 °C</td>
<td>n.r</td>
</tr>
<tr>
<td>6</td>
<td>-</td>
<td>K₂CO₃</td>
<td>MeOH</td>
<td>25 °C</td>
<td>92 %</td>
</tr>
</tbody>
</table>

Crude yields were determined by ¹⁹F NMR spectroscopic analysis using PhOCF₃ as an internal standard.
II.3.1.3.2 Post-Functionalization of the SCF$_2$CO$_2$H moiety

Herein we report decarboxylative halogenation reactions and oxidative decarboxylation reaction to access SCF$_2$-X bond formation and SCF$_2$-C coupling respectively.

II.3.1.3.2.1 Decarboxylative halogenation reactions

Carboxylic acids are pervasive in nature and find a wide use in industry in the production of pharmaceuticals, additives, polymers etc. Moreover, compounds bearing a carboxyl group can function as precursors to several molecules through post-functionalization of COOH motif. Decarboxylative halogenation reactions as Hunsdiecker reaction are well known in organic chemistry. Recently, decarboxylative halogenation in presence of adjacent fluorine atoms (CF$_2$COOH) has been reported. Gouverneur and coll. by means of an elegant procedure accessed trifluoromethylarenes through an electrophilic decarboxylation reaction in both cold and hot chemistry using Selectfluor as a fluoride source.\cite{224} However, when we started this project such a reaction has never been performed in presence of a SCF$_2$COOH group. Thus, it could be interesting to evaluate the influence of adjacent sulfur in this reaction and explore the reaction conditions that could be the first pass to access the radiolabeled [$^{18}$F]CF$_3$S moiety. Adaption of the reaction conditions reported by Gouverneur and coll., did not give the desired result. Although the entire starting material was consumed no trace of the trifluoromethylthiolated compounds was observed. However, multiple peaks were observed between -110 and -112 ppm in $^{19}$F NMR (Table 17, entry 1) suggesting an aromatic fluorination of our starting material. Neither increasing the amounts of AgNO$_3$ (Table 17, entry 2), increasing the concentration of the reaction media (Table 17, entry 7), decreasing the reaction temperature to 25 °C and 5 °C (Table 17, entries 3-4), or changing the source of silver (Table 17, entries 5-6) we could access the expected compound. However, in all the cases full consumption of the starting material and presence of multiple peaks between -110 and -112 ppm was observed. Nevertheless, we could not isolate any of the by-products to further comprehend the reaction mechanism.

Another unexplored topic in fluorine chemistry is the synthesis of SCF$_2$I group. The iododifluoromethylthio group is almost unknown to organic chemists and no evidence concerning its characterization was found in literature. Tentative for insertion of an iodine atom resulted unsuccessful, by using both I$_2$ and NSI as iodine sources in presence of silver salt (Table 17, entries 8-9). Neither the addition of K$_2$S$_2$O$_8$ or BHF$_4$ to the reaction media gave the expected compound (Table 17, 10-11 and 19). Nor using the potassium salt as a starting material did not favor the formation of the desired compound (Table 17, 12-13), presumably due to steric hindrance and the less nucleophilic character of the iodine atom.
### Table 17 Decarboxylative halogenation reactions

<table>
<thead>
<tr>
<th>Entry</th>
<th>Halogen Source (equiv)</th>
<th>Ag salt (equiv.)</th>
<th>Additive 2 (equiv.)</th>
<th>Solvent</th>
<th>T (°C)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Selectfluor</td>
<td>AgNO₃</td>
<td>-</td>
<td>(CH₃)₂CO/H₂O 1/1</td>
<td>55 °C</td>
<td>n.r</td>
</tr>
<tr>
<td>2</td>
<td>Selectfluor</td>
<td>AgNO₃</td>
<td>-</td>
<td>(CH₃)₂CO/H₂O 1/1</td>
<td>55 °C</td>
<td>n.r</td>
</tr>
<tr>
<td>3</td>
<td>Selectfluor</td>
<td>AgNO₃</td>
<td>-</td>
<td>(CH₃)₂CO/H₂O 1/1</td>
<td>25 °C</td>
<td>n.r</td>
</tr>
<tr>
<td>4</td>
<td>Selectfluor</td>
<td>AgNO₃</td>
<td>-</td>
<td>(CH₃)₂CO/H₂O 1/1</td>
<td>5 °C</td>
<td>n.r</td>
</tr>
<tr>
<td>5</td>
<td>Selectfluor</td>
<td>Ag₂CO₃</td>
<td>-</td>
<td>(CH₃)₂CO/H₂O 1/1</td>
<td>55 °C</td>
<td>n.r</td>
</tr>
<tr>
<td>6</td>
<td>Selectfluor</td>
<td>AgOAc</td>
<td>-</td>
<td>(CH₃)₂CO/H₂O 1/1</td>
<td>55 °C</td>
<td>n.r</td>
</tr>
<tr>
<td>7</td>
<td>Selectfluor</td>
<td>AgNO₃</td>
<td>-</td>
<td>(CH₃)₂CO/H₂O 1/1</td>
<td>55 °C</td>
<td>n.r</td>
</tr>
<tr>
<td>8</td>
<td>I₂</td>
<td>AgNO₃</td>
<td>-</td>
<td>CH₃CN</td>
<td>80 °C</td>
<td>n.r</td>
</tr>
<tr>
<td>9</td>
<td>NSI</td>
<td>AgNO₃</td>
<td>-</td>
<td>CH₃CN</td>
<td>80 °C</td>
<td>n.r</td>
</tr>
<tr>
<td>10</td>
<td>NSI</td>
<td>AgNO₃</td>
<td>K₂S₂O₈</td>
<td>(CH₃)₂CO/H₂O 1/1</td>
<td>55 °C</td>
<td>n.r</td>
</tr>
<tr>
<td>11</td>
<td>I₂</td>
<td>AgNO₃</td>
<td>K₂S₂O₈</td>
<td>(CH₃)₂CO/H₂O 1/1</td>
<td>55 °C</td>
<td>n.r</td>
</tr>
<tr>
<td>12</td>
<td>NSI</td>
<td>AgNO₃</td>
<td>K₂S₂O₈</td>
<td>(CH₃)₂CO/H₂O 1/1</td>
<td>55 °C</td>
<td>n.r</td>
</tr>
<tr>
<td>13</td>
<td>NSI</td>
<td>AgNO₃</td>
<td>K₂S₂O₈</td>
<td>(CH₃)₂CO/H₂O 1/1</td>
<td>55 °C</td>
<td>n.r</td>
</tr>
<tr>
<td>14</td>
<td>NBS</td>
<td>AgNO₃</td>
<td>HBF₄</td>
<td>CH₂Cl₂/H₂O 10/1</td>
<td>80 °C</td>
<td>45%</td>
</tr>
<tr>
<td>15</td>
<td>NBS</td>
<td>AgNO₃</td>
<td>HBF₄</td>
<td>(CH₃)₂CO/H₂O 1/1</td>
<td>55 °C</td>
<td>n.r</td>
</tr>
<tr>
<td>16</td>
<td>NBS</td>
<td>AgNO₃</td>
<td>TFOH</td>
<td>PhCF₃/H₂O 10/1</td>
<td>80 °C</td>
<td>1%</td>
</tr>
<tr>
<td>17</td>
<td>NBS</td>
<td>AgNO₃</td>
<td>HBF₄</td>
<td>CH₂Cl₂/H₂O 1/1</td>
<td>80 °C</td>
<td>20%</td>
</tr>
<tr>
<td>18</td>
<td>NBS</td>
<td>AgNO₃</td>
<td>HBF₄</td>
<td>CH₂Cl₂/H₂O 10/1</td>
<td>80 °C</td>
<td>90%</td>
</tr>
<tr>
<td>19</td>
<td>NSI</td>
<td>AgNO₃</td>
<td>HBF₄</td>
<td>CH₂Cl₂/H₂O 10/1</td>
<td>80 °C</td>
<td>n.r</td>
</tr>
</tbody>
</table>

Reactions were checked by ¹⁹F NMR after 4 h and 16 h. Reaction was run at a [0.25M]. The potassium salt of the acid was used as a starting material.
The decarboxylative bromination is also very appealing because it could lead to a precursor that can be used in coupling reactions. Such compounds can be used also as starting materials in a Ag-mediated halogen-exchange radiolabeling as demonstrated by Gouverneur and collaborators, giving rise to compounds bearing an \[^{18}\text{F}]\text{CF}_3\text{S} group. Adapting very recently published conditions that have been used in decarboxylative fluorination and substituting Selectfluor with NBS, we observed a peak at -23.05 ppm in $^{19}$F NMR, area corresponding to molecules bearing a SCF$_2$Br group (Table 17, entry 14). Choosing CH$_2$Cl$_2$/H$_2$O as a solvent in a 10/1 ratio is crucial for the reaction trend. Using a 1/1 ratio of the same solvents the desired compound was formed only in 20% yield (Table 17, entry 17). Furthermore, substituting the solvent with a mixture of acetone/H$_2$O or PhCF$_3$/H$_2$O no peaks or non-quantifiable signals were observed (Table 17, entry 15-16). When the amount of NBS was increased up to 4 equiv. correspondingly the dosed yield increased up to 90% (Table 17, entry 18). Once the compound was isolated, we realized that the observed $^1$H NMR spectra did not correspond to the expected compound. Hence, the peak corresponding to the hydrogen in meta respect SCF$_2$Br group was missing. Considering the electron-rich character 22c a SEAr reaction took place simultaneously leading to the bromination of the arene ring. The structure of the new compound was confirmed by $^1$H NMR, $^{13}$C NMR and GC-MS (Scheme 67).

![Scheme 67 Decarboxylative bromination reaction](image)

**II.3.1.3.2 Oxidative decarboxylation with SF$_2$C-C bond formation**

As mentioned before, there is a great interest in developing SF$_2$C-C coupling reactions, that could ease the way to access to SCF$_2$-bridged molecules.

As shown in Table 18, the reaction between aryl iodides or alkyl bromides and compound 22c in DMF in presence of CuI did not lead to the formation of any desired product (entries 1 and 3-4). Also, the potassium salt of compound 22c has been used as starting material, without success. However, after 16 hours no traces of starting material 22c were observed by $^{19}$F NMR.
Table 18 SF₂C-C bond formation

<table>
<thead>
<tr>
<th>Entry</th>
<th>R-X (eq)</th>
<th>T (°C)</th>
<th>Time (h)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Br</td>
<td>170 °C</td>
<td>16 h</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>Br</td>
<td>170 °C</td>
<td>16 h</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>Br</td>
<td>80 °C</td>
<td>16 h</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>Br</td>
<td>80 °C</td>
<td>16 h</td>
<td>-</td>
</tr>
</tbody>
</table>

1 K salt was used instead of the carboxylic acid as starting material.

A last post-functionalization reaction that we tried is the oxidative decarboxylation in presence of EBX-TIPS to access difluoromethylthio alkynes, interesting building blocks that could lead to further structural modifications.

To our knowledge, in literature there is only one example concerning the synthesis of difluoromethylthio alkynes, starting from a substituted benzyl thiol and a difluoropropargyl bromide. Thus, with the last advances in the formation of difluoromethyl alkyne in mind and the interest of such motifs we adapted some existing procedures to our system. Reacting 22c with EBX-TIPS in presence of K₂S₂O₈ we observed the formation of a peak at -58.80 ppm in ¹⁹F NMR to our delight (Table 19, entry 1). Addition of AgNO₃ to the reaction media improved the yield from 33 % to 60 % (Table 19, entry 2). Encouraged by the obtained results we planned the synthesis of various compounds by modifying the EBX reagent. The Ag-catalysed reaction between 22c and EBX-hexyne in acetone/H₂O mixture did not give the expected results although no starting material was found in the reaction mixture (Table 19, entries 3-4). A peak at -58.18 ppm was observed in ¹⁹F NMR that could correspond to our compound although we do not have any evidence concerning to it. When the reaction was run in absence of AgNO₃, 40 % of the starting material was still found in the reaction media. The use of Ph-EBX led to the
formation of undefined complex mixtures also, and the starting material was consumed in both cases (Table 19, entries 5-6).

Table 19 Decarboxylative oxidation hypervalent alkynyl iodines

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Catalyst (equiv.)</th>
<th>Additive (equiv.)</th>
<th>Solvent</th>
<th>Temp (°C)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-</td>
<td>-</td>
<td>K₂S₂O₈ 2 equiv.</td>
<td>CH₃CN/H₂O</td>
<td>55 °C</td>
<td>25c 33 %</td>
</tr>
<tr>
<td>2</td>
<td>AgNO₃ 25 mol %</td>
<td>K₂S₂O₈ 2 equiv.</td>
<td>(CH₃)₂CO/H₂O</td>
<td>55 °C</td>
<td>25c 60 %</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>AgNO₃ 25 mol %</td>
<td>K₂S₂O₈ 2 equiv.</td>
<td>(CH₃)₂CO/H₂O</td>
<td>55 °C</td>
<td>25b 8 %</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>-</td>
<td>K₂S₂O₈ 2 equiv.</td>
<td>(CH₃)₂CO/H₂O</td>
<td>55 °C</td>
<td>n.r</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Ph</td>
<td>AgNO₃ 25 mol %</td>
<td>K₂S₂O₈ 2 equiv.</td>
<td>(CH₃)₂CO/H₂O</td>
<td>55 °C</td>
<td>Complex mixture</td>
</tr>
<tr>
<td>6</td>
<td>Ph</td>
<td>AgNO₃ 25 mol %</td>
<td>K₂S₂O₈ 2 equiv.</td>
<td>CH₃CN/H₂O</td>
<td>55 °C</td>
<td>Complex mixture</td>
</tr>
</tbody>
</table>

Crude yields were determined by ¹⁹F NMR spectroscopic analysis using PhOCF₃ as an internal standard.

TIPS-EBX was reacted in presence of indoles bearing a SCF₂COOH group. In the case of the unprotected indole 23c, compound 25a was obtained with a modest yield of 13 %. N-methyl indole gave compound 25b with a 26 % yield.
III. Conclusions

At the beginning of this project no literature data concerning the direct insertion of SCF$_2$FG group was present in literature. Thus, since the beginning we concentrated our efforts in the development and improvement of such chemistry. In the first chapter, we reported the synthesis of the first two sulfenamides-based reagents (1a and 1d) bearing a SCF$_2$FG (FG= SO$_2$Ph, CO$_2$Me) group. Both reagents were successfully used in electrophilic reactions as donors of +SCF$_2$FG in presence of electron-rich (hetero) aryl compounds, alkenes, terminal alkynes and ketones. We have also exploited the post-functionalization capacity of the phenylsulfonyl, CO$_2$Me and COOH moieties to access differently substituting compounds. Among others, compounds bearing SCF$_2$H and, for the first time, SCF$_2$D were prepared after reductive desulfonylation of SO$_2$Ph moiety. Substitution of SO$_2$Ph with a SiMe$_3$ also was performed. Through post-functionalization of the SCF$_2$CO$_2$Me group we accessed to a different structure using different reactions as, reduction to alcohol, aminolysis and saponification reactions. More interestingly, decarboxylative halogenation and C-C bond formation by oxidative decarboxylation reactions were successfully performed leading to a new class of compounds.
IV. References:


Chapter I. Synthesis of SCF$_2$R derivatives and their application in electrophilic reactions


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Chapter I. Synthesis of SCF₂R derivatives and their application in electrophilic reactions


CHAPTER II

SYNTHESIS OF BENZYLFLUOROALKYLSELENIDE REAGENTS AND THEIR APPLICATION IN ELECTROPHILIC REACTIONS
Chapter II. Synthesis of benzylfluoroalkyl selenide reagents: Application in \( _{S_{2}}^{A}_{r} \) reactions

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Herein we report the synthesis, characterization and the in-situ use of novel fluoroalkylselenolating pre-reagents. The generation of a well-known reactive species CF₃SeCl in situ led to interesting results. Trifluoromethylselenolated molecules (SeCF₃), superior homologs (SeRᵢ) as well as functionalized moieties (SeCF₂FG) were obtained using different sources of SeCF₂R. The reported bibliographic data are prior October 2016.

Results and discussion part is preceded by the bibliographic data concerning fluoroalkylselenolated compounds.

I. Bibliography SeCF₃ and SeCF₂R

Selenium was discovered in 1817 by Berzelius who named it in honor of the Greek moon goddess, Selene. This might be due to the similitudes he noticed with tellurium, named in honor of Tellus the Latin goddess of earth. However, selenium is far more similar to sulfur than tellurium, the previous chalcogen of the 16th group in the periodic table. Despite this, the interest towards selenium in organic chemistry remains still low in comparison to sulfur. Among various issues that limited the interest towards selenium might be also the awareness concerning its toxicity. However, selenium has been proven to be an essential oligoelement in living species. Selenium is found in the 21st proteinogenic discovered aminoacid selenocysteine,[¹] which is integral part of several enzymes, as glutathione peroxidases, tetraiodothyronine 5’ iodinases, thioredoxin reductases etc. Scientists referred to selenium as the “essential poison” due to its small range between R.D.A (Recommended Dietary Allowance) (50 μg/day) and toxic limit (800 μg/day). Despite the higher abundance of sulfur in nature, the presence of selenium is significant in different biological processes due to the ability of selenium to resist to permanent oxidation.[²]

Thus, considering the importance of such element in natural processes, the development of synthetic methodologies and reagents to access fluoroalkylselenolated compounds appeared to be of interest.

As mentioned above, the association of fluorine and selenium is less explored than in the case of the sulfur. Herein, you find a review of various synthetic pathways and reagents to access CF₃Se and RCF₂Se containing molecules. In the second part, we will report our recent results obtained in direct fluoroalkylselenolations.
I.1 Introduction of CF₃ group into Selenium-containing derivatives

Herein we report the most relevant works, to our knowledge, concerning the trifluoromethylation of Se-centers. Trifluoromethylation of Se-centers has been obtained through nucleophilic and radical reactions. Based on our bibliographic research, no electrophilic trifluoromethylation has been reported.

I.1.1 Radical trifluoromethylation of Se-centers

Radical trifluoromethylation of Se-centers is less developed respect to the trifluoromethylation of sulfur containing compounds. To our knowledge only a few reports has been published involving a couple of different CF₃ sources.

I.1.1.1 Trifluoromethaneselenosulfonates and sodium trifluoromethanesulfinate

In late 90ies, trifluoromethaneselenosulfonates has been prepared in our labs reacting sodium trifluoromethanesulfinate with either selenyl chlorides or diselenides under oxidative conditions (Scheme 1).[3]

\[
\begin{align*}
F_3C-\text{S} & \quad \text{a) Ph-Se-Se-R/Br₂} \\
& \quad \text{b) Ph-Se-Cl} \\
& \quad \text{c) R-Se-Se-R/Ph(OCOCF₃)₂} \\
\end{align*}
\]

Then phenyltrifluoromethaneselenosulfonate has been used as a CF₃ radical source in the trifluoromethylation of diselenides. Trifluoromethylselenolated compound has been obtained through a S₉2 reaction mechanism as reported by the authors. Taking in consideration the reaction sensitivity to light and formation of the various by-products further strengthens the conclusion of the authors concerning the reaction mechanism (Scheme 2).[3]

\[
\begin{align*}
\text{SeSe} & \quad \text{+ O-S} \quad \text{hv} \quad \text{PhCF₃} \\
& \quad \text{SePh} \quad \text{58 %} \quad \text{SeSePh} \quad \text{3 %} \quad \text{F₃C-} \quad \text{4 %}
\end{align*}
\]

Moreover the yield has been improved further up to 85 % adding two equiv. of diphenyl diselenide. In this case there is no need of irradiation. And the reaction proceeds through an SET
process with the phenyltrifluoromethaneselenosulfonate acting as an oxidant and the diselenide as a reducer as reported by the authors.\cite{4}

Sodium trifluoromethanesulfinate, a well-known trifluoromethylating reagent developed in our labs, has been used in the radical trifluoromethylation of benzeneselenol compound. Cai and coll. reported the trifluoromethylation of only one example of seleno-containing compounds among various sulfur-centers. Mechanistic elucidations reveal that I\textsubscript{2} released from iodine pentoxide generated the CF\textsubscript{3} radical via a SET mechanism. Iodine also reacts with the benzeneselenol to form, in situ, Ph-Se-Se-Ph or Ph-SeI, which underwent trifluoromethylation in presence of the CF\textsubscript{3} radical (Scheme 3).\cite{5}

\[
\text{SeH} + \text{CF}_3\text{SO}_2\text{Na} \xrightarrow{\text{I}_2\text{O}_5, \text{DMSO}} \text{SeCF}_3
\]

\textbf{Scheme 3 Trifluoromethylation of benzeneselenol}

\subsection*{1.1.1.2 Trifluoroiodomethane}

CF\textsubscript{3}I is a colourless gas, part of the family of the halomethanes, which were proposed as a substitution of the environmentally hazardous CF\textsubscript{3}Br. Even though being a gas and facing several handling problems during its use, CF\textsubscript{3}I is one of the most used reagents as trifluoromethylating source. It has been used also in the trifluoromethylation of Se-centers through the formation of a CF\textsubscript{3} radical.

Magnier et al. reported the trifluoromethylation of diselenides in presence of CF\textsubscript{3}I, mediated by the use of sodium hydroxymethanesulfinate (Rongalite\textsuperscript{a}) (Scheme 4, eq. a).\cite{6} However, the methodology has been mostly applied to the synthesis of perfluoroalkyl selenides. As reported by the authors, a S\textsubscript{H2} (homolytic substitution) reaction mechanism\cite{6b} or a S\textsubscript{RN1} process involving a radical chain propagation could be involved.\cite{6a}

\[
\text{SeH} + \text{CF}_3\text{I} + \text{TDAE} \xrightarrow{\text{DMF}} \text{SeCF}_3
\]

\textbf{Scheme 4 Use of trifluoroiodomethyl as a trifluoromethylating source}

Later, Dolbier and coll. disclosed a new route for the trifluoromethylation of aryl and alkyl diselenides in excellent yields (Scheme 4, eq. b). CF\textsubscript{3}I/TDEA system gave the desired compounds in a high yield. Moreover, using the double of equiv. of CF\textsubscript{3}I they have reported the
trifluoromethylation of both parts of the diselenide thus obtaining almost 200 % of conversion respect to the moles of the diselenide.\(^{[7]}\)

**I.1.2 Nucleophilic trifluoromethylation of Se-centers**

Nucleophilic trifluoromethylation of Se-centers is limited to a few papers as in the case of the radical trifluoromethylation. However, a wider range of trifluoromethylating sources has been used in these reactions. The use of Ruppert-Prakash reagent, fluoroform, trifluoromethylcopper and other reagents will be disclosed below.

**I.1.2.1 Trifluoromethyl trimethylsilane**

Trifluoromethyl trimethylsilane (CF\(_3\)TMS), known also as Ruppert-Prakash reagent, is a very versatile and useful trifluoromethylating source. Since its discovery, it has been extensively used in trifluoromethylation reactions and very recently also in the difluoromethylation of C-\(^{[8]}\), N-\(^{[9]}\) and S-centers.\(^{[10]}\) Taking advantage of the high efficiency of CF\(_3\)TMS as trifluoromethylating agent, its commercial availability and its easy-handling character, it was used in the trifluoromethylation of diselenides some years ago by our group. Thus, employing 2 equiv. of TBAF as a desilylating agent in THF, (PhSe)\(_2\) was trifluoromethylated giving the desired compound in a 40 % isolated yield (Scheme 5, eq. a).\(^{[11]}\) However, considering the low reaction yields obtained more efforts were made in order to increase it. Thus, using the selenocyanates as starting materials not only led to an improvement in terms of yield but also the amount of TBAF was reduced 10-fold (Scheme 5, eq. b). The released cyanide anion is also able to desilylate CF\(_3\)TMS, therefore explaining the use of TBAF in catalytic amounts.\(^{[12]}\)

![Scheme 5 Ruppert-Prakash reagent as a trifluoromethylating source](image)

Rueping and coll. reported the trifluoromethylation of a selenocyanates with TMSCF\(_3\) in presence of Cs\(_2\)CO\(_3\) in good yield (Scheme 5, eq. a). However, the trifluoromethylation of the selenocyanates served as a starting point to the authors for the exploration of the best reaction conditions implied in the transformation of the diazonium salts into trifluoromethylselenolates (Scheme 6, eq. b).
Therefore a Cu\(^{1}\)/Cu\(^{II}\)-mediated Sandmeyer type reaction involving the trifluoromethylselenolation of aryl and heteroaryl diazonium tetrafluoroborates has been successfully developed. The methodology tolerates various functional groups and works well with both electron-rich and electron poor substrates (Scheme 6, eq. b). The authors also reported the one pot trifluoromethylselenolation of the aniline (Scheme 6, eq. c).\(^{13}\)

### 1.1.2.2 Trifluoromethane and hemiaminals of fluoral

As reported in the previous chapter, fluoroform is an industrial by-product in the production of Teflon, refrigerants, etc. Thus, a lot of effort has been made to transform this waste in a useful trifluoromethylating reagent in order to consume it. Among other reactions, fluoroform found use also in the trifluoromethylation of selenocyanates and diselenides.

Fluoroform was used in the trifluoromethylation of carbonyl compounds, disulfides and also diselenides in the early 2000 in our labs. Trifluoromethylation occurs through the in situ formation of a tetrahedral DMF adduct arising from reaction of CF\(_3\)H with DMF in presence of a base. Such adduct acts as a reservoir-like source of CF\(_3\) (Scheme 7, eq. a).\(^{14}\)

Rozen and coll. accessed to alkyl, aryl and heteroaryl trifluoromethylselenolated compounds starting from the corresponding selenocyanates and the fluoroform-derived CuCF\(_3\) (Scheme 7, eq. b). Similar reaction conditions have been applied also to diselenides leading to the desired products in high yields (Scheme 7, eq. c).\(^{15}\)
Hemiaminals of fluoral has been developed in our labs in the early 2000 and could be easily prepared from fluoral or fluoroform. The trifluoromethylation ability of the hemiaminals has been successfully tested in presence of non-enolizable carbonyl compounds, disulfides and diselenides.

Trifluoromethylselenolated compounds were obtained in a good yield starting from the proper diselenides and TBAT as fluoride source.[16]

![Scheme 8 Hemiaminal as a trifluoromethylating source](image)

**I.1.2.3  Diethyl trifluoromethylphosphonate**

Diethyl trifluoromethylphosphate has been used as a trifluoromethylating reagent mostly in the trifluoromethylation of ketones and aldehydes. Nevertheless, Beier and coll. reported an example of the trifluoromethylation of diphenyl diselenide with a modest yield, using t-BuOK as a base.[17]

![Scheme 9 Diethyl trifluoromethylphosphonate as a trifluoromethylating agent](image)

**I.2  Direct insertion of SeCF₃ group**

Direct insertion of the trifluoromethylseleno group onto molecules remains the favorite approach with respect to the Se-CF₃ bond formation, thus avoiding the pre-synthesis of selenolated compounds. Electrophilic and especially nucleophilic reactions are the most developed ways to access trifluoromethylselenolated compounds. Herein, we report the use of various reagents as well as the different synthetic pathways exploited to obtain SeCF₃R adducts.

**I.2.1  Nucleophilic trifluoromethylselenolation reactions**

During recent years, interest has been increasing towards trifluoromethylselenolation through nucleophilic approach. Different research groups contributed to this field by developing new reagents that act as CF₃Se donors as well as relevant synthetic strategies giving the possibility to access to a wide range of CF₃Se containing compounds. Below we will report the most relevant synthetic procedures and use of different reagents that contributed in the improvement of this field.
I.2.1.1 Trifluoromethylselenocopper

As in the case of nucleophilic trifluoromethylthiolation reactions, the association between organometallic chemistry and trifluoromethylseleno group led to important results. Hence, various classes of substrates have been trifluoromethylselenolated. Although the most used metal is Cu, trifluoromethylseleno adamantane has been prepared reacting iodoadamantane and Hg(SeCF₃)₂\textsuperscript{[18]}. One of the ways for preparing the CuSCF₃ is reacting the trifluoromethyl diselenide with copper powder in DMF (Scheme 10). Yagupolskii and coll. reported the synthesis of trifluoromethylselenocopper in a quantitative yield. Nevertheless, CuSeCF₃ could be isolated only as a complex containing one molecule of solvent\textsuperscript{[19]}. Trifluoromethyl diselenide, itself, has been prepared whether reacting mercury bis(trifluoromethyl) with SeBr₄\textsuperscript{[20]} or (CF₃Se)₃N with CF₃SeBr (Scheme 10).\textsuperscript{[21]}

\[
\text{Hg(CF}_3\text{)}_2 + \text{SeBr}_4 \rightarrow \text{F}_3\text{C}\cdot\text{Se} \cdot \text{Se} \cdot \text{CF}_3 \\
\text{2(CF}_3\text{Se)}_3\text{N} + \text{CF}_3\text{SeBr} \rightarrow 2\text{CuSeCF}_3
\]

They also described the synthesis of mono-, tri- and hexa-trifluoromethylselenolated arenes starting from the corresponding iodo-derivatives in presence of CuSeCF₃ (Scheme 11). However, improved yields are reported running a one-pot reaction: in situ preformation of the complex and subsequent addition of the iodoarene.\textsuperscript{[19]}

\[
\text{O}_2\text{N} \quad \text{I} \quad \text{CuSeCF}_3 \quad \text{DMF} \quad \text{O}_2\text{N} \\
\text{SeCF}_3 \\
95 \%
\]

\[
\text{O}_2\text{N} \quad \text{I} \quad \text{CuSeCF}_3 \quad \text{NMP} \quad \text{SeCF}_3 \\
\text{F}_3\text{CSe} \quad \text{SeCF}_3 \\
74 \%
\]

\[
\text{SeCF}_3 \quad \text{SeCF}_3 \\
87 \%
\]

Weng and coll. performed a catalytic Cu-mediated trifluoromethylselenolation of aryl, heteroaryl and alkyl halides in presence of elemental selenium, TMSCF₃, KF, Ag₂CO₃ and phenantroline as a ligand in DMF (Scheme 12). The methodology seems to be compatible with a wide range of
functional groups. The presence of silver salt might to be involved in the formation of the active complex \([\text{phen} \text{Cu}(\text{SeCF}_3)]_2\), key intermediate in the reaction. Moreover, when catalytic amounts of CuI and phenantroline in absence of silver salt were used, the expected compound was obtained with 50 % yield. Furthermore, the use of the isolated of Cu complex as a reactive species, gave similar yields when compared to the in-situ formation of the complex.\[22\]

Based on the results shown above and the previous works in Cu-catalyzed nucleophilic trifluoromethylthiolation of various starting materials, Weng and coll. also reported the synthesis of various Cu(I) trifluoromethylselenolate complexes and studied their reactivity as CF₃Se⁻ donors towards various starting materials.

All the complexes has been prepared in a reaction involving CuI, TMSCF₃, Se₈, KF and dinitrogen ligands in CH₃CN (Scheme 13, eq. a).\[23\]
Although all complexes led to high reaction yields (except the neocuprine coordinating complex) in presence of iodo-toluene, the authors chose the [(bpy)Cu(SeCF₃)]₂ considering the ease in the preparation and being the most economically-advantageous as a source of SeCF₃. Cu-mediated trifluoromethylselenolation of aryl and heteroaryl iodides and bromides as well as alkyl bromides have been successfully performed. The reaction conditions showed compatibility with various functional groups (Scheme 13, eq. b).[23]

For instance, propargylic trifluoromethyl selenoethers has been prepared starting from the propargylic chloro derivatives in good yields. The same group reported also Cu-mediated trifluoromethylselenolation of allylic bromides (Scheme 13, eq. c and d).[24] Cu-mediated trifluoromethylselenolation of vinyl halides has been performed leading to vinyl trifluoromethyl selenoethers in good yields.[25] Trifluoromethylseleno-α,β-unsaturated carbonyl compounds have been prepared starting from the bromo derivatives (Scheme 13, eq. f).[26] Copper-mediated oxidative trifluoromethylselenolation of terminal alkynes has been reported in presence of DMP and KF (Scheme 13, eq. g).[27] In order to fully exploit the capacity of the previously prepared complex, the same group reported the Cu-mediated β-trifluoromethylseleno-α,β-unsaturated ketones starting from the brominated starting materials (Scheme 13, eq. h). The proposed reaction mechanism passes through the formation of an enolate between the Cu complex and the β-bromo ketone, leading to the desired product after bromide elimination.[28] Trifluoromethylselenolated heteroaromatics have been prepared reacting the bromo derivatives and the dimeric complex in presence of dioxane as a solvent (Scheme 13, eq. i).[29]

1.2.1.2 Tetramethyl ammonium trifluoromethylselenate (0)

Tetramethyl ammonium trifluoromethylselenolate (Me₄N)SeCF₃ has been firstly prepared by Tyrra et al. reacting TMSCF₃, elemental selenium (Se₈) and Me₄NF in THF or glyme with a yield of 70% (Scheme 14, eq. a).[30] For instance, during the last few years the interest towards (Me₄N)SeCF₃ has been continuously increasing and several groups used it as a SeCF₃ source in nucleophilic trifluoromethylselenolation reactions.

Rueping and coll. reported the Cu-mediated oxidative trifluoromethylselenolation of terminal alkynes by both using the isolated (Me₄N)SeCF₃ as well as preparing it in situ (Scheme 14, eq. b). However, the use of the preformed reagent gave higher yields. Also, the trifluoromethylselenolation of boronic acids as well as boronic pinacol esters has been successfully performed (Scheme 14, eq. c).[31] Goossen and coll. accessed to α-trifluoromethylseleno esters by means of a catalytic Cu-mediated method starting from the α-diazo esters (Scheme 14, eq. d).[32] Schoenebeck and coll. reported a straightforward Pd-mediated
coupling strategy for obtaining aryl and heteroaryl trifluoromethylselenolated adducts starting from the iodo-derivatives. A benchstable Pd\textsuperscript{I}-I dimer has been used as a catalyst, which apparently leads to the in situ formation of Pd\textsuperscript{I}-SeCF\textsubscript{3} dimer acting as a trifluoromethylselenating species (Scheme 14, eq. e).\textsuperscript{[33]}

I.2.2 Radical trifluoromethylselenolation reactions

On the contrary to nucleophilic trifluoromethylselenolation reactions, direct insertion of SeCF\textsubscript{3} group into molecules through a radical pathway has not been extensively studied. To our knowledge only one recent publication has been reported using (Me\textsubscript{4}N)SeCF\textsubscript{3} as a source of SeCF\textsubscript{3}. Goossen and coll. accessed to trifluoromethylselenolated compounds in a Sandmeyer-type reaction starting from the aromatic and heteroaromatic diazonium salts in presence of catalytic amounts of copper thiocyanate. As expected, a single electron transfer mechanism is involved leading to the expected compounds (Scheme 15).\textsuperscript{[34]}

Scheme 15 Sandmeyer trifluoromethylselenolation reaction

108
I.2.3 Electrophilic trifluoromethylselenolation reactions

Electrophilic trifluoromethylselenolating reactions are far way less developed than nucleophilic trifluoromethylthiolating reactions. Thus, the development of new reagents as well as new synthetic approaches to access CF$_3$Se-containing compounds through an electrophilic pathway would be highly desirable considering the advantages of this methodology.

I.2.3.1 Trifluoromethaneselenyl chloride

Trifluoromethaneselenyl chloride is the sole reagent used in electrophilic trifluoromethylselenolation reactions as a source of SeCF$_3$. The first synthesis of CF$_3$SeCl has been reported in the late 50ies by Emeleus and coll.$^{[35]}$ as well as Yarovenko and coll.$^{[36]}$ reacting trifluoromethyl diselenide with Cl$_2$. Trifluoromethyl diselenide has been prepared by heating elemental selenium in presence of CF$_3$I or trifluoromethylacetoxy silver (Scheme 16, eq. a). However, the synthetic pathway presents a low overall yield, especially due to the first synthetic step. In order to overcome such a problem, Magnier et al. reacted dibenzyldiselenide with CF$_3$I in presence of sodium hydroxymethanesulfinate obtaining benzyl trifluoromethylselenide, which was reacted with sulfuryl chloride to give CF$_3$SeCl with an overall yield of more than 90 % (Scheme 16).$^{[6a]}$

Despite the great steps forward in improving the synthesis, its good capacity in acting as trifluoromethylselenolating reagent has not been fully exploited and no novel reactions have been performed since then.

![Scheme 16 Synthesis of trifluoromethaneselenyl chloride](image)

Indeed, all the reactions performed with CF$_3$SeCl date more than 30 years ago, when still the way to obtain such a highly volatile reagent was far way less advantageous. Yagupolskii and coll.
reported the trifluoromethylselenolation of aromatic amines through a $S_{N}Ar$ reaction reacting phenyl amines and CF$_3$SeCl in Et$_2$O (Scheme 17, eq. a).$^{[37]}$ More electron-rich compounds as phenol gave a lack of selectivity leading to trifluoromethylseleno trisubstituted compounds (Scheme 17, eq. c).$^{[38]}$ Also few Grignard reagents have been successfully transformed to trifluoromethylselenolated compounds in diethyl ether (Scheme 17, eq. b). Haas and coll. reported an acid mediated insertion of SeCF$_3$ moiety to an aromatic core (Scheme 17, eq. d).$^{[39]}$
I.3 Se-CF$_2$R bond formation; indirect approach

Concerning Se-CF$_2$R (where R = FG, R$_F$) containing molecules only the indirect approach has been reported to literature up to date. Herein we report the fluoroalkylation reactions as tools to access SeCF$_2$R containing molecules.

I.3.1 Se-CF$_2$R bond formation through a radical pathway

Herein we report the Se-CF$_2$R bond formation through a radical pathway mechanism.

I.3.1.1 HCF$_2$Cl as difluorocarbene source

As in the case of the thiolates, reactions involving difluorocarbene sources have been developed in order to access fluoroalkylselenolations. Chlorodifluoromethane, a restricted-use refrigerating gas is one of the first compounds used as a difluorocarbene source. Suzuki and coll. reported the difluoromethylation of preformed selenolates in presence of sodium hydroxide.\(^{[40]}\)

![Scheme 18 Chlorodifluoromethane as a difluorocarbene precursor](image)

I.3.1.2 Dibromodifluoromethane

Dibromodifluoromethane is another well-known difluorocarbene precursor and it has been described in the previous chapter when used in the difluoromethylation of S-centers. Qing and coll. reported the synthesis of PhSeCF$_2$Br, starting from selenophenol or diselenides in presence of CF$_2$Br$_2$ as a difluorocarbene precursor.

![Scheme 19 Dibromodifluoromethane as a difluorocarbene source](image)

The only use of NaH for deprotonating the selenophenol led to the expected compounds with a 25 % yield (Scheme 19, eq. a).\(^{[41]}\) However, the authors improved the yield after addition of
NaBH₄ to the reaction mixture in order to reduce PhSeSePh and other by-products to reactive species (Scheme 19, eq. b). Also NaBH₄-mediated reduction of the diselenide followed by subsequent addition of CF₂Br₂ led to the desired compound in a reasonable yield (Scheme 19, eq. c).

### 1.3.1.3 Sodium chlorodifluoroacetate

SCDA (sodium chlorodifluoroacetate) has been also used as a difluorocarbene source in the difluoromethylation of thiols as shown above. However, only one example of difluoromethylation of selenols has been reported by the authors (Scheme 20).

![Scheme 20 SCDA as a difluorocarbene source](image)

### 1.3.1.4 Aryl difluoromethyl chlorides used as radical sources

ArCF₂Cl compounds were found to be radical sources in presence of light and underwent radical reactions in presence of a in situ preformed selenolate. ArCF₂ radical has been formed after dissociation of C-Cl bond induced by light-mediated electron transfer from the selenolate. As expected, a radical chain propagation mechanism is involved leading to the expected selenolated compounds (Scheme 21).

![Scheme 21 ArCF₂Cl used as a difluorocarbene source](image)
I.3.1.5  $R_f$I used as perfluorinating reagent in radical perfluoroalkylations

C-$R_f$ and S-$R_f$ containing molecules have already been reported in literature and several ways to obtain them do already exist. In the case of perfluoroalkylselenides few data have been reported in literature.

In the early 60ies, perfluoroalkyl selenolated derivatives has been firstly synthesized by Emeleus and coll. with the aim to compare their physico-chemical properties with the corresponding trifluoromethyl selenides.\textsuperscript{[45]} Magnier et al. reported the synthesis of perfluoroalkyl selenides starting from the corresponding iodides and diselenides (Scheme 22, eq. a).\textsuperscript{[6]} Later on, Dolbier and coll. accessed to perfluoroalkyl selenolated compounds using the TDAE/$R_f$I methodology (Scheme 22, eq. b).\textsuperscript{[7a]}

I.3.2  $\text{Se-CF}_2R$ bond formation through a nucleophilic pathway

Difluoroalkylation of Se-centres through a nucleophilic pathway has been even less explored respect to the already revisited radical pathway. Herein we report a short overview of the existing procedures in literature.

I.3.2.1  Hemiaminals and $\alpha$-Difluorodiaroylmethanes

After using the hemiaminals of fluoral as trifluoromethylating reagents, our group studied also the possibility of using these compounds as difluoroalkylating reagents in presence of various electrophiles.
Phenylselenyl chloride underwent difluoroalkylation leading to the desired compound in a good yield (Scheme 23). The importance of such transformation should be also highlighted because it leads to adducts that can go post-functionalization.

Lu and coll. reported the synthesis of difluoromethyl phenyl selenide using α,α-difluorodibenzoylmethane as a difluoromethylating reagent. Nevertheless, only one substrate has been reported with only the dosed yield.

\[
\begin{align*}
\text{Ph} & \quad \text{O} \\
\begin{array}{c}
\text{F}
\end{array} & \quad \begin{array}{c}
\text{F}
\end{array} \\
\begin{array}{c}
\text{Ph}
\end{array} & \quad \begin{array}{c}
\text{Ph}
\end{array} \\
\text{F} & \quad \text{F} \\
\text{PhSeSePh} & \quad \text{PhSeCF}_2\text{H}
\end{align*}
\]

Scheme 24 Difluoromethylation of diselenides

### I.3.2.2 Metal-catalyzed perfluoroalkylations

As shown in the section above, Rueping and coll. reported the trifluoromethylation of the in situ formed selenocyanates starting from the diazonium salts. In the same paper also three perfluoroalkylations examples have been reported using the same methodology (Scheme 25).

\[
\begin{align*}
\text{R} & \quad \text{N}_2 \quad \text{BF}_4 \\
\text{CuCl/CuCl}_2 & \quad 1,10\text{-phen} \quad 10 \text{ mol} \% \\
\text{KSeCN, Cs}_2\text{CO}_3 & \quad \text{CH}_3\text{CN} \\
\text{TMSC}_2\text{F}_5 & \quad \text{SeC}_2\text{F}_5
\end{align*}
\]

Scheme 25 Perfluoroalkylation reactions

A Pd-catalyzed cross-coupling reaction method has been used to obtain the superior homologs of CF$_3$Se starting from selenyl stannanes and iodoperfluoroalkanes. Two examples have been reported with a good yield (Scheme 26).

\[
\begin{align*}
\text{Bu}_{\text{Se}} & \quad \text{Sn-Bu} \\
\text{Bu} & \quad \text{Bu} \\
\text{Sn} & \quad \text{Sn} \\
\text{Bu} & \quad \text{Bu} \\
\end{align*}
\]

\[
\begin{align*}
\text{R}_\text{F} & \quad \text{(PPh}_3\text{)}_2\text{PdCl}_2 \\
\text{DMF} & \quad 90 \%
\end{align*}
\]

Scheme 26 Perfluoroalkylation of selenyl stannates
II. Results and Discussion: SeCF$_2$R insertion

As shown in the bibliographic part, most of the methodologies reporting the insertion the SeCF$_3$ group insertion into molecules have been obtained through nucleophilic pathway. Various trifluoromethylselenolating reagents have already been reported. C-SeCF$_3$ bond formation through a nucleophilic pathway led to different classes of compounds as (hetero)aromatics, propargyl, allyl, vinyl and alkyl as well as $\alpha,\beta$-unsaturated carbonyl CF$_3$Se-containing compounds. Up to the present time only a few examples of electrophilic substitution reactions have been reported. As a matter of fact, only CF$_3$SeCl has been used with the aim to access CF$_3$Se-containing compounds.

Concerning C-SeCF$_2$R (where R= FG) bond formation no bibliographic data has been found up to present time to our knowledge. Thus, the development of reagents acting as $^+\text{SeCF}_2\text{R}$ donors remains relevant.

II.1 Synthesis of benzyl fluoroalkyl selenides

Herein we report the synthesis of benzyl fluoroalkyl selenides, compounds that act as pre-reagents donating the SeCF$_2$R group in presence of SO$_2$Cl$_2$ to form the reactive species CF$_3$SeCl.

II.1.1 State of the art: Synthesis of the CF$_3$SeCl

In the late 50ies two groups independently reported the synthesis of trifluoromethaneselenyl chloride reacting trifluoromethyl diselenide and chlorine.\textsuperscript{[35-36]} Indeed, CF$_3$SeCl has been obtained with 90 % yield following this method during the last step of the synthesis. In spite of that, the synthetic method includes the use of gases as chlorine and the use of volatile and toxic starting materials as F$_3$CSeSeCF$_3$.

\[
\begin{array}{c}
\text{ClSeCF}_3 \\
\text{SO}_2\text{Cl}_2 \\
\text{95 \%} \\
\end{array} \rightarrow \begin{array}{c}
\text{ClSeCF}_3 \\
\text{Cl}_2 \\
\text{90 \%} \\
\end{array} \rightarrow \begin{array}{c}
\text{CF}_3\text{SeSeCF}_3 \\
\end{array}
\]

Scheme 27 Synthesis of trifluoromethaneselenyl chloride

In order to overcome these drawbacks Magnier \textit{et al.} reported an improved synthesis of CF$_3$SeCl. Notably the use of more easy-to-handle starting materials, as trifluoromethyl benzyl selenide and sulfuryl chloride, was beneficial in both terms of manipulation and overall yield. Despite these steps forward, CF$_3$SeCl still did not find any further use as trifluoromethylselenolating reagent. This might be due to the handling difficulties deriving from its highly volatile character considering that a boiling point between 31–31.5 °C has been reported in literature.\textsuperscript{[35-36]} Another
important topic is the supposed toxicity of CF₃SeCl (by analogy with CF₃SCl), even if, up to the present time, no toxicity-related data have been reported to literature. As a result of what mentioned above, its use has been rather limited to the synthesis a few examples reported in literature. Nevertheless, keeping in mind its good reactivity, efforts need to be done in order to revalorize such a reagent, minimizing the disadvantages. Therefore, the preparation of CF₃SeCl and its in situ use could avoid the isolation and the direct contact with the reagent, rendering less essential the eventual toxicity of the reagent.

Based on the results obtained by Magnier et al. the use of benzyl fluoroalkyl selenides as pre-reagents in presence of SO₂Cl₂ could be an attractive strategy. Thus, the CF₃SeCl, in situ prepared, would react with the proper arenes leading to the formation of Ar-SeCF₃ compounds.

### II.1.2 Synthesis of benzyl fluoroalkyl selenides

Magnier et al. accessed to benzyl perfluoroalkyl selenides starting from dibenzyl diselenide and CF₃I as shown above. Furthermore, benzyl trifluoromethyl selenides were prepared in our laboratory years ago through a TBAF-catalyzed reaction between benzyl selenocyanates and TMSCF₃ (Scheme 28).[12] Benzyl selenocyanate itself can be easily obtained in a quantitative yield, starting from benzyl bromide and potassium selenocyanate.

![Scheme 28 Synthesis of benzyl trifluoromethyl selenide](image)

Keeping in mind the willingness to access RCF₂Se-containing molecules through an electrophilic pathway and considering the commercial availability of various fluoroalkylsilanes, we planned to synthesize different benzyl-SeCF₂R (Scheme 29).

![Scheme 29 Benzyl fluoroalkyl selenides](image)

As mentioned above and with the previous obtained results in mind, we planned the synthesis of the pre-reagents 2a-g. Compound 2a was obtained reacting the Ruppert-Prakash reagent with Se¹ in presence of catalytic amounts of TBAF. It should be noticed that the reaction was be
Chapter II. Synthesis of benzylfluoroalkyl selenide reagents: Application in S$_2$Ar reactions

Scaled-up with similar yield (Table 1, entry 1-3). Such a result emphasizes the robustness of the methodology. Compound 2b was obtained in a good yield in the same way reacting TMSCF$_2$Br with BnSeCN and the synthesis scaled up to 20 mmol (Table 1, entry 4-5). Moreover, we could easily access to compounds 2d, 2f and 2g by using the previous reaction conditions and the proper silylated reagents. Additionally, in all of the cases good to excellent yields were obtained (Table 1, entry 10-13).

Table 1 Synthesis of benzyl fluoroalkyl selenides

<table>
<thead>
<tr>
<th>Entry</th>
<th>BnScCN (mmol)</th>
<th>TMSCF$_2$-R (2 equiv.)</th>
<th>F$^-$ source (equiv.)</th>
<th>Solvent</th>
<th>Time h</th>
<th>Yield$^2$ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>9.9 mmol CF$_3$</td>
<td>TBAF 20 mol %</td>
<td>THF</td>
<td>7 h</td>
<td>2a</td>
<td>73 %</td>
</tr>
<tr>
<td>2</td>
<td>9.9 mmol CF$_3$</td>
<td>TBAF 20 mol %</td>
<td>THF</td>
<td>7 h</td>
<td>2a</td>
<td>82 %</td>
</tr>
<tr>
<td>3</td>
<td>70 mmol CF$_3$</td>
<td>TBAF 20 mol %</td>
<td>THF</td>
<td>7 h</td>
<td>2a</td>
<td>70 %</td>
</tr>
<tr>
<td>4</td>
<td>5 mmol CF$_2$Br</td>
<td>TBAF 20 mol %</td>
<td>THF</td>
<td>4 h</td>
<td>2b</td>
<td>80 %</td>
</tr>
<tr>
<td>5</td>
<td>20 mmol CF$_2$Br</td>
<td>TBAF 20 mol %</td>
<td>THF</td>
<td>4 h</td>
<td>2b</td>
<td>88 %</td>
</tr>
<tr>
<td>6</td>
<td>0.5 mmol CF$_3$SO$_2$Ph</td>
<td>TBAF 20 mol %</td>
<td>THF</td>
<td>15 h</td>
<td>2c</td>
<td>(6 %)</td>
</tr>
<tr>
<td>7</td>
<td>0.5 mmol CF$_3$SO$_2$Ph</td>
<td>CsF 1 equiv.</td>
<td>Diglyme</td>
<td>15 h</td>
<td>2c</td>
<td>(40 %)</td>
</tr>
<tr>
<td>8</td>
<td>0.5 mmol CF$_3$SO$_2$Ph</td>
<td>CsF 20 mol %</td>
<td>Diglyme</td>
<td>15 h</td>
<td>2c</td>
<td>(84 %)</td>
</tr>
<tr>
<td>9</td>
<td>5.5 mmol CF$_3$SO$_2$Ph</td>
<td>CsF 20 mol %</td>
<td>Diglyme</td>
<td>15 h</td>
<td>2c</td>
<td>80 %</td>
</tr>
<tr>
<td>10</td>
<td>2 mmol CF$_3$CO$_2$Me</td>
<td>TBAF 20 mol %</td>
<td>THF</td>
<td>15 h</td>
<td>2d</td>
<td>62 %</td>
</tr>
<tr>
<td>11</td>
<td>4.5 mmol CF$_2$CF$_3$</td>
<td>TBAF 20 mol %</td>
<td>THF</td>
<td>16 h</td>
<td>2f</td>
<td>83 %</td>
</tr>
<tr>
<td>12</td>
<td>14.2 mmol CF$_2$CF$_3$</td>
<td>TBAF 20 mol %</td>
<td>THF</td>
<td>16 h</td>
<td>2f</td>
<td>78 %</td>
</tr>
<tr>
<td>13</td>
<td>3.7 mmol CF$_2$CF$_2$CF$_3$</td>
<td>TBAF 20 mol %</td>
<td>THF</td>
<td>16 h</td>
<td>2g</td>
<td>87 %</td>
</tr>
</tbody>
</table>

$^1$ A 1M solution of TBAF in THF was used. $^2$ Isolated yields; In parentheses the dosed yields determined by $^{19}$F NMR using PhOCF$_3$ as an internal standard.

In contrast to other silanes, TMSCF$_3$SO$_2$Ph showed to be more stable considering that in presence of 0.2 equiv. of TBAF only 6% of dosed yield was observed (Table 1, entry 6). The use
of a stronger fluoride source as CsF in diglyme led to compound 2c with a 40 % dosed yield with a stoichiometric amount (Table 1, entry 7). However, the optimal reaction conditions resulted to be catalytic amounts of CsF in diglyme. In this case compound 2c was obtained with 80 % isolated yield (Table 1, entry 9).

Considering the recent importance that have been given to the CF₂H as a bioisostere in mimicking various endogenous functional groups and the recent advances in SCF₂H chemistry, we came up with the idea of developing a pre-reagent that acts as a SeCF₂H donor. To directly access compound 2e we reacted benzyl selenocyanate and difluoromethyl silane in presence of catalytic and excess amounts of TBAF.

Table 2 Synthesis of BnSeCF₂H

<table>
<thead>
<tr>
<th>Entry</th>
<th>F⁻ source² (equiv.)</th>
<th>Solvent</th>
<th>Temp °C</th>
<th>Yield³ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>TBAF 20 mol %</td>
<td>THF</td>
<td>23 °C</td>
<td>(2 %)</td>
</tr>
<tr>
<td>2</td>
<td>TBAF 2 equiv.</td>
<td>THF</td>
<td>23 °C</td>
<td>(7 %)</td>
</tr>
<tr>
<td>3</td>
<td>TBAF 2 equiv.</td>
<td>THF</td>
<td>50 °C</td>
<td>(12 %)</td>
</tr>
<tr>
<td>4</td>
<td>TBAF 20 mol %</td>
<td>THF</td>
<td>65 °C</td>
<td>(8 %)</td>
</tr>
<tr>
<td>5</td>
<td>TBAF 20 mol %</td>
<td>DMF</td>
<td>120 °C</td>
<td>(3 %)</td>
</tr>
<tr>
<td>6</td>
<td>CsF 20 mol %</td>
<td>Diglyme</td>
<td>23 °C</td>
<td>(3 %)</td>
</tr>
<tr>
<td>7</td>
<td>CsF 1 equiv.</td>
<td>Diglyme</td>
<td>23 °C</td>
<td>(28 %)</td>
</tr>
<tr>
<td>8</td>
<td>CsF 20 mol %</td>
<td>DMF</td>
<td>23°C</td>
<td>(16 %)</td>
</tr>
<tr>
<td>9</td>
<td>CsF 1 equiv.</td>
<td>DMF</td>
<td>23°C</td>
<td>(28 %)</td>
</tr>
<tr>
<td>10</td>
<td>CsF 3 equiv.</td>
<td>DMF</td>
<td>23°C</td>
<td>(12 %)</td>
</tr>
<tr>
<td>11</td>
<td>CsF 3 equiv.</td>
<td>DMF</td>
<td>80 °C</td>
<td>(12 %)</td>
</tr>
<tr>
<td>12</td>
<td>CsF 1 equiv.</td>
<td>DMF</td>
<td>80 °C</td>
<td>(9 %)</td>
</tr>
<tr>
<td>13¹</td>
<td>CsF 3 equiv.</td>
<td>DMF</td>
<td>23°C</td>
<td>19 % (33 %)</td>
</tr>
<tr>
<td>14</td>
<td>CsF 1 equiv.</td>
<td>DMF</td>
<td>23°C</td>
<td>19 % (33 %)</td>
</tr>
</tbody>
</table>

¹ 1 equiv. of CuSCN is added. ² A 1M solution of TBAF in THF was used. ³ Isolated yields; In parentheses the dosed yields determined by ¹⁹F NMR using PhOCF₃ as an internal standard.

Only low yields or traces of the expected compound were observed in contrast to the previously synthesized pre-reagents (Table 2, entry 1-5). This might be due to the more stable character of the TMS CF₂H, as discussed above in this dissertation. CsF used in catalytic amounts gave
approximately the same results as in the case of TBAF (Table 2, entry 6 and 8). On the other hand, the use of stoichiometric amounts of CsF at 23 °C gave compound 2e with a 28 % dosed yield in diglyme as well as DMF (Table 2, entry 7 and 9). It was found that an excess of CsF as well as higher temperatures only hampers the reaction (Table 2, entry 8-12). Moreover, neither the use of CuSCN it was found beneficial for the reaction yield (Table 2, entry 13). Despite these efforts, compound 2e was finally obtained and isolated with a modest yield of 19 %. Regardless the low yield we should emphasize the fact that the first SeCF₂H donor was developed in order to easily furnish SeCF₂H containing molecules.
II.1.2.1 CF$_3$SeCl: in situ preparation of the reactive species

In light of the results obtained by Magnier et al. we started exploring the best reaction conditions for the in situ preparation of CF$_3$SeCl (2a'). By simply mixing equimolar amounts of benzyltrifluoromethyl selenide and sulfuryl chloride in THF the instant formation of trifluoromethaneselenyl chloride was observed (Table 3, entry 1 and 2). On the other hand, increasing the amount of SO$_2$Cl$_2$ gave a lower yield in the same period of time. This is related to the formation of a by-product CF$_3$SeCl$_3$ (2a''). Moreover, the formation of compound 2a'' increases proportionally with the time up to 4 hours (Table 3, entries 3-6).

Table 3 Formation of ClSeCF$_3$

<table>
<thead>
<tr>
<th>Entry</th>
<th>SO$_2$Cl$_2$ (equiv.)</th>
<th>Solvent</th>
<th>Time</th>
<th>2a' (%)</th>
<th>2a'' (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1 equiv.</td>
<td>THF</td>
<td>4 min.</td>
<td>(95 %)</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>1 equiv.</td>
<td>THF</td>
<td>15 min</td>
<td>(95 %)</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>2 equiv.</td>
<td>THF</td>
<td>4 min.</td>
<td>(82 %)</td>
<td>(10 %)</td>
</tr>
<tr>
<td>4</td>
<td>2 equiv.</td>
<td>THF</td>
<td>15 min</td>
<td>(58 %)</td>
<td>(40 %)</td>
</tr>
<tr>
<td>5</td>
<td>2 equiv.</td>
<td>THF</td>
<td>1.5 h</td>
<td>(46 %)</td>
<td>(52 %)</td>
</tr>
<tr>
<td>6</td>
<td>2 equiv.</td>
<td>THF</td>
<td>3 h</td>
<td>(59 %)</td>
<td>(41 %)</td>
</tr>
<tr>
<td>7</td>
<td>1 equiv.</td>
<td>CH$_2$Cl$_2$</td>
<td>15 min</td>
<td>(19 %)</td>
<td>-</td>
</tr>
<tr>
<td>8</td>
<td>1 equiv.</td>
<td>CH$_2$Cl$_2$</td>
<td>1.5 h</td>
<td>(62 %)</td>
<td>-</td>
</tr>
<tr>
<td>9</td>
<td>1 equiv.</td>
<td>CH$_2$Cl$_2$</td>
<td>3 h</td>
<td>(67 %)</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>1 equiv.</td>
<td>CH$_2$Cl$_2$</td>
<td>4 h</td>
<td>(67 %)</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>2 equiv.</td>
<td>CH$_2$Cl$_2$</td>
<td>15 min</td>
<td>(34 %)</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>2 equiv.</td>
<td>CH$_2$Cl$_2$</td>
<td>1.5 h</td>
<td>(83 %)</td>
<td></td>
</tr>
<tr>
<td>13'</td>
<td>2 equiv.</td>
<td>CH$_2$Cl$_2$</td>
<td>3 h</td>
<td>(88 %)</td>
<td></td>
</tr>
</tbody>
</table>

*In parentheses the dosed yields determined by $^{19}$F NMR using PhOCF$_3$ as an internal standard.

Important to mention is the faster reaction rate in THF than in CH$_2$Cl$_2$ using 1 equiv. of SO$_2$Cl$_2$ (Table 3, entries 2 and 7). The slower product formation as well as the lower yield, 67 % after 3 h respect to 95 % after 4 minutes were observed in CH$_2$Cl$_2$. On the contrary to THF, use of 2 equivalents of SO$_2$Cl$_2$ in CH$_2$Cl$_2$ do not lead to the formation of by-products 2a'', but the yield of compound 2a' increases up to 88 % in 3 hours.
As reported by Magnier et al., the mechanism could be supposed to start with the sulfuryl chloride dissociation in Cl₂ and SO₂. Generated chlorine attacks the selenium leading to the formation of a cationic intermediate which expels CF₃SeCl through nucleophilic attack of chloride anion in benzylic position, generating also BnCl.⁶ᵇ

When 2 equiv. of SO₂Cl₂ were used in THF, a second equiv. of Cl₂, coming from the excess of SO₂Cl₂, reacts with CF₃SeCl to give the unreactive species CF₃SeCl₃.

II.1.2.2 Benzyltrifluoromethyl selenide used as a CF₃SeCl source in Sₐ-Ar reactions

Herein we report the use of CF₃SeCl (2a') in Sₐ-Ar reactions in presence of electron-rich arenes. Various compounds were prepared following such a straightforward strategy, thus enabling the scientific community to access CF₃Se-compounds through easy-to-handle reagents.

After in situ formation of CF₃SeCl, by action of SO₂Cl₂ onto BnSeCF₃ in THF in 15 minutes, arenes or heteroarenes were added in reacting media (Scheme 32).

The formation of corresponding trifluoromethylselenolated compounds was observed with electron-rich compounds. Good to excellent yields were obtained and the dosed yields were often quantitative (Scheme 32). Addition of dimethoxybenzene to the already-formed 2a' after 15 minutes led to 40a with a yield of 80%. Resorcinol and 1-naphtol reacted well with CF₃SeCl leading to the formation of the desired compounds 40b and 40d with 85% and 75% yield respectively. Using 2.2 equiv. of both BnSeCF₃ and SO₂Cl₂, with resorcinol led to the bis(trifluoromethylselenolated) compound 40c in a 75% yield. Also, N-dimethylaniline reacted with the 2a' giving compound 40e with 84% yield. Less electron-rich compounds did not react...
in the same conditions. In order to increase the reactivity of CF₃SeCl we tried a Lewis acid-mediated reaction. Under these conditions, the use of catalytic amounts of BF₃.Et₂O gave compounds 40l and 40m with a yield of 60% and 64%. Nevertheless, compound 40k, arising from non electron-rich toluene, could be obtained with only 4% of yield. Also, the trifluoromethylselenolation of heteroaromatic compounds like pyrroles and indoles in presence of CF₃SeCl was studied. The two classes of compounds find interest in pharmaceutical and agrochemical synthesis. Thus, could be of particular interest to obtain the trifluoromethylselenolated version of such compounds. Then, pyrrole 40f was synthesized with a good yield of 65%. Trifluoromethylselenolated indoles (40h-j) were also obtained in excellent yields.

Scheme 32 SₐAr reactions using ClSeCF₃. Yields shown are of isolated products; values in parentheses are yields as determined by ¹⁹F NMR spectroscopy using PhOCF₃ as an internal standard. ²a (2.2 equiv), SO₂Cl₂ (2.2 equiv). ²b 2a (1.2 equiv), SO₂Cl₂ (1.2 equiv), BF₃. Et₂O (0.3 equiv), CICH₂CH₂Cl, 80 °C.
II.1.2.3 Fluoroalkylselenolation of arenes

As shown above the direct insertion of SeCF$_2$R pre-functionalized groups into molecules has not been reported yet. With this in mind we planned the insertion of various fluoroalkylselenolated groups into molecules.

II.1.2.3.1 BrCF$_2$SeCl used in S$_a$/Ar reactions

Bromodifluoromethylselenolated arenes were prepared from the preformed reagent BrCF$_2$SeCl and the proper arenes. Up to date no literature data has been reported concerning the formation of BrCF$_2$Se-molecules. Bromo derivatives find a wide use in synthesis as starting materials especially in cross-coupling reactions. Thus, the preparation of Ar-SeCF$_2$Br compounds is of particular importance because would furnish pre-functionalized materials to use in further synthesis.

In general, the obtained yields are similar to the ones for the trifluoromethylselenolated adducts with electron-rich arenes. As in that case heterocyclic compounds were also
bromodifluoromethylselenolated. Pyrrole 30g gave only the compound 40g arising from bis-substitution. Less electron-rich did not react in these conditions and only low yields were observed when BF₃·Et₂O was used as an activator.

As previously mentioned, such bromodifluoromethylselenolated molecules constitute important starting materials for further functionalization. For instance, Gouverneur and coll. reported the radiolabeling of BrCF₂O and BrCF₂S containing molecules with [¹⁸F]F through a nucleophilic halex-exchange mediated mechanism. Consequently, the obtained molecules 41 could be used to access, for the first-time, to [¹⁸F]CF₃Se moiety. This application will be reported in Chapter 3.

II.1.2.3.2 RₚSeCl used in SₐrAr reactions

To our knowledge only one electrophilic perfluoroalkylselenolation reaction has been reported to literature. Magnier et al. reported the perfluorooctylselenolation of sodium diethylmalonate using C₈F₁₇SeCl.[⁶b]

In our series of above reported pre-reagents, we reported the synthesis of two perfluoroalkylselenolated donors. Both these compounds would respectively give C₂F₅SeCl and C₃F₇SeCl in presence of SO₂Cl₂.

The in situ formed reactive species would react with electron-rich arenes to give the desired compounds as shown above in the case of SeCF₃.

For instance, resorcinol and indole were added to the reaction mixture containing the preformed C₂F₅SeCl leading to compounds 42b and 42h with excellent yields. Likewise, using C₃F₇SeCl we could obtain compounds 43a and 43h with 88 % and 89 % yield respectively. Worth to mention,
that we reported the first direct fluoroalkylselenolations of arenes. For sure this methodology should be extended to other arenes in order to have a larger panel of ArSeRF compounds.

II.1.2.3.3 **RCF₂Se insertion through S<sub>e</sub>Ar reactions.**

As in the case of perfluoroalkylselenolation, direct RCF₂Se (R= H, FG) insertion into molecules has not been reported. Herein, we report the synthesis of molecules bearing SeCF₂H, SeCF₂CO₂Me and SeCF₂SO₂Ph groups. As in the case of difluoromethylthiolated molecules, the SeCF₂H group could be of particular interest considering a possible H bonding donor character. On the other hand, the presence of functional groups adjacent to the SeCF₂ moiety could be valuable because leads to interesting compounds through post-functionalization reactions.

Thus, pre-reagents 2c, 2d and 2e in THF gave the corresponding reactive species 2c'-2e', after the addition of SO₂Cl₂. The formation of HCF₂SeCl (2e') requires 45 minutes. After the addition of resorcinol or indole into the reaction media we obtained compounds 44b and 44h in good yields. The formation of the two other reactive species 2d' and 2e', requires also more time, 30
minutes for both. For instance, addition of arenes into reaction media after 30 minutes led to compounds 45 and 46 in good to excellent yields (Scheme 36).

As reported above, those two functional groups have proved to be valuable in post-functionalization reactions in the chemistry of SCF₂R. Thus, we could predict the same role in accessing post-functionalized CF₂Se-containing molecules.

II.1.3 Post-functionalization reactions

Post-functionalization reactions occupy an important role in the first chapter. Through post-functionalization reactions we could access to various compounds that might find interest in organic synthesis or pharmaceuticals. An interesting transformation was obtained after a reductive desulfonylation in presence of a source of deuterium to access SCF₂D compounds.

Consequently, based on the recent interest towards deuterated molecules and our successful methodology to access DCF₂S-containing compounds we decided to extend such a methodology to obtain, for the first time, DCF₂Se adducts. Thus, adapting the reaction conditions previously used we accessed compound [D]47h with a 58% yield.

![Scheme 37 Synthesis of SeCF₂D compound. Yields shown are of isolated products; values in parentheses are yields as determined by ¹⁹F NMR spectroscopy using PhOCF₃ as an internal standard](image)

III. Conclusions

As a conclusion, we came out with a new one-pot strategy to access various fluoroalkylselenolated compounds with good to excellent yields. The above reported results were obtained using a known source of fluoroalkylselenolating reagent. Thus, revalorization of an old reagent led to interesting results. We reported the synthesis of seven different pre-reagents 2a-2g, as sources of the corresponding reactive species generated in situ, 2a′-2g′. Only one of the above reported pre-reagents was known prior to literature. The preformed reactive species RCF₂SeCl acted as fluoroalkylselenolating reagents in presence of arenes and heteroarenes. By means of the above described strategy, we reported the trifluoromethylselenolation of arenes and heteroarenes and most of the compounds were not reported in literature. Resorcinol and indole were used as starting material to access perfluoroalkylselenolation as well as difluoromethylselenolating
compounds for the first time in a direct insertion. Also, pre-functionalized molecules bearing SeCF$_2$Br, SeCF$_2$SO$_2$Ph and SeCF$_2$CO$_2$Me were reported.

In the light of the results obtained in post-functionalization reactions reported in the first chapter we performed a Mg-mediated reductive desulfonylation reaction in CD$_3$OD reporting the first procedure to access deuterodifluoromethylselenolated molecules.
IV. References:


CHAPTER III

TRIFLUOROMETHYLCHALCOGENS;
LATE-STAGE $^{18}$F-FLUORINATION OF
SCF2R AND SeCF2R GROUPS
Chapter III. Trifluoromethylchalcogens; Late-stage [18F]F radiolabeling

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As previously mentioned, part of our freshly synthesized compounds were used as starting materials in nucleophilic $^{18}$F-labeling. Herein we report the various efforts made to access SCF$_2^{18}$F and SeCF$_2^{18}$F containing molecules.

Results and Discussion part is preceded by a short overview of the data found in literature concerning radiolabeling of fluorochalcogen groups through $^{18}$F late-stage fluorination.

I. Bibliography

I.1 Introduction to Positron Emission Tomography principles, non-metallic radionuclides and applications

Nuclear medicine involves the application of radioactive substances in the detection and treatment of diseases. The most common techniques in nuclear imaging are single photon emission computed tomography (SPECT) and positron emission tomography (PET). Unlike SPECT imaging, positron emission tomography gives a higher resolution and a better quantification of the image. Positron emission tomography has been developed the last 40 years as a valuable imaging technique in detecting functional abnormalities at molecular levels. During the last years, PET imaging became an important diagnostic tool especially for physicians considering the facility to detect illnesses as brain disorders, cancer as well as heart diseases at early stages. The non-invasive character of the PET imaging fits perfectly to the needs of the patients, which preferably would like to avoid invasive detection methods. Unlike structural imaging techniques as magnetic resonance imaging (MRI), computerized imaging (CT) or ultrasound (US), which provide useful anatomical information, PET gives a more detailed picture regarding the physiological and biological processes in living species by monitoring the distribution and concentration of the labeled probes over time. As a result, PET imaging could provide benefits to drug development, in vivo pharmacological imaging as well as in pre-clinical studies fields.

The development of PET radiotracers consists on the incorporation of radioactive isotopes into the molecule. Incorporation of low atomic mass elements as C, N and O into the molecules is advantageous due to their presence in most of the organic molecules. For instance, the labeling of radiotracers with these elements does not bring any structural modification within the molecule, thus no modification of the biological activity will be reported. Nevertheless, their short half-life remains the biggest drawback and needs an in situ radioisotope production, fast reaction synthesis and diagnostic tools in proximity.
Another non-metallic radioisotope is $^{18}\text{F}$, which presents several advantages respect to the other radionuclides. Often fluorine-18 is referred as the radionuclide of choice due to the characteristics that confers to the radiotracer. Especially the longer half-life makes $^{18}\text{F}$ the favorite radioisotope for clinical research as well as allowing to access $^{18}\text{F}$-radiolabeled tracers through a multistep synthesis. Moreover, its longer half-life permits to transport $^{18}\text{F}$ also out of the site of production, thus not limiting the use only in sites equipped with a cyclotron. Other advantage is that multiple patients can be scanned with only one produced dose per day. Lately, the cold chemistry of fluorine has been expanding rapidly, allowing the access to various biologically active fluorinated molecules although the presence of fluorine in naturally occurring compounds is low. Furthermore, as previously said in introduction, the insertion of fluorine onto organic compounds modifies their properties then, often, enhancing the ADME (adsorption, distribution, metabolism and excretion) properties of the molecules.

$[^{18}\text{F}]$fluodeoxyglucose ($[^{18}\text{F}]$FDG) is the most used radiotracer in medical imaging. In the early beginnings $[^{18}\text{F}]$FDG has been obtained through electrophilic fluorination of 3,4,6-tri-O-acetyl-D-glucal with $[^{18}\text{F}]$F$_2$ gas (Figure 1). However, considering the low reported yields in $^{18}\text{F}$ electrophilic fluorination, the radiotracer has been labeled through nucleophilic fluorination leading to higher radiochemical yield. The nucleophilic fluorination is the preferred way to access $[^{18}\text{F}]$FDG starting from the acetylated sugar 1,3,4,6-tetra-O-acetyl-2-O-trifluoromethane-sulfonyl-β-D-mannopyranose and $[^{18}\text{F}]$F/K$_{222}$. 

### Tableau 1: Low atomic mass radionuclides used in PET \[^{5}\]

<table>
<thead>
<tr>
<th>Radionuclide</th>
<th>Half-life, ($t_{1/2}$) (min)</th>
<th>Nuclear reaction</th>
<th>Target</th>
<th>Product</th>
<th>Decay product</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^{18}\text{F}$</td>
<td>110</td>
<td>$^{20}\text{Ne} (d,\alpha)^{18}\text{F}$</td>
<td>Ne (+F$_2$)</td>
<td>$[^{18}\text{F}]$F$_2$</td>
<td>$^{18}\text{O}$</td>
</tr>
<tr>
<td>$^{11}\text{C}$</td>
<td>20.4</td>
<td>$^{14}\text{N} (p,\alpha)^{11}\text{C}$</td>
<td>N$_2$ (+O$_2$)</td>
<td>$[^{11}\text{C}]$CO$_2$</td>
<td>$^{11}\text{B}$</td>
</tr>
<tr>
<td>$^{13}\text{N}$</td>
<td>9.97</td>
<td>$^{16}\text{O} (p,\alpha)^{13}\text{N}$</td>
<td>H$_2$O</td>
<td>$[^{13}\text{N}]$NO$_x$</td>
<td>$^{13}\text{C}$</td>
</tr>
<tr>
<td>$^{15}\text{O}$</td>
<td>2.04</td>
<td>$^{15}\text{N} (d,n)^{15}\text{O}$</td>
<td>N$_2$ (+O$_2$)</td>
<td>$[^{15}\text{O}]$O$_2$</td>
<td>$^{15}\text{N}$</td>
</tr>
</tbody>
</table>
Once the radiotracer is prepared, it is administered to the patient by intravenous injection and decays in the body by positron emission. However, the emitted positron (β⁺) is not detected directly but travels into the tissues (a few mm) and collides with an electron. The collision between the positron and the electron results in an annihilation event that produces two γ ray photons with 511 keV energies that travels in opposite direction (180 °) to each other. The simultaneous detection of the two emissions that travels throughout the body (line of coincidence) by the PET scanner helps to locate the interested area in the body. The PET scanner consists of a crown of detectors that helps to identify various simultaneously occurring annihilation events in order to construct a PET image.

I.2 Syntheses of SCF₂⁺¹⁸F, OCF₂⁺¹⁸F and OCHF⁺¹⁸F compounds by nucleophilic substitution reactions: State of art

During the last few years the interest towards compounds containing fluorine has been growing rapidly. A plethora of methodologies to access organic compounds containing fluorine or a fluorinated group has already been reported. Fluoride itself and the trifluoromethyl group are the most common substituents in fluorine chemistry. However, the association of fluorine with other elements of the periodic table has been also explored. For example, fluorinated groups as OCF₃ and SCF₃ confer to the molecules a higher lipophilicity respect to their analog CF₃. Thus, an
increase in lipophilicity represents an advantage for pharmaceuticals and agrochemicals. Despite the steps forward made in cold fluorine chemistry, \(^{18}\text{F}\)-labeled compounds are still challenging to be obtained. Herein we describe the only two works found in literature regarding the radiolabeling of SCF\(_3\), OCF\(_3\) as well as OCF\(_2\)H with fluorine-18.

1.2.1 \(^{18}\text{F}\)-labeling of aryl-OCF\(_2\)Br and aryl-OCHFBBr compounds

Among various groups involved in the \(^{18}\text{F}\)-radiolabeling of compounds, the group of Prof. Gouverneur gave a huge contribution in the development of different methodologies to access \(^{18}\text{F}\)-labeled molecules bearing various fluorinated groups. Recently Gouverneur and coll. reported the \(^{18}\text{F}\)-labeling of Ar-OCF\(_2\)Br through a Ag-mediated halogen-exchange reaction.\(^6\) Thus, various aryl-OCF\(_2\)^{18}\text{F} compounds have been synthesized (Scheme 1). Riluzole, the first drug approved for the treatment of amyotrophic lateral sclerosis has been also radiolabeled.

![Scheme 1 18F-labeling of Ar-OCF2Br adducts](image)

Also, aryl-OCF\(_2\)^{18}\text{F} compounds have been synthesized by using the same strategy. Nine substrates have been radiolabeled and good yields have been reported by the authors (Scheme 2).\(^6\)

![Scheme 2 18F-labeling of Ar-OCF2HCl adducts](image)

1.2.2 \(^{18}\text{F}\)-labeling of aryl-SCF\(_2\)Br compounds

As described in the previous chapters, the F\(_3\)CS-containing molecules are characterized by high lipophilicity (Hansch parameter \(\pi = 1.44\)), an important parameter in drug discovery in determining the transport of bioactive molecules through membranes. The last few years we have assisted to the development of a plethora methodologies to access direct SCF\(_3\) containing molecules. Nevertheless, \(^{18}\text{F}\)-labeled SCF\(_3\) motifs have been reported only in two papers. Gouverneur and coll. accessed for the first time the aryl-SCF\(_2\)^{18}\text{F} -containing adducts by a Ag-mediated halogen exchange nucleophilic fluorination reaction (Scheme 3). As in the case of OCF\(_3\)
and OCF₂H $^{18}$F-radiolabeled compounds, the strategy gave high yields and showed compatibility with various functional groups.⁶

![Scheme 3 $^{18}$F-labeling of Ar-SCF₂Br adducts](image)

At the same time Liang *et coll.* accessed to benzylic, allylic, aliphatic as well as heterocyclic $[^{18}$F] F₃CS containing substrates starting from the corresponding halides. Difluoromethylene phosphobetaine (PDFA) has been employed as a difluorocarbene source and in presence of an external fluoride source forms CF₃⁻ anion. The anion reacts with S₈ to give CF₃S⁻ nucleophilic source, which gives the expected products through a nucleophilic substitution reaction.⁷ Thus, in terms of scope the two reported methodologies could be considered complementary.

![Scheme 4 Synthesis of R-SCF₃$[^{18}$F] compounds](image)
II. Results and discussion

As mentioned previously the association of CF$_3$ and chalcogens increases the lipophilicity of the molecules. Both OCF$_3$ and SCF$_3$ are characterized of high lipophilicity with the respective Hansch parameters 1.04 and 1.44. Following the same way of reasoning we have deduced that also SeCF$_3$ motif confers a higher lipophilicity to the molecules. With this in mind and inspired by interesting results obtained from Gouverneur and coll., we decided to test the $^{18}$F-labeling of SeCF$_2$Br motif by halogen-exchange.

Also, the $^{18}$F-labeling of SCF$_2$FG (FG= SO$_2$Ph, CO$_2$Me) to access $^{[18F]}$F$_3$CS labeled compounds was tested and a brief description will be reported below.

II.1 $^{18}$F-labeling of aryl-SCF$_2$FG substrates

When we started this project, no $^{18}$F-labeling of SCF$_3$ groups had been yet published. Because we had succeeded to achieve molecules bearing SCF$_2$SO$_2$Ph moieties, we decided to try to substitute the PhSO$_2$ part by $^{[18F]}$F$^-$, expecting the push-pull effect of sulfur atom would favor such reaction. However, whatever the tested conditions, no labelling has been observed.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Additive</th>
<th>RCY* (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CuOTf(CH$_3$CN)$_4$</td>
<td>n.r</td>
</tr>
<tr>
<td>2</td>
<td>AgOTf</td>
<td>n.r</td>
</tr>
<tr>
<td>3</td>
<td>TfOH</td>
<td>n.r</td>
</tr>
<tr>
<td>4</td>
<td>-</td>
<td>n.r</td>
</tr>
</tbody>
</table>

* RCY*: radiochemical yield. Volume (300 μL).

Various works in decarboxylative fluorination has been reported in literature especially in cold chemistry. On the other hand, in hot chemistry only a few methods describing decarboxylative fluorination in presence of $^{18}$F has been reported. Gouverneur and coll. lately reported the Ag-mediated $^{18}$F-labeling of ArCF$_2$COOH compounds through decarboxylative fluorination using $^{[18F]}$Selectfluor as a reagent accessing to $^{[18F]}$F$_3$CS-Ar substrates. Groves and coll. described a Mn-catalyzed decarboxylative fluorination of aliphatic carboxylic acids using nucleophilic $^{[18F]}$F$^-$ as a fluoride source. Based on the results obtained by Groves and coll. we tried to adapt their
optimal reaction conditions in order to access (hetero)aryl-SCF$_2^{18}$F substrates. For instance, using 2 mol % of Mn catalyst, and PhIO as an oxidant (Table 1, entry 1) we did not observe any formation of the $^{18}$F-labeled product after 10 min. Neither increasing the amounts of catalyst as well as the reaction times was beneficial to the reaction (Table 1, entry 2). Also, increasing the amounts of the oxidant as well as decreasing the volume of the solvent mixture did not lead to obtain the desired compound (Table 1, entry 3-5).

Table 1 Decarboxylative fluorination using [$^{18}$F]F$^-$

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst (equiv.)</th>
<th>PhIO (equiv.)</th>
<th>Time (min)</th>
<th>Volume (μL)</th>
<th>RCY$^a$ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2 mol %</td>
<td>0.33 equiv</td>
<td>10</td>
<td>400</td>
<td>n.r</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>0.33 equiv</td>
<td>50</td>
<td>400</td>
<td>n.r</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>0.33 equiv</td>
<td>20</td>
<td>300</td>
<td>n.r</td>
</tr>
<tr>
<td>4</td>
<td>1</td>
<td>1</td>
<td>15</td>
<td>300</td>
<td>n.r</td>
</tr>
<tr>
<td>5</td>
<td>1</td>
<td>1</td>
<td>15</td>
<td>400</td>
<td>n.r</td>
</tr>
</tbody>
</table>

$^a$ RCY: radiochemical yield.

II.2 $^{18}$F-labeling of aryl-SeCF$_2$Br substrates

Herein we report the first Ag-mediated $^{18}$F-labeling of SeCF$_2$Br compounds. Inspired by the results described by Gouverneur and coll. in the synthesis of $^{18}$F di- and trifluoromethylethers and $^{18}$F trifluoromethylthioethers we planned the $^{18}$F-labeling of trifluoromethylselenides by adapting the same reaction conditions.

With the results obtained by Gouverneur and coll. in mind, we chose AgOTf as the best source of silver capable to promote the halex exchange at room temperature. Thus, as shown in Table 2 the best yield was obtained using 2 equiv. of AgOTf after 20 min in dichloromethane (entry 1). The reaction did not give the desired product in absence of AgOTf, thus confirming the importance of the silver in the reaction.
Table 2 Optimisation of the reaction conditions

<table>
<thead>
<tr>
<th>Entry</th>
<th>Additive (equiv.)</th>
<th>RCY(^a) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>AgOTf 1 equiv.</td>
<td>45% ± 4 % (n = 2)</td>
</tr>
<tr>
<td>2</td>
<td>AgOTf 2 equiv.</td>
<td>35% ± 2 % (n = 2)</td>
</tr>
<tr>
<td>3</td>
<td>-</td>
<td>n.r</td>
</tr>
</tbody>
</table>

\(^a\) RCY : radiochemical yield.

With the optimized reaction conditions in hand, we tried to extend the \(^{18}\text{F}\) labeling methodology to a wider number of substrates. Indole substrates gave the expected compounds \(41\text{ha}, 41\text{ia}\) and \(41\text{ja}\) with a radiochemical yield of 20 %. Despite the modest radiochemical yield is worth to note that the radiolabeling of indoles was not reported in the case of the SCF\(_2\)Br containing compounds.

![Figure 2](image_url)

Aromatic substrates bearing acidic OH functional groups did not lead to the desired compounds or gave lower yields, probably due to deprotonation of OH by basic, naked, \(^{18}\text{F}\). No trace of the radiolabeled compound \(41\text{ba}\) was observed after 20 minutes of reaction. On the other hand,
41d gave the radiolabeled compound with a 14% yield and also the formation of other by-products was observed. Also in the case of 41ea only traces of the radiolabeled adduct were observed.

Also, the $^{18}$F-labeling of SeCF$_2$Br in benzylic and allylic position was reported. Surprisingly, bromodifluorobenzyl selenide gave compound 50a with a 29% radiochemical yield. Thus, such a result is important because it shows that the halex-exchange methodology reported by Gouverneur and coll. is efficient also for $^{18}$F labeling in benzylic position. Compound 50b was not observed, only unidentified complex mixtures were formed.

III. Conclusions

To conclude, in this chapter we accessed for the first time to the radiolabeling of SeCF$_2$Br containing molecules in collaboration with the University of Oxford. Nucleophilic $^{18}$F-fluorination of the substrates was obtained through Ag-mediated halex exchange reaction. We reported the first example of 18F-labeling over trifluoromethyl selenides, to our knowledge. However, experiments will be on-going in order to expand the substrate scope and improve the yield.
Chapter III. Trifluoromethylchalcogens; Late-stage [18F]F- radiolabeling

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I. Generalities

I.1 Analytic techniques

NMR spectra were recorded on Bruker AVL300 and AV400 at the “Centre Commun de RMN”, Universite Lyon1. All measurements were performed at room temperature if not otherwise mentioned. The internal standard is deuterated chloroform (CDCl₃) if not otherwise mentioned. Chemical shifts are reported in parts per million (ppm) referred to TMS regarding ¹H and ¹³C and CF₃Cl regarding ¹⁹F. Coupling constants are reported in Hertz. Multiplicity of the signals is given as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet). Dosed yields in ¹⁹F NMR were reported using trifluoromethoxybenzene as internal standard (PhOCF₃, δ= -58.30, ppm, s). Nomenclature was assigned following the IUPAC nomenclature rules. Signal peak attribution was assigned after an arbitrary numeration of all the carbons found on the molecule using ChemBioDraw 14.0.

Melting points were measured using a Kofler bench apparatus with a temperature gradient between 45 °C-270 °C. Internal standards were used to calibrate the apparatus as reported in each case. The melting points were not corrected.

GC-MS analyses were measured using Agilent GC-MS mass spectra if reported.
I.2 Working procedures and conditions

**Commercially available compounds** were purchased from different companies and used without any other further purification.

**Dry solvents** were purchased from Sigma-Aldrich and used without any other distillation.

**Flash column chromatography** was performed using silica gel 60M (0.04-0.063) as a stationary phase, from Macheray-Nagel company. The purification was carried out under compressed air pressure with the aim to fasten the purification process.

**Thin layer chromatography** was carried out on ALUGRAM SIL G/UV254 ready foils from Macheray-Nagel Company.
II. Syntheses and characterization of the products

II.1 Synthesis and characterization of reagent 1a and the precursors involved in the preparation

[(bromodifluoromethyl)sulfanyl]benzene S1

Experimental procedure:
Based on a slightly modified reaction procedure, thiophenol (9.34 ml, 100 mmol) is slowly added to a suspension of NaH 60% (6 g, 150 mmol) in anhydrous DMF (100 mL) at 0 °C over a period of 30 min. The mixture is reported to room temperature and let stirring for 15 min. After 15 min. the reaction mixture is cooled to -35 °C (internal temp.), followed by the addition of CF2Br2 (27.4 mL, 300 mmol). The reaction mixture is stirred for 3 h at -35 °C and 30 min from -35 °C to room temperature. The reaction flask is cooled in an ice-water bath and the excess of NaH quenched by dropwise addition of water (100 mL). The aqueous phase is extracted with Et2O (3 x 100 mL) and the combined organic layers washed with water (3 x 100 mL), brine (100 mL), and dried over MgSO4. Filtration and solvent evaporation left a crude product that was purified by distillation as reported in literature.

<table>
<thead>
<tr>
<th>Identification:</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="S1" alt="SCF2Br" /></td>
<td>60 %</td>
</tr>
</tbody>
</table>

Fractional distillation, b.p = 97 °C / 34 mmHG
Colorless liquid

1H NMR (300 MHz, CDCl3) δ = 7.66 (d, J = 6.8 Hz, 2H), 7.53–7.47 (m, 1H), 7.48–7.42 (m, 2H).
19F NMR (282 MHz, CDCl3) δ = -22.13 (s, 2F)

Bromodifluoromethanesulfonylbenzene S2

Experimental procedure:
To a solution of bromodifluoromethylthiobenzene (S1) (19.2 g, 80 mmol) in dry CH2Cl2 (160 mL) was slowly added m-CPBA (598.9 g, 240 mmol) at 0 °C. The reaction is stirred at room temperature for 24 h. The reaction mixture is concentrated, dissolved in EtOAc (300 mL) and washed with NaOH 10 % (200 mL), saturated NaCl (200 mL) and dried over MgSO4. The solvent was removed in vacuo and the compound was purified via silica gel column chromatography.
Experimental Part

### [(benzenesulfonyl)difluoromethyl]trimethylsilane Si1

**Experimental procedure:**
Following a slightly modified procedure, to the solution of PhSO₂CF₂Br (18.9 g, 70 mmol) and TMSCl (22.2 mL, 175 mmol) in THF (210 mL) at -78 °C, under N₂ atmosphere, n-BuLi (1.6M hexane solution, 96.3 mL, 154 mmol) is added. After the addition of n-BuLi (over a period of 1.5 h), the reaction mixture is stirred for 2 h more at -78 °C. Then the reaction mixture was carefully added into cold water. The mixture was extracted with Et₂O (100mL x 3), and the combined organic phase was washed with brine, water, and then dried over Na₂SO₄. After the removal of the solvent under vacuum, the crude product was further fractionally distilled to afford the pure compound.

#### Identification:
In accordance with literature data

<table>
<thead>
<tr>
<th>Yield</th>
<th>Fractional distillation b.p 96-97 °C / 1.3 mbar</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yield</td>
<td>80 %</td>
</tr>
</tbody>
</table>

**1H NMR** (300 MHz, CDCl₃) δ = 7.98–7.90 (m, 2H), 7.77–7.68 (m, 1H), 7.64–7.55 (m, 2H), 0.43 (s, 9H).

**19F NMR** (282 MHz, CDCl₃) δ = -112.32 (s, 2F)

---

### N-{{[(benzenesulfonyl)difluoromethyl]sulfanyl}aniline 1a}

**Experimental procedure:**
In an oven-dried flask under N₂ containing THF, DAST (9.15 mL, 66 mmol) is slowly added and the mixture is stirred for 10 min at room temperature. Silane (Si1) (15 gr, 60 mmol) is added to the solution and the reaction is stirred for 1 more hour. The reaction was quenched with aniline and left at room temperature over night. The reaction mixture was extracted with EtOAc (100 mL x 3) and the organic layers washed with water, brine and dried over Na₂SO₄. After the removal of the solvent under vacuum the compound was purified *via* silica gel column chromatography.

#### Identification:
In accordance with literature data

<table>
<thead>
<tr>
<th>Yield</th>
<th>Fractional distillation b.p 96-97 °C / 1.3 mbar</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yield</td>
<td>80 %</td>
</tr>
</tbody>
</table>

**1H NMR** (300 MHz, CDCl₃) δ = 7.98–7.90 (m, 2H), 7.77–7.68 (m, 1H), 7.64–7.55 (m, 2H), 0.43 (s, 9H).

**19F NMR** (282 MHz, CDCl₃) δ = -112.32 (s, 2F)
**Experimental Part**

<table>
<thead>
<tr>
<th>Identification:</th>
<th>Yield 60 %</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="1a" /></td>
<td>Flash column chromatography: CyHex/EtOAc: 98/2 to 95/5</td>
</tr>
<tr>
<td></td>
<td>Brownish oil</td>
</tr>
<tr>
<td><img src="image" alt="1H NMR" /></td>
<td>$\delta$ = 8–7.97 (m, 2H$<em>2$), 7.79–7.74 (m, 1H$</em>{10}$), 7.63–7.59 (m, 2H$_2$), 7.28–7.24 (m, 2H$_2$), 7.11–7.08 (m, 2H$_2$), 6.97–6.93 (m, 1H$_2$), 5.21 (s, 1H$_1$).</td>
</tr>
<tr>
<td><img src="image" alt="13C NMR" /></td>
<td>$\delta$ = 145.5 (C$<em>2$), 135.8 (C$</em>{10}$), 132.4 (C$_7$), 130.8 (C$_9$), 129.6 (C$_6$), 129.3 (C$<em>5$), 127.5 (t, $J</em>{C,F}$ = 331.9 Hz, C$_6$), 122.0 (C$_3$), 115.5 (C$_3$).</td>
</tr>
<tr>
<td><img src="image" alt="19F NMR" /></td>
<td>$\delta$ = -89.84 (s, 2F).</td>
</tr>
</tbody>
</table>

**Elemental analysis**
calcld (%) C$_{13}$H$_{11}$F$_2$NO$_2$S$_2$: C 49.51, H 3.52, N 4.44, S 20.34. Found: C 49.39, H 3.32, N 4.59, S 20.57

**II.1.1 (Benzenesulfonyl)difluoromethylthiolation of aromatic and heteroaromatic compounds**

**II.1.1.1 General synthetic procedures**

**Experimental Procedure 1:**
To an oven-dried flask containing a solution of 1a (0.5 mmol, 1 equiv.) in dry CH$_2$Cl$_2$ (1M), the nucleophile is added (0.5 mmol, 1 equiv.) and followed by the addition of P-toluenbenzensulfonic acid (1.25 mmol, 2.5 equiv.). After closing the reaction vessel hermetically, the mixture is left under stirring at 50 °C for 16 h. The reaction mixture was extracted with EtOAc or Et$_2$O (10 mL x 2). The fractions were collected together, washed with water and brine and dried over Na$_2$SO$_4$ or MgSO$_4$. After the removal of the solvent under vacuum the compounds were purified via silica gel column chromatography as specified in each case.

**Experimental Procedure 2:**
To an oven-dried flask containing a solution of 1a (0.5 mmol, 1 equiv.) in dry CH$_3$CN, the nucleophile (0.5 mmol, 1 equiv.) is added. After the addition of TMSCl (0.5 mmol, 1 equiv.) the resulting mixture is stirred for 16 h at 25 °C or at 80 °C, depending on the substrate. The reaction mixture is quenched by addition of water and is extracted with EtOAc (10 mL x 2). The organic fractions are collected washed with water and dried over Na$_2$SO$_4$. After the removal of the solvent under vacuum the compounds were purified via silica gel column chromatography as specified in each case.

**Experimental Procedure 3:**
To an oven-dried flask containing a solution of 1a (0.5 mmol, 1 equiv.) in dry CH$_2$Cl$_2$, the nucleophile (0.5 mmol, 1 equiv.) is added. After the addition of TfOH (0.5 mmol, 1 equiv.), the
Experimental Part

resulting mixture is stirred for 16 h at 50 °C. The reaction mixture is quenched by the addition of water and extracted with EtOAc (10 mL x 2). The organic fractions are collected washed with water and brine and dried over Na₂SO₄. After the removal of the solvent under vacuum the compounds were purified via silica gel column chromatography as specified in each case.

3-{{(benzenesulfonyl)difluoromethyl}sulfanyl}-1H-indole 3a

<table>
<thead>
<tr>
<th>Identification</th>
<th>Exp. Proced. 1</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="Structure" /></td>
<td>Eluent for flash column chromatography: CyHex/EtOAc: 8/2</td>
<td>85 %</td>
</tr>
<tr>
<td>Brown solid</td>
<td>Melting point: 110 °C</td>
<td></td>
</tr>
<tr>
<td>¹H NMR (400 MHz, CDCl₃) δ = 8.63 (bs, 1H NH), 7.98–7.95 (m, 2H₁₂), 7.77–7.75 (m, 1H₆), 7.73–7.69 (m, 1H₁), 7.58–7.53 (m, 2H₁₃), 7.52 (bd, J = 2.7 Hz, 1H₇), 7.38–7.35 (m, 1H₂), 7.25–7.22 (m, 2H₁₂).</td>
<td></td>
<td></td>
</tr>
<tr>
<td>¹³C NMR (101 MHz, CDCl₃) δ = 136.3 (C₄), 135.4 (C₁₄), 134.1 (t, J_C,F = 1.7 Hz, C₂), 133.3 (C₁₁), 130.9 (C₁₂), 130.2 (C₁₃), 129.4 (C₁₄), 128.2 (t, J_C,F = 325 Hz, C₆), 123.5 (C₈), 121.7 (C₉), 119.6 (C₇), 111.9 (C₈), 94.2 (t, J_C,F = 3.9 Hz, C₇).</td>
<td></td>
<td></td>
</tr>
<tr>
<td>¹⁹F NMR (376 MHz, CDCl₃) δ = -79.35 (s, 2F).</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Elemental analysis calcd (%) C₁₅H₁₁F₂NO₂S₂: C 53.09, H 3.27, N 4.13, S 18.90. Found: C 52.98, H 3.18, N 4.25, S 18.63.

2-{{(benzenesulfonyl)difluoromethyl}sulfanyl}-3-methyl-1H-indole 3b

<table>
<thead>
<tr>
<th>Identification</th>
<th>Exp. Proced. 1</th>
<th>Yield</th>
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<tbody>
<tr>
<td><img src="image" alt="Structure" /></td>
<td>Eluent for flash column chromatography: CyHex/EtOAc: 8/2</td>
<td>57 %</td>
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<td>Reddish solid</td>
<td>Melting point: 116 °C</td>
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<tr>
<td>¹H NMR (400 MHz, CDCl₃) δ = 8.52 (bs, 1H NH), 7.99–7.96 (m, 2H₁₂), 7.77–7.73 (m, 1H₁), 7.61–7.57 (m, 2H₁₂), 7.39–7.35 (m, 1H₆), 7.32–7.28 (m, 1H₁), 7.17–7.13 (m, 1H₂), 2.45 (s, 3H₈).</td>
<td></td>
<td></td>
</tr>
<tr>
<td>¹³C NMR (101 MHz, CDCl₃) δ = 138.0 (C₈), 135.7 (C₁₄), 132.4 (C₁₁), 131.0 (C₁₂), 129.6 (C₁₃), 128.2 (C₁₂), 127.4 (t, J_C,F = 329 Hz, C₆), 125.1 (C₁), 125.0 (C₇), 120.1 (C₈), 120.0 (C₉), 112.6 (t, J_C,F = 4.5 Hz, C₇), 111.5 (C₈), 9.7 (C₈).</td>
<td></td>
<td></td>
</tr>
<tr>
<td>¹⁹F NMR (376 MHz, CDCl₃) δ = -80.47 (s, 2F).</td>
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</tbody>
</table>

Elemental analysis calcd (%) C₁₆H₁₃F₂NO₂S₂: C 54.38, H 3.71, N 3.96, S 18.15. Found: C 54.63, H 3.44, N 4.21, S 18.01.
2-(2-{{[benzenesulfonyl]difluoromethyl}sulfanyl}-5-methoxy-1H-indol-3-yl)acetic acid 3c

<table>
<thead>
<tr>
<th>Identification:</th>
<th>Exp. Proced. 1</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-(2-{{[benzenesulfonyl]difluoromethyl}sulfanyl}-5-methoxy-1H-indol-3-yl)acetic acid 3c</td>
<td>Flash column chromatography: Cyclohexane/EtOAc: 8/2</td>
<td>99 %</td>
</tr>
<tr>
<td></td>
<td>Brown solid</td>
<td>Melting point: 152 °C</td>
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<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1H NMR (400 MHz, CD3OD) δ = 7.97 (d, J = 7.6 Hz, 1H13), 7.85-7.77 (m, 1H15), 7.70-7.61 (m, 1H6), 7.26 (d, J = 8.9 Hz, 1H3), 7.02 (d, J = 2.4 Hz, 1H5), 6.90 (dd, J = 8.9, 2.4 Hz, 1H7), 4.90 (s, 1H1), 3.85 (s, 2H9), 3.80 (s, 1H13).</td>
<td></td>
<td></td>
</tr>
<tr>
<td>13C NMR (101 MHz, CD3OD) δ = 175.1 (C10), 155.6 (C1), 137.1 (C15), 134.8 (C4), 133.6 (C11), 131.9 (C13), 130.8 (C14), 128.7 (C3), 120.7 (C6), 116.7 (C2), 114.3 (t, JCF = 3.3 Hz, C3), 113.5 (C9), 101.3 (C8), 56.0 (C9), 31.5 (C13).</td>
<td></td>
<td></td>
</tr>
<tr>
<td>19F NMR (376 MHz, CDCl3) δ = -76.18 (s, 2F).</td>
<td></td>
<td></td>
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<tr>
<td>Elemental analysis calcd (%) C18H15F2NO5S2: C 50.58, H 3.54, N 3.28 S 15.00. Found: C 50.52, H 3.81, N 3.12, S 14.88.</td>
<td></td>
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</table>

2-amino-3-(2-{{[benzenesulfonyl]difluoromethyl}sulfanyl}-1H-indol-3-yl)propanoic acid 3d

<table>
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<tr>
<th>Identification:</th>
<th>Exp. Proced. 1</th>
<th>Yield</th>
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</thead>
<tbody>
<tr>
<td>2-amino-3-(2-{{[benzenesulfonyl]difluoromethyl}sulfanyl}-1H-indol-3-yl)propanoic acid 3d</td>
<td>Flash column chromatography:CH2Cl2/MeOH: 9/1</td>
<td>80 %</td>
</tr>
<tr>
<td></td>
<td>White solid</td>
<td>Melting point: 188 °C</td>
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<tr>
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</tr>
<tr>
<td>1H NMR (400 MHz, CD3OD) δ = 7.99–7.97 (m, 2H14), 7.86–7.82 (m, 1H15), 7.74–7.66 (m, 3H13, 16), 7.41 (bd, J = 8.1 Hz, 1H4), 7.35–7.24 (m, 1H4), 7.14 (bt, J = 7.5 Hz, 1H3), 4.15-4.07 (m, 1H10), 3.67 (dd, J = 15.0, 5.4 Hz, 1H4), 3.42 (dd, J = 15.0, 8.5 Hz, 1H4).</td>
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<tr>
<td>13C NMR (101 MHz, CD3OD) δ = 173.0 (C10), 139.7 (C4), 137.3 (C17), 133.4 (C14), 131.9 (C13), 131.3 (C6), 130.9 (C15), 128.1 (t, JCF = 345.0 Hz, C12), 125.6 (C3), 121.3 (C2), 120.9 (C6), 120.2 (C3), 115.4 (t, JCF = 3.4 Hz, C3), 112.9 (C9), 55.7 (C9), 27.9 (C13).</td>
<td></td>
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</tr>
<tr>
<td>19F NMR (376 MHz, CDCl3) δ = -79.62 (s, 2F).</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elemental analysis calcd (%) C18H16F2N2O4S2: C 50.69, H 3.78, N 6.57 S 15.04. Found: C 50.97, H 4.06, N 6.79, S 14.91.</td>
<td></td>
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**Experimental Part**

3-[(benzenesulfonyl)difluoromethyl)sulfanyl]-6-bromo-1H-indole 3e

**Identification:**

Ex. Proced. 1

<table>
<thead>
<tr>
<th>Yield</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Flash column chromatography: CyHex/EtOAc: 9/1</td>
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</tr>
<tr>
<td>Yellow solid Melting point: 124 °C</td>
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</tr>
<tr>
<td>1H NMR (400 MHz, CDCl3) δ = 8.74 (s, 1H NH), 7.96–7.94 (m, 2H), 7.77–7.73 (m, 1H), 7.64–7.57 (m, 3H), 7.54 (d, J = 2.8 Hz, 1H), 7.49 (d, J = 1.6 Hz, 1H), 7.33 (dd, J = 8.5, 1.7 Hz, 1H).</td>
<td></td>
</tr>
<tr>
<td>13C NMR (101 MHz, CDCl3) δ = 136.8 (C), 135.7 (C), 134.6 (t, J = 1.7 Hz, C), 132.5 (C), 130.8 (C), 129.5 (C), 128.9 (C), 127.7 (t, J = 325.2 Hz, C), 125.1 (C), 120.9 (C), 117.0 (C), 114.9 (C), 94.46 (t, J = 4.1 Hz, C).</td>
<td></td>
</tr>
<tr>
<td>19F NMR (376 MHz, CDCl3) δ = -79.93 (s, 2F).</td>
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</table>

Elemental analysis calcd (%): C15H10BrF2NO2S2: C 43.07, H 2.41, N 3.35, S 15.33, Br 19.10. Found: C 42.92, H 2.70, N 3.27, S 14.98, Br 19.33.

3-[(benzenesulfonyl)difluoromethyl)sulfanyl]-4-ethyl-2,5-dimethyl-1H-pyrrole

**Identification:**

Ex. Proced. 2

<table>
<thead>
<tr>
<th>Yield</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Flash column chromatography: CyHex/EtOAc: 95/5 to 9/1</td>
<td></td>
</tr>
<tr>
<td>Black solid Melting point: 118 - 120 °C</td>
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</tr>
<tr>
<td>1H NMR (400 MHz, CDCl3) δ = 8.15 (s, 1H NH), 7.98–7.95 (m, 1H), 7.77–7.71 (m, 1H), 7.62–7.58 (m, 2H), 2.37 (q, J = 7.6 Hz, 2H), 2.20 (s, 3H), 2.09 (s, 3H), 1.04 (s, 3H)</td>
<td></td>
</tr>
<tr>
<td>13C NMR (101 MHz, CDCl3) δ = 135.5 (C), 132.4 (C), 131.2 (C), 130.9 (C), 130.1 (C), 129.47 (C), 126.90 (t, J = 326.4 Hz, C), 123.14 (C), 99.89 (t, J = 4.5 Hz, C), 18.1 (C), 15.4 (C), 11.6 (C), 10.0 (C).</td>
<td></td>
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<tr>
<td>19F NMR (376 MHz, CDCl3) δ = -82.70 (s, 2F).</td>
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</table>

Elemental analysis calcd (%): C15H17F2NO2S2: C 52.16, H 4.96, N 4.05, S 18.57. Found: C 52.08, H 5.18, N 3.80, S 18.41.

3-[(benzenesulfonyl)difluoromethyl)sulfanyl]-2,5-dimethyl-1H-pyrrole 3g

**Identification:**

Ex. Proced. 2

<table>
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<tr>
<th>Yield</th>
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</thead>
<tbody>
<tr>
<td>Flash column chromatography: CyHex/EtOAc: 9/1 to 8/2</td>
<td></td>
</tr>
<tr>
<td>Brown solid Melting point: 113 °C</td>
<td></td>
</tr>
<tr>
<td>1H NMR (400 MHz, CDCl3) δ = 8.03 (s, 1H NH), 8.00–7.97 (m, 2H), 7.76–7.71 (m, 1H), 7.61–7.57 (m, 2H), 5.95 (bs, 1H), 2.31 (s, 3H), 2.18 (s, 3H)</td>
<td></td>
</tr>
<tr>
<td>13C NMR (101 MHz, CDCl3) δ = 135.6 (C), 135.3 (C), 133.1 (C), 130.8 (C), 129.4 (C), 128.01 (t, J = 323.3 Hz, C), 126.8 (C), 113.1 (C), 96.02 (t, J = 3.7 Hz, C), 13.1 (C), 11.2 (C).</td>
<td></td>
</tr>
<tr>
<td>19F NMR (376 MHz, CDCl3) δ = -80.44 (s, 2F).</td>
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</table>

Elemental analysis calcd (%): C15H17F2NO2S2: C 52.16, H 4.96, N 4.05, S 18.57. Found: C 52.08, H 5.18, N 3.80, S 18.41.
Experimental Part

Elemental analysis calcd (%) C_{15}H_{14}F_{2}O_{2}S_{2}: C 49.99, H 3.92, S 17.79. Found: C 50.12, H 2.88, S 19.13.

1-\{[(benzenesulfonyl)difluoromethyl]sulfanyl\}-2,4-dimethoxybenzene 3i

Identification:

Exp. Proced. 1

Yield 80 %

Flash column chromatography: CyHex/EtOAc: 9/1*

Brown solid Melting point: 113 °C

\(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta = 7.98\) (d, \(J = 7.1\) Hz, 2H, 11), 7.73 (t, \(J = 7.5\) Hz, 1H, 13), 7.61-7.54 (m, 3H, 4, 12), 6.50 (dd, \(J = 8.5, 2.6\) Hz, 1H, 3), 6.47 (d, \(J = 2.6\) Hz, 1H, 14), 3.83 (s, 2H, 7), 3.83 (s, 1H, 8).

\(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \(\delta = 164.2\) (C, 2), 162.9 (C, 6), 140.9 (C, 4), 135.4 (C, 13), 133.0 (C, 10), 130.9 (C, 11), 129.3 (C, 12), 128.1 (C, 9), 105.7 (C, 3), 102.6 (C, 5), 99.3 (C, 6), 56.1 (C, 7), 55.7 (C, 8).

\(^{19}\)F NMR (471 MHz, CDCl\(_3\)) \(\delta = -79.61\) (s, 2F).

Elemental analysis calcd (%) C_{15}H_{13}F_{2}NO_{2}S_{2}: C 49.20, H 4.13, N 4.41, S 20.21. Found: C 49.07, H 4.32, N 4.33, S 20.56.

*in order to avoid the purification via silica gel column chromatography, the crude was triturated in pentane and the solid was filtered off. The pure compound was washed with a minimal quantity of pentane and obtained with a 77 % yield.

4-\{[(benzenesulfonyl)difluoromethyl]sulfanyl\]benzene-1,3-diol 3j

Identification:

Exp. Proced. 1

Yield 89 %

Flash column chromatography: CyHex/EtOAc: 8/2

Pale yellow solid Melting point: 150-152 °C

\(^1\)H NMR (500 MHz, DMSO) \(\delta = 10.20\) (s, 1H, 1OH), 9.98 (s, 1H, 3OH), 8.01-7.99 (m, 2H, 3), 7.92 (bt, \(J = 7.5\) Hz, 1H, 9), 7.76 (bt, \(J = 7.9\) Hz, 2H, 10), 7.16 (bd, \(J = 8.5\) Hz, 1H, 4), 6.41 (bd, \(J = 2.6\) Hz, 1H, 11), 6.27 (dd, \(J = 8.5, 2.5\) Hz, 1H, 12).

\(^{13}\)C NMR (126 MHz, DMSO) \(\delta = 162.1\) (C, 2), 161.7 (C, 6), 140.1 (C, 4), 136.3 (C, 13), 131.7 (C, 10), 130.6 (C, 11), 130.0 (C, 12), 128.0 (t, \(J_{C,F} = 323.6\) Hz, C, 3), 108.2 (C, 9), 102.9 (C, 1), 96.2 (t, \(J_{C,F} = 2.5\) Hz, C, 1).

\(^{19}\)F NMR (471 MHz, DMSO) \(\delta = -79.24\) (s, 2F).

Elemental analysis calcd (%) C_{13}H_{10}F_{2}O_{2}S_{2}: C 46.98, H 3.03, S 19.30. Found: C 47.01, H 2.88, S 19.13.
Experimental Part

2-\{[(benzenesulfonyl) difluoromethyl] sulfanyl\} naphthalen-1-ol 3k

<table>
<thead>
<tr>
<th>Identification:</th>
<th>Exp. Proced. 2</th>
<th>Yield 89%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1H NMR (500 MHz, (CD$<em>3$)$<em>2$CO) δ = 10.39 (s, 1H$</em>{10}$), 8.32 (d, J = 8.4 Hz, 1H$</em>{6}$), 8.04 (d, J = 7.3 Hz, 2H$<em>{8}$), 7.95 - 7.86 (m, 1H$</em>{13}$), 7.54 (ddd, J = 8.2, 6.8, 1.2 Hz, 1H$_{7}$).</td>
<td></td>
<td></td>
</tr>
<tr>
<td>13C NMR (126 MHz, (CD$<em>3$)$<em>2$CO) δ = 158.4 (C$</em>{7}$), 140.8 (C$</em>{9}$), 138.0 (C$<em>{4}$), 136.87 (C$</em>{15}$), 133.34 (C$<em>{12}$), 131.6 (C$</em>{13}$), 130.6 (C$<em>{14}$), 129.5 (t, J$</em>{C-F} = 324.5$ Hz, C$<em>{11}$), 128.8 (C$</em>{1}$), 126.7 (C$<em>{3}$), 126.2 (C$</em>{2}$), 126.2 (C$<em>{5}$), 123.7 (C$</em>{6}$), 109.3 (C$<em>{8}$), 109.12 (C$</em>{10}$).</td>
<td></td>
<td></td>
</tr>
<tr>
<td>19F NMR (471 MHz, (CD$_3$)$_2$CO) δ = -79.27 (s, 2F).</td>
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</table>

Flash column chromatography: CyHex/EtOAc: 9/1
Pale brown solid Melting point: 134 °C

4-\{[(benzenesulfonyl) difluoromethyl] sulfanyl\} phenol 3l

<table>
<thead>
<tr>
<th>Identification:</th>
<th>Exp. Proced. 3</th>
<th>Yield 84%</th>
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<tr>
<td>1H NMR (400 MHz, CDCl$<em>3$) δ = 7.98–7.96 (m, 2H$</em>{10}$), 7.78–7.73 (m, 1H$<em>{11}$), 7.63–7.58 (m, 2H$</em>{12}$), 7.56 (d, J = 8.6 Hz, 2H$<em>{2}$), 6.84 (d, J = 8.7 Hz, 2H$</em>{3}$).</td>
<td></td>
<td></td>
</tr>
<tr>
<td>13C NMR (101 MHz, CDCl$<em>3$) δ = 158.6 (C$</em>{6}$), 139.5 (C$<em>{4}$), 135.7 (C$</em>{12}$), 132.6 (C$<em>{9}$), 130.9 (C$</em>{8}$), 129.5 (C$<em>{11}$), 128.1 (t, J$</em>{C-F} = 324.1$ Hz, C$<em>{5}$), 116.6 (C$</em>{1}$), 113.71 (t, J$<em>{C-C}$ = 3.2 Hz, C$</em>{7}$).</td>
<td></td>
<td></td>
</tr>
<tr>
<td>19F NMR (376 MHz, CDCl$_3$) δ = -78.25 (s, 2F).</td>
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</table>

Flash column chromatography: CyHex/EtOAc: 9/1 to 8/2
Pale yellow solid Melting point: 131-133 °C

Elemental analysis calcd (%) C$_{13}$H$_{10}$F$_{2}$O$_{3}$S$_{2}$: C 49.36, H 3.19, S 20.27. Found: C 49.21, H 3.46, S 20.13.

1-\{[(benzenesulfonyl) difluoromethyl] sulfanyl\} 4-iodo-2-methoxybenzene 3m

<table>
<thead>
<tr>
<th>Identification:</th>
<th>Exp. Proced. 3</th>
<th>Yield 30%</th>
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<tbody>
<tr>
<td>1H NMR (400 MHz, CDCl$<em>3$) δ = 8.02 – 7.99 (m, 2H$</em>{10}$), 7.77–7.74 (m, 2H$<em>{11}$), 7.63–7.59 (m, 2H$</em>{12}$), 7.47 (d, J = 2.7 Hz, 1H$<em>{1}$), 6.91 (dd, J = 8.7, 2.8 Hz, 1H$</em>{1}$), 3.80 (s, 3H$_{5}$).</td>
<td></td>
<td></td>
</tr>
<tr>
<td>13C NMR (101 MHz, CDCl$<em>3$) δ = 161.8 (C$</em>{6}$), 139.4 (C$<em>{9}$), 135.6 (C$</em>{13}$), 132.5 (C$<em>{10}$), 131.1 (C$</em>{8}$), 129.5 (C$<em>{11}$), 128.2 (t, J$</em>{C-F} = 325.2$ Hz, C$<em>{5}$), 126.2 (C$</em>{1}$), 120.1 (t, J$<em>{C-F} = 2.5$ Hz, C$</em>{3}$), 115.2 (C$<em>{1}$$^\prime$), 111.0 (C$</em>{7}$), 55.8 (C$_{7}$).</td>
<td></td>
<td></td>
</tr>
<tr>
<td>19F NMR (376 MHz, CDCl$_3$) δ = -79.13 (s, 2F).</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Flash column chromatography: CyHex/EtOAc: 9/1
Pale yellow solid Melting point: 96-98 °C

Elemental analysis calcd (%) C$_{14}$H$_{11}$F$_{2}$IO$_{3}$S$_{2}$: C 36.85, H 2.43, S 17.50. Found: C 37.07, H 2.51, S 17.23.
4-\{(benzenesulfonyl)difluoromethyl]sulfanyl\}-2-nitrobenzene-1,3-diol 3n

**Identification:** Exp. Proced. 3

<p>| | | |</p>
<table>
<thead>
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<tbody>
<tr>
<td></td>
<td>Flash column chromatography: CyHex/EtOAc: 9/1</td>
<td>Yield 45%</td>
</tr>
<tr>
<td></td>
<td>Reddish solid</td>
<td>Melting point: 116 °C</td>
</tr>
</tbody>
</table>

1H NMR (400 MHz, CDCl 3) \(\delta = 7.98–7.96 \text{ (m, 2H)}, 7.77–7.72 \text{ (m, 1H)}, 7.63–7.57 \text{ (m, 2H)}, 7.45 \text{ (d, } J = 8.1 \text{ Hz, 1H)}, 6.68 \text{ (d, } J = 8.1 \text{ Hz, 1H}).

13C NMR (101 MHz, CDCl 3) \(\delta = 159.4 \text{ (C)}, 159.4 \text{ (C)}, 139.2 \text{ (C)}, 135.5 \text{ (C)}, 132.8 \text{ (C)}, 130.9 \text{ (C)}, 129.4 \text{ (C)}, 128.2 \text{ (t, } J_{C,F} = 324.8 \text{ Hz, C)}, 124.9 \text{ (C)}, 115.9 \text{ (C)}, 110.7 \text{ (C)}.

19F NMR (376 MHz, CDCl 3) \(\delta = -79.13 \text{ (s, 2F)}.

**Elemental analysis** calcld (%) C_{13}H_{9}F_{2}NO_{6}S_{2}: C 41.38, H 2.40, N 3.71, S 17.00. Found: C 41.57, H 2.11, N 3.96, S 17.28.

II.1.2 Addition of (Benzenesulfonyl)difluoromethylthio moiety to alkenes and alkynes

II.1.2.1 General synthetic procedures

**Experimental Procedure 1:**
To an oven-dried flask containing a solution of 1a (0.5 mmol, 1 equiv.) in dry CH₂Cl₂ (1M), the nucleophile is added (0.5 mmol, 1 equiv.) followed by the addition of P-toluenbenzensolfonic acid (1.25 mmol, 2.5 equiv.). The reaction vessel is hermetically closed and the reaction is run overnight at 50 °C. The reaction is quenched with water and extracted with EtOAc or Et₂O (10 mL x 2). The organic fractions were collected together, washed with water and brine and dried over Na₂SO₄ or MgSO₄. After the removal of the solvent under vacuum the compounds were purified via silica gel column chromatography as specified in each case.

**Experimental Procedure 4:**
To an oven-dried flask containing a solution of 1a (0.5 mmol, 1 equiv.) and nucleophile (0.5 mmol, 1 equiv.) in dry DCE (1M), sodium tosylate is added (0.75 mmol, 1.5 equiv.). The resulting mixture is stirred vigorously for 5 min at room temperature. After 5 min of stirring, BF₃·Et₂O (2.5 mmol, 5 equiv.) is added dropwise, and the reaction left under stirring at 80 °C for 24 hours. Et₂O and water are added, followed by the extraction of the organic phase. The organic phases were collected together, washed with water and dried over Na₂SO₄ or MgSO₄. After the removal of the solvent under vacuum the compounds were purified via silica gel column chromatography as specified in each case.
Experimental Part

(1R,2R)-2-[[[benzenesulfonyl]difluoromethyl]sulfanyl]cyclohexyl 4-methylbenzene-1-sulfonate 5a

<table>
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<tr>
<th>Identification</th>
<th>Exp. Proced. 1</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flash column chromatography: CyHex/EtOAc: 9/1</td>
<td></td>
<td>45 %</td>
</tr>
<tr>
<td>Pale yellow oil</td>
<td></td>
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</tbody>
</table>

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta = 7.97–7.92\) (m, 2H, \(2H_2\)), 7.80–7.76 (m, 2H, \(2H_1\)), 7.76–7.72 (m, 1H, \(1H_1\)), 7.60 (t, \(J = 7.9\) Hz, 2H, \(2H_3\)), 7.50 (d, \(J = 8.0\) Hz, 2H, \(2H_4\)), 4.52 (td, \(J = 6.6, 3.4\) Hz, 1H, \(1H_2\)), 3.61–3.52 (m, 1H, \(1H_3\)), 2.40 (s, 3H, \(3H_2\)), 2.30–2.22 (m, 1H, \(1H_4\)), 2.06–2.02 (m, 1H, \(1H_5\)), 1.71–1.62 (m, 3H, \(3H_3, 3H_4, 3H_5\)).

\(^13\)C NMR (101 MHz, CDCl\(_3\)) \(\delta = 144.8\) (C, \(C_{15}\)), 135.6 (C, \(C_{11}\)), 134.1 (C, \(C_{12}\)), 132.5 (C, \(C_{13}\)), 130.9 (C, \(C_9\)), 129.9 (C, \(C_8\)), 129.5 (C, \(C_{10}\)), 129.4 (t, \(J_{C,F} = 325.1\) Hz, C, \(C_7\)), 128.0 (C, \(C_{14}\)), 80.7 (C, \(C_5\)), 46.3 (t, \(J_{C,F} = 2.7\) Hz, C, \(C_6\)), 30.5 (C, \(C_4\)), 29.7, 23.0 (C, \(C_3\)), 21.6 (C, \(C_{16}\)), 21.4 (C, \(C_3\)).

\(19\)F NMR (376 MHz, CDCl\(_3\)) \(\delta = -77.97\) (d, \(J_{F,F} = 207.0\) Hz, AB system, 1F), -79.00 (d, \(J_{F,F} = 207.0\) Hz, AB system, 1F).

Elemental analysis calcd (%) C\(_{20}\)H\(_{22}\)F\(_2\)O\(_5\)S\(_3\): C 50.40, H 4.65, S 20.18. Found: C 50.56, H 4.93, S 20.04.


<table>
<thead>
<tr>
<th>Identification</th>
<th>Exp. Proced. 1</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flash column chromatography: CyHex/EtOAc: 95/5</td>
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<td>43 %</td>
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<tr>
<td>Reddish oil</td>
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<td></td>
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</tbody>
</table>

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta = 7.98–7.96\) (m, 2H, \(2H_2\)), 7.82-7.76 (m, 3H, \(C_9, C_{17}, C_{19}\)), 7.65–7.61 (m, 2H, \(2H_3\)), 7.34 (ddd, \(J = 8.6, 0.7\) Hz, \(2H_20\)), 4.69 (t, \(J = 6.0\) Hz, \(1H_1\)), 3.26 (ddd, \(J = 5.6, 4.3, 1.0\) Hz, \(1H_1\)), 2.44 (s, 3H, \(3H_22\)), 1.71 (q, \(J = 6.1\) Hz, \(2H_10\)), 1.33-1.16 (m, 16H, \(2H, 9H, 8H\)), 0.88 (t, \(J = 7.0\) Hz, \(3H_3\)).

\(^13\)C NMR (101 MHz, CDCl\(_3\)) \(\delta = 145.1\) (C, \(C_{21}\)), 135.8 (C, \(C_{17}\)), 133.7 (C, \(C_{18}\)), 132.1 (C, \(C_{14}\)), 131.0 (C, \(C_{19}\)), 130.0 (C, \(C_{20}\)), 129.6 (C, \(C_{16}\)), 129.1 (t, \(J_{C,F} = 324\) Hz, C, \(C_7\)), 128.1 (C, \(C_{15}\)), 81.0 (C, \(C_8\)), 34.2 (t, \(J_{C,F} = 3.6\) Hz, \(C_{12}\)), 33.5 (C, \(C_{10}\)), 32.0 (C, \(C_9\)), 29.7 (C, \(C_6\)), 29.4 (C, \(C_5\)), 29.2 (C), 24.6 (C, \(C_6\)), 22.8 (C, \(C_3\)), 21.8 (C, \(C_9\)), 14.3 (C, \(C_3\)).

\(19\)F NMR (376 MHz, CDCl\(_3\)) \(\delta = -80.20\) (d, \(J_{F,F} = 210.0\) Hz, AB system, 1F), -80.95 (d, \(J_{F,F} = 210.0\) Hz, AB system, 1F).

Elemental analysis calcd (%) C\(_{26}\)H\(_{36}\)F\(_2\)O\(_5\)S\(_3\): C 55.49, H 6.45, S 17.09. Found: C 55.31, H 6.55, S 17.20.
1-(((4R,5R)-5-((benzenesulfonyl)difluoromethyl)sulfanyl)octan-4-yl)oxy)sulfonyl)-4-methylbenzene 5c

**Identification:** Exp. Proced. 1

- **Yield:** 54%
- **Flash column chromatography:** CyHex/EtOAc: 95/5 to 9/1
- **Melting point:** 58 °C

**1H NMR** (400 MHz, CDCl₃) δ = 8.00 (d, J = 7.2 Hz, 2H₁₁), 7.81–7.76 (m, 3H₁₃,₁₅), 7.63 (t, J = 7.9 Hz, 2H₂₂), 7.33 (d, J = 8.0 Hz, 2H₁₆), 4.74 (dt, J = 9.0, 3.4 Hz, 1H₁), 3.61 (ddd, J = 10.1, 4.5, 3.1 Hz, 1H₁₂), 2.44 (s, 3H₁₈), 1.80–1.68 (m, 2H₃,₄), 1.58 (dd, J = 9.6, 4.8 Hz, 2H₅,₆), 1.42–1.25 (m, 3H₄,₅,₆), 1.13–1.09 (m, 1H₆), 0.85 (t, J = 7.2 Hz, 3H₇), 0.80 (t, J = 7.3 Hz, 3H₈).

**13C NMR** (101 MHz, CDCl₃) δ = 145.0 (C₁₇), 135.8 (C₁₃), 133.9 (C₁₄), 132.2 (C₁₀), 131.0 (C₁₁), 129.9 (C₁₆), 129.6 (C₁₂), 129.6 (t, J₉,F = 324 Hz, C₉), 128.0 (C₁₅), 84.1 (C₁), 48.2 (t, J₉,F = 2.1 Hz, C₂) 31.7 (C₄), 31.7 (C₃), 21.8 (C₁₈), 18.8 (C₅), 18.3 (C₆).

**19F NMR** (376 MHz, CDCl₃) δ = -80.20 (d, J₈,F = 210.0 Hz, AB system, 1F), -80.95 (d, J₈,F = 210.0 Hz, AB system, 1F).

**Elemental analysis** calcd (%) C₂₂H₂₈F₂O₅S₃: C 52.15, H 5.57, S 18.99. Found: C 51.94, H 5.28, S 19.06.

1-(((4R,5S)-5-((benzenesulfonyl)difluoromethyl)sulfanyl)octan-4-yl)oxy)sulfonyl)-4-methylbenzene 5d

**Identification:** Exp. Proced. 1

- **Yield:** 30%
- **Flash column chromatography:** CyHex/EtOAc: 95/5 to 9/1
- **Melting point:** 90 °C

**1H NMR** (400 MHz, CDCl₃) δ = 7.98 – 7.96 (m, 2H₁₁), 7.80 – 7.78 (m, 2H₁₅), 7.77 – 7.75 (m, 1H₁₉), 7.64 – 7.59 (m, 2H₁₂), 7.30 (bd, J = 0.9 Hz, 2H₁₆), 4.83 (ddd, J = 8.0, 5.6, 2.5 Hz, 1H₁), 3.62 – 3.58 (m, 1H₂), 2.43 (s, 3H₁₈), 1.83 (dddd, J = 14.0, 10.1, 7.8, 5.1 Hz, 1H₁₂), 1.69 – 1.19 (m, 7H₃,₄,₅,₆), 0.91 – 0.85 (m, 6H₇,₈).

**13C NMR** (101 MHz, CDCl₃) δ = 144.9 (C₁₇), 135.7 (C₁₃), 133.9 (C₁₄), 132.3 (C₁₀), 131.0 (C₁₁), 129.8 (C₁₆), 129.5 (C₁₂), 129.4 (t, J₉,F = 324 Hz, C₉), 128.1 (C₁₅), 84.1 (C₁), 49.5 (t, J₉,F = 2.2 Hz, C₂) 31.7 (C₄), 31.7 (C₃), 21.8 (C₁₈), 20.2 (C₅), 18.6 (C₆), 13.8 (C₁₉), 13.7 (C₁₅).

**19F NMR** (376 MHz, CDCl₃) δ = -77.05 (d, J₈,F = 207.0 Hz, AB system, 1F), -78.73 (d, J₈,F = 207.0 Hz, AB system, 1F).

**Elemental analysis** calcd (%) C₂₂H₂₈F₂O₅S₃: C 52.15, H 5.57, S 19.25. Found: C 51.94, H 5.28, S 19.06.

**Experimental Procedure 5:**

To an oven-dried flask containing a solution of 1a (0.5 mmol, 1 equiv.) in dry CH₂Cl₂, the nucleophile (0.5 mmol, 1 equiv.) is added following by the addition of TfOH (1 mmol, 2 equiv.). The resulting mixture is stirred for 16 h at 23 °C. Water is added and organic phase is extracted.
with EtOAc (10 mL x 2). The organic fractions are collected, washed with water and dried over Na$_2$SO$_4$ or MgSO$_4$. After the removal of the solvent under vacuum the compounds were purified via silica gel column chromatography as specified in each case.

**2-[(benzenesulfonyl)difluoromethyl]sulfanyl]-1,2,3,4-tetrahydronaphthalene 5e**

<table>
<thead>
<tr>
<th>Identification:</th>
<th><strong>Exp. Proced. 5</strong></th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
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<td>Flash column chromatography: CyHex/EtOAc: 9/1 to 8/2</td>
<td>71 %</td>
</tr>
<tr>
<td>Brown-redish oil</td>
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<td></td>
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</tbody>
</table>

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ = 8.03 (d, $J$ = 7.8 Hz, 2H$_{13}$), 7.78 (t, $J$ = 7.5 Hz, 1H$_{12}$), 7.64 (t, $J$ = 7.9 Hz, 2H$_{14}$), 7.16–7.14 (m, 2H$_{11}$), 7.12–7.07 (m, 2H$_{10}$), 4.03–3.96 (m, 1H$_{8}$), 3.33 (dd, $J$ = 16.6, 5.2 Hz, 1H$_{7}$), 3.04–2.95 (m, 3H$_{2}$, 7), 2.35 (dd, $J$ = 13.4, 4.3 Hz, 1H$_{6}$), 2.07–1.98 (m, 1H$_{5}$).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ = 135.6 (C$_{15}$), 134.9 (C$_{16}$), 134.0 (C$_{1}$), 132.5 (C$_{12}$, C$_{13}$), 131.0 (C$_{14}$), 130.2 (t, $J_{C,F}$ = 323.1 Hz C$_{11}$), 129.5 (C$_{15}$), 129.1 (C$_{2}$), 129.0 (C$_{1}$), 126.5 (C$_{6}$), 125.6 (C$_{10}$), 126.2 (C$_{3}$), 41.92 (t, $J_{C,F}$ = 2.6 Hz, C$_{8}$), 37.26 (C$_{7}$), 30.71 (C$_{10}$), 28.06 (C$_{9}$).

$^{19}$F NMR (376 MHz, CDCl$_3$) $\delta$ = -77.73 (d, $J_{F,F}$ = 209.0 Hz, AB system, 1F), -78.32 (d, $J_{F,F}$ = 209.0 Hz, AB system, 1F).

**Elemental analysis** calcd (%) C$_{17}$H$_{16}$F$_{2}$O$_2$S$_2$: C 57.61, H 4.55, S 18.09. Found: C 57.69, H 4.72, S 19.31.

**Difluoro[(5E)-oct-5-en-4-ylsulfanyl]methanesulfonylbenzene 6d**

<table>
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<tr>
<th>Identification:</th>
<th><strong>Exp. Proced. 3</strong> Yield 35 %</th>
<th><strong>Exp. Proced. 5</strong> Yield (58 %)</th>
</tr>
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<tr>
<td></td>
<td>Flash column chromatography: CyHex/EtOAc: 95/5 to 9/1</td>
<td></td>
</tr>
<tr>
<td>Colorless oil</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ = 8.02–7.98 (m, 2H$_{11}$), 7.78–7.74 (m, 1H$_{10}$), 7.64–7.59 (m, 2H$_{12}$), 5.73–5.65 (m, 1H$_{1}$), 4.05 (t, $J_{C,F}$ = 8.8, 5.9 Hz, 1H$_{2}$), 2.03 (ddd, $J_{C,F}$ = 7.7, 6.4, 1.5 Hz, 2H$_{3}$), 1.76–1.57 (m, 2H$_{1}$), 1.44–1.38 (m, 2H$_{2}$), 0.97 (t, $J$ = 7.4 Hz, 3H$_{8}$), 0.91 (t, $J$ = 7.4 Hz, 3H$_{9}$).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ = 135.5 (C$_{13}$), 135.5 (C$_{3}$), 132.7 (C$_{10}$), 131.0 (C$_{12}$), 129.1 (C$_{16}$), 128.8 (C$_{1}$), 48.9 (t, $J_{C,F}$ = 2.0 Hz, C$_{2}$), 37.6 (C$_{6}$), 25.4 (C$_{5}$), 20.3 (C$_{4}$), 13.7 (C$_{7}$), 13.4 (C$_{8}$).

$^{19}$F NMR (376 MHz, CDCl$_3$) $\delta$ = -75.94 (d, $J_{F,F}$ = 206.0 Hz, AB system, 1F), -78.30 (d, $J_{F,F}$ = 206.0 Hz, AB system, 1F).

**Elemental analysis** calcd (%) C$_{15}$H$_{20}$F$_{2}$O$_2$S$_2$: C 53.87, H 6.03, S 18.09. Found: C 53.74, H 5.75, S 18.85.
(([(1E)-1-[(benzenesulfonyl)difluoromethyl]sulfanyl]hept-1-en-2-yl]oxy)sulfonyl)benzene 8a

<table>
<thead>
<tr>
<th>Identification:</th>
<th>Exp. Proced. 4</th>
<th>Yield</th>
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<tr>
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<td>Flash column chromatography: CyHex/EtOAc: 95/5</td>
<td>60 %</td>
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</table>

**^1H NMR** (400 MHz, CDCl₃) δ = 7.98–7.95 (m, 2H₁₁), 7.84–7.80 (m, 2H₁₀), 7.78–7.75 (m, 1H₁), 7.62–7.60 (m, 2H₁₂), 7.38–7.34 (m, 2H₁₁), 6.01 (s, 1H₁₃), 2.45 (s, 3H₁₈), 2.41–2.37 (m, 2H₅), 1.46–1.38 (m, 2H₁₄), 1.30–1.15 (m, 4H₂, 3), 0.83 (t, J = 7.0 Hz, 3H₁).

**^13C NMR** (101 MHz, CDCl₃) δ = 159.3 (t, J_C, F = 1.7 Hz, C₆), 145.9 (C₁₂), 135.9 (C₁₅), 132.6 (C₉), 132.0 (C₁₄), 130.9 (C₁₃), 130.1 (C₁₁), 129.6 (C₁₀), 128.5 (C₁₆), 127.7 (t, J_C, F = 325.9 Hz C₈), 103.7 (t, J_C, F = 4.6 Hz C₁₇), 31.2 (C₅), 25.8 (C₁₂), 22.3 (C₃), 21.8 (C₁₃), 13.9 (C₁₄).

**^19F NMR** (376 MHz, CDCl₃) δ = -81.05 (s, 2F).

**Elemental analysis** calcd (%) C₂₁H₂₄F₂O₅S₃: C 51.41, H 4.93, S 19.61. Found: C 51.27, H 5.01, S 19.83.

{{(E)-2-[(benzenesulfonyloxy)-2-cyclohexylethenyl]sulfanyl]difluoromethanesulfonylbenzene 8b

<table>
<thead>
<tr>
<th>Identification:</th>
<th>Exp. Proced. 4</th>
<th>Yield</th>
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<tbody>
<tr>
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<td>42 %</td>
</tr>
<tr>
<td>Pale yellow oil</td>
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<td></td>
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</tbody>
</table>

**^1H NMR** (400 MHz, CDCl₃) δ = 7.99–7.97 (m, 2H₁₁), 7.85–7.83 (m, 2H₁₀), 7.81–7.77 (m, 1H₁₃), 7.65–7.61 (m, 2H₁₂), 7.38–7.36 (m, 2H₁₁), 6.16 (s, 1H₁₃), 2.84–2.77 (m, 1H₁₄), 2.46 (s, 3H₁₈), 1.72–1.60 (m, 4H₂, 3, 5), 1.50–1.42 (m, 2H₁₄), 1.30–1.16 (m, 4H₂, 3, 5).

**^13C NMR** (101 MHz, CDCl₃) δ = 162.9 (t, J_C, F = 1.7 Hz, C₁), 145.8 (C₁₂), 135.8 (C₁₃), 133.0 (C₁₄), 132.2 (C₁₃), 131.0 (C₁₃), 130.0 (C₁₁), 129.6 (C₁₀), 128.6 (C₁₅), 127.8 (t, J_C, F = 325.6 Hz C₈), 98.89 (t, J_C, F = 4.7 Hz C₁₇), 40.3 (C₁₂), 29.1 (C₁₄), 25.7 (C₁₃), 25.5 (C₁₂), 21.9 (C₁₄).

**^19F NMR** (376 MHz, CDCl₃) δ = -81.06 (s, 2F).

## Experimental Part

> **{(1E)-2-[((benzenesulfonyl)oxy]-4-phenylbut-1-en-1-yl)sulfanyl]difluoromethanesulfonylbenzene 8c**

<table>
<thead>
<tr>
<th>Identification:</th>
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<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
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<td></td>
<td>42%</td>
</tr>
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<td>Pale yellow oil</td>
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### 1H NMR

\[
\delta = 7.96-7.93 \text{ (m, 2H)} 13, 7.86-7.84 \text{ (m, 2H)} 19, 7.8-7.76 \text{ (m, 1H)} 11, 7.65-7.60 \text{ (m, 2H)} 10, 7.40-7.37 \text{ (m, 2H)} 16, 7.28-7.24 \text{ (m, 2H)} 1, 7.21-7.18 \text{ (m, 1H)} 12, 7.12-7.09 \text{ (m, 2H)} 1, 5.99 \text{ (t, } J = 1.0 \text{ Hz, 1H)} 10, 2.79-2.70 \text{ (m, 4H)} 7, 8, 2.47 \text{ (s, 3H)} 20.
\]

### 13C NMR

\[
\delta = 158.1 \text{ (C)} 9, 146.0 \text{ (C)} 19, 139.8 \text{ (C)} 5, 135.9 \text{ (C)} 15, 132.6 \text{ (C)} 10, 132.1 \text{ (C)} 12, 131.0 \text{ (C)} 11, 130.2 \text{ (C)} 2, 129.6 \text{ (C)} 14, 128.7 \text{ (C)} 13, 128.6 \text{ (C)} 17, 127.6 \text{ (t, } J_{C,F} = 325.8 \text{ Hz, C)} 11, 126.6 \text{ (C)} 7, 105.0 \text{ (C)} 10, 33.5 \text{ (C)} 8, 32.4 \text{ (C)} 2, 21.9 \text{ (C)} 20.
\]

### 19F NMR

\[
\delta = -81.25 \text{ (s, 2F)}.
\]

**Elemental analysis**

calcd (%) C$_{24}$H$_{22}$F$_2$O$_5$S$_3$: C 54.95, H 4.23, S 18.34. Found: C 54.83, H 4.16, S 18.26.
II.1.3 Phenylsulfonyl reduction and access to SCF₂H

Experimental Procedure 1

Catalytic I₂ (30 mol %) was added to magnesium turnings (2.5 mmol, 10 equiv.) and heated up with a heat gun for 10 min under stirring. Then a solution of starting material (0.25 mmol, 1 equiv.) in MeOH (2.5 mL) was added and the mixture was stirred for 1.5 h at room temperature. A second portion of Mg (5 mmol, 20 equiv.) was added and the reaction stirred for further 2.5 h. The reaction was quenched by the addition of NH₄Cl (10 mL) reaction mixture and the organic phase was extracted with Et₂O (15 x 3). The organic phases were collected, washed with water, brine and dried over MgSO₄. Solvent removal under vacuum led to the pure final compounds without the need of any further purification if not specified differently.

Experimental Procedure 2:

For the synthesis of deuterated molecules, we followed the above reported procedure step by step by only substituting MeOH with CD₃OD.

1-[(difluoromethyl)sulfanyl]-2,4-dimethoxybenzene 9a

<table>
<thead>
<tr>
<th>Identification:</th>
<th>Exp. Proced. 1</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compound pure after work-up</td>
<td></td>
<td>88 %</td>
</tr>
<tr>
<td>Colorless oil</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**¹H NMR** (400 MHz, CDCl₃) δ = 7.47–7.45 (m, 1H₄), 6.80 (t, J₁₁,⁻ F = 58.0 Hz, 1H₃), 6.51–6.49 (m, 2H₁, 3), 3.88 (s, 3H₉), 3.83 (s, 3H₈).

**¹³C NMR** (101 MHz, CDCl₃) δ = 163.2 (C₂), 161.2 (C₆), 139.0 (C₄), 120.8 (t, J₇, F = 275.1 Hz, C₁₁), 105.5 (C₇), 105.2 (C₈), 99.4 (C₉), 56.1 (C₁₂), 55.7 (C₁₀).

**¹⁹F NMR** (376 MHz, CDCl₃) δ = -93.16 (d, J₁₁,⁻ H = 58.0 Hz).

**Elemental analysis** calcd (%) C₉H₁₀F₂O₂S: C 49.08, H 4.58, S 14.56. Found: C 49.18, H 4.84, S 14.83.

2-{2-[(difluoromethyl)sulfanyl]-5-methoxy-1H-indol-3-yl}acetic acid 9b

<table>
<thead>
<tr>
<th>Identification:</th>
<th>Exp. Proced. 1</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compound pure after work-up</td>
<td>Melting point: 92 °C</td>
<td>95 %</td>
</tr>
<tr>
<td>Black-brown solid</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**¹H NMR** (400 MHz, CDCl₃) δ = 8.40 (s, 1HOH), 7.23 (d, J = 8.8 Hz, 1H₃), 6.99 (d, J = 2.4 Hz, 1H₄), 6.95 – 6.92 (m, 1H₂), 6.75 (t, J₁₁,⁻ F = 57.3 Hz, 1H₁₁), 3.91 (s, 2H₁₂), 3.83 (s, 3H₁₉).

**¹³C NMR** (101 MHz, CDCl₃) δ = 177.1 (C₁₀), 154.7 (C₁), 132.4 (C₄), 127.6 (C₉), 120.4 (t, J₁₁,⁻ F = 278.4 Hz C₁₁), 117.5 (t, J₁₁,⁻ C = 4.0 Hz C₁₁), 117.1 (C₈), 115.6 (C₉), 112.4 (C₈), 100.57 (C₁₂), 55.9 (C₁₉), 30.8 (C₁₀).
$^{19}$F NMR (376 MHz, CDCl$_3$) $\delta = -93.16$ (d, $J = 58.0$ Hz).

**Elemental analysis** calcd (%) C$_9$H$_{10}$F$_2$O$_2$S: C 49.08, H 4.58, S 14.56. Found: C 49.18, H 4.84, S 14.83.

### 3-[(difluoromethyl)sulfanyl]-2,5-dimethyl-1H-pyrrole

**Identification:** Exp. Proced. 1

- Flash column chromatography: CyHex/EtOAc: 9/1 to 8/2
- Reddish oil

| H NMR (400 MHz, CDCl$_3$) $\delta =$ | 7.86 (s, 1H NH), 6.58 (t, $J = 57.8$ Hz, 1H$_7$), 5.92 (dd, $J = 2.7$, 1.2 Hz, 1H$_d$), 2.30 (s, 3H$_6$), 2.22 (s, 1H$_5$).
| C NMR (101 MHz, CDCl$_3$) $\delta =$ | 133.4 (C$_1$), 126.6 (C$_4$), 121.7 (t, $J_{C,F} =$ 274.7 Hz, C$_7$), 112.5 (C$_d$), 98.9 (t, $J_{C,F} =$ 3.7 Hz, C$_2$), 13.0 (C$_6$), 11.4 (C$_5$).
| F NMR (376 MHz, CDCl$_3$) $\delta =$ | -92.83 (d, $J = 57.4$ Hz, 2F).

**Elemental analysis** calcd (%) C$_7$H$_9$F$_2$NS: 47.44, H 5.12, N 7.90, S 18.09. Found: 47.58, H 5.05, N 7.68, S 18.24.

### (1R,2R)-2-[(difluoromethyl)sulfanyl]cyclohexan-1-ol

**Identification:** Exp. Proced. 1

- Compound pure after work-up
- Colorless oil

| H NMR (400 MHz, CDCl$_3$) $\delta =$ | 6.99 (dd, $J_{H,F} =$ 58.5, 55.7 Hz, 1H$_7$), 3.42 (td, $J = 9.7$, 4.5 Hz, 1H$_{6a}$), 2.89 (ddd, $J = 12.3$, 9.8, 4.1 Hz, 1H$_{6b}$), 2.51 (s, 1H$_{5a}$), 2.19–2.08 (m, 2H$_{1,2}$), 1.79–1.69 (m, 2H$_{2,3}$), 1.51–1.47 (m, 1H$_d$), 1.33–1.27 (m, 4H$_{1,2,3}$).
| C NMR (101 MHz, CDCl$_3$) $\delta =$ | 121.0 (dd, $J_{C,F} =$ 274.1, 270.6 Hz, C$_7$), 73.6 (C$_d$), 50.5 (C$_6$), 34.5 (C$_4$), 33.49 (C$_3$), 26.1 (C$_2$), 24.2 (C$_1$).
| F NMR (376 MHz, CDCl$_3$) $\delta =$ | -88.96 (dd, $J_{F,F} =$ 245.6, 58.5 Hz, ABX system, 1F), -91.69 (dd, $J_{F,F} =$ 245.6, 55.7 Hz, ABX system, 1F).

**Elemental analysis** calcd (%) C$_7$H$_{12}$F$_2$OS: 46.14, H 6.64, S 17.60. Found: C 45.96, H 6.89, S 17.82.
# 2-[(difluoromethyl)sulfanyl]-1,2,3,4-tetrahydronaphthalene 9e

<table>
<thead>
<tr>
<th>Identification</th>
<th>Exp. Proced. 1</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>11 SCF₂H</td>
<td>Compound pure after work-up</td>
<td>86 %</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>1H NMR (400 MHz, CDCl₃) δ</th>
<th>7.18–7.08 (m, 4H, 1, 2, 3, 6), 6.93 (t, J₉,F = 56.2 Hz, 1H, 11), 3.71–3.64 (m, 1H, 8), 3.30–3.24 (m, 1H, 10), 3.02–2.93 (m, 3H, 7, 10), 2.33–2.27 (m, 1H, 8), 2.02–1.93 (m, 1H, 8).</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>13C NMR (101 MHz, CDCl₃) δ</th>
<th>135.2 (C₄), 134.4 (C₅), 129.1 (C₆), 129.0 (C₂), 126.4 (C₁), 126.1 (C₃), 121.0 (t, J₉,C = 272.5 Hz, C₁₁), 38.3 (t, J₉,C = 2.5 Hz, C₈), 37.3 (C₇), 30.7 (C₉), 28.3 (C₁₀).</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>19F NMR (376 MHz, CDCl₃) δ</th>
<th>-91.01 (dd, J₁,F, F = 254.5, 56.2 Hz, ABX system, 1F), -91.55 (dd, J₁,F, F = 254.5, 56.2 Hz, ABX system, 1F).</th>
</tr>
</thead>
</table>

Elemental analysis: calcd (%) C₁₁H₁₂F₂S: C 61.66, H 5.65, S 14.96. Found: C 61.84, H 5.48, S 15.11.

# 1-{{[(difluoro(D)methyl)sulfanyl]-2,4-dimethoxybenzene

<table>
<thead>
<tr>
<th>Identification</th>
<th>Exp. Proced. 2</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>7 O SCF₂D [D]₉a</td>
<td>Compound pure after work-up</td>
<td>88 %</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>1H NMR (400 MHz, CDCl₃) δ</th>
<th>7.46–7.44 (m, 1H, 4), 6.50–6.48 (m, 2H, 1, 3), 3.87 (s, 3H, 6), 3.82 (s, 3H, 8).</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>13C NMR (101 MHz, CDCl₃) δ</th>
<th>163.1 (C₂), 161.2 (C₆), 138.9 (C₄), 120.5 (tt, J₉,C,F = 273.4 Hz, J₈,C,D = 32.2 Hz, C₉), 105.5 (C₁), 105.2 (t, Jₙ,F,C = 3.5 Hz, C₈), 99.4 (C₃), 56.1 (C₆), 55.6 (C₇).</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>19F NMR (282 MHz, CDCl₃) δ</th>
<th>-93.93 (t, J₁,F, D = 9.1 Hz, 2F).</th>
</tr>
</thead>
</table>


# 3-{{[(difluoro(D)methyl)sulfanyl]-2,5-dimethyl-1H-pyrrole

<table>
<thead>
<tr>
<th>Identification</th>
<th>Exp. Proced. 2</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>7 SCF₂D [D]₉c</td>
<td>Compound pure after work-up</td>
<td>81 %</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>1H NMR (400 MHz, CDCl₃) δ</th>
<th>7.86 (s, 1H, NH), 5.92 (dd, J = 2.5, 1.2 Hz, 1H), 2.29 (s, 3H, ₉), 2.21 (s, 3H, ₁₀).</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>13C NMR (101 MHz, CDCl₃) δ</th>
<th>133.4 (C₇), 126.6 (C₄), 121.3 (tt, J₉,C,F = 273.6 Hz, J₈,C,D = 30.1 Hz, C₆), 112.5 (C₇), 98.9 (t, J₉,C,F = 3.35 Hz, C₈), 13.1 (C₄), 11.4 (C₅).</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>19F NMR (282 MHz, CDCl₃) δ</th>
<th>-93.65 (t, J₁,F, D = 9.1 Hz, 2F).</th>
</tr>
</thead>
</table>

Elemental analysis: calcd (%) C₇H₈DF₂NS: 47.17, H 5.65, N 7.86, S 17.99. Found: C 47.22, H 5.41, N 7.96, S 18.36.
(1R,2R)-2-[[difluoro(D)methyl]sulfanyl]cyclohexan-1-ol

<table>
<thead>
<tr>
<th>Identification: (1R,2R)-2-[[difluoro(D)methyl]sulfanyl]cyclohexan-1-ol</th>
<th>Exp. Proced. 2</th>
<th>Yield 81%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compound pure after work-up</td>
<td>Redish oil</td>
<td></td>
</tr>
<tr>
<td>( ^1H ) NMR (400 MHz, CDCl(_3)) ( \delta = 3.43 - 3.38 ) (m, 1H), 2.88 (ddd, ( J = 12.3, 9.8, 4.1 ) Hz, 1H), 2.17–2.08 (m, 2H), 1.78–1.70 (m, 2H), 1.49 (ddd, ( J = 25.4, 12.4, 3.8 ) Hz, 1H), 1.36–1.26 (m, 3H).</td>
<td>( ^13C ) NMR (101 MHz, CDCl(_3)) ( \delta = 120.7 ) (tt, ( J_C,F = 271.2 ) Hz, ( J_C,D = 31.4 ) Hz), 73.6 (C), 50.4 (C), 34.5 (C), 33.5 (C), 26.1 (C), 24.2 (C).</td>
<td>( ^19F ) NMR (376 MHz, CDCl(_3)) ( \delta = -89.76 ) (dt, ( J = 246.3, J_F = 8.5 ) Hz, ABX system, 1F), -91.69 (dt, ( J = 246.2, J_D,F = 8.7 ) Hz, ABX system, 1F).</td>
</tr>
</tbody>
</table>

3-[[difluoro(D)methyl]sulfanyl]-1H-indole

<table>
<thead>
<tr>
<th>Identification: 3-[[difluoro(D)methyl]sulfanyl]-1H-indole</th>
<th>Exp. Proced. 2</th>
<th>Yield 86%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compound pure after work-up</td>
<td>Brown oil</td>
<td></td>
</tr>
<tr>
<td>( ^1H ) NMR (400 MHz, CDCl(_3)) ( \delta = 8.50 ) (s, 1H), 7.81–7.99 (m, 1H), 7.47 (d, ( J = 2.6 ) Hz, 1H), 7.42 (dd, ( J = 7.9, 1.4 ) Hz, 1H), 7.31–7.24 (m, 2H).</td>
<td>( ^13C ) NMR (101 MHz, CDCl(_3)) ( \delta = 136.2 ) (C), 132.0 (C), 129.8 (C), 123.3 (C), 121.4 (C), 120.8 (tr, ( J_C,F = 274.2 ) Hz, ( J_C,D = 32.4 ) Hz, C), 119.5 (C), 111.7 (C), 96.7 (t, ( J = 3.3 ) Hz, C).</td>
<td>( ^19F ) NMR (282 MHz, CDCl(_3)) ( \delta = -92.84 ) (t, ( J_D,F = 9.1 ) Hz, 2F).</td>
</tr>
</tbody>
</table>

### II.1.4 Post-functionalization of the phenylsulfonyl moiety

**Experimental Procedure:**

To an oven-dried flask containing Mg turnings (12mg, 0.5mmol, 2 equiv.), TMSCl (159 µL, 1.25 mmol, 5 equiv.) is added under N\(_2\) atmosphere and stirred for 2 minutes at 0 °C. Compound 3i dissolved in DMF (0.25M) is slowly added to the mixture and stirred for 30 minutes at 0 °C and 1.5 h at room temperature. To the reaction mixture Et\(_2\)O and water is added and the organic layers are dried over Na\(_2\)SO\(_4\). Solvent removal under vacuum led to the pure final compound without the need of any further purification.
{(2,4-dimethoxyphenyl)sulfanyl}difluoromethyl]trimethylsilane

<table>
<thead>
<tr>
<th>Identification:</th>
<th>Exp. Proced. 2</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compound pure after work-up</td>
<td></td>
<td>93 %</td>
</tr>
<tr>
<td>brown oil</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1H NMR (400 MHz, CDCl₃) δ = 7.51–7.49 (m, 1H₄), 6.50 (m, 2H₁₃), 3.85 (s, 3H₈), 3.81 (s, 3H₉), 0.25 (s, 9H₁₀).</td>
<td></td>
<td></td>
</tr>
<tr>
<td>13C NMR (101 MHz, CDCl₃) δ = 162.8 (C₂), 162.0 (C₆), 140.1 (C₄), 134.1 (t, J = 300.6 Hz, C₇), 105.2 (C₃), 99.31 (C₁), 99.0 (t, J = 8.4 Hz, C₅), 56.1 (C₉), 55.5 (C₁₀), -4.1 (C₁₀).</td>
<td></td>
<td></td>
</tr>
<tr>
<td>19F NMR (376 MHz, CDCl₃) δ = -87.51 (s, 2F).</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Elemental analysis calcd (%) C₁₂H₁₈F₂O₂SSi: C 49.29, H 6.20, S 10.97, Si 9.60. Found: C 49.49, H 6.06, S 10.70, Si 9.26.
II.2 Synthesis and characterization of reagent 1d

Methyl 2,2-difluoro-2-[((phenylamino)sulfanyl)acetate 1d

Experimental Procedure

In an oven-dried flask under N₂, DAST (8.7 mL, 66 mmol, 1.1 equiv.) is slowly added to a mixture of CH₂Cl₂ (120 mL) and DIPEA (11.5 mL, 66 mmol, 1.1 equiv.) and stirred for 20 min at –25 °C. Methyl difluoro(trimethylsilyl)acetate (10.7 mL, 60 mmol, 1 equiv.) is slowly added to the solution and the reaction stirred for 1.5 hour. Aniline (5.47 mL, 60 mmol, 1 equiv.) is added to the mixture and the reaction is left under stirring for 16 hours at room temperature. The reaction mixture was extracted with Et₂O (100 mL x 3). The organic fractions were collected and washed with water, brine and dried over Na₂SO₄. After the removal of the solvent under vacuum the compound was purified via silica gel column chromatography.

Identification:

<table>
<thead>
<tr>
<th>Yield</th>
<th>40 %</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Identification:</th>
<th>Yield 40 %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flash chromatography: Pentane/Diethyl Ether: 100% to 95/5.</td>
<td>Yield 40 %</td>
</tr>
<tr>
<td>Redish oil</td>
<td>Yield 40 %</td>
</tr>
</tbody>
</table>

1H NMR (400 MHz, CDCl₃) δ = 7.27-7.22 (m, 2H₁, 2H₂), 7.05 (dt, J = 7.7, 1.1 Hz, 2H₃), 6.92 (tt, J = 7.4, 1.1 Hz, 1H₂), 5.12 (s, 1HₙH), 3.71 (s, 3H₇).

13C NMR (101 MHz, CDCl₃) δ = 162.4 (t, J = 32 H, C₆), 145.5 (C₄), 129.3 (C₃), 121.6 (C₂), 120.0 (t, J = 290 Hz, C₅), 115.2 (C₀), 53.9 (C₇).

19F NMR (376 MHz, CDCl₃) δ = -92.54 (s, 2F).

II.2.1 SEAr reactions using reagent 1d

Experimental Procedure 1:

To a flask containing a solution of reagent 1d (0.5 mmol, 1 equiv.) in dry CH₂Cl₂ (1M), the nucleophile (0.5 mmol, 1 equiv.) is added. TMSCl (1 mmol, 2 equiv.) is added to the resulting mixture and the solution was stirred for 16 h at 50 °C, depending on the substrate. The reaction mixture was extracted with Et₂O (10 mL x 3). The organic fractions were collected and washed with water, brine and dried over MgSO₄. After the removal of the solvent under vacuum the compounds were purified via silica gel column chromatography.

Experimental Procedure 2:

To a flask containing a solution of reagent 1d (0.5 mmol, 1 equiv.) in dry CH₂Cl₂ (1M), the nucleophile is added (0.5 mmol, 1 equiv.). P-TsOH (1.25 mmol, 2.5 equiv.) is added and the flask is heated at 50 °C overnight. The reaction mixture is quenched with water was extracted with Et₂O (10 mL x 3). The organic fractions were collected and washed with water, brine and dried.
over MgSO₄. After the removal of the solvent under vacuum the compounds were purified *via* silica gel column chromatography (except where reported differently).

**Experimental Procedure 3:**

To a flask containing a solution of 1d (0.5 mmol, 1 equiv.) in dry CH₂Cl₂ (1M), the nucleophile (0.5 mmol, 1 equiv.) is added. TfOH (0.5 mmol, 1 equiv.) is added to the resulting mixture and the solution is stirred for 16 h at 50 °C. The reaction mixture is extracted with Et₂O (10 mL x 3). The organic fractions were collected and washed with water, brine and dried over MgSO₄. After the removal of the solvent under vacuum the compounds were purified *via* silica gel column chromatography (except where indicated differently).

**Methyl 2,2-difluoro-2-(1H-indol-3-ylsulfanyl)acetate 20a**

<table>
<thead>
<tr>
<th>Identification:</th>
<th>Exp. Proced. 1</th>
<th>Yield 80 %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flash chromatography: Pentane/Diethyl Ether: 8/2.</td>
<td>Pale brown solid</td>
<td>m.p. 82 °C, calibration substance: Acetanilid at 114.5 °C</td>
</tr>
<tr>
<td><strong>¹H NMR</strong> (400 MHz, CDCl₃) δ = 8.59 (s, 1H NH), 7.65 (dd, J = 6.1, 3.1 Hz, 1H4), 7.27 (bd, J = 2.7 Hz, 1H11), 7.24-7.20 (m, 1H3), 7.17-7.13 (m, 2H1, 2), 3.60 (s, 3H10).</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>¹³C NMR</strong> (101 MHz, CDCl₃) δ = 162.9 (t, J = 33 Hz, C11), 136.1 (C4), 133.3 (C11), 129.6 (C3), 123.3 (C2), 121.5 (C3), 119.9 (t, J = 287 Hz, C9), 119.1 (C9), 112.0 (C3), 94.93 (t, J = 4 Hz, C7), 53.9 (C10).</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>¹⁹F NMR</strong> (376 MHz, CDCl₃) δ = -84.36 (s, 2F)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Methyl 2,2-difluoro-2-[(3-methyl-1H-indol-2-yl)sulfanyl]acetate 20b**

<table>
<thead>
<tr>
<th>Identification:</th>
<th>Exp. Proced. 2</th>
<th>Yield 63 %</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>¹H NMR</strong> (400 MHz, CDCl₃) δ = 8.16 (s, 1H NH), 7.60 (dq, J = 8.0, 0.9 Hz, 1H4), 7.36-7.27 (m, 2H2, 3), 7.15 (ddd, J = 8.0, 6.8, 1.2 Hz, 1H11), 3.79 (s, 1H12), 2.43 (s, 3H9).</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>¹³C NMR</strong> (101 MHz, CDCl₃) δ = 162.3 (t, J = 32 Hz, C11), 137.6 (C4), 128.1 (C11), 124.7 (C3), 123.6 (C2), 121.27 (t, J = 289 Hz, C10), 120.0 (C3), 120.0 (C2), 113.7 (t, J = 3 Hz, C3), 111.2 (C3), 54.2 (C12), 9.6 (C9).</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>¹⁹F NMR</strong> (376 MHz, CDCl₃) δ = -81.69 (s, 2F)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Methyl 2-[(4-bromo-1H-indol-3-yl)sulfanyl]-2,2-difluoroacetate 20c

<table>
<thead>
<tr>
<th>Identification:</th>
<th>Exp. Proced. 1</th>
<th>Yield 94%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flash chromatography: Pentane/Diethyl Ether: 9/1 to 8/2.</td>
<td>m.p. 132-134 °C, calibration substance: acetanilide at 114.5 °C</td>
<td></td>
</tr>
<tr>
<td>Pale brown solid</td>
<td>δ = 7.84 (s, 1H), 7.58 (dd, J = 8.2, 0.9 Hz, 1H), 7.37 (dd, J = 7.6, 0.9 Hz, 1H), 7.12 (t, J = 7.9, 1H), 3.76 (s, 3H)</td>
<td></td>
</tr>
<tr>
<td>1H NMR (400 MHz, CD$_3$CO)</td>
<td>δ = 161.9 (t, J = 33 Hz, C$_{10}$), 137.3 (C$_7$), 137.3 (C$_4$), 126.3 (C$_2$), 125.9 (C$_1$), 123.6 (C$_6$), 119.2 (t, J = 285.8 Hz, C$_8$), 113.3 (C$<em>9$), 112.2 (C$<em>3$), 94.2 (t, J = 3.8 Hz, C$</em>{11}$), 53.3 (C$</em>{12}$)</td>
<td></td>
</tr>
<tr>
<td>13C NMR (101 MHz, CD$_3$CO)</td>
<td>δ = -81.03 (s, 2F)</td>
<td></td>
</tr>
</tbody>
</table>

### Methyl 2,2-difluoro-2-[(1-methyl-1H-indol-3-yl)sulfanyl]acetate 20f

<table>
<thead>
<tr>
<th>Identification:</th>
<th>Exp. Proced. 1</th>
<th>Yield 89%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flash chromatography: Pentane/EtOAc: 85/15 to 8/2.</td>
<td>m.p. 60°C, calibration substance: azobenzol at 68.0°C</td>
<td></td>
</tr>
<tr>
<td>Pale yellow solid</td>
<td>δ = 7.68 (d, J = 7.5 Hz, 1H), 7.29-7.16 (m, 4H), 3.71 (s, 3H), 3.62 (s, 3H)</td>
<td></td>
</tr>
<tr>
<td>1H NMR (400 MHz, CDCl$_3$)</td>
<td>δ = 162.7 (t, J$<em>{C,F}$ = 33 Hz, C$</em>{10}$), 137.3 (C$_7$), 137.2 (C$_4$), 130.5 (C$_3$), 122.9 (C$<em>2$), 121.2 (C$<em>1$), 119.8 (t, J$</em>{C,F}$ = 287 Hz, C$<em>6$), 119.4 (C$<em>9$), 110.0 (C$<em>8$), 93.0 (t, J$</em>{C,F}$ = 4 Hz, C$</em>{11}$), 53.7 (C$</em>{12}$), 33.3 (C$</em>{11}$)</td>
<td></td>
</tr>
<tr>
<td>13C NMR (101 MHz, CDCl$_3$)</td>
<td>δ = -84.14 (s, 2F)</td>
<td></td>
</tr>
</tbody>
</table>

### Methyl 2-[(4-ethyl-2,5-dimethyl-1H-pyrrol-3-yl)sulfanyl]-2,2-difluoroacetate 2j

<table>
<thead>
<tr>
<th>Identification:</th>
<th>Exp. Proced. 1</th>
<th>Yield 25%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flash chromatography: Pentane/EtOAc: 100/0 to 9/1.</td>
<td>Black oil</td>
<td></td>
</tr>
<tr>
<td>1H NMR (400 MHz, CDCl$_3$)</td>
<td>δ = 7.86 (s, 1H$<em>{NH}$), 3.79 (s, 3H$</em>{11}$), 2.38 (q, J = 7.6 Hz, 2H$<em>2$), 2.18 (s, 3H$</em>{10}$), 2.07 (s, 3H$_{11}$), 1.05 (t, J = 7.6 Hz, 3H$_2$)</td>
<td></td>
</tr>
<tr>
<td>13C NMR (101 MHz, CDCl$_3$)</td>
<td>δ = 162.7 (t, J$<em>{C,F}$ = 33 Hz, C$</em>{10}$), 129.7 (C$_7$), 129.5 (C$_2$), 123.2 (C$<em>1$), 119.8 (t, J$</em>{C,F}$ = 288 Hz, C$<em>6$), 101.6 (t, J$</em>{C,F}$ = 4 Hz, C$<em>7$), 53.9 (C$</em>{11}$), 18.1 (C$<em>3$), 15.4 (C$<em>8$), 11.5 (C$</em>{12}$), 9.9 (C$</em>{11}$)</td>
<td></td>
</tr>
<tr>
<td>19F NMR (376 MHz, CDCl$_3$)</td>
<td>δ = -84.20 (s, 2F)</td>
<td></td>
</tr>
</tbody>
</table>
### Methyl 2-[(2,4-dimethoxyphenyl)sulfanyl]-2,2-difluoroacetate 20k

<table>
<thead>
<tr>
<th>Identification:</th>
<th>Exp. Proced. 2</th>
<th>Yield 80%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Flash chromatography: Pentane/Et₂O: 100/0 to 9/1.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Yellow solid m.p. &lt; 46°C, calibration substance: azobenzol at 68.0°C</td>
<td></td>
</tr>
<tr>
<td><img src="image" alt="Chemical Structure" /></td>
<td><img src="image" alt="Chemical Structure" /></td>
<td><img src="image" alt="Chemical Structure" /></td>
</tr>
<tr>
<td><strong>1H NMR</strong> (400 MHz, CDCl₃) δ = 7.49 (d, J = 8.4 Hz, 1H₄), 6.52 (d, J = 2.5 Hz, 1H₉), 6.50 - 6.46 (m, 2H₁), 3.85 (s, 3H₇), 3.83 (s, 3H₈), 3.81 (s, 3H₁₁).</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>13C NMR</strong> (101 MHz, CDCl₃) δ = 163.9 (C₂), 162.5 (t, J_C, F = 33.3 Hz, C₁₀), 162.3 (C₁), 140.7 (C₄), 119.5 (t, J_C, F = 287.2 Hz, C₉), 105.7 (C₁), 103.6(t, J_C, F = 3 Hz, C₅), 99.3 (C₁), 56.1 (C₇), 55.6 (C₈), 53.7 (C₁₁).</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>19F NMR</strong> (376 MHz, CDCl₃) δ = -84.10 (s, 2F).</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Methyl 2-[(2,4-dihydroxyphenyl)sulfanyl]-2,2-difluoroacetate 20l

<table>
<thead>
<tr>
<th>Identification:</th>
<th>Exp. Proced. 2</th>
<th>Yield 81%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Flash chromatography: Pentane/Et₂O: 100/0 to 8/2 to 7/3.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Yellow solid m.p. 62-64 °C, calibration substance: azobenzol at 68.0°C</td>
<td></td>
</tr>
<tr>
<td><img src="image" alt="Chemical Structure" /></td>
<td><img src="image" alt="Chemical Structure" /></td>
<td><img src="image" alt="Chemical Structure" /></td>
</tr>
<tr>
<td><strong>1H NMR</strong> (400 MHz, CDCl₃) δ = 7.36 (d, J = 8.5 Hz, 1H₄), 6.52 (d, J = 2.7 Hz, 1H₉), 6.44 (dd, J = 8.5, 2.6 Hz, 1H₁), 3.84 (s, 3H₉).</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>13C NMR</strong> (101 MHz, CDCl₃) δ = 162.1 (t, J_C, F = 32.4 Hz, C₀), 160.7 (C₂), 159.7 (C₃), 139.6 (C₄), 119.7 (t, J_C, F = 288.7 Hz, C₉), 109.6 (C₃), 102.8 (C₁), 99.8 (t, J_C, F = 2.7 Hz, C₅), 54.1 (C₀).</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>19F NMR</strong> (376 MHz, CDCl₃) δ = -82.96 (s, 2F).</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Methyl 2,2-difluoro-2-[(4-hydroxyphenyl)sulfanyl]acetate 20m

<table>
<thead>
<tr>
<th>Identification:</th>
<th>Exp. Proced. 2</th>
<th>Yield 66%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Flash chromatography: Pentane/Et₂O: 100/0 to 8/2.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pale yellow solid m.p. 58-60 °C, calibration substance: azobenzol at 68.0°C</td>
<td></td>
</tr>
<tr>
<td><img src="image" alt="Chemical Structure" /></td>
<td><img src="image" alt="Chemical Structure" /></td>
<td><img src="image" alt="Chemical Structure" /></td>
</tr>
<tr>
<td><strong>1H NMR</strong> (400 MHz, CDCl₃) δ = <strong>1H NMR</strong> (300 MHz, CDCl₃) δ = 7.47 (d, J = 8.9 Hz, 1H₄), 6.84 (d, J = 8.8 Hz, 1H₁), 3.83 (s, 1H₇).</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>13C NMR</strong> (101 MHz, CDCl₃) δ = 162.6 (t, J_C, F = 33 Hz, C₀), 158.2 (C₂), 138.9 (C₃), 120.2 (t, J_C, F = 287 Hz, C₉), 116.6 (C₁), 115.2 (C₈), 54.0 (C₀).</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>19F NMR</strong> (376 MHz, CDCl₃) δ = -83.25 (s, 2F).</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Methyl 2,2-difluoro-2-[1-(hydroxynaphthalen-2-yl)sulfanyl]acetate 20n

<table>
<thead>
<tr>
<th>Identification:</th>
<th>Exp. Proced. 2</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flash chromatography: Pentane/Et₂O: 100/0 - 8/2.</td>
<td>Pale yellow solid, m.p. 132-134 °C, calibration substance: acetanilide at 68.0°C</td>
<td>83 %</td>
</tr>
</tbody>
</table>

**¹H NMR (400 MHz, (CD₃)₂CO) δ**: 9.92 (s, 1H OH), 8.41 (ddd, J = 8.6, 1.3, 0.7 Hz, 1H₂), 8.34 (ddd, J = 8.4, 1.4, 0.7 Hz, 1H₁), 7.78 (d, J = 7.9 Hz, 1H₈), 7.69 (ddd, J = 8.4, 6.8, 1.4 Hz, 1H₃), 7.58 (ddd, J = 8.2, 6.8, 1.2 Hz, 1H₉), 7.03 (d, J = 7.9 Hz, 1H₈), 3.68 (s, 3H₁₃).  

**¹³C NMR (101 MHz, (CD₃)₂CO) δ**: 162.6 (t, J_C,F = 33 Hz, C₁₂), 157.9 (C₇), 140.4 (C₉), 137.8 (C₉), 128.7 (C₅), 126.3 (C₇), 126.3 (C₉), 123.7 (C₉), 121.2 (t, J_C,F = 286 Hz, C₁₁), 111.3 (t, J_C,F = 3 Hz, C₁₀), 109.3 (C₈), 54.2 (C₁₁).  

**¹⁹F NMR (376 MHz, (CD₃)₂CO) δ**: -83.85 (s, 2F).

II.2.2 Acid activation of α-ketones

**Experimental Procedure 1:**
To a flask containing a solution of reagent 1d (0.3 mmol, 1 equiv.) in dry CH₃CN (0.5 M), the ketone is added (0.3 mmol, 1 equiv.). After stirring for 5 minutes, TMSCl (0.6 mmol, 2 equiv.) is slowly added and the flask is heated at 90 °C overnight. The reaction mixture is extracted with Et₂O (10 mL x 3). The organic fractions are collected and washed with water, brine and dried over MgSO₄. After the removal of the solvent under vacuum the compounds were purified via silica gel column chromatography (except where reported differently).

Methyl 2,2-difluoro-2-[(2-oxo-2-phenylethyl)sulfanyl]acetate 21a

<table>
<thead>
<tr>
<th>Identification:</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flash chromatography: Pentane/Et₂O: 100/0 to 95/5.</td>
<td>42 %</td>
</tr>
</tbody>
</table>

**¹H NMR (400 MHz, CDCl₃) δ**: 7.98-7.95 (m, 2H₉,₆), 7.65-7.60 (m, 1H₁), 7.53-7.48 (m, 2H₉,₆), 4.47 (s, 2H₁), 3.91 (s, 3H₁₁).  

**¹³C NMR (101 MHz, CDCl₃) δ**: 192.6 (C₇), 162.2 (t, J_C,F = 33 Hz, C₁₀), 135.2 (C₃), 134.2 (C₇), 129.1 (C₆,₈), 128.6, (C₅) 120.1 (t, J_C,F = 286.7 Hz, C₈), 54.2 (C₁₁), 37.3 (C₉).  

**¹⁹F NMR (376 MHz, CDCl₃) δ**: -83.14 (s, 2F).
## Experimental Part

### Methyl 2-[[2-(3-chlorophenyl)-2-oxoethyl]sulfanyl]-2,2-difluoroacetate 21b

**Identification:**

Flash chromatography: Pentane/Et$_2$O: 100/0 to 95/5.

| Yield | 40% |

Pale yellow liquid

**$^{1}$H NMR** (400 MHz, CDCl$_3$) $\delta$ = 7.93 (t, $J$ = 1.9 Hz, 1H$_6$), 7.83 (ddd, $J$ = 7.8, 1.7, 1.0 Hz, 1H$_7$), 7.60 (ddd, $J$ = 8.0, 2.2, 1.1 Hz, 1H$_2$), 7.45 (t, $J$ = 7.9 Hz, 1H$_3$), 4.42 (d, $J$ = 0.6 Hz, 2H$_8$), 3.92 (s, 3H$_11$).

**$^{13}$C NMR** (101 MHz, CDCl$_3$) $\delta$ = 191.5 (C$_7$), 162.1 (t, $J_{C,F}$ = 33.0 Hz, C$_{10}$), 136.7 (C$_1$), 135.5 (C$_5$), 134.1 (C$_2$), 130.4 (C$_3$), 126.7 (C$_4$), 119.9 (t, $J_{C,F}$ = 287.0 Hz, C$_9$), 54.28 (C$_{11}$), 37.10 (t, $J_{C,F}$ = 3.0 Hz, C$_8$).

**$^{19}$F NMR** (282 MHz, CDCl$_3$) $\delta$ = -83.10 (s, 2F).

### Methyl 2-[[2-(1-benzofuran-3-yl)-2-oxoethyl]sulfanyl]-2,2-difluoroacetate 2c

**Identification:**

Flash chromatography: Pentane/EtOAc: 8/2

Brown oil

**$^{1}$H NMR** (400 MHz, CDCl$_3$) $\delta$ = 7.72 (ddd, $J$ = 7.9, 1.3, 0.8 Hz, 1H$_6$), 7.62 (d, $J$ = 1.0 Hz, 1H$_7$), 7.60-7.56 (m, 1H$_2$), 7.51 (ddd, $J$ = 8.4, 7.1, 1.3 Hz, 1H$_3$), 4.37 (d, $J$ = 0.7 Hz, 2H$_{10}$), 3.91 (s, 3H$_{13}$).

**$^{13}$C NMR** (101 MHz, CDCl$_3$) $\delta$ = 183.7 (C$_9$), 162.0 (t, $J_{C,F}$ = 33.0 Hz, C$_{12}$), 155.9 (C$_4$), 150.9 (C$_8$), 129.1 (C$_2$), 126.9 (C$_3$), 124.4 (C$_1$), 123.7 (C$_5$), 119.84 (t, $J_{C,F}$ = 287.2 Hz, C$_{10}$), 114.3 (C$_{13}$), 112.6 (C$_{15}$), 54.3 (C$_{13}$), 36.06 (t, $J_{C,F}$ = 3.2 Hz, C$_{10}$).

**$^{19}$F NMR** (376 MHz, CDCl$_3$) $\delta$ = -82.99 (s, 2F).

### 2-[(1,1-difluoro-2-methoxyethyl)sulfanyl]-1-phenylpropan-1-one 2d

**Identification:**

Flash chromatography: Pentane/Et$_2$O: 100/0 to 95/5.

Pale yellow liquid

**$^{1}$H NMR** (400 MHz, CDCl$_3$) $\delta$ = 8.22-7.83 (m, 2H$_{4,6}$), 7.65-7.56 (m, 1H$_3$), 7.53-7.45 (m, 2H$_{1,5}$), 5.07 (q, $J$ = 7.1 Hz, 1H$_9$), 3.86 (s, 3H$_{12}$), 1.68 (d, $J$ = 7.1 Hz, 2H$_8$).

**$^{13}$C NMR** (101 MHz, CDCl$_3$) $\delta$ = 196.9 (C$_7$), 162.1 (t, $J_{C,F}$ = 32.8 Hz, C$_{11}$), 154.4 (C$_4$), 143.0 (C$_2$), 129.0 (C$_3$), 128.9 (C$_{1,3}$), 120.5 (t, $J_{C,F}$ = 287.5 Hz, C$_{15}$), 54.2 (C$_{12}$), 43.1 (t, $J_{C,F}$ = 2.2 Hz, C$_{9}$), 20.0 (C$_{11}$).

**$^{19}$F NMR** (376 MHz, CDCl$_3$) $\delta$ = -80.78 (d, $J$ = 221.2 Hz, AB system 1F), -81.61 (d, $J$ = 221.2 Hz, AB system 1F).
II.2.3 Post-functionalization of the SCF\textsubscript{2}CO\textsubscript{2}Me motif

II.2.3.1 Reduction od SCF\textsubscript{2}CO\textsubscript{2}Me to alcohol

Experimental Procedure:
Compound 20\textit{k} or 20\textit{f} (0.5 mmol, 1 equiv.) was dissolved in dry MeOH (0.1 M) and followed by the addition of NaBH\textsubscript{4} in portions at 0 °C. The reaction mixture is allowed to reach 25 °C and let under stirring overnight. After quenching the excess of NaBH\textsubscript{4} with HCl 1M, the mixture was extracted with EtOAc (3x10). The organic layers were collected, washed with water and brine and dried over Na\textsubscript{2}SO\textsubscript{4} or MgSO\textsubscript{4}. After the removal of the solvent under vacuum the compounds were purified \textit{via} silica gel column chromatography (except where reported differently).

2-[(2,4-dimethoxyphenyl)sulfanyl]-2-fluoroethan-1-ol 22\textit{a}

<table>
<thead>
<tr>
<th>Identification:</th>
<th>Yield 99 %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pure compound after the work-up.</td>
<td></td>
</tr>
<tr>
<td>Pale yellow liquid</td>
<td></td>
</tr>
</tbody>
</table>

\textbf{\textsuperscript{1}H NMR} (400 MHz, CDCl\textsubscript{3}) \(\delta = 7.68-7.40\ (m, 1H_{4}), 6.57-6.22\ (m, 2H_{i,\phi}), 3.90\ (s, 3H_{9}), 3.83\ (s, 3H_{10}), 3.59\ (t, J_{H,F} = 11.4\ Hz, 3H_{3}).

\textbf{\textsuperscript{13}C NMR} (101 MHz, CDCl\textsubscript{3}) \(\delta = 163.6\ (C_{2}), 161.52\ (C_{6}), 141.2\ (C_{4}), 129.2\ (t, J_{C,F} = 281.2\ Hz, C_{9}), 106.1\ (C_{5}), 105.2\ (t, J_{C,F} = 3.9\ Hz, C_{3}), 99.4\ (C_{1}), 63.7\ (t, J_{C,F} = 32.3\ Hz, C_{8}), 56.4\ (C_{9}), 55.7\ (C_{10}).

\textbf{\textsuperscript{19}F NMR} (376 MHz, CDCl\textsubscript{3}) \(\delta = -86.25\ (t, J_{F,H} = 11.3\ Hz, 2F).

2,2-difluoro-2-(1H-indol-3-ylsulfanyl)ethan-1-ol 23\textit{a}

<table>
<thead>
<tr>
<th>Identification:</th>
<th>Yield 74 %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flash chromatography: Pentane/EtOAc: 70/30 to 60/40.</td>
<td></td>
</tr>
<tr>
<td>Pure compound after the work-up.</td>
<td></td>
</tr>
<tr>
<td>Brown oil</td>
<td></td>
</tr>
</tbody>
</table>

\textbf{\textsuperscript{1}H NMR} (400 MHz, CDCl\textsubscript{3}) \(\delta = 8.57\ (bs, 1H_{NH}), 7.81\ (m, 1H_{4}), 7.44-7.38\ (m, 2H_{1,\phi}), 7.30-7.24\ (m, 2H_{i,\phi}), 3.83\ (t, J_{H,F} = 12.2\ Hz, 2H_{i,\phi}), 2.39\ (bs, 1H_{OH}).

\textbf{\textsuperscript{13}C NMR} (101 MHz, CDCl\textsubscript{3}) \(\delta = 136.2\ (C_{5}), 132.7\ (C_{6}), 129.9\ (C_{4}), 128.3\ (t, J_{C,F} = 279.5\ Hz, C_{9}), 123.3\ (C_{7}), 121.5\ (C_{8}), 119.4\ (C_{1}), 111.8\ (C_{3}), 96.2\ (m, C_{3}), 64.5\ (t, J_{C,F} = 30\ Hz, C_{10}).

\textbf{\textsuperscript{19}F NMR} (376 MHz, CDCl\textsubscript{3}) \(\delta = -85.89\ (t, J_{F,H} = 12\ Hz, 2F).

II.2.3.2 Aminolysis reactions

Experimental Procedure:
Compound 20\textit{k} or 20\textit{f} (0.5 mmol, 1 equiv.) was dissolved in dry MeOH (0.1 M) and followed by the addition of benzylamine (1 mmol, 0.5 equiv.) the reaction was run at room temperature for 3
hours and 16 hours respectively. HCl 1M was added to the reaction mixture and the organic layers were extracted with EtOAc (3x10). The organic layers were collected, washed with water and brine and dried over Na₂SO₄ or MgSO₄. After the removal of the solvent under vacuum the compounds were purified via silica gel column chromatography (except where reported differently).

**N-benzyl-2-[(2,4-dimethoxyphenyl)sulfanyl]-2,2-difluoroacetamide**

<table>
<thead>
<tr>
<th>Identification:</th>
<th>Yield quant.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flash chromatography: Pentane/Et₂O: 8/2.</td>
<td>Pale yellow solid m.p. 96-98 °C, calibration substance: acetanilide at 114.5 °C</td>
</tr>
</tbody>
</table>

1H NMR (400 MHz, CDCl₃) δ = 7.49 (d, J = 8.5 Hz, 1H), 7.32-7.29 (m, 1H), 6.47 (dd, J = 8.6, 2.6 Hz, 1H), 6.43 (d, J = 2.5 Hz, 1H), 4.40 (d, J = 5.8 Hz, 2H), 3.81 (s, 3H), 3.73 (s, 3H).

13C NMR (101 MHz, CDCl₃) δ = 163.7 (C₈), 162.1 (C₂), 161.9 (C₆), 140.5 (C₄), 136.6 (C₁₀), 128.8 (C₁₂), 127.9 (C₁₁), 105.6 (C₆), 103.6 (t, J = 3 Hz, C₁), 99.3 (C₆), 56.0 (C₉), 55.7 (C₁₆), 43.8 (C₁₇).

19F NMR (376 MHz, CDCl₃) δ = -82.84 (s, 2F).

**N-benzyl-2,2-difluoro-2-(1H-indol-3-ylsulfanyl)acetamide**

<table>
<thead>
<tr>
<th>Identification:</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flash chromatography: Pentane/EtOAc: 75/25 to 65/35.</td>
<td>95 %</td>
</tr>
<tr>
<td>Pale oil m.p.</td>
<td>Pale orange, calibration substance: acetanilide at 114.5 °C</td>
</tr>
</tbody>
</table>

1H NMR (400 MHz, CDCl₃) δ = 9.15 (bs, 1H), 7.79 (d, J = 7.4 Hz, 1H), 7.41 (d, J = 7.7 Hz, 1H), 7.33 (bs, 1H), 7.28-7.21 (m, 5H), 6.98 (dd, J = 6.6, 2.9 Hz, 2H), 6.38 (bs, 1H), 4.28 (d, J = 5.6 Hz, 2H).

13C NMR (101 MHz, CDCl₃) δ = 162.5 (t, J₆,F = 29 Hz, C₁₂), 136.3 (C₁₀), 133.5 (C₅), 129.7 (C₉), 128.9 (C₁₆), 128.0 (C₁₇), 127.9 (C₁₅), 123.2 (C₂), 122.4 (t, J₆,F = 288 Hz, C₁₁), 121.4 (C₆), 119.2 (C₉), 112.1 (C₆), 95.0 (m, C₆), 44.0 (C₁₈).

19F NMR (376 MHz, CDCl₃) δ = -84.39 (s, 2F).

**II.2.3.3 Saponification reactions**

**Experimental Procedure:** To a flask are added the ester derivative (20c, 20k or 20f) (0.69 mmol, 1.0 equiv.), MeOH (2 mL) and a solution of K₂CO₃ 1M in water (2.05 mL, 2.05 mmol, 3.0 equiv.). The reaction mixture is stirred at 23°C for 18 h. It is then partitioned between aqueous NaOH 2N and EtOAc. The organic layer is extracted with aqueous NaOH 2N and the combined aqueous layers are acidified with aqueous HCl 2N until pH 1-2. The aqueous layer is
extracted with EtOAc and the combined organic layers are washed with water, dried over MgSO₄, filtered and concentrated to dryness to afford the desired carboxylic acid.

2-[(2,4-dimethoxyphenyl)sulfanyl]-2,2-difluoroacetic acid 22c

<table>
<thead>
<tr>
<th>Identification</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flash chromatography: Pentane/EtOAc: 75/25 to 65/35.</td>
<td>87 %</td>
</tr>
<tr>
<td>Redish oil or redish solid</td>
<td>m.p. 74 °C, calibration substance: azobenzol at 68.0 °C</td>
</tr>
<tr>
<td>1H NMR (400 MHz, CDCl₃) δ = 9.27 (s, 1H OH), 7.50 (d, J = 8.4 Hz, 1H), 6.52-6.33 (m, 2H), 3.82 (s, 3H), 3.81 (s, 3H).</td>
<td></td>
</tr>
<tr>
<td>13C NMR (101 MHz, CDCl₃) δ = 165.8 (t, J₅,F = 34 Hz, C₁₀), 164.0 (C₂), 162.2 (C₆), 140.6 (C₄), 118.9 (t, J₄,F = 288 Hz, C₉), 105.8 (C₉), 103.3 (t, J₅,F = 3 Hz, C₄), 99.3 (C₁), 56.0 (C₇), 55.6 (C₈).</td>
<td></td>
</tr>
<tr>
<td>19F NMR (376 MHz, CDCl₃) δ = -85.77 (s, 2F).</td>
<td></td>
</tr>
</tbody>
</table>

2,2-difluoro-2-(1H-indol-3-ylsulfanyl)acetic acid 23c

<table>
<thead>
<tr>
<th>Identification</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>Filtration in pentane</td>
<td>92 %</td>
</tr>
<tr>
<td>Brown solid</td>
<td>m.p. 78-80 °C, calibration substance: azobenzol at 68.0°C</td>
</tr>
<tr>
<td>1H NMR (300 MHz, (CD₃)₂CO) δ = 10.93 (bs, 1H OH), 9.24 (bs, 1H NH), 7.74-7.71 (m, 2H), 7.51 (m, 1H), 7.25-7.16 (m, 2H).</td>
<td></td>
</tr>
<tr>
<td>13C NMR (101 MHz, (CD₃)₂CO) δ = 163.1 (t, J₅,F = 32 Hz, C₁₀), 137.7 (C₂), 137.5 (C₁), 135.0 (C₃), 134.9 (C₃), 130.9 (C₄), 123.4 (C₃), 121.6 (C₃), 121.1 (t, J₃,F = 285 Hz, C₉), 119.6 (C₆), 113.0 (C₈), 113.0 (C₈), 94.6 (m, C₉).</td>
<td></td>
</tr>
<tr>
<td>19F NMR (376 MHz, (CD₃)₂CO) δ = -84.28 (s, 2F).</td>
<td></td>
</tr>
</tbody>
</table>

2,2-difluoro-2-[(1-methyl-1H-indol-3-yl)sulfanyl]acetic acid 23f

<table>
<thead>
<tr>
<th>Identification</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>Filtration in pentane</td>
<td>92 %</td>
</tr>
<tr>
<td>Brown solid</td>
<td>m.p. 90-92 °C, calibration substance: azobenzol at 68.0°C</td>
</tr>
<tr>
<td>1H NMR (300 MHz, (CD₃)₂CO) δ = 11.50 (s, 1H_H), 7.77 (d, J = 7.5 Hz, 1H), 7.61 (s, 1H), 7.46 (d, J = 7.5 Hz, 1H), 7.32-7.21 (m, 2H), 3.85 (s, 3H).</td>
<td></td>
</tr>
<tr>
<td>13C NMR (101 MHz, (CD₃)₂CO) δ = 163.3 (t, J₅,F = 32Hz, C₁₀), 138.5 (C₂), 138.3 (C₂), 131.4 (C₃), 123.3 (C₃), 121.6 (C₃), 121.0 (t, J₃,F = 284 Hz, C₉), 119.8 (C₉), 111.0 (C₈), 93.1 (bs), 33.3 (C₁₁).</td>
<td></td>
</tr>
<tr>
<td>19F NMR (376 MHz, (CD₃)₂CO) δ = -84.03 (s, 2F).</td>
<td></td>
</tr>
</tbody>
</table>
II.2.3.4 Decarboxylative bromination reaction

**Experimental Procedure:**
In an oven-dried flask compound 23c (0.5 mmol, 1.0 equiv.), AgNO₃ (0.1 mmol, 20 mol %), Selectfluor II (1.75 mmol, 3.5 equiv.) is added. The flask is evacuated and backfilled with pure N₂ for 3 times. Then dry CH₂Cl₂ (5.0 mL), water (0.5 mL) and HBF₄ (50% aq.) (1.5 mmol, 3.0 equiv.) are added with syringe. The mixture is heated at 80 °C for 12 h. The reaction is quenched by addition of water and the organic phase is extracted with CH₂Cl₂ (3x10 mL). The combined organic phase is dried over Na₂SO₄. After the removal of the solvent under vacuum the compounds were purified via silica gel column chromatography.

1-bromo-5-[(bromodifluoromethyl)sulfanyl]-2,4-dimethoxybenzen 24c

<table>
<thead>
<tr>
<th>Identification</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>Filtration in pentane</td>
<td>65 %</td>
</tr>
<tr>
<td>Brown solid</td>
<td>m.p. 62 °C, calibration substance: azobenzol at 68.0 °C</td>
</tr>
<tr>
<td><strong>¹H NMR</strong> (400 MHz, CDCl₃) δ = 7.75 (s, 1H₄), 6.50 (s, 1H₁), 3.95 (s, 3H₈), 3.91 (s, 3H₉)</td>
<td></td>
</tr>
<tr>
<td><strong>¹³C NMR</strong> (101 MHz, CDCl₃) δ = 161.8 (C₂), 160.0 (C₆), 142. (C₄), 125.6 (C₃) 119.6 (t, J_C,F = 340.3 Hz, C₇), 107.3 (C₅), 102.3 (C₇), 96.6 (C₁), 56.6 (C₈), 56.51 (C₉)</td>
<td></td>
</tr>
<tr>
<td><strong>¹⁹F NMR</strong> (376 MHz, CDCl₃) δ = -22.56 (s, 2F)</td>
<td></td>
</tr>
</tbody>
</table>

II.2.3.5 Oxidative decarboxylation reactions

**Synthesis of the Hypervalent iodonium reagents:**
All the hyperiodonium reagents and their precursors have been synthesized as following the procedures reported by Wasser and coll.[4] without any further modification, obtaining the same yields.

**General experimental procedure:**
In an oven-dried flask, carboxylic acid 23 (0.2 mmol, 1 equiv.), AgNO₃ (0.05 mmol, 25 mol %), K₂S₂O₈ (0.4 mmol, 2 equiv.), EBX reagent (0.2 mmol, 1 equiv.) and then H₂O (1 mL), acetone (1 mL) was added. The reaction mixture is stirred at 50 °C for 16h. H₂O and EtOAc are added to the reaction vessel and the organic layers were extracted with EtOAc (3x10 mL). The combined organic layer were washed with water and brine and dried with anhydrous Na₂SO₄ or MgSO₄ and evaporated in vacuum. After the removal of the solvent under vacuum the compounds were purified via silica gel column chromatography (except where reported differently).
### 3-[(2,4-dimethoxyphenyl)sulfanyl]-3,3-difluoroprop-1-yn-1-yl]tris(propan-2-yl)silane 25c

<table>
<thead>
<tr>
<th>Identification:</th>
<th>Yield</th>
<th>Flash chromatography: Pentane/Et₂O: 100 to 95/5.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brown solid</td>
<td>m.p. &lt; 46 °C, calibration substance: azobenzol at 68.0 °C</td>
<td></td>
</tr>
<tr>
<td><strong>¹H NMR</strong> (400 MHz, CDCl₃) δ = 7.54-7.52 (m, 1H₄), 6.51-6.48 (m, 2H₁,₃), 3.86 (s, 3H₆), 3.82 (s, 3H₂), 1.06-1.03 (m, 21H₁₂-20).</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>¹³C NMR</strong> (101 MHz, CDCl₃) δ = 163.6 (C₆), 162.1 (C₂), 140.3 (C₄), 117.2 (t, J₉,F = 266 Hz, C₉), 106.2 (C₅), 105.5 (C₃), 99.3 (C₆), 97.1 (t, J₄,F = 38 Hz, C₄₀), 93.7 (t, J₉,F = 5 Hz, C₁₀), 56.2 (C₇), 55.6 (C₈), 18.5 (C₁₅-20), 11.0 (C₁₂-14).</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>¹⁹F NMR</strong> (376 MHz, (CD₃)₂CO) δ = -58.43 (s, 2F).</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### 3-[(1,1-difluoro-3-[(tri-tert-butylsilyl)prop-2-yn-1-yl]sulfanyl]-1H-indole 25a

<table>
<thead>
<tr>
<th>Identification:</th>
<th>Yield</th>
<th>Flash chromatography: Pentane/EtOAc: 90/10 to 80/2.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yellow solid</td>
<td>m.p. not determined.</td>
<td></td>
</tr>
<tr>
<td><strong>¹H NMR</strong> (500 MHz, CDCl₃) δ = 8.48 (bs, 1H NH), 7.84 (m, 1H₆), 7.51 (d, J = 2.7 Hz, 1H₄), 7.40 (m, 1H₃), 7.28-7.22 (m, 2H₁₂,₂₀), 1.03-1.01 (m, 21H₁_2₀).</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>¹³C NMR</strong> (126 MHz, CDCl₃) δ = 136.2 (C₄), 132.7 (C₇), 130.0 (C₅), 123.2 (C₁), 121.5 (C₂), 119.9 (C₆), 116.9 (t, J₈,F = 266 Hz, C₆₀), 111.6 (C₃), 98.4 (t, J₈,F = 2 Hz, C₉), 97.1 (t, J₈,F = 38 Hz, C₄₀), 93.9 (t, J₈,F = 5 Hz, C₁₀), 18.5 (C₁₅-20), 11.0 (C₁₂-14).</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>¹⁹F NMR</strong> (376 MHz, CDCl₃) δ = -59.49 (s, 2F).</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### 3-[(1,1-difluoro-3-[(tris(propan-2-yl)silyl)prop-2-yn-1-yl]sulfanyl]-1-methyl-1H-indole 25b

<table>
<thead>
<tr>
<th>Identification:</th>
<th>Yield</th>
<th>Flash chromatography: Pentane/EtOAc: 98/2 to 95/5.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yellow solid</td>
<td>m.p. 64 °C, calibration substance: azobenzol at 68.0 °C</td>
<td></td>
</tr>
<tr>
<td><strong>¹H NMR</strong> (500 MHz, CDCl₃) δ = 7.73 (d, J = 7.7 Hz, 1H₆), 7.25-7.13 (m, 4H₂,₃,₁,₂₀), 3.71 (s, 3H₁₂), 0.93 (massif, 21H₁₂-20).</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>¹³C NMR</strong> (126 MHz, CDCl₃) δ = 137.3 (C₄), 136.8 (C₇), 130.8 (C₅), 122.8 (C₁), 121.1 (C₂), 120.0 (C₆), 117.1 (t, J₈,F = 266 Hz, C₆₀), 109.7 (C₃), 97.2 (t, J₈,F = 38 Hz, C₄₀), 96.0 (t, J₈,F = 2 Hz, C₉), 93.8 (t, J₈,F = 5 Hz, C₁₀), 33.3 (C₂₀), 18.5 (C₁₅-20), 11.0 (C₁₂-14).</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>¹⁹F NMR</strong> (376 MHz, CDCl₃) δ = -59.69 (s, 2F).</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
II.3 Synthesis and characterization of pre-reagents 2a-g

{[(trifluoromethyl)selanyl]methyl}benzene 2a

**Experimental procedure:**

To an oven-dried flask equipped with a magnetic stirrer are added 2-phenylacetonitrile (70.0 mmol, 1.0 equiv.) and dry THF (140 mL). The flask is evacuated and refilled with nitrogen three times and TMSCF₃ (20.7 mL, 140 mmol, 2.0 equiv.) is added. The reaction mixture is cooled to 0°C and TBAF in THF 1M (14.0 mL, 14.0 mmol, 0.2 equiv.) is added dropwise. After 10 minutes at 0°C under nitrogen, the reaction is allowed to warm to 20°C and stirred for 7 hours. The reaction mixture is then partitioned between water and pentane and the aqueous layer is extracted with pentane. The combined organic layers are washed with H₂O, brine and dried over MgSO₄, filtered through a pad of silica (rinsed with pentane) and concentrated to dryness (under moderate vacuum). After the removal of the solvent under vacuum the crude residue is purified via silica gel column chromatography.

<table>
<thead>
<tr>
<th>Identification</th>
<th>As reported in literature[5]</th>
<th>Yield 70 %</th>
</tr>
</thead>
<tbody>
<tr>
<td>![SeCF₃] 2a</td>
<td>Flash chromatography: Pentane 100 %</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Colorless liquid</td>
<td></td>
</tr>
<tr>
<td></td>
<td>¹H NMR (300 MHz, CDCl₃) δ = 7.37-7.27 (m, 5H), 4.26 (s, 2H).</td>
<td></td>
</tr>
<tr>
<td></td>
<td>¹⁹F NMR (282 MHz, CDCl₃) δ = -34.47 (s, 3F).</td>
<td></td>
</tr>
</tbody>
</table>

{{[bromodifluoromethyl]selanyl]methyl}benzene 2b

**Experimental procedure:**

To an oven-dried flask equipped with a magnetic stirrer is added 2-phenylacetonitrile (1.08 gr, 10 mmol, 1.0 equiv.). The flask is evacuated and refilled with nitrogen three times before adding THF (20 mL) and TMSCF₂Br (3.1 mL, 20 mmol, 2.0 equiv.) to the reaction mixture. The reaction mixture is cooled to 0°C and TBAF in THF 1M (2 mL, 2 mmol, 0.2 equiv.) is added dropwise. After 10 minutes at 0°C under nitrogen, the reaction is allowed to warm to 20°C and stirred for 4 hours. The reaction mixture is then partitioned between water and pentane and the aqueous layer is extracted with pentane. The combined organic layers are washed with H₂O, brine, dried over MgSO₄ and concentrated to dryness (under moderate vacuum). After the removal of the solvent under vacuum the crude residue is purified via silica gel column chromatography.
Experimental Part

Identification: Yield

Flash chromatography: Pentane 100 %
Colorless liquid

\[^1\text{H} \text{NMR} \ (400 \text{ MHz, CDCl}_3) \delta = 7.36-7.28 \ (m, 5\text{H}_\text{Ar}), 4.31 \ (s, 2\text{H}_2).
\[^{13}\text{C} \text{ NMR} \ (101 \text{ MHz, CDCl}_3) \delta = 135.6 \ (C_{12}), 131.9 \ (C_{11}), 131.0 \ (C_9), 129.5 \ (C_{10}), 129.4 \ (C_6), 129.0 \ (C_{13}, 7), 128.0 \ (C_2), 126.01 \ (t, J_{C,F} = 339 \text{ Hz}, C_9), 30.7 \ (C_7).
\[^{19}\text{F} \text{ NMR} \ (282 \text{ MHz, CDCl}_3) \delta = -34.47 \ (s, 3\text{F}).

Elemental Analysis calcd (%) for C\(_8\)H\(_7\)BrF\(_2\)Se: C, 32.03; H, 2.35; Br, 26.63; Se, 26.32. Found: C, 31.95; H, 2.47; Se, 26.11.

(2-(benzylselanyl))difluoromethanesulfonylethylbenzene 2c

**Experimental procedure:**

To a flask equipped with a magnetic stirrer is added 2-phenylacetonitrile (1.08 gr, 5.5 mmol, 1.0 equiv.). The flask is evacuated and refilled with nitrogen three times before adding diglyme (11 mL), and TMSCF\(_2\text{SO}_2\text{Ph} \ (10 \text{ mmol, 2.0 equiv.) to the reaction mixture. The reaction mixture is cooled to 0°C and CsF (166 mg, 1.1 mmol, 0.2 equiv.) is carefully added. After 10 minutes at 0°C under nitrogen, the reaction is allowed to warm to 20°C and stirred for 15 hours. The reaction mixture is then partitioned between water and Et\(_2\)O and the aqueous layer is extracted with Et\(_2\)O. The combined organic layers are washed with H\(_2\)O, brine, dried over MgSO\(_4\) and concentrated to dryness. After the removal of the solvent under vacuum the crude residue is purified via silica gel column chromatography.

Identification: Yield

Flash chromatography: 9/1.
White solid m.p. 64°C, calibration substance: azobenzol 68°C

\[^1\text{H} \text{NMR} \ (400 \text{ MHz, CDCl}_3) \delta = 8.02 \ (dt, J = 8.5, 1.0 \text{ Hz}, 2\text{H}_9), 7.82 - 7.74 \ (m, \text{5H}_\text{Ar}), 7.41 - 7.27 \ (m, \text{5H}_\text{Ar}), 4.45 \ (s, 2\text{H}_7).
\[^{13}\text{C} \text{ NMR} \ (101 \text{ MHz, CDCl}_3) \delta = 135.6 \ (C_{12}), 131.9 \ (C_{11}), 131.0 \ (C_9), 129.5 \ (C_{10}), 129.4 \ (C_6), 129.0 \ (C_{13}, 7), 128.0 \ (C_2), 126.01 \ (t, J_{C,F} = 339 \text{ Hz}, C_9), 30.7 \ (C_7).
\[^{19}\text{F} \text{ NMR} \ (376 \text{ MHz, CDCl}_3) \delta = -78.53 \ (s, 2\text{F}).

Elemental Analysis: calcd (%) for C\(_{14}\)H\(_{12}\)F\(_2\)O\(_2\)SSe: C, 46.55; H, 3.35; Se, 21.86, S 8.87. Found: C, 46.65; H, 3.58; Se, 21.64, S 9.07.

Methyl 2-(benzylselanyl)-2,2-difluoroacetate 2d

**Experimental procedure:**
To a flask equipped with a magnetic stirrer 2-phenylacetonitrile (980 mg, 5 mmol, 1.0 equiv.) is added. The flask is evacuated and refilled with nitrogen three times before adding THF (10 mL) and TMSCF₂Br (1.77 mL, 10 mmol, 2.0 equiv.) to the flask. The reaction mixture is cooled to 0°C and TBAF in THF 1M (1 mL, 1 mmol, 0.2 equiv.) is added dropwise. After 10 minutes at 0°C under nitrogen, the reaction is allowed to warm to 20°C and stirred for 15 hours. The reaction mixture is then partitioned between water and EtOAc and the aqueous layer is extracted with EtOAc. The combined organic layers are washed with H₂O, brine, dried over MgSO₄ and concentrated to dryness. After the removal of the solvent under vacuum the crude residue is purified via silica gel column chromatography.

**Identification:**

<table>
<thead>
<tr>
<th>Identification</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flash chromatography: Pentane/Et₂O 99/1 – 98/2</td>
<td>62%</td>
</tr>
</tbody>
</table>

| ¹H NMR (400 MHz, CDCl₃) δ = 7.36-7.24 (m, 5H Ar), 4.24 (s, 2H), 3.88 (s, 3H). |
| ¹³C NMR (101 MHz, CDCl₃) δ = 163.0 (t, J = 31 Hz, C₉), 136.4 (C₅), 129.3 (C₄, 6), 128.9 (C₁, 3), 127.7 (C₂), 115.1 (t, J = 302 Hz, C₈), 54.0 (C₁₀), 28.8 (t, J = 3 Hz, C₇). |
| ¹⁹F NMR (376 MHz, CDCl₃) δ = -83.07 (s, 2F). |

**Elemental Analysis** calcd (%) for C₁₀H₁₀F₂O₂Se: C, 43.03; H, 3.61; Se, 28.29. Found: C, 43.32; H, 3.92; Se, 28.10.

**{(difluoromethyl)selanyl}methyl]benzene 2e**

**Experimental procedure:**

To a dry flask equipped with a magnetic stirrer 2-phenylacetonitrile (2.05 g, 10.45 mmol, 1.0 equiv.) and dry THF (21 mL) are added. The flask is evacuated and refilled with nitrogen three times and TMSCF₂H (2.85 mL, 20.9 mmol, 2.0 equiv.) is added. The reaction mixture is cooled to 0°C and CsF (1.59 g, 10.45 mmol, 1.0 equiv.) is carefully added. After 30 minutes at 0°C under nitrogen, the reaction is allowed to warm to 20°C and stirred for 15 hours. The reaction mixture is then partitioned between water and pentane and the aqueous layer is extracted with pentane. The combined organic layers are washed with brine, dried over MgSO₄, filtered and concentrated to dryness (under moderate vacuum). After the removal of the solvent under vacuum the crude residue is purified via silica gel column chromatography.
Identification: Yield

<table>
<thead>
<tr>
<th>2e</th>
<th>Flash chromatography: Pentane/CH₂Cl₂ 97/3 - 95/5</th>
</tr>
</thead>
<tbody>
<tr>
<td>1H NMR (400 MHz, CDCl₃) δ = 7.37-7.31 (m, 5H Ar), 7.08 (t, J_H, F = 55.2 Hz, 1H), 4.12 (s, 2H).</td>
<td></td>
</tr>
<tr>
<td>13C NMR (101 MHz, CDCl₃) δ = 137.4 (C_5), 129.1 (C_4, 6), 128.9 (C_1, 3), 127.5 (C_2), 115.8 (t, J_C, F = 287 Hz, C_9, 26.4 (t, J_C, F = 3 Hz, C).</td>
<td></td>
</tr>
<tr>
<td>19F NMR (376 MHz, CDCl₃) δ = -92.95 (d, J_F, H = 55.3 Hz, 2F).</td>
<td></td>
</tr>
</tbody>
</table>

Flash yellow liquid

Yield 19 %

**Elemental Analysis**

Calcd (%) for C₈H₈F₂Se: C, 43.46; H, 3.65; Se, 35.71. Found: C, 43.29; H, 3.40; Se, 35.63.

*{(pentafluoroethyl)selanylmethyl}benzene 2f*

**Experimental procedure:**

To a flask equipped with a magnetic stirrer are added 2-phenylacetonitrile (2.8 g, 14.2 mmol, 1.0 equiv.) and dry THF (30 mL). The flask is evacuated and refilled with nitrogen three times and TMSCF₂CF₃ (4.9 mL, 28.5 mmol, 2.0 equiv.) is added. The reaction mixture is cooled to 0°C and TBAF in THF 1M (2.8 mL, 2.8 mmol, 0.2 equiv.) is added dropwise. After 10 minutes at 0°C, the reaction is allowed to warm to 20°C and stirred for 16 hours. The reaction mixture is then partitioned between water and pentane and the aqueous layer is extracted with pentane. The combined organic layers are washed with brine, dried over MgSO₄, filtered through a pad of silica (rinsed with pentane) and concentrated to dryness (under moderate vacuum). After the removal of the solvent under vacuum the crude residue is purified via silica gel column chromatography.

Identification: Yield

<table>
<thead>
<tr>
<th>2f</th>
<th>Flash chromatography: Pentane 100 %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1H NMR (400 MHz, CDCl₃) δ = 7.39-7.28 (m, 5H Ar), 4.28 (s, 2H).</td>
<td></td>
</tr>
<tr>
<td>13C NMR (101 MHz, CDCl₃) δ = 135.5 (C_5), 129.3 (C_4, 6), 129.1 (C_1, 3), 128.0 (C_2), 119.1 (qt, J_C, F = 285 Hz, J_C, F = 35 Hz, C_10), 116.5 (tq, J_C, F = 303 Hz, J_C, F = 43 Hz, C_9), 28.6 (t, J_C, F = 3 Hz, C).</td>
<td></td>
</tr>
<tr>
<td>19F NMR (376 MHz, CDCl₃) δ = -83.66 (t, J_F, H = 4.3 Hz, 3F_10), -91.75 (q, J_F, H = 4.3 Hz, 2F).</td>
<td></td>
</tr>
</tbody>
</table>

Colorless liquid

Yield 83 %

**Elemental Analysis**

Calcd (%) for C₉H₇F₅Se: C, 37.39; H, 2.44; Se, 27.31. Found: C, 37.54; H, 2.53; Se, 35.63.

*{(heptafluoropropyl)selanylmethyl}benzene 2g*

**Experimental procedure:**

To a flask equipped with a magnetic stirrer are added 2-phenylacetonitrile (720 mg, 3.7 mmol, 1.0 equiv.) and dry THF (7 mL) are added. The flask is evacuated and refilled with nitrogen three
Experimental Part

times and TMSCF₂CF₂CF₃ (1.5 mL, 7.3 mmol, 2.0 equiv.) is added. The reaction mixture is cooled to 0°C and TBAF in THF 1M (0.73 mL, 0.73 mmol, 0.2 equiv.) is added dropwise. After 10 minutes at 0°C, the reaction is allowed to warm to 20°C and stirred for 16 hours. The reaction mixture is then partitioned between water and pentane and the aqueous layer is extracted with pentane. The combined organic layers are washed with brine, dried over MgSO₄, filtered through a pad of silica (rinsed with pentane) and concentrated to dryness (under moderate vacuum). After the removal of the solvent under vacuum the crude residue is purified via silica gel column chromatography.

<table>
<thead>
<tr>
<th>Identification:</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flash chromatography: Pentane 100 %</td>
<td>87 %</td>
</tr>
<tr>
<td>Colorless liquid</td>
<td></td>
</tr>
<tr>
<td><strong>¹H NMR</strong> (400 MHz, CDCl₃) δ = 7.38-7.27 (massif, 5H Ar), 4.30 (s, 2H H₂).</td>
<td></td>
</tr>
<tr>
<td><strong>¹³C NMR</strong> (101 MHz, CDCl₃) δ = 135.5 (C 5), 129.4 (C 4, 6), 129.1 (C 1, 3), 128.1 (C 2), 119.4 (tt, J C, F) = 304 Hz, J C, F = 38 Hz, C 4), 117.8 (qt, J C, F = 288 Hz, J C, F = 35 Hz, C 11), 108.9 (tsex, J C, F = 262 Hz, J C, F = 36 Hz, C 10), 28.6 (m, C 7).</td>
<td></td>
</tr>
<tr>
<td><strong>¹⁹F NMR</strong> (376 MHz, CDCl₃): δ = -79.78 (t, J F, F = 9.3 Hz, 3F 11), -87.74 (m, 2F 9), -122.77 (bs, 2F 10).</td>
<td></td>
</tr>
</tbody>
</table>

**II.3.1 Fluoroalkylselenolationation reactions**

**General experimental procedure 1:**
To a flask equipped with a magnetic stirrer are added the pre-reagent 2a-g (0.5 mmol, 1.0 equiv.), sulfuryl chloride (0.5 mmol, 1.0 equiv.) and dry THF (0.5 mL, 1M). The reaction mixture is stirred at 23°C for 15 minutes, it is then cooled to 0°C followed by the addition of the nucleophile (0.5 mmol, 1.0 equiv.). The reaction mixture is stirred for 10 minutes at 0°C until complete conversion of the intermediate ClSeCF₃. The reaction mixture is then partitioned between water and Et₂O and the aqueous layer is extracted with Et₂O. The combined organic layers are washed with brine, dried over MgSO₄, filtered and concentrated to dryness. After the removal of the solvent under vacuum the crude residue is purified via silica gel column chromatography (if not differently indicated).

**Experimental procedure 2:**
To a flask equipped with a magnetic stirrer were added 1 (0.6 mmol, 1.2 equiv.), sulfuryl chloride (0.6 mmol, 1.2 equiv.), and dry DCE (0.5 mL, 1 M). The reaction mixture was stirred at 23 °C for 3.5 h followed by the addition of 3 (0.5 mmol, 1.0 equiv.) and BF₃·Et₂O (0.15 mmol, 30 mol %).
The reaction mixture was heated to 80 °C for 15 h. The reaction mixture was then partitioned between water and pentane, and the aqueous layer was extracted with pentane. The combined organic layers were washed with brine, dried over MgSO4, filtered, and concentrated to dryness. After the removal of the solvent under vacuum the crude residue is purified via silica gel column chromatography (if not differently indicated).

2,4-dimethoxy-1-[(trifluoromethyl)selanyl]benzene 40a

<table>
<thead>
<tr>
<th>Identification</th>
<th>Exp. Proced. 1:</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flash chromatography: Pentane/toluene: 90/10 to 85/15.</td>
<td></td>
<td>80 %</td>
</tr>
<tr>
<td>Colorless liquid</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

$^1$H NMR (300 MHz, CDCl₃): $\delta = 7.61$ (d, $J = 8.1$ Hz, 1H), 6.52-6.48 (m 2H), 3.87 (s, 3H), 3.84 (s, 3H).

$^{19}$F NMR (282 MHz, CDCl₃): $\delta = -36.54$ (s, 3F).

4-[(trifluoromethyl)selanyl]benzene-1,3-diol 40b

$^1$H NMR (400 MHz, CDCl₃): $\delta = 7.52$ (d, $J = 8.5$ Hz, 1H), 6.58 (d, $J = 2.7$ Hz, 1H), 6.45 (dd, $J = 8.5$, 2.7 Hz, 1H), 6.25 (bs, 1H), 5.44 (bs, 1H).

$^{13}$C NMR (101 MHz, CDCl₃): $\delta = 160.6$ (C₂, 4), 158.8 (C₆), 140.3 (C₉), 121.9 (q, $J_{C,F} = 336$ Hz, C₇), 109.8 (C₁), 102.7 (C₃), 100.3 (C₅).

$^{19}$F NMR (376 MHz, CDCl₃): $\delta = -36.74$ (s, 3F).

4,6-bis[(trifluoromethyl)selanyl]benzene-1,3-diol 40c

$^1$H NMR (400 MHz, CDCl₃): $\delta = 8.01$ (s, 1H), 6.84 (s, 1H), 6.47 (bs, 2H).

$^{13}$C NMR (101 MHz, CDCl₃): $\delta = 162.1$ (C₂, 4), 149.3 (C₆), 121.7 (q, $J_{C,F} = 336$ Hz, C₇), 102.6 (C₃), 101.9 (bs C₁, 5).

$^{19}$F NMR (376 MHz, CDCl₃): $\delta = -36.47$ (s, 6F).

Elemental Analysis calc'd (%) for C₈H₆F₆O₂Se₂: C, 23.78; H, 1.00; Se, 39.09. Found: C, 23.67; H, 0.89; Se, 39.14.
4-[(trifluoromethyl)selanyl]naphthalen-1-ol 40d

<table>
<thead>
<tr>
<th>Identification:</th>
<th>Exp.Proced. 1:</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flash chromatography: Pentane/EtOAc 95/5 to 85/15.</td>
<td></td>
<td>75 %</td>
</tr>
<tr>
<td>Brown solid</td>
<td>m.p. 64-66 °C, calibration substance: azobenzol at 68.0°C.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ = 8.46 (d, $J = 8.4$ Hz, 1H), 8.26 (ddd, $J = 8.3$, 1.4, 0.7 Hz, 1H), 7.91 (d, $J = 7.8$ Hz, 1H), 7.66 (ddd, $J = 8.4$, 6.8, 1.4 Hz, 1H), 7.57 (ddd, $J = 8.3$, 6.8, 1.2 Hz, 1H), 6.80 (d, $J = 7.8$ Hz, 1H).</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$^{13}$C NMR (101 MHz, CDCl$<em>3$) $\delta$ = 154.8 (C$</em>{10}$), 139.4 (C$<em>8$), 136.8 (C$<em>4$), 128.3 (C$<em>2$), 128.3 (C$<em>3$), 126.1 (C$<em>9$), 125.3 (C$</em>{11}$), 122.7 (q, $J</em>{C,F} = 335$ Hz, C$</em>{11}$), 122.4 (C$</em>{9}$), 113.2 (q, $J</em>{C,F} = 2$ Hz, C$_2$), 108.9 (C$_9$).</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$^{19}$F NMR (376 MHz, CDCl$_3$) $\delta$ = -36.38 (s, 3F).</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Elemental Analysis calcd (%) for C$_{11}$H$_7$F$_3$OSe: C, 45.38; H, 2.42; Se, 27.12. Found: C, 45.59; H, 2.65; Se, 27.31.

N,N-dimethyl-4-[(trifluoromethyl)selanyl]aniline 40e

<table>
<thead>
<tr>
<th>Identification:</th>
<th>Exp.Proced. 1:</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>In accordance with the literature data$^{[6]}$</td>
<td></td>
<td>84 %</td>
</tr>
<tr>
<td>Brown solid</td>
<td>m.p. 64-66 °C, calibration substance: azobenzol at 68.0°C.</td>
<td></td>
</tr>
<tr>
<td>$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ = 7.57 (m, 2H), 6.68 (m, 2H), 3.01 (s, 6H).</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$^{19}$F NMR (282 MHz, CDCl$_3$) $\delta$ = -37.84 (s, 3F).</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

3-ethyl-2,5-dimethyl-4-[(trifluoromethyl)selanyl]-1H-pyrrole 40f

<table>
<thead>
<tr>
<th>Identification:</th>
<th>Exp.Proced. 1:</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flash chromatography: Pentane/Et$_2$O: 100/0 to 98/2.</td>
<td></td>
<td>67 %</td>
</tr>
<tr>
<td>Dark brown liquid</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$^1$H NMR (400 MHz, CDCl$<em>3$) $\delta$ = 7.85 (bs, 1H$</em>{NH}$), 2.44 (q, $J = 7.6$ Hz, 2H$_2$), 2.24 (s, 3H$_2$), 2.16 (s, 3H$_2$), 1.10 (t, $J = 7.6$ Hz, 3H$_2$).</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ = 129.6 (C$_1$), 129.4 (C$_4$), 123.0 (C$<em>2$), 122.3 (q, $J</em>{C,F} = 338$ Hz, C$<em>2$), 100.5 (q, $J</em>{C,F} = 2$ Hz, C$_2$), 18.2 (C$_8$), 15.4 (C$_9$), 11.4 (C$_9$), 10.5 (C$_2$).</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$^{19}$F NMR (376 MHz, CDCl$_3$) $\delta$ = -38.58 (s, 3F).</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Elemental Analysis calcd (%) for C$_9$H$_{12}$F$_3$NSe: C, 40.01; H, 4.48; N 5.18; Se, 29.23. Found: C, 39.76; H, 4.71; N 5.46; Se, 29.52.
Experimental Part

3-[(trifluoromethyl)selanyl]-1H-indole 40h

<table>
<thead>
<tr>
<th>Identification</th>
<th>Exp.Proced. 1:</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flash chromatography: Pentane/EtOAc: 90/10 to 85/15.</td>
<td>Yield 67 %</td>
<td></td>
</tr>
<tr>
<td>Brown solid</td>
<td>m.p. 64 °C, calibration substance: azobenzol at 68.0 °C</td>
<td></td>
</tr>
<tr>
<td>1H NMR (400 MHz, CDCl₃) δ = 8.44 (bs, 1H NH), 7.82 (m, 1H), 7.48 (d, J = 2.7 Hz, 1H), 7.43 (m, 1H), 7.36-7.30 (m, 2H)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>13C NMR (101 MHz, CDCl₃) δ = 136.1 (C₄), 133.0 (C₇), 130.1 (C₅), 123.4 (C₆), 122.4 (q, JₓC,F = 335 Hz, C₁₀), 121.6 (C₂), 120.1 (C₆), 111.7 (C₃), 93.2 (q, JₓC,F = 2 Hz, C₈)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>19F NMR (376 MHz, CDCl₃) δ = -37.54 (s, 3F)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Elemental Analysis calcld (%) for C₉H₆F₃NSe: C, 40.93; H, 2.29, N 5.30; Se, 29.90. Found: C, 41.02; H, 2.48, N 5.13; Se, 29.74.

4-bromo-3-[(trifluoromethyl)selanyl]-1H-indole 40g

<table>
<thead>
<tr>
<th>Identification</th>
<th>Exp.Proced. 1:</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flash chromatography: Pentane/EtOAc: 85/15 to 80/20.</td>
<td>Yield 91 %</td>
<td></td>
</tr>
<tr>
<td>Brown solid</td>
<td>m.p. 98-100°C, calibration substance: azobenzol at 68.0°C</td>
<td></td>
</tr>
<tr>
<td>1H NMR (400 MHz, CDCl₃): δ = 8.65 (bs, 1H NH), 7.56 (d, J = 2.8 Hz, 1H), 7.43-7.38 (m, 2H), 7.10 (t, J = 7.9 Hz, 1H)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>13C NMR (101 MHz, CDCl₃): δ = 137.1 (C₄), 135.5 (C₇), 126.6 (C₅), 126.2 (C₆), 124.2 (C₂), 122.0 (q, JₓC,F = 335 Hz, C₈), 115.0 (C₃), 111.3 (C₉), 93.3 (q, JₓC,F = 2 Hz, C₈)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>19F NMR (376 MHz, CDCl₃): δ = -38.70 (s, 3F)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Elemental Analysis calcld (%) for C₉H₅BrF₃NSe: C, 31.51; H, 1.47, Br 23.30, N 4.08; Se, 23.02. Found: C, 31.70; H, 1.70, Br 23.22, N 4.21; Se, 22.96.

Methyl 3-[(trifluoromethyl)selanyl]-1H-indole-5-carboxylate 40j

<table>
<thead>
<tr>
<th>Identification</th>
<th>Exp.Proced. 1:</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flash chromatography: Pentane/EtOAc: 80/20 to 70/30.</td>
<td>Yield 89 %</td>
<td></td>
</tr>
<tr>
<td>Pale pink solid</td>
<td>m.p. 170°C, calibration substance: benzanilid at 163.0°C</td>
<td></td>
</tr>
<tr>
<td>1H NMR (400 MHz, (CD₃)₂CO): δ = 11.34 (bs, 1H NH), 8.42 (s, 1H), 8.42 (s, 1H), 7.95-7.92 (m, 2H), 7.64 (d, J = 8.9 Hz, 1H), 3.91 (s, 3H)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>13C NMR (101 MHz, (CD₃)₂CO): δ = 167.8 (C₁₀), 140.3 (C₄), 137.1 (C₇), 130.6 (C₅), 124.7 (C₂), 124.2 (C₆), 123.4 (q, JₓC,F = 334 Hz, C₈), 122.6 (C₉), 113.1 (C₃), 93.5 (C₉), 52.2 (C₁₂)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>19F NMR (376 MHz, (CD₃)₂CO): δ = -38.93 (s, 3F)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Elemental Analysis calcld (%) for C₁₁H₈F₃NO₂Se: C, 41.01; H, 2.50, N 4.35; Se, 24.51. Found: C, 40.88; H, 2.66, N 4.16; Se, 24.81.
1-methyl-4-[(trifluoromethyl)selanyl]benzene 40l

<table>
<thead>
<tr>
<th>Identification</th>
<th>Exp.Proced. 1:</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="Structural formula of 1-methyl-4-[(trifluoromethyl)selanyl]benzene 40l" /></td>
<td>In accordance to literature[^6]</td>
<td>60 %</td>
</tr>
<tr>
<td>Flash chromatography: Cyclohexane/toluene 98/2.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pale pink solid</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ = 7.66 (m, 2H), 6.91 (m, 2H), 3.83 (s, 3H)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$^{19}$F NMR (282 MHz, CDCl$_3$) $\delta$ = −37.18 (s, 3F)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1,3,5-trimethyl-2-[(trifluoromethyl)selanyl]benzene 40l

<table>
<thead>
<tr>
<th>Identification</th>
<th>Exp.Proced. 1:</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="Structural formula of 1,3,5-trimethyl-2-[(trifluoromethyl)selanyl]benzene 40l" /></td>
<td>In accordance to literature data.[^7]</td>
<td>64 %</td>
</tr>
<tr>
<td>Flash chromatography: Pentane 100 %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ = 7.05 (s, 2H), 2.60 (s, 6H), 2.34 (s, 3H).</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$^{19}$F NMR (282 MHz, CDCl$_3$) $\delta$ = −35.16 (s, 3F).</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1-[(bromodifluoromethyl)selanyl]-2,4-dimethoxybenzene 41a

<table>
<thead>
<tr>
<th>Identification</th>
<th>Exp.Proced. 1:</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="Structural formula of 1-[(bromodifluoromethyl)selanyl]-2,4-dimethoxybenzene 41a" /></td>
<td>30 min. needed for BrF$_2$CSeCl formation</td>
<td>80 %</td>
</tr>
<tr>
<td>Flash chromatography: Cyclohexane/Toluene: 9/1.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Off white solid</td>
<td>m.p. &lt; 46°C, calibration substance: azobenzol at 68.0°C</td>
<td></td>
</tr>
<tr>
<td>$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ = 7.63 (m, 1H$_6$), 6.52-6.49 (m, 2H$_1,3$), 3.86 (s, 3H$_8$), 3.84 (s, 3H$_7$).</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ = 163.8 (C$_2$), 161.2 (C$_4$), 140.5 (C$<em>6$), 109.3 (t, $J</em>{C,F}$ = 359 Hz, C$_9$), 106.9 (C$_1$), 105.8 (C$_3$), 99.2 (C$_5$), 56.2 (C$_8$), 55.6 (C$_7$).</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$^{19}$F NMR (376 MHz, CDCl$_3$) $\delta$ = -18.20 (s, 2F).</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Elemental Analysis calcd (%) for C$_9$H$_9$BrF$_2$O$_2$Se: C, 31.24; H, 2.62; Br 23.09; Se, 22.82. Found: C, 31.49; H, 2.92; Br 23.17; Se, 22.96.

4-[(bromodifluoromethyl)selanyl]benzene-1,3-diol 41b

<table>
<thead>
<tr>
<th>Identification</th>
<th>Exp.Proced. 1:</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="Structural formula of 4-[(bromodifluoromethyl)selanyl]benzene-1,3-diol 41b" /></td>
<td>30 min. needed for BrF$_2$CSeCl formation</td>
<td>88 %</td>
</tr>
<tr>
<td>Flash chromatography: Cyclohexane/Toluene: 9/1.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pale yellow solid</td>
<td>m.p. 116-118 °C, calibration substance: acetanilide 114.5°C</td>
<td></td>
</tr>
<tr>
<td>$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ = 7.52 (d, $J = 8.5$ Hz, 1H$_6$), 6.58 (dd, $J = 2.7$, 0.5 Hz, 1H$<em>6$), 6.45 (dd, $J = 8.5$, 2.7, 0.5 Hz, 1H$<em>1$), 6.27 (bs, 1H$</em>{OH}$), 5.52 (bs, 1H$</em>{OH}$).</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ = 161.0 (C$_2$), 158.8 (C$_4$), 140.3 (C$_6$), 109.7 (C$<em>9$), 108.8 (t, $J</em>{C,F}$ = 359 Hz, C$_9$), 104.4 (C$_1$), 102.7 (C$_3$).</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$^{19}$F NMR (376 MHz, CDCl$_3$) $\delta$ = -18.20 (s, 2F).</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Elemental Analysis calcd (%) for C$_7$H$_5$BrF$_2$O$_2$Se: C, 26.44; H, 1.59; Br 25.13; Se, 24.83. Found: C, 26.53; H, 1.87; Br 25.39; Se, 24.97.
4-[(bromodifluoromethyl)selanyl]naphthalen-1-ol 41d

**Identification:**

Flash chromatography: Cyclohexane/EtOAc: 95/5.

**Exp.Proced. 1:** 130 min. needed for BrF₂CSeCl formation

<table>
<thead>
<tr>
<th>Yield</th>
<th>81 %</th>
</tr>
</thead>
</table>

| m.p. 96°C, calibration substance: azobenzol at 68.0°C |

| Brown solid |  |

| δ | 8.46 (bd, J = 8.5 Hz, 1H₈), 8.26 (ddd, J = 8.2, 1.4, 0.7 Hz, 1H₆), 7.92 (d, J = 7.8 Hz, 1H₄), 7.65 (ddd, J = 8.5, 6.8, 1.4 Hz, 1H₃), 7.56 (ddd, J = 8.2, 6.8, 1.2 Hz, 1H₂), 6.82 (d, J = 7.8 Hz, 1H₁), 5.99 (bs, 1H₉). |

| 19F NMR (376 MHz, CDCl₃) δ | -18.09 (s, 2F). |

**Elemental Analysis**

Calcd (%) for C₁₁H₇BrF₂OSe: C, 37.53; H, 2.00; Br 22.70; Se, 22.43. Found: C, 37.28; H, 1.87; Br 22.82; Se, 22.73.

4-[(bromodifluoromethyl)selanyl]-N,N-dimethylaniline 41e

**Identification:**

Purification: Trituration in a small quantity of pentane and filtration

<table>
<thead>
<tr>
<th>Yield</th>
<th>72 %</th>
</tr>
</thead>
</table>

| m.p. 76-78°C, calibration substance: azobenzol at 68.0°C |

| Yellow solid |  |

| δ | 7.60 (d, J = 8.5 Hz, 2H₂, 4), 6.74 (d, J = 8.5 Hz, 2H₁, 3), 3.02 (s, 6H₉, 10). |

| 19F NMR (376 MHz, CDCl₃) δ | -19.35 (s, 2F). |

**Elemental Analysis**

Calcd (%) for C₉H₁₀BrF₂NSe: C, 32.85; H, 3.06; Br 24.28; N 4.26; Se, 24.00. Found: C, 32.69; H, 3.11; Br 24.20; N 4.35; Se, 23.79.

3,4-bis[(bromodifluoromethyl)selanyl]-2,5-dimethyl-1H-pyrrole 41g

**Identification:**

Flash chromatography: Cyclohexane/EtOAc: 9/1.

<table>
<thead>
<tr>
<th>Yield</th>
<th>76 %</th>
</tr>
</thead>
</table>

| Yellow pale oil |  |

| δ | 8.53 (bs, 1HNH), 2.45 (s, 6H₅, 6). |

| 19F NMR (376 MHz, CDCl₃) δ | -18.97 (s, 4F). |

**Elemental Analysis**

Calcd (%) for C₈H₇Br₂F₄NSe₂: C, 18.81; H, 1.38; Br 31.28; N 2.74; Se, 30.91. Found: C, 19.05; H, 1.57; Br 31.33; N 2.59; Se, 30.98.
Experimental Part

3-[(bromodifluoromethyl)selanyl]-1H-indole 41h

**Identification:**

- **Exp.Proced. 1:** 30 min. needed for BrF₂CSeCl formation.
- **Yield:** 87%

- Flash chromatography: Cyclohexane/EtOAc: 9/1 - 8/2.
- Brown solid m.p. 50°C, calibration substance: azobenzol at 68.0°C
- ¹H NMR (400 MHz, CDCl₃) δ = 8.54 (bs, 1H NH), 7.81 (m, 1H₅), 7.53 (d, J = 2.7 Hz, 1H₆), 7.44 (m, 1H₇), 7.34-7.27 (m, 2H₁, ₂).
- ¹³C NMR (101 MHz, CDCl₃) δ = 136.1 (C₄), 133.2 (C₇), 130.0 (C₅), 123.5 (C₁), 121.7 (C₂), 120.3 (C₃), 111.6 (C₆), 109.9 (t, J₉,F = 359 Hz, C₉), 98.0 (C₈).
- ¹⁹F NMR (376 MHz, CDCl₃) δ = -18.92 (s, 2F).

**Elemental Analysis**
Calcd (%) for C₉H₆BrF₂NSe: C, 33.26; H, 1.86, Br 24.58, N 4.31 Se 24.29. Found: C, 33.18; H, 2.02, Br 24.90, N 4.49; Se, 24.21.

4-bromo-3-[(bromodifluoromethyl)selanyl]-1H-indole 41i

**Identification:**

- **Exp.Proced. 1:** 30 min. needed for BrF₂CSeCl formation.
- **Yield:** 76%

- Flash chromatography: Cyclohexane/EtOAc: 8/2.
- Dark brown solid m.p. 90-92°C, calibration substance: azobenzol at 68.0°C
- ¹H NMR (400 MHz, CDCl₃) δ = 8.67 (bs, 1H NH), 7.60 (d, J = 2.8 Hz, 1H₇), 7.44-7.40 (m, 2H₁, ₃), 7.11 (t, J = 7.9 Hz, 1H₂).
- ¹³C NMR (101 MHz, CDCl₃) δ = 137.0 (C₄), 135.8 (C₇), 126.7 (C₁), 126.2 (C₅), 124.2 (C₂), 115.1 (C₆), 111.3 (C₃), 109.7 (t, J₉,F = 359 Hz, C₉), 98.0 (C₈).
- ¹⁹F NMR (376 MHz, CDCl₃) δ = -20.24 (s, 2F).

**Elemental Analysis**

Methyl 3-[(bromodifluoromethyl)selanyl]-1H-indole-5-carboxylate

**Identification:**

- **Exp.Proced. 1:** 30 min. needed for BrF₂CSeCl formation.
- **Yield:** 94%

- Purification: Trituration in a small quantity of pentane and filtration
- Pale pink solid m.p. 188-190°C, calibration substance: salophen at 191.0°C
- ¹H NMR (400 MHz, CDCl₃) δ = 8.83 (bs, 1H NH), 8.51 (bs, 1H₆), 7.64 (m, 1H₇), 7.44 (m, 1H₅), 7.34-7.27 (m, 2H₁, ₂).
- ¹³C NMR (101 MHz, CDCl₃) δ = 167.9 (C₁₀), 138.8 (C₄), 134.5 (C₇), 129.8 (C₅), 124.9 (C₂), 120.0 (C₆), 123.2 (C₃), 111.5 (C₆), 109.5 (t, J₉,F = 359 Hz, C₉), 99.5 (C₈), 52.3 (C₁₁).
- ¹⁹F NMR (376 MHz, CDCl₃) δ = -19.07 (s, 2F).

**Elemental Analysis**
Calcd (%) for C₁₁H₈BrF₂NO₂Se: C, 34.49; H, 2.11, Br 20.86, N 3.66 Se 20.61. Found: C, 34.37; H, 2.34, Br 21.05, N 3.75; Se, 20.85.
### 4-[(pentfluoroethyl)selenyl]benzene-1,3-diol 42b

<table>
<thead>
<tr>
<th>Identification:</th>
<th>Exp.Proced. 1:</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flash chromatography: Pentane/Acetone: 80/20.</td>
<td></td>
<td>86 %</td>
</tr>
<tr>
<td>White solid</td>
<td>m.p. 92°C, calibration substance: benzil at 95.0°C</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>NMR:</th>
<th>1H</th>
<th>13C</th>
<th>19F</th>
</tr>
</thead>
<tbody>
<tr>
<td>δ</td>
<td>7.49 (d,  J = 8.5 Hz, 1H6), 6.58 (d,  J = 2.7 Hz, 1H1), 6.44 (dd,  J = 8.5, 2.7 Hz, 1H1), 6.22 (bs, 1H1O,H), 5.42 (bs, 1H1O,H).</td>
<td>160.7 (C2), 159.2 (C4), 140.8 (C6), 118.7 (qt, J_{C,F} = 286 Hz, J_{C,F} = 34 Hz, C8), 115.4 (tq, J_{C,F} = 305 Hz, J_{C,F} = 42 Hz, C8), 109.8 (C1), 102.7 (C3), 102.7 (C3), 99.2 (t, J_{C,F} = 3 Hz, C3).</td>
<td>-82.80 (t, J_{F,F} = 3.8 Hz, 3F8), -91.61 (q, J_{F,F} = 3.8 Hz, 2F7).</td>
</tr>
</tbody>
</table>

**Elemental Analysis**
calcd (%) for C_{8}H_{5}F_{5}O_{2}Se: C, 31.29; H, 1.64; Se, 25.71. Found: C, 31.19; H, 1.77; Se, 26.03.

### 4-[(heptafluoropropyl)selenyl]benzene-1,3-diol 43b

<table>
<thead>
<tr>
<th>Identification:</th>
<th>Exp.Proced. 1:</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flash chromatography: Pentane/Acetone: 80/20.</td>
<td></td>
<td>88 %</td>
</tr>
<tr>
<td>White solid</td>
<td>m.p. 72°C, calibration substance: azobenzol at 68.0°C</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>NMR:</th>
<th>1H</th>
<th>13C</th>
<th>19F</th>
</tr>
</thead>
<tbody>
<tr>
<td>δ</td>
<td>7.50 (d,  J = 8.5 Hz, 1H6), 6.58 (s,  J = 2.7 Hz, 1H1), 6.45 (dd,  J = 8.5, 2.7 Hz, 1H1), 6.23 (s, 1H1O,H), 5.51 (s, 1H1O,H).</td>
<td>160.8 (C2), 159.3 (C4), 141.0 (C6), 118.2 (tr, J_{C,F} = 306 Hz, J_{C,F} = 40 Hz, C8), 117.5 (qt, J_{C,F} = 289 Hz, J_{C,F} = 35 Hz, C9), 108.8 (tsex, J_{C,F} = 263 Hz, J_{C,F} = 38 Hz, C9), 102.7 (C3), 99.1 (C3).</td>
<td>-79.85 (t, J_{F,F} = 9.2 Hz, 3F9), 122.28 (s, 2F8).</td>
</tr>
</tbody>
</table>

**Elemental Analysis**
calcd (%) for C_{9}H_{5}F_{7}O_{2}Se: C, 30.27; H, 1.41; Se, 22.11. Found: C, 30.50; H, 1.71; Se, 22.33.

### 3-[(pentfluoroethyl)selenyl]-1H-indole

<table>
<thead>
<tr>
<th>Identification:</th>
<th>Exp.Proced. 1:</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flash chromatography: Pentane/EtOAc: 90/10.</td>
<td></td>
<td>88 %</td>
</tr>
<tr>
<td>Pale pink solid</td>
<td>m.p. 74-76°C, calibration substance: azobenzol at 68.0°C</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>NMR:</th>
<th>1H</th>
<th>13C</th>
<th>19F</th>
</tr>
</thead>
<tbody>
<tr>
<td>δ</td>
<td>8.51 (bs, 1H NH), 7.79 (m, 1H 6), 7.50 (d,  J = 2.7 Hz, 1H1), 7.43-7.28 (m, 2H1, 2).</td>
<td>136.1 (C4), 133.6 (C7), 130.4 (C8), 123.4 (C1), 121.7 (C2), 120.2 (C4), 119.1 (qt, J_{C,F} = 286 Hz, J_{C,F} = 35 Hz, C10), 115.4 (tq, J_{C,F} = 304 Hz, J_{C,F} = 41 Hz, C8), 111.6 (C6), 92.1 (t, J_{C,F} = 4 Hz, C6).</td>
<td>-82.75 (t, J_{F,F} = 3.9 Hz, 3F10), -92.62 (q, J_{F,F} = 3.9 Hz, 2F9).</td>
</tr>
</tbody>
</table>

**Elemental Analysis**
calcd (%) for C_{11}H_{6}F_{7}NSe: C, 36.28; H, 1.66; N 3.85; Se, 21.69. Found: C, 36.14; H, 1.49; N 4.12; Se, 21.51
3-[(heptafluoropropyl)selanyl]-1H-indole

<table>
<thead>
<tr>
<th>Identification:</th>
<th>Exp.Proced. 1:</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Flash chromatography: Pentane/EtOAc: 90/10.</td>
<td>89 %</td>
</tr>
<tr>
<td>Redish solid</td>
<td>m.p. 46-48°C, calibration substance: azobenzol at 68.0°C</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1H NMR (400 MHz, CDCl₃) δ = 8.49 (bs, 1H NH), 7.82 (m, 1H₂), 7.48 (d, J = 2.7 Hz, 1H₇), 7.42 (m, 1H₂), 7.36-7.30 (m, 2H₂).</td>
<td></td>
</tr>
<tr>
<td></td>
<td>13C NMR (101 MHz, CDCl₃) δ = 136.2 (C₂), 133.8 (C₄), 130.5 (C₄), 123.4 (C₃), 121.7 (C₂), 120.2 (C₆), 118.1 (tt, J₇,F = 305 Hz, J₉,F = 38 Hz, C₉), 117.7 (qt, J₂,F = 289 Hz, J₆,F = 35 Hz, C₁₁), 111.7 (C₃), 109.0 (tsex, J₇,F = 263 Hz, J₉,F = 38 Hz, C₁₀), 92.1 (t, J₈,F = 4 Hz, C₈).</td>
<td></td>
</tr>
<tr>
<td></td>
<td>19F NMR (282 MHz, CDCl₃) δ = -79.87 (t, J₈,F = 9.1 Hz, 3F₁₁), -88.46 (qt, J₉,F = 9.1 Hz, 2F₉), -122.42 (bs, 2F₁₀).</td>
<td></td>
</tr>
</tbody>
</table>

Elemental Analysis Calcd (%) for C₁₀H₆F₅NSe: C, 38.24; H, 1.93; N 4.46; Se, 25.14. Found: C, 38.13; H, 2.14; N 4.71; Se, 25.34.

Experimental procedure 3:
To a flask equipped with a magnetic stirrer is added 2e (0.4 mmol, 1.0 equiv) and dry THF (0.2 mL). The solution is cooled to 0 °C, followed by the addition of sulfuryl chloride (0.4 mmol, 1.0 equiv) and dry THF (0.2 mL). The reaction mixture was stirred at 0 °C for 45 min, and the nucleophile (0.4 mmol, 1.0 equiv) was added. The reaction mixture was stirred at 0 °C until complete conversion of the intermediate 2e (the conversion takes around 2 h; it was checked by 19F NMR with PhOCF₃ as internal standard). The reaction mixture was then partitioned between water and Et₂O, and the aqueous layer was extracted with Et₂O. The combined organic layers were washed with brine, dried over MgSO₄, filtered, and concentrated to dryness. After the removal of the solvent under vacuum the crude residue is purified via silica gel column chromatography (if not differently indicated).

4-[(difluoromethyl)selanyl]benzene-1,3-diol 44b

<table>
<thead>
<tr>
<th>Identification:</th>
<th>Exp.Proced. 3:</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Flash chromatography: Pentane/EtOAc: 90/10 – 85/15.</td>
<td>83 %</td>
</tr>
<tr>
<td>Pale yellow oil</td>
<td>m.p. 65°C, 1H₂, 6.5 (d, J = 2.6 Hz, 1H₁), 6.43 (dd, J = 8.5, 2.6 Hz, 1H₁), 6.37 (bs, 1H₂).</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1H NMR (400 MHz, CDCl₃) δ = 7.46 (d, J = 8.5 Hz, 1H₂), 6.95 (t, J₆,F = 55.2 Hz, 1H₂), 6.57 (d, J = 2.6 Hz, 1H₁), 6.43 (dd, J = 8.5, 2.6 Hz, 1H₁), 6.37 (bs, 1H₂).</td>
<td></td>
</tr>
<tr>
<td></td>
<td>13C NMR (101 MHz, CDCl₃) δ = 159.9 (Cₙ), 158.5 (Cₙ), 140.0 (Cₙ), 116.4 (t, J₉,F = 292 Hz, Cₙ), 109.6 (Cₙ), 102.5 (Cₙ), 100.5 (t, J₉,F = 3 Hz, Cₙ).</td>
<td></td>
</tr>
<tr>
<td></td>
<td>19F NMR (282 MHz, CDCl₃) δ = -90.05 (d, J₆,F = 55.4 Hz).</td>
<td></td>
</tr>
</tbody>
</table>

Elemental Analysis Calcd (%) for C₇H₆F₂O₂Se: C, 35.17; H, 2.53; Se, 33.03. Found: C, 34.94; H, 2.62; Se, 32.88.
### 3-[(difluoromethyl)selanyl]-1H-indole

**Identification:**

Flash chromatography: Pentane/EtOAc: 75/25.

**Yield** 83%

<table>
<thead>
<tr>
<th>Compound</th>
<th>Flash chromatography</th>
<th>Elemental Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pentane/EtOAc: 75/25</td>
<td>Calcd (%) for C9H7F2NSe: C, 43.92; H, 2.87, N 5.69; Se, 32.08. Found: C, 43.75; H, 3.12, N 5.74; Se, 32.28.</td>
</tr>
</tbody>
</table>

#### Compounds

- **Methyl 2-[(2,4-dihydroxyphenyl)selanyl]-2,2-difluoroacetate 45b**

  **Identification:**
  
  Flash chromatography: Cyclohexane/EtOAc: 8/2.

  **Yield** 60%

<table>
<thead>
<tr>
<th>Compound</th>
<th>Flash chromatography</th>
<th>Elemental Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cyclohexane/EtOAc: 8/2</td>
<td>Calcd (%) for C9H8F2O4Se: C, 36.38; H, 2.71; Se, 26.58. Found: C, 36.63; H, 2.89; Se, 26.48.</td>
</tr>
</tbody>
</table>

- **Methyl 2,2-difluoro-2-(1H-indol-3-ylselanyl)acetate 45h**

  **Identification:**
  
  Flash chromatography: Pentane/EtOAc 80/20 to 75/25

  **Yield** 89%

<table>
<thead>
<tr>
<th>Compound</th>
<th>Flash chromatography</th>
<th>Elemental Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pentane/EtOAc 80/20 to 75/25</td>
<td>Calcd (%) for C11H9F2NO2Se: C, 43.44; H, 2.98, N 4.61; Se, 25.96. Found C 43.60; H, 3.22, N 4.36; Se, 26.06.</td>
</tr>
</tbody>
</table>

---
4-((((benzenesulfonyl)difluoromethyl)selanyl)benzene-1,3-diol

<table>
<thead>
<tr>
<th>Identification:</th>
<th>Exp.Proced. 3:</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Purification: Trituration in a small quantity of pentane and filtration</td>
<td>90%</td>
</tr>
<tr>
<td></td>
<td>Off white solid</td>
<td>mp 149–151 °C, calibration substance: acetanilide at 114.5 °C</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1H NMR (400 MHz, CDCl₃) δ = 7.97 (m, 2H), 7.81 (m, 1H), 7.67 (m, 2H), 7.35 (d, J = 8.5 Hz, 1H), 6.39 (d, J = 2.6 Hz, 1H), 6.28 (dd, J = 8.5, 2.6 Hz, 1H)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>13C NMR (101 MHz, CDCl₃) δ = 163.2 (C₂), 162.0 (C₆), 142.0 (C₄), 136.8 (C₁₁), 133.5 (C₈), 131.9 (C₉), 130.6 (C₁₀), 126.4 (t, J₉,F = 340 Hz, C₇), 109.3 (C₃), 103.6 (C₉), 99.5 (t, J₉,C = 2 Hz, C₅)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>19F NMR (282 MHz, CDCl₃) δ = −75.51 (s, 2F)</td>
</tr>
</tbody>
</table>

Elemental Analysis calcld (%) for C₁₃H₁₀F₂O₄Se: C, 41.17; H, 2.66, S 8.45 Se 20.82. Found: C, 41.27; H, 2.90, S 8.25; Se, 20.96.

3-((((benzenesulfonyl)difluoromethyl)selanyl)-1H-indole

<table>
<thead>
<tr>
<th>Identification:</th>
<th>Exp.Proced. 3:</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Purification: Trituration in a small quantity of pentane and filtration</td>
<td>90%</td>
</tr>
<tr>
<td></td>
<td>Pale brown solid</td>
<td>mp 122–124 °C, calibration substance: acetanilide at 114.5 °C</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1H NMR (400 MHz, CDCl₃) δ = 8.75 (bs, 1H, NH), 7.95 (d, J = 7.7 Hz, 1H), 7.79 (m, 1H), 7.74 (t, J = 7.7 Hz, 1H), 7.57 (t, J = 7.7 Hz, 2H), 7.52 (m, 1H), 7.41 (m, 1H), 7.29–7.25 (m, 2H)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>13C NMR (101 MHz, CDCl₃) δ = 136.1 (C₄), 135.5 (C₁₃), 134.2 (C₉), 132.0 (C₁₀), 130.8 (C₁₁), 130.5 (C₃), 129.4 (C₁₂), 124.9 (t, J₉,F = 342 Hz, C₉), 123.2 (C₈), 121.5 (C₂), 120.2 (C₅), 111.8 (C₉), 92.3 (m, C₈)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>19F NMR (282 MHz, CDCl₃) δ = −78.03 (s, 2F)</td>
</tr>
</tbody>
</table>

Elemental Analysis calcld (%) for C₁₅H₁₁F₂NO₂Se: C, 46.64; H, 2.87, N 3.63, S 8.30 Se 20.44. Found: C, 46.43; H, 2.74, N 3.71, S 8.14; Se, 20.27.

3-((((difluoro(D)methyl)selanyl)1H-indole

**Experimental procedure:**
To a flask are added magnesium turnings (93 mg, 3.9 mmol, 10 equiv) and iodine (14.8 mg, 0.12 mmol, 30 mol %), and is heated up with a heat gun for 10 min under stirring. The flask is evacuated and refilled with nitrogen three times before adding a solution of 46h (150 mg, 0.38 mmol, 1 equiv) in CD₃OD (3.8 mL, 0.1 M). The mixture is stirred for 1.5 h at 23 °C, then a second portion of magnesium (187 mg, 7.8 mmol, 20 equiv) is added and the reaction is stirred for a further 2 h. A saturated aqueous solution of NH₄Cl (10 mL) is added, and the reaction mixture is extracted with Et₂O (15 mL × 3). The combined organic layers are washed with water.
and brine, dried over MgSO₄, filtered, and concentrated to dryness. After the removal of the solvent under vacuum the crude residue is purified via silica gel column chromatography.

<table>
<thead>
<tr>
<th>Identification</th>
<th>Exp.Proced. 3:</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yellow oil</td>
<td>Flash chromatography: Pentane/EtOAc 85/15 to 75/25</td>
<td>58 %</td>
</tr>
</tbody>
</table>

**1H NMR (400 MHz, CDCl₃)** δ = 8.43 (bs, 1H NH), 7.79 (m, 1H), 7.44−7.41 (m, 2H), 7.33−7.26 (m, 2H).

**13C NMR (101 MHz, CDCl₃)** δ = 136.2 (C₄), 132.2 (C₇), 130.4 (C₅), 123.3 (C₃), 121.3 (C₂), 120.2 (C₆), 116.9 (tt, Jₐ,F = 289 Hz, Jₐ,D = 32 Hz, C₈), 93.3 (t, Jₐ,F = 4 Hz, C₉).

**19F NMR (282 MHz, CDCl₃)** δ = −91.33 (t, Jₐ,D = 8.5 Hz, 2F)

**Elemental Analysis** calcd (%) for C₉H₆DF₂NSe: C, 43.74; H, 3.26; N 5.67; Se, 31.95. Found: C, 43.54; H, 2.98; N 5.80; Se, 32.06.
References:


**English Abstract:**

During the last years a lot of progress has been done in the fluorine field. Various groups contributed by developing methodologies or fluorinated reagents that find a wide use nowadays within the scientific community. Among them, we were concentrated in exploiting the association of fluorine with heteroatoms. Such an interest is totally comprehensible considering the changes that fluorine is able to induce to organic compounds. Fluorine is well known for increasing the lipophilicity of the compounds bearing it and one of the most lipophilic motifs is \( \text{SCF}_3 \). During the last years we have developed three bench-stable trifluoromethylthiolating reagents that were used in synthetic chemistry from us and other groups as well.

Starting from the results obtained in this field, recently we expanded our interest towards the development of reagents that act as fluoroalkylthiolating reagents in electrophilic reactions. Thus, two reagents bearing a \( \text{SCF}_2\text{FG} \) (FG = functional group) motif were developed and successfully used in various reactions. Thus, such reagents not only opened the way to access functionalized new fluoroalkylthiolated molecules, but also the obtained compounds could be post-transformed.

In this dissertation we also studied the association of fluorine with another chalcogen, namely Selenium. Fluoroalkylselenolated compounds are less studied respect to the thiolated analogs. Herein, we report a new one-pot strategy to access various trifluoromethylselenolated compounds through in situ formation of \( \text{CF}_3\text{SeCl} \) starting from the easy-to-handle pre-reagent trifluoromethyl benzyl selenide. Also analogs and homologs of the reagent were synthesized and successfully used in reactions leading \( \text{RCF}_2\text{Se} \)-adducts.

Some of the synthesized compounds were also used as starting materials in nucleophilic \( ^{18}\text{F} \)-labeling reactions. Thus we accessed for the first time to \( \text{SeCF}_2^{^{18}\text{F}} \) molecules opening the way to selenium in \( ^{18}\text{F} \) radiolabeled products.

**Key words**: (benzenesulfonyl)difluoromethanesulfenamide, difluoromethylthiolation, \( ^{18}\text{F} \)-labeling, trifluoromethylselenolation, fluoroalkylselenolation, trifluoromethaneselenyl chloride.

**French Abstract**:

Au cours des dernières années, de nombreux progrès ont été réalisés dans le domaine de la chimie du fluor. Diverses équipes ont contribué au développement de nouvelles méthodologies ainsi qu’à la mise au point de réactifs de fluoration trouvant de larges applications au sein de la communauté scientifique. Au cours de ces travaux, nous nous sommes intéressés à l’association du fluor à des hétéroatomes. Cet intérêt s’explique par les propriétés de ces groupements. En effet, ils permettent ainsi d’augmenter la lipophilie des molécules sur lesquelles ils sont introduits, en particulier le motif \( \text{SCF}_3 \). Durant les dernières années, nous avons développé trois réactifs de
trifluorométhylthiolation stables qui ont pu être par la suite utilisé en synthèse aussi bien par notre groupe que par d'autres équipes.

A partir de ces résultats, nous avons récemment étendu cette thématique vers le développement de réactifs de fluoroalkylthiolation en conditions électrophiles. Ainsi, deux réactifs portant le motif SCF₂FG (FG=groupe fonctionnel) ont été développés et utilisés avec succès dans diverses réactions. Aux vues de ces résultats, ces réactifs permettent l'accès à de nouvelles molécules fluoroalkylthiolées fonctionnalisées ; mais également à leur post-transformation.

Nous avons également étudié l'association du fluor avec un autre élément de la famille des chalcogènes ; le sélénium. Les composés fluoroalkylséléniés sont moins étudiés que leurs analogues soufrés. Dans ces travaux, nous reportons une nouvelle stratégie monotopique pour accéder à diverses molécules trifluorométhylséléniés via la formation in situ de l'intermédiaire CF₃SeCl à partir d'un pré-réactif facile à manipuler, le trifluorométhylséléniure de benzyle. Des analogues et homologues de ce pré-réactif ont été synthétisés et utilisés pour conduire à des composés SeCF₂R. Certains des produits synthétisés ont été employés comme réactifs de départ dans des réactions nucléophiles de radiomarquage au fluor-18. Ainsi, nous avons pu accéder pour la première fois à des molécules comportant le groupement SeCF₂¹⁸F offrant la possibilité d'utiliser le sélénium dans des molécules marquées au fluor-18.