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Syntéza a reaktivita hypervalentních fluoridů síry
Synthesis and reactivity of hypervalent sulfur fluorides

Disertační práce

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Doctoral thesis

Supervisor: Ing. Petr Beier, Ph.D.

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Prohlášení:

Prohlašuji, že jsem závěrečnou práci zpracoval samostatně a že jsem uvedl všechny použité informační zdroje a literaturu. Tato práce ani její podstatná část nebyla předložena k získání jiného nebo stejného akademického titulu.

V Praze, 26.02.2019

Podpis

“So remember to look up at the stars and not down at your feet. Try to make sense of what you see and wonder about what makes the universe exist. Be curious. And however difficult life may seem, there is always something you can do and succeed at. It matters that you don’t just give up. Unleash your imagination. Shape the future.”

Stephen Hawking – *Brief Answers to the Big Questions* (2018)

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Abbreviations

Å	Ångström
Acac	acetylacetonate
anh	anhydrous
Atm	atmosphere
DAST	diethylaminosulfur trifluoride
DCM	dichloromethane
DME	dimethoxyethane
DMF	dimethylformamide
equiv	equivalent(s)
et al.	et alii (Latin), and others
EWGs	electron withdrawing groups
GC-MS	gas chromatography–mass spectrometry
IC_{50}	half maximal inhibitory concentration
IC_{90}	inhibitory concentration 90 (90% response)
IUPAC	International Union of Pure and Applied Chemistry
LCDs	Liquid Crystal displays
LED	Light-emitting diode
m.p.	melting point
mCPBA	*meta*-Chloroperoxybenzoic acid
NMR	Nuclear Magnetic Resonance
ox.	oxidant
pin_2B_2	Bis(pinacolato)diboron
rt	room temperature
S_EAr	Electrophilic aromatic substitution
S_NAr	Nucleophilic aromatic subsitution
TBAF	tetra-*n*-butylammonium fluoride
TEMPO	(2,2,6,6-Tetramethylpiperidin-1-yl)oxyl
TMINO	1,1,3-trimethylisoindole N-oxide
VNS	Vicarious nucleophilic substitution

Abstract

The pentafluorosulfanyl (SF_5) group displays remarkable and unique properties, including large dipole moment, high electronegativity, high thermal and chemical stability, as well as high lipophilicity. However, only a few synthetic methods for the preparation of aromatic pentafluorosulfanyl building blocks have been developed to date. This work aims at improving availability and accessibility of aryl sulfurpentafluoride building blocks.

In the first part of the work, the synthesis of aryl sulfurpentafluorides by the direct fluorination of diaryl disulfides with elemental fluorine is described. Nowadays, this synthetic strategy is used by industry on a multi-kilogram scale. However, the scope of the reaction is only limited to 3- and 4-nitro-1-(pentafluorosulfanyl)benzenes. In this work, the synthesis of various *para*-, *meta*- and *ortho*-substituted-(pentafluorosulfanyl)benzenes following the same approach was carried out.

In the second part, the derivatization of aryl sulfurpentafluoride building blocks was investigated. Direct fluorination of 3-nitro-1-(pentafluorosulfanyl)benzene afforded 3-fluoro-5-nitro-1-(pentafluorosulfanyl)benzene. The titled compound was derivatized by two different processes: nucleophilic aromatic substitution (S_NAr) of fluorine and vicarious nucleophilic substitution of hydrogen (VNS).

Abstrakt

Pentafluorsulfanylová skupina vykazuje pozoruhodné a jedinečné vlastnosti, zahrnující velký dipólový moment, vysokou elektronegativitu, lipofilitu nebo termální a chemickou stabilitu. Doposud bylo nicméně vyvinuto pouze několik syntetických metod pro přípravu arylpentafluorsulfanylových sloučenin. Cílem této práce je zvýšení dostupnosti a přístupnosti arylpentafluorsulfanylových sloučenin.

V první části této práce je popsána syntéza arylsulfopentafluoridů pomocí fluorace diaryldisulfidů elementárním fluorem. Dnes se tato syntetická strategie používá v průmyslu v multikilogramovém měřítku. Tato syntetická metoda je však omezena pouze na 3- a 4-nitro-1-(pentafluorsulfanyl)benzeny. Stejným způsobem byla v této práci provedena syntéza různě *para*-, *meta*- a *ortho*-substituovaných-(pentafluorsulfanyl)benzenů.

Druhá část práce se zabývá derivatizací arylsulfopentafluoridů, kde pomocí přímé fluorace 3-nitro-1-(pentafluorsulfanyl)benzenu vzniká 3-fluor-5-nitro-1-(pentafluorsulfanyl)benzen. Tato sloučenina byla dále drivatizována dvěma odlišnými přístupy: nukleofilní aromatickou substitucí (S_NAr) a pomoci takzvané VNS reakce.

1 Introduction

The presence of fluorine atoms in the structures of organic molecules has, quite often, dramatic consequences on the physicochemical properties in comparison with the parent non-fluorinated analogues.[1,2] Fluoromethane, synthesised by Dumas and Péligot in 1835 from the reaction of dimethyl sulfate and anhydrous potassium fluoride, can be considered the first synthetic organic fluoride.[3–5] Progress in the introduction of fluorine atoms into organic molecules during the following century was slow. This can be explained by the lack of synthetic methods and the difficulty in harnessing important fluorinating reagents such as elemental fluorine (Moissan,[6] 1886) or anhydrous hydrogen fluoride (HF).[7] The development of the Balz-Schiemann method,[8] the control of reactivity of fluorine (F_2) in organic reactions,[9] the synthesis of anhydrous hydrogen fluoride[10,11] and the discovery of polytetrafluoroethylene (PTFE) set the basis of a nowadays vast and expanding field.[9]

Over the time, many organofluorine compounds have been synthesised, including some highly polyfluorinated scaffolds, such as -CF_3, -OCF_3, -SCF_3, -CH_2CF_3 or -CF_2CF_3 and ultimately of relevance to this work -SF_5.[12–14] The discovery of practical synthetic methods[15–17] and applications[12] of pentafluorosulfanyl derivatives stimulated the scientific community for further development of this chemistry. In 2015, the preparation and utility of organic pentafluorosulfanyl-containing compounds were extensively reviewed by Welch and co-workers.[12] Nevertheless, the number of synthetic methods and commercially available SF_5-containing building blocks is still very limited. In this context, this work focuses on improving availability and accessibility of these hypervalent sulfur pentafluorides.

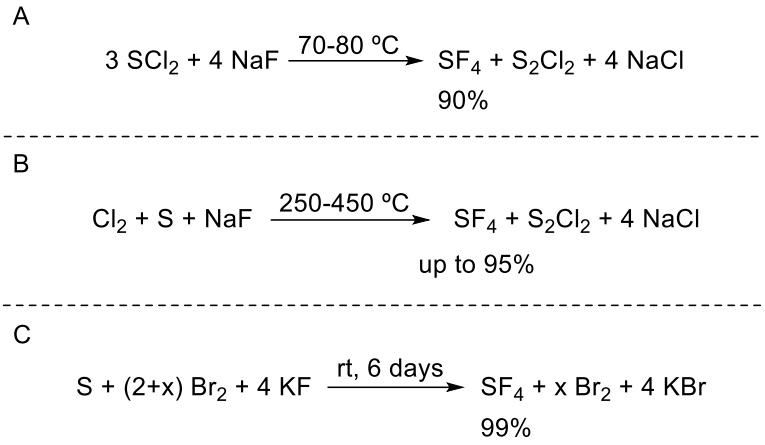
1.1 Hypervalent sulfur fluorides

Sulfur hexafluoride (SF_6) is considered the first synthetic sulfur fluoride. Despite being firstly produced by Moissan in 1891,[18] the preparation and the study of sulfur hexafluoride were reported jointly with Lebeau in 1902.[19] Pentafluorosulfanyl compounds (R-SF_5) could be considered as organic derivatives of sulfur hexafluoride; however, due to the extreme stability of SF_6, its use in the synthesis of pentafluorosulfanyl derivatives is still very limited. Recently, some reports on this topic appeared.[20,21] In general, sulfur(VI) fluorides are more stable and less reactive than sulfur(IV) fluorides. For instance, sulfur tetrafluoride (SF_4) readily reacts with moisture.[22] In contrast, SF_6 is stable and hydrolyses very slowly.[23]

According to the nomenclature adopted by the IUPAC, molecules with a sulfur centre in a different oxidation state than +2 should be named conforming to the lambda (λ) convention.[24] Consequently, the SF_5 scaffold should be named as pentafluoro-λ^6-sulfanyl and SF_5-containing compounds, as pentafluoro-λ^6-sulfanes. For simplicity, only preferred IUPAC names (PINs) were used for the description of SF_5-containing compounds in the Experimental section of this dissertation. The properties of the pentafluorosulfanyl (SF_5) group, its introduction into organic molecules as well as their reactivity and applications are presented in this chapter.

1.1.1 Tetrafluoro-λ^4-sulfane (SF_4)

The first reproducible synthesis of sulfur tetrafluoride was carried out by the reaction of elemental fluorine with sulfur (S_8).[25] Sulfur tetrafluoride is a colourless and hydrolytically unstable gas (bp = -38 ºC) and its toxicity is comparable to that of phosgene.[26] Other reported strategies without the use of F_2 are the reaction of sulfur chlorides and molecular chlorine or sulfur with sodium fluoride (Scheme 1A and 1B).[26–29] In addition, a practical method to avoid lower valence sulfur fluorides during the purification process was described by Dmowski.[30] Later on, Winter reported a mild and practical synthesis with the use of bromine, potassium bromide and elemental sulfur at room temperature (Scheme 1C).[31]



Scheme 1. Various syntheses of SF_4

SF_4 undergoes halogen exchange with halomethanes, -alkanes and -alkenes as well as aryl chlorides.[28] The use of SF_4 as deoxofluorinating agent in the reaction with alcohols or carbonyl compounds has been described in the literature;[32] however, due to its toxicity, its use has been superseded by *N,N*-diethylaminosulfur trifluoride (Et_2NSF_3, commonly known as DAST).[33] To date, sulfur tetrafluoride is the main starting material used for the synthesis of pentafluorosulfanylated halides. These compounds are the main precursors of alkyl pentafluorosulfanylated derivatives.

1.1.2 Hexafluoro-λ^6-sulfane (SF_6)

Sulfur hexafluoride is described as a colourless, odourless, tasteless, non-toxic and non-flammable gas obtained from the reaction of sulfur (S_8) with F_2.[19,34] This method is still used nowadays with an annual production of over 10 000 metric tons (2010).[35] Sulfur hexafluoride has an octahedral geometry of the ligands surrounding the sulfur centre. It displays an extraordinary stability, with a decomposition temperature between 500-700 ºC.[36] However, it is worth noting that this stability is a consequence of its kinetic properties rather than thermodynamic ones.[23] Due to the strong sulfur-fluorine bond (360 kJ/mol) dissociative reaction pathways are limited. In addition, reactions with nucleophiles or electrophiles are precluded due to the coordinative saturation of the sulfur centre. Owing to its inertness, SF_6 is considered one of the most potent greenhouse gases and it has been included in the list of gases whose emissions should be reduced to fight against

global warming according to the Kyoto Protocol. The atmospheric lifetime of sulfur hexafluoride is about 3200 years, with the highest global warming potential (GWP) known of 22 800.[37–39]

The utility of sulfur hexafluoride in electronic and electrical industries as an insulating gas is well known.[40,41] It exhibits arc-quenching capability[42] for electron trapping and it is extensively used in switchgear, transformers, transmission lines, capacitors, substations and high-voltage circuit breakers. SF_6 acts like a fluorine-radical source in etching industry[43] or as a component of gas mixtures in the blanketing of alloys[35,42,44]. In addition, its utility as fire-extinguishing agent or as a tracer for gas tracer techniques (i.e., leak detection) has been also described.[45]

To date, sulfur hexafluoride has very limited applications in organic synthesis. Publications describing its use as fluorinating agent arose in recent years.[46,47] In addition, catalytic degradation[48,49] of sulfur hexafluoride by rhodium (I) complexes and metal-free activation by using superbasic phosphines have been reported.[50] The use of sulfur hexafluoride as a pentafluorosulfanylating agent has just started to appear in the literature; however, is not still a routinely protocol and needs further development.[20,21] Efficient chemical activation and mild and environmentally friendly depletion of SF_6 remains a challenge.

1.1.3 Derivatives of SF_6

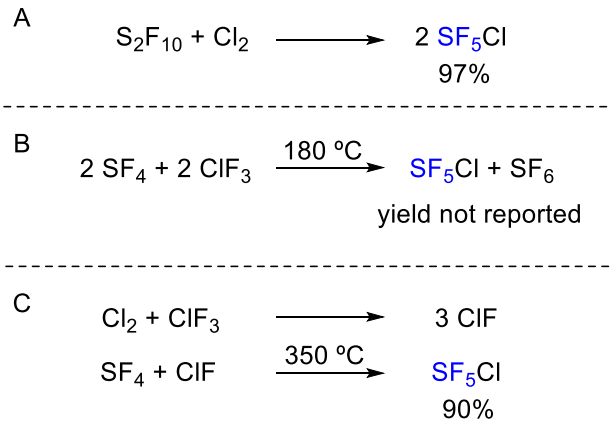
a. Decafluoro-λ^6-disulfane (S_2F_{10})

The reaction of F_2 and sulfur (S_8) generates a variety of sulfur fluorides, among which SF_6, SF_4, S_2F_2 and S_2F_{10} are present. Disulfur decafluoride was obtained as a by-product in the gas form after distillation in 0.1% yield.[51] In addition, it can be synthesized by photoreduction of SF_5Cl[52,53] or SF_5Br[54] in quantitative yield. Disulfur decafluoride is a highly toxic, colourless, volatile liquid (bp = 30.1 ºC) with a sulfur dioxide-like odour. It has a very poor solubility in water but it is soluble in many organic solvents.[42,55] It is formed by two staggered SF_5 fragments wherein each sulfur centre is surrounded by five fluorine atoms, which adopt an octahedral geometry. The bond between the sulfur centres

is weak ($d_{(S-S)}$ = 2.21 Å) and, as a consequence, S_2F_{10} is less stable and more reactive in comparison with SF_6.[23] Moreover, it is stable to acid but it catalytically hydrolyzes in the presence of water and alkalis. It decomposes in the presence of copper or mercury above 150 ºC to afford disproportionation products, SF_4 and SF_6.[42,53,56] Disulfur decafluoride readily reacts with molecular chlorine to form sulfur chloride pentafluoride (SF_5Cl).[57] Formation of SF_5-containing derivatives was observed upon reaction with some olefins and benzene.[53]

b. Chloro-pentafluoro-λ^6-sulfane (SF_5Cl)

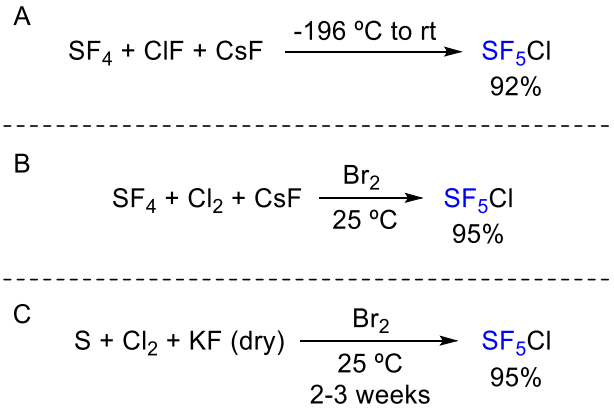
The synthesis of SF_5Cl was firstly reported by Cotton[57] from the reaction of S_2F_{10} and Cl_2). Chloro sulfur pentafluoride was obtained as a toxic colourless gas (bp = -21 ºC) in almost quantitative yield (Scheme 2A). Due to the high toxicity of S_2F_{10}, the efforts were focused on the development of new synthetic routes starting from sulfur tetrafluoride. SF_5Cl was obtained as the product of the reaction of SF_4 and ClF_3 at 180 ºC in a sealed vessel (Scheme 2B).[53] Preformation of ClF by the reaction of molecular chlorine with ClF_3 reduced SF_4 consumption by half (Scheme 2C). However, the reaction had to be conducted at high temperature. Flow process technology was successfully applied to this process on hundred–gram scale.[58]



Scheme 2. Preparation of SF_5Cl from S_2F_{10} and SF_4

In the upcoming years, further optimization led to synthetic routes involving the use of metal fluorides (Scheme 3). The presence of a metal fluoride is crucial to decrease the

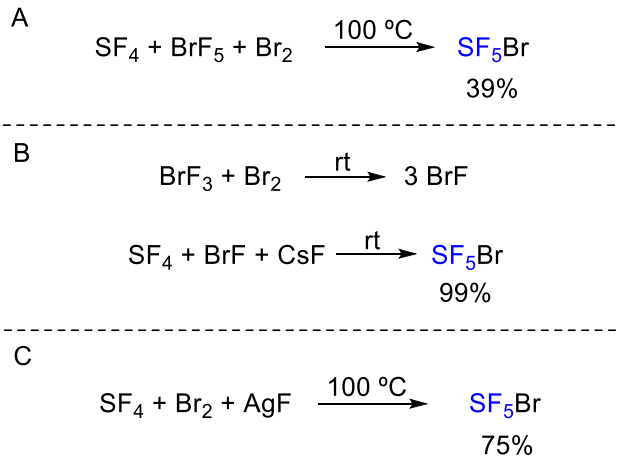
temperature of the reaction. In addition, the use of inexpensive Cl_2 and Br_2 (whose role has not been determined yet) resulted in an increase of the efficiency of the process.[59] An alternative synthesis using sulfur, dry KF and Cl_2 in the presence of bromine afforded SF_5Cl in excellent yield. In this case, SF_4 was found to be an intermediate in the reaction (Scheme 3C).[60,61]



Scheme 3. Synthesis of SF_5Cl from SF_4

c. Bromo-pentafluoro-λ^6-sulfane (SF_5Br)

Sulfur bromide pentafluoride (SF_5Br) was firstly synthesised as the product of the reaction of S_2F_{10} and Br_2.[62] In an analogous synthesis to that of SF_5Cl, the reaction was conducted in a sealed tube at 138 ºC. SF_5Br was recovered as a volatile, colourless liquid (bp = 31 ºC) and is toxic. However, the reaction was not complete even with excess of Br_2 or with an increase of the temperature up to 150 ºC due to thermal decomposition of SF_5Br at temperatures above 135 ºC. This equilibrium becomes irreversible at temperatures above 150 ºC. In contrast, SF_5Cl is stable up to 400 ºC.[63] SF_5Br can be synthesized from the reaction of SF_4 with BrF_5 and bromine in a Monel tube at 100 ºC (Scheme 4A).[64] Preformation and ultimate reaction of BrF with SF_4 and CsF affords SF_5Br in quantitative yield (Scheme 4B).[65] In addition, sulfur tetrafluoride reacts with bromine and silver(I) fluoride at 100 ºC to form sulfur bromide pentafluoride in good yield (Scheme 4C).[60]

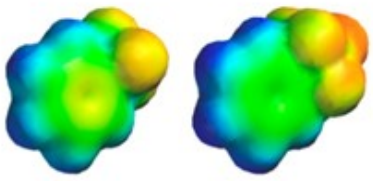


Scheme 4. Preparation of SF_5Br from SF_4

The chemistry of the pentafluorosulfanylating agents (SF_5Cl and SF_5Br) is governed by their tendency to form SF_5 radicals. SF_5Cl generally undergoes clean radical-type reactions. The difference in reactivity might be explained by the polarity of the sulfur-halogen bond.[12] The nature of the SF_5 scaffold might induce electrophilic reaction pathways in the bromine centre and to a lesser extent in the chlorine. In conclusion, SF_5Br is less stable but more reactive than SF_5Cl. Addition of these reagents to unsaturated systems is described in the Section 1.3.

1.2 Properties of the pentafluorosulfanyl group

The SF_5 group is frequently regarded as a "super-CF_3" group and these two groups are frequently compared (Table 1). The pentafluorosulfanyl group has an octahedral geometry of the ligands around the sulfur centre. Generally, the scaffold constitutes a typical AB_4 system where two types of fluorine can be distinguished, four basal (equatorial) and one apical (axial) in ^{19}F NMR.[66] Due to the particular array of fluorines in the scaffold, the rotation barrier is reduced and therefore receptor interactions can be optimized.[12] The estimated rotation barrier of the C-S bond in Ar-SF_5 is around 7.5 kJ/mol. In systems presenting di-*ortho*-substitution, as in (2,6-difluorophenyl)pentafluorosulfanes, the rotation barrier is estimated to be increased up to 33.1 kJ/mol.[67] The volume of the group is 49.2 cm^3/mol, bigger than that of the CF_3 but slightly smaller than the *tert*-Bu group.[68–70]



(a) (b)

Figure 1. Electrostatic potential map of (a) Ph-CF_3 vs (b) Ph-SF_5[71]

The profile of electron density around the SF_5 moiety presents a squared pyramidal configuration, whereas that of the CF_3 analogue describes a conical shape (Figure 1).[71] The pentafluorosulfanyl scaffold has a strong electron-withdrawing capability close to the nitro group.[72] However, in aliphatic systems, the inductive power was estimated to be nearly the same as the trifluoromethyl group.[73] The trend in electronegativity for aromatic systems is consistent with the values of the Hammet substituent constants. The SF_5 group presents a higher inductive[74,75] (σ_I) and lower resonance contributions[74,76] (σ_R) than the parent CF_3-analog. For instance, the dipole moment (μ) in Ph-SF_5 is significantly enhanced, with a calculated value of 3.44 D vs 2.60 D for Ph-CF_3.[74]

Table 1. Properties of SF_5 vs CF_3 analogues

Parameter	**SF_5**	**CF_3**
Geometry of ligands	Octahedral	Tetrahedral
Volume (cm^3/mol)	49.20	20.49
Electron density profile	Pyramidal	Conical
Dipole moment (D)	3.44 (Ph-SF_5)	2.60 (Ph-CF_3)
Electronegativity	3.65	3.36
Hansch hydrophobicity parameter (π)	1.51	1.09
Hammet substituent constants		
σ_p	0.68	0.54
σ_m	0.61	0.41
σ_I	0.55	0.39
σ_R	0.11	0.12

The pentafluorosulfanyl derivatives are in general more lipophilic than the trifluoromethyl analogues. This is reflected in the measurement of the Hansch hydrophobicity constants (π), with values of 1.51 and 1.09, respectively for SF_5 and CF_3.[77] However, there are some examples in the literature where the trend is the opposite.[70] SF_5-derivatives exhibit a great thermal and chemical stability. Thermal decomposition experiments in closed vessels under pressure were performed for CF_3SF_5 and $CF_3CF_2SF_5$. Noticeable formation of SF_4 from CF_3SF_5 occurred at temperatures over 400 ºC.[78] In terms of chemical stability, the SF_5 group is considered highly stable. Slow hydrolysis of Ph-SF_5 to benzenesulfonyl fluoride and phenylsulfonic acid took place upon treatment at 100 ºC with 100% H_2SO_4. Under analogous conditions, hydrolysis of the trifluoromethyl analogue took place within 5 minutes.[15,74] Treatment of 4-aminophenyl sulfurpentafluoride with 2M aqueous sodium hydroxide solution for 2 days at room temperature resulted in recovery of starting material in high yield.[79] In contrast, the CF_3-analog hydrolyses within 2 hours at room temperature upon treatment with 1M sodium hydroxide to afford 4-aminobenzoic acid.[80] The potential defluorination of the trifluoromethyl-derivatives allows the formation of covalent attachment sites by Michael addition; however, this process is not possible in pentafluorosulfanylated systems.

Aromatic SF_5-derivatives are resistant to the attack by strong Brønstedt acids and bases.[81] In contrast, they are sensitive toward strong Lewis acids.[82] Metal-catalyzed hydrogenation or C-C coupling reaction conditions have been used for further transformations of these systems.[67,79,83–85] The use of organolithium reagents such as *n*-butyllithium is not compatible with the SF_5 group; nevertheless, *tert*-butyllithium can be successfully used.[84] When the SF_5 group is directly attached to aromatic systems, it barely acts as a leaving group. Only a few examples have been reported in aliphatic systems.[15,79,86,87] In contrast, nucleophilic aromatic substitution (S_NAr) of the nitro group was carried out in nitro-SF_5-benzenes.[88]

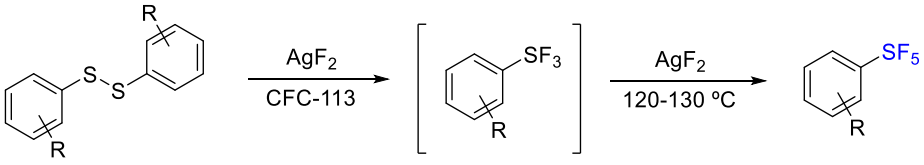
According to studies on the photodegradation of SF_5-aromatic systems reported in literature, only environmentally friendly products have been detected.[87] On the other hand, biodegradation studies on pentafluorosulfanyl-substituted aminophenol showed the potential of bacteria for the degradation of these derivatives. The postulated catabolic pathway might involve the release of fluoride ion which has the potential to produce toxic by-products. However, further studies are in progress.[89]

In the next few years, the pentafluorosulfanyl scaffold could play a relevant role in drug design. The SF_5 group has an extraordinary potential as a bioisosteric replacement for CF_3, *t*-Bu, NO_2 and halogen groups on aromatic systems. Examples where the SF_5-derivatives showed higher metabolic stability, potency and selectivity as well as lower toxicity are increasingly appearing in the literature.[12,90]

1.3 Synthesis of pentafluorosulfanylated compounds

1.3.1 Aromatic SF_5-containing compounds

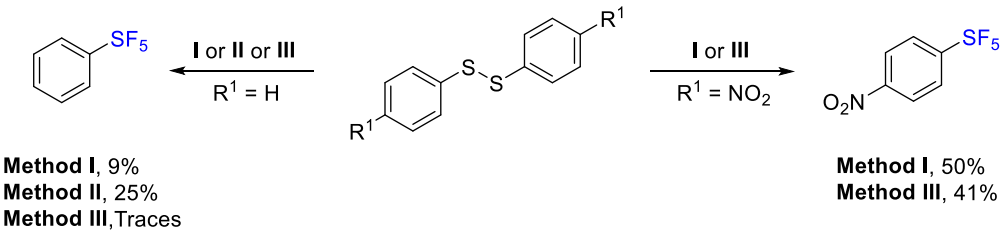
The first synthesis of (pentafluorosulfanyl)benzene was carried out by the reaction of diphenyl disulfide and AgF_2.[15,17] The stepwise procedure involves the formation of trifluorosulfanyl intermediates and the ultimate formation of the pentafluorosulfanyl product upon heating (Scheme 5).[74] Ar-SF_3 hydrolyses in the presence of moisture; however, they are stable and the isolation is possible. The main drawbacks of this method are the use of expensive AgF_2, the harsh conditions required in the final step of the reaction and low yields. When the reaction was carried out in an inert solvent, such as nonane, the efficiency of the process increased.[91] The presence of a coinage metal (Cu, Ag or Au) in the synthesis is crucial, since it catalyses the formation of aryl thiolate intermediates from the corresponding disulfide.[92]



Scheme 5. Sheppard's original synthesis of SF_5-benzenes

Ou and Janzen[93] reported the use of XeF_2 as a replacement of AgF_2 in the original Sheppard synthesis. The method was suitable for the fluorination of sulfur, selenium and tellurium compounds; however, (pentafluorosulfanyl)benzene was obtained only in 25% yield upon treatment of diphenyl disulfide with XeF_2 and catalytic Et_4NCl.

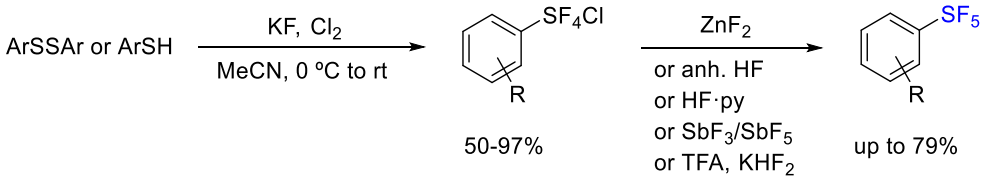
Later on, Philp's group and co-workers reported the direct fluorination of aromatic disulfides and thiols in reasonable yields using elemental fluorine.[79,94] The substrate scope investigated was mostly limited to 3- and 4-nitro-(pentafluorosulfanyl)benzene. This method has also proven suitable for the use of microreactors, displaying a higher efficiency and a safer use of elemental fluorine.[95]



I: AgF_2, 130 °C; **II**: XeF_2, cat. Et_4NCl, rt; **III**: F_2/N_2 (1:9, v/v), MeCN, -5 °C.

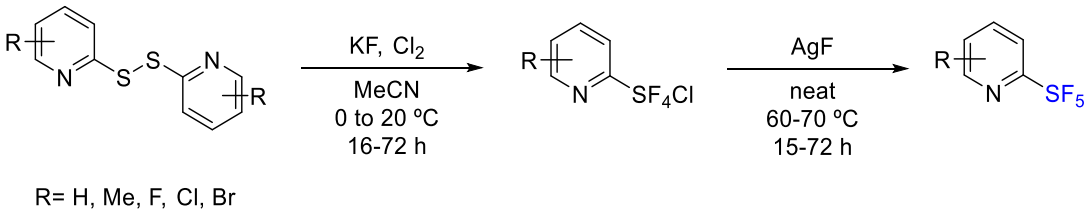
Scheme 6. Synthesis of Ar-SF_5 by oxidative fluorination

A significant advance was achieved by Umemoto[16] and co-workers who reported a step-wise procedure, in which the corresponding thiol or disulfide is oxidized by Cl_2 in the presence of an alkali metal fluoride to form an aryl (tetrafluorosulfanyl)chloride intermediate. The last step of the reaction involves a halogen exchange in the presence of a Lewis acid fluoride and can be carried out under various conditions (Scheme 7).



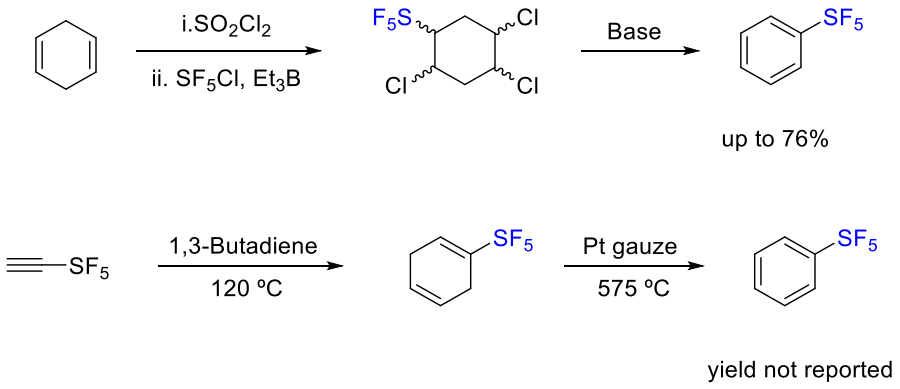
Scheme 7. Umemoto's oxidative fluorination process

This strategy was later on used by Dolbier[96] for the synthesis of 2-pyridylsulfur pentafluorides (Scheme 8). In the first step, 2-pyridylsulfur chlorotetrafluoride intermediates were formed; however, ^{19}F NMR confirmed a competing formation of pyridylsulfur trifluoride intermediates (Py-SF_3).[97] Interestingly, 3,3'- and 4,4'-dipyridyl disulfides did not form the corresponding (tetrafluorosulfanyl)chloride intermediate.



Scheme 8. Synthesis of SF_5-pyridines using the Umemoto's strategy

In the second step, the (tetrafluorosulfanyl)chloride intermediate was transformed into the SF_5-pyridines by the fluorination with AgF upon heating. Later, Shibata's group improved the method by the use of IF_5 as fluorinating agent to accomplish the last step of the reaction leading to previously inaccessible SF_5-pyridines bearing strong electron withdrawing groups, such as CF_3, SF_5 and NO_2.[98] Umemoto's method is nowadays the main strategy for the synthesis of Ar-SF_5 and SF_5-containing heteroaromatics, such as pyridines and pyrimidines, on a multigram-scale.

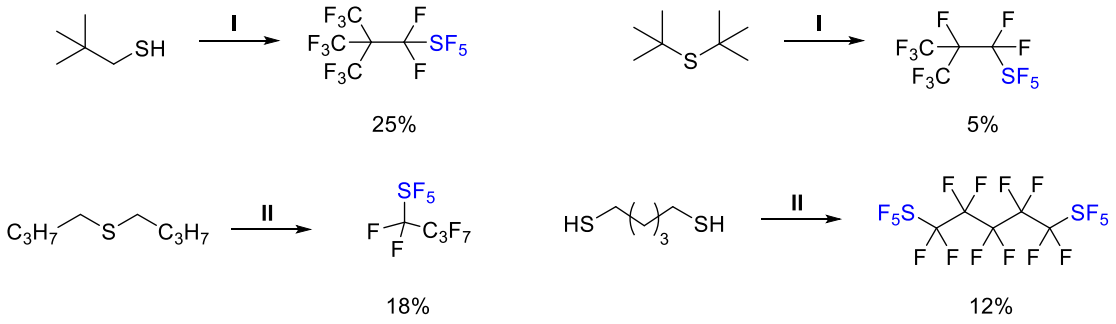


Scheme 9. Other syntheses of SF_5-benzene

Other methods reported in the literature for the synthesis of Ph-SF_5 are depicted in Scheme 9. 1-Pentalfuorosulfanyl acetylene underwent cycloaddition with 1,3-butadiene[99], followed by thermal rearomatization at high temperature to afford (pentafluorosulfanyl)benzene. Analogously, SF_5Cl addition[100] to 1,4-cyclohexadiene, followed by base promoted elimination afforded the titled compound.

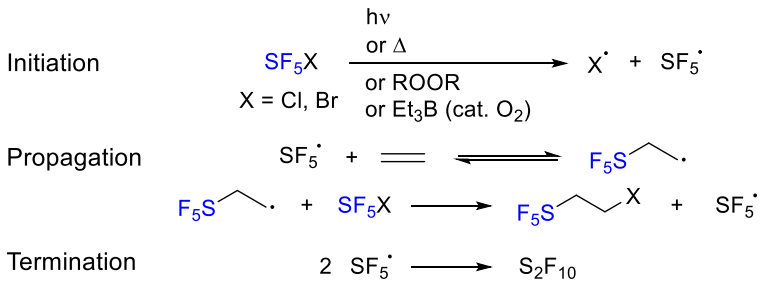
1.3.2 Aliphatic SF_5-containing compounds

The synthesis of aliphatic SF_5-containing compounds has been mainly carried out by the direct fluorination of sulfur-containing precursors and the radical addition of SF_5X (X = Cl or Br) or S_2F_{10} to unsaturated systems. Quite recently, publications on the activation of SF_6 towards the synthesis of SF_5-alkyl derivatives appeared in the literature. However, this strategy is still not a routine protocol.



Scheme 10. Fluorination of alkyl thiols and dialkyl disulfides

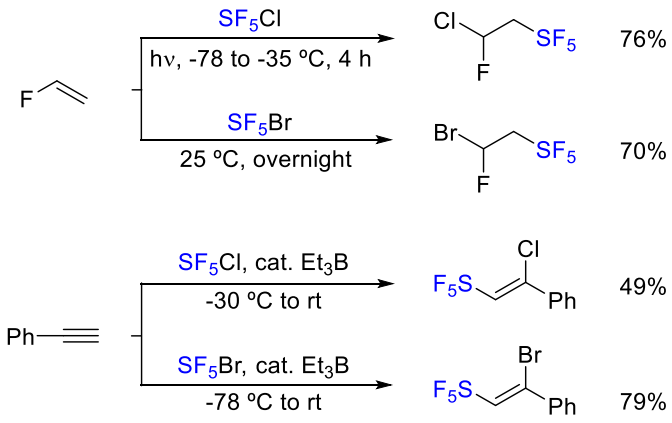
The direct fluorination of alkyl thiols and dialkyl disulfides with F_2[101] or electrochemical fluorination[102–104] with anhydrous HF (Simmons process)[105] afforded long-chain per-fluoroalkyl-SF_5 compounds (Scheme 10). Both strategies resulted in the formation of a complex mixture of highly fluorinated SF_5-containing alkanes likely due to fragmentation reactions and rearrangement of side products.



Scheme 11. General mechanism for the addition of SF_5X (X = Cl, Br) to unsaturated systems

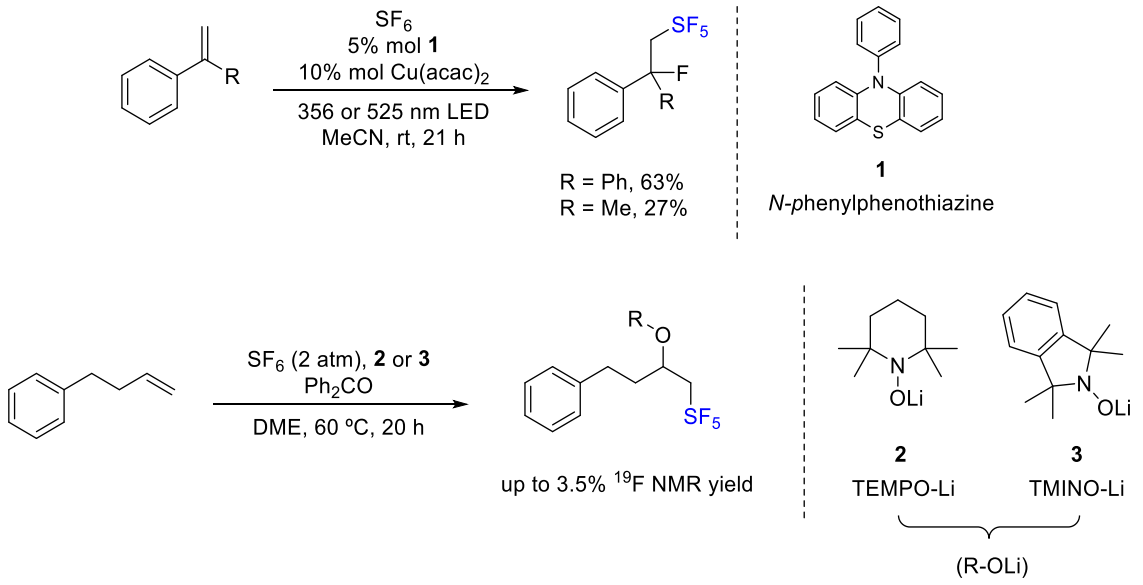
The main advantages of radical addition of SF_5X (X = Cl, Br) or S_2F_{10} to unsaturated systems are milder reaction conditions and broader substrate scope (Scheme 12). On the other hand, toxicity of these reagents is the main drawback. The formation of the pentafluorosulfanyl radical ($SF_5^{\cdot}$) can be carried out by homolytic cleavage of the sulfur-halogen bond. This process can be photochemical-, thermal- or chemical-induced.[12,63] In the propagation step, $SF_5^{\cdot}$ reacts with the unsaturated system affording a new SF_5-alkyl radical, which ultimately reacts with another molecule of pentafluorosulfanyl halide. The termination step involves the reaction of two pentafluorosulfanyl radicals affording disulfur decafluoride (Scheme 11).[106]

The use of S_2F_{10} for the functionalization of unsaturated systems is very limited due to its high toxicity and the harsh conditions required in the process. It reacts with deactivated olefins at high temperatures leading to bis-SF_5 adducts in yields up to 25%.[53]



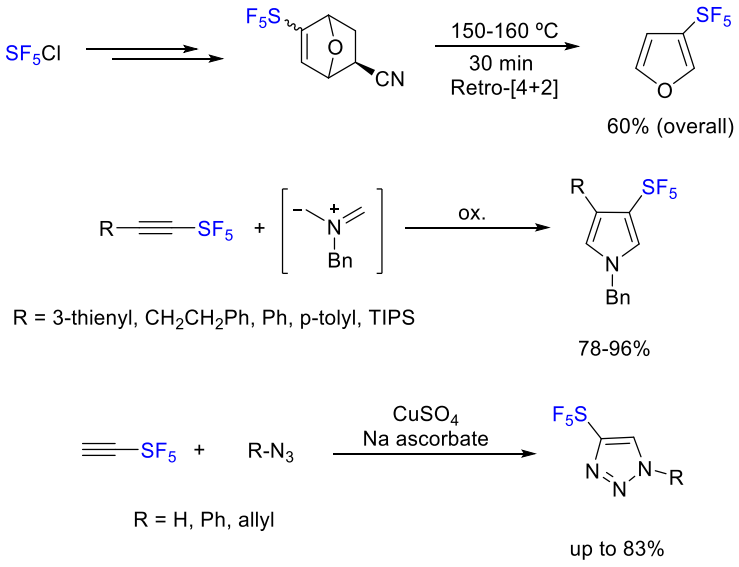
Scheme 12. Examples of SF_5X (X = Cl, Br) addition to unsaturated systems

The activation of SF_6 for the synthesis of SF_5-alkyl and -alkenyl derivatives represents a new and groundbreaking strategy in the field (Scheme 13). The strategies involve photoinduced electron transfer[21] or reductive activation[20] of SF_6 for the generation of radical species that ultimately react with terminal alkenes; however, the methods require further development.



Scheme 13. Early attempts on synthesis of SF_5-derivatives from SF_6

The strategies for the synthesis of SF_5-containing heterocycles are limited to cycloaddition and oxidative fluorination reactions. The synthesis of SF_5-furan derivatives involves a retro-Diels-Alder step in the process.[107] SF_5-thiophenes,[108] -pyrroles,[109] -pyrazoles,[99,110] -triazoles,[111] -isoxazoles[112] and -isoxazolines have been synthesized by cycloaddition reactions of SF_5-alkynes with a suitable partner (Scheme 14). Nowadays, the most relevant synthesis of SF_5-pyridines is carried out by oxidative fluorination using Umemoto's method.[16,96,98]



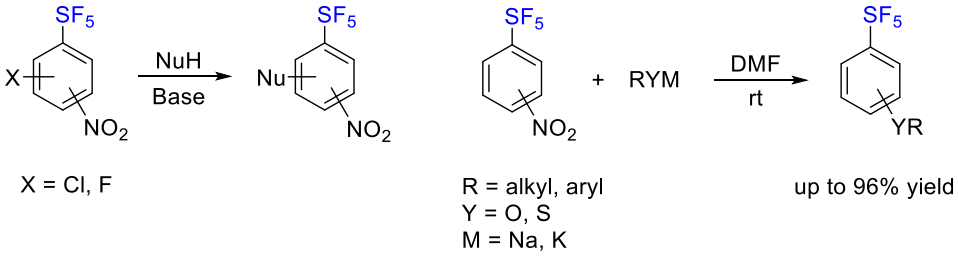
Scheme 14. Examples of syntheses of SF_5-heteroaromatics

1.4 Reactivity of pentafluorosulfanylated compounds

1.4.1 Aromatic SF_5-containing compounds

Due to the lack of practical synthetic methods and availability of Ar-SF_5 building blocks, the chemistry of these derivatives has been mainly developed by derivatization of commercially available 3- and 4-nitro-(pentafluorosulfanyl)benzene.

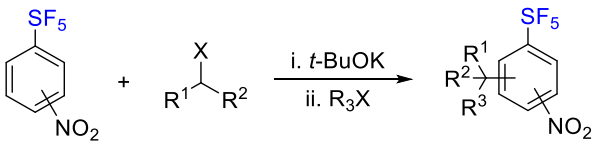
Reduction of SF_5-nitrobenzenes gave access to SF_5-anilines, which were converted into SF_5-diazonium salts upon treatment with $NaNO_2$ and a strong acid, such as HCl, HBF_4 or H_2SO_4. Diazonium salts are key intermediates for the preparation of SF_5-containing halides, phenols, thiophenols and azo compounds or as pseudohalide-type electrophiles in coupling reactions. This strategy is commonly used to synthesise a wide variety of (pentafluorosuflanyl)benzenes.[12,17,91]



Scheme 15. S_NAr reactions of SF_5-nitrobenzenes

Nucleophilic aromatic substitution (S_NAr) of the nitro group in *meta*- and *para*-nitro-(pentafluorosulfanyl)benzenes was reported by our group in 2010.[88] The reactions were carried out using alkali metal nucleophiles and proceeded in good yield and selectivity. Alternatively, substitution of the halogen atom in halo-nitro-(pentafluorosulfanyl)benzenes has been reported by Trasher.[113,114] Both strategies are depicted in Scheme 15.

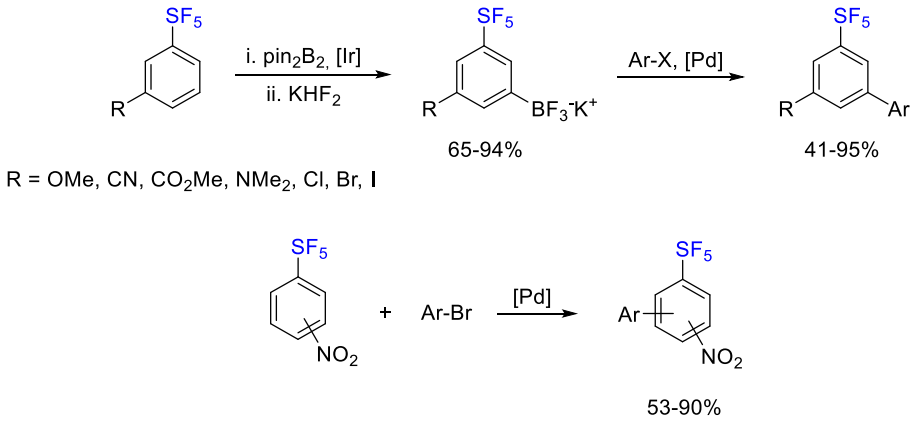
Analogously, vicarious nucleophilic substitution of hydrogen (VNS) in *p*- and *m*-nitro-(pentafluorosulfanyl)benzenes was investigated by our group in 2011. The reactions generally proceed in good to excellent yields with high regioselectivity under kinetic conditions (Scheme 16).[115]



X = Cl, Br, OPh
R^1 = H, Me, Cl, Br
R^2 = Cl, Br, SO_2Ph, CN, CO_2R, $P(O)(OEt)_2$
R^3 = H, Me, $PhCH_2$, CH_2=$CHCH_2$

Scheme 16. VNS reactions of SF_5-nitrobenzenes

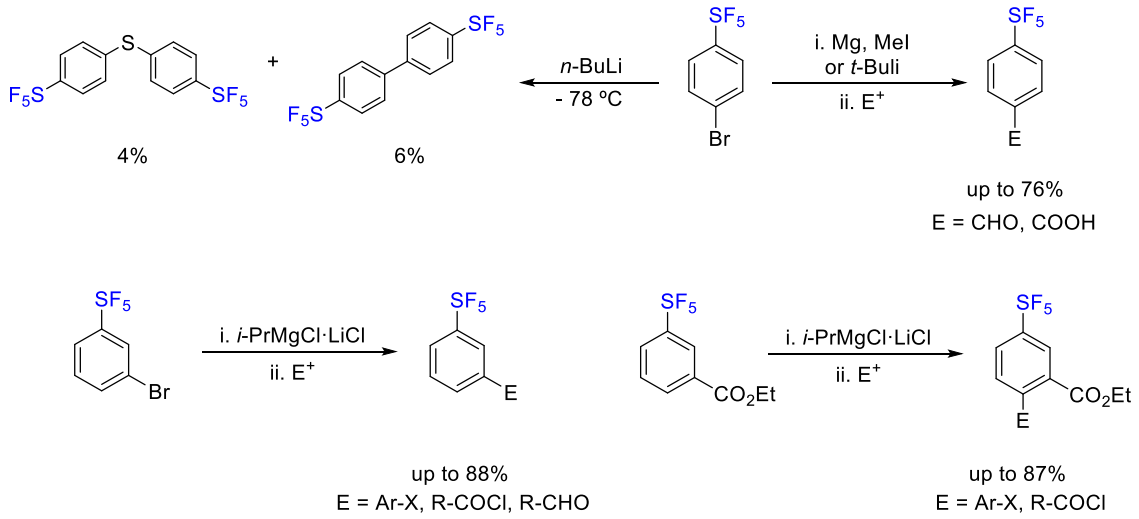
Electrophilic bromination and nitration of (pentafluorosulfanyl)benzene was described by Sheppard.[17] The regioselectivity in the process is dominated by the strong *meta*-directing inductive effect of the SF_5 scaffold. Similar conditions were applied for the further derivatization of 3-bromo- or 3-nitro-(pentafluorosulfanyl)benzene by subsequent bromination and/or nitration.[100,116]



Scheme 17. Metal catalysed C-H activation of SF_5-derivatives

Reports on metal catalysed C-H activation of nitro-(pentafluorosulfanyl)benzenes are present in the literature (Scheme 17). Ir-catalysed C-H borylation of *m*-substituted-SF_5-benzenes to afford SF_5-substituted potassium aryltrifluoroborates in one-pot was reported by Carreira.[117] These substrates were ultimately used in Suzuki-Miyaura cross-coupling reactions. At the same time, Wang[118] reported the Pd-catalysed arylation of *m*- and *p*-

nitro-(pentafluorosulfanyl)benzene with aryl bromides. The reaction afforded SF_5-substituted derivatives in, generally, high yield and regioselectivity. Examples of Sonogashira, Suzuki and Heck coupling reactions of halo-SF_5-benzene derivatives have also been published.[79]

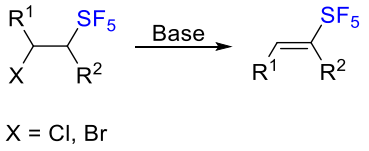


Scheme 18. Examples of use of organometallics in transformations of SF_5-arenes

The use of organometallics in Ar-SF_5 is very restricted since the scaffold is susceptible to reduction by these reagents (Scheme 18). Conversion of 4-bromo(pentaflurosulfanyl)benzene into the corresponding Grignard reagent was achieved only in the presence of catalytic methyl iodide (MeI).[119] On the other hand, attempts of lithiation of 4-bromo(pentaflurosulfanyl)benzene with *n*-butyllithium led to reduction products. The use of alkyllithium reagents is exclusively limited to *tert*-butyllithium.[84] 3-Bromo(pentaflurosulfanyl)benzene successfully underwent halogen-magnesium exchange with *i*-PrMgCl·LiCl. This base is commonly known as Turbo-Grignard reagent. In addition, SF_5-containing benzoates underwent directed metalation with $TMP_2Mg·2LiCl$ (TMP = 2,2,6,6-tetramethylpiperidyl).[120] All the examples mentioned above are depicted in (Scheme 18).

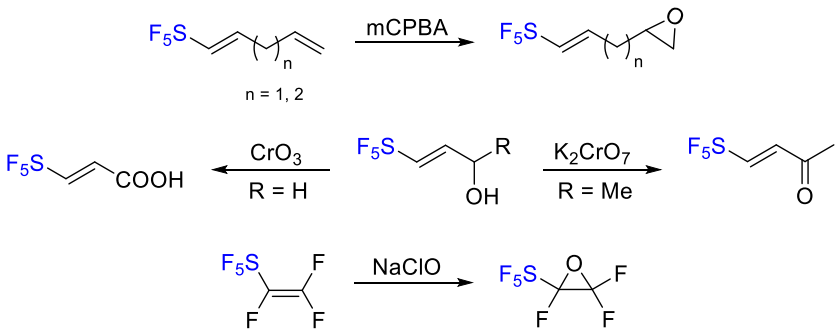
1.4.2 Aliphatic SF_5-containing compounds

The reactivity of SF_5-alkanes, whose synthesis was described in the Section 1.3.2, is mainly governed by base-promoted β-elimination of HX (X = Cl, Br) (Scheme 19). Over the last decades, this strategy allowed the preparation of many diverse SF_5-olefins using a wide range of bases and conditions.[12] Only in a few cases, a mixture of olefins was obtained, some of which contained the SF_5 group. This strategy allowed the preparation of SF_5-alkynes under similar conditions.[121,122]



Scheme 19. Base-promoted β-elimination in SF_5-alkanes

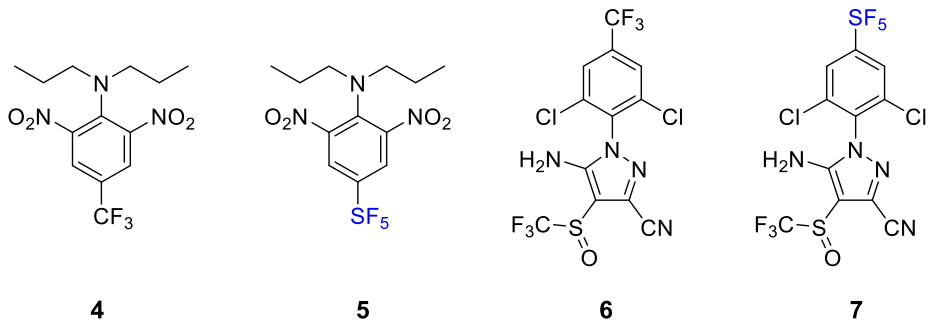
Halogen and tosylate displacement reactions with O-, C- and N-nucleophiles in SF_5-alkanes have been described in the literature.[123–126] Generally, only SF_5-containing derivatives were obtained. SF_5-containing olefins underwent addition reactions to the double bond (Scheme 20); however, a protective behaviour of the scaffold in these systems has been observed. Upon treatment with oxidant, the double bond remained intact.[127,128] In contrast, the SF_5 group facilitated hypochlorite epoxidation of SF_5-trifluoroethylene.[129]



Scheme 20. Example of oxidation reactions of SF_5-alkenes

1.5 Applications of pentafluorosulfanyl derivatives

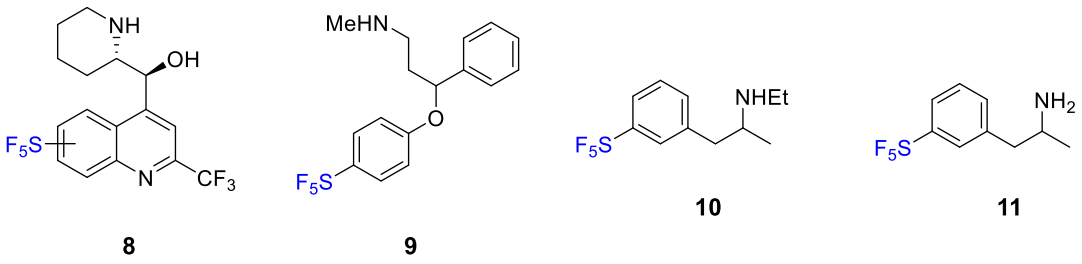
Since 1963, many patents describing the utility of SF_5-derivatives as pesticides (herbicides, fungicides, parasiticides and insecticides) have been published.[12] Of special relevance, is the synthesis and evaluation of the SF_5-containing Trifluralin analogue **5** (Figure 2).[130] It displayed a better performance in pre-emergence applications, as well as a higher herbicidal activity (nearly 5-fold greater towards grass weeds) compared to the parent CF_3-analog **4**. Another example of pentafluorosulfanyl-containing heterocycle herbicide is the SF_5-analog of commercially available Fipronil **6**. Biological studies reported a higher activity against cockroaches and houseflies for the pentafluorosulfanylated analogue **7**.[91]



4 **5** **6** **7**

Figure 2. Examples of pesticides and SF_5-analogs

Due to the extraordinary properties of the SF_5 scaffold and its potential role as a bioisosteric replacement, the number of publications in the field of medicinal chemistry has grown exponentially over the last years. Important examples of pentafluorosulfanyl analogues are the SF_5-analogs of mefloquine **8**, fluoxetine **9**, fenfluramine **10** and norfenfluramine **11** (Figure 3). 6- and 7-SF_5-analogs of Mefloquine **8**, an important antimalarial agent, exhibited a greater selectivity and higher inhibitory potency compared to the parent CF_3-analog[131] as reflected by lower values of IC_{50} and IC_{90}.[132] SF_5-analogs of fluoxetine, fenfluramine and norfenfluramine were successfully synthesized and their biological activity was evaluated.[68] Fluoxetine, commercially known by trade names Sarafem or Prozac, is an anti-depressive agent that belongs to the selective serotonin reuptake inhibitors (SSRI) class.



8 **9** **10** **11**

Figure 3. SF_5-analogues of marketed pharmaceuticals

On the other hand, fenfluramine **10** and norfenfluramine **11** are appetite suppressants for the treatment of obesity. **9, 10** and **11** are able to selectively bind the serotonin (5-HT) receptors, which are involved in biological functions besides brain activity.[133] Up to ten-fold enhanced affinity for 5-HT_6 receptors was observed in the case of **10** and **11** compare to their CF_3-analogues. Both compounds are promising candidates for the treatment of motor disorders, depression, Alzheimer's disease, etc.

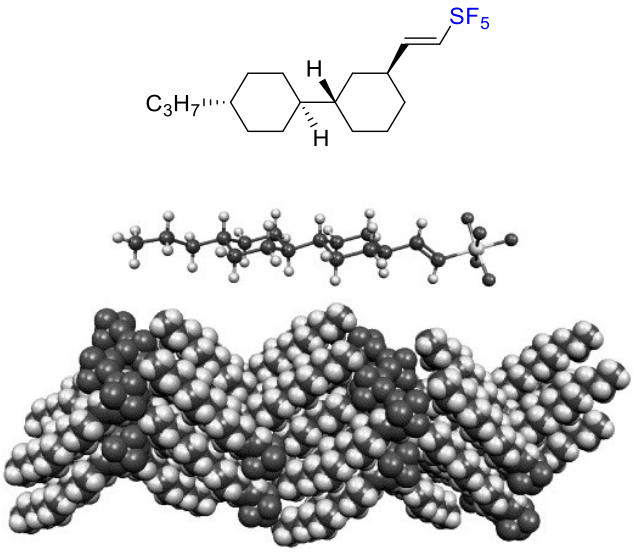
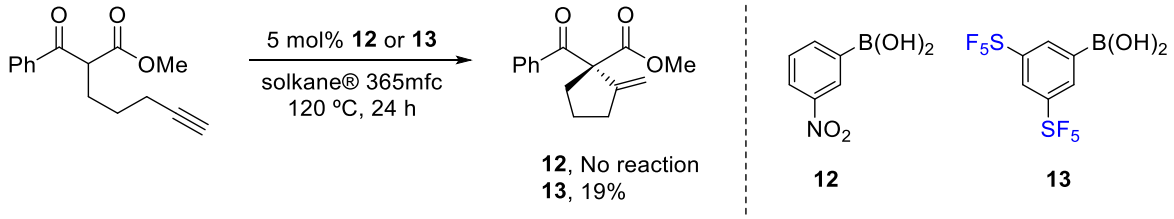


Figure 4. Crystal structure of an SF_5-vinyl substituted liquid crystal reported by Kirsch[84]

The utility in the preparation of liquid crystals is among the very early-discovered applications of SF_5-derivatives. The perfect combination of high dielectric anisotropy ($\Delta\varepsilon$) and very low birefringence (Δn), of relevance for LCDs construction, as well as an extraordinary chemical stability, afforded a new class of liquid crystals based on SF_5-alkenes (i.e., Figure 4).[134]



Scheme 21. Catalysed Conia-Ene cyclisation reaction

The first example of the use SF_5-arenes in organocatalysis was reported by Shibata. Compound **13** exhibited a good catalytic activity for the Conia-ene carbocyclization of 1,3-dicarbonyl compounds bearing terminal alkynes (Scheme 21).[135] Due to the properties of the SF_5 scaffold in terms of lipophilicity and steric demand, this moiety is potentially a good alternative for the nitro or *t*-Bu groups in the catalyst design.

2 Aims of the work

- Preparation of *ortho*-, *meta*- and *para*-substituted disulfides and thiols.

- Investigation of the scope and limitation of direct fluorination of substituted thiols and disulfides for the synthesis of arylsulfur pentafluorides.

- Derivatization of aromatic (pentafluorosulfanyl)-containing building blocks by direct fluorination.

- Derivatization of fluoro-(pentafluorosulfanyl)benzenes by nucleophilic aromatic substitution (S_NAr) and vicarious nucleophilic substitution (VNS).

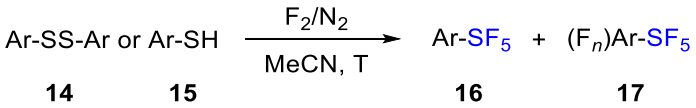
3 Results and discussion

3.1 Synthesis of substituted aromatic-SF_5 derivatives by direct fluorination

3.1.1 Direct fluorination of thiols and disulfides using elemental fluorine

In order to investigate the scope and limitation of the synthesis of aromatic pentafluorosulfanyl derivatives by direct fluorination, a library of *ortho*-, *meta*- and *para*-substituted aromatic thiols and disulfides were fluorinated using elemental fluorine. In addition, this work also provides a convenient access to these initial substrates, which are in some cases expensive or commercially unavailable. The main synthetic route towards the synthesis of thiols or disulfides was nucleophilic substitution of commercially available or previously synthesized halobenzenes with sulfur nucleophiles, such as Na_2S and *t*-BuSK, or by reduction of benzenesulfonyl chlorides (see Experimental section for more details).

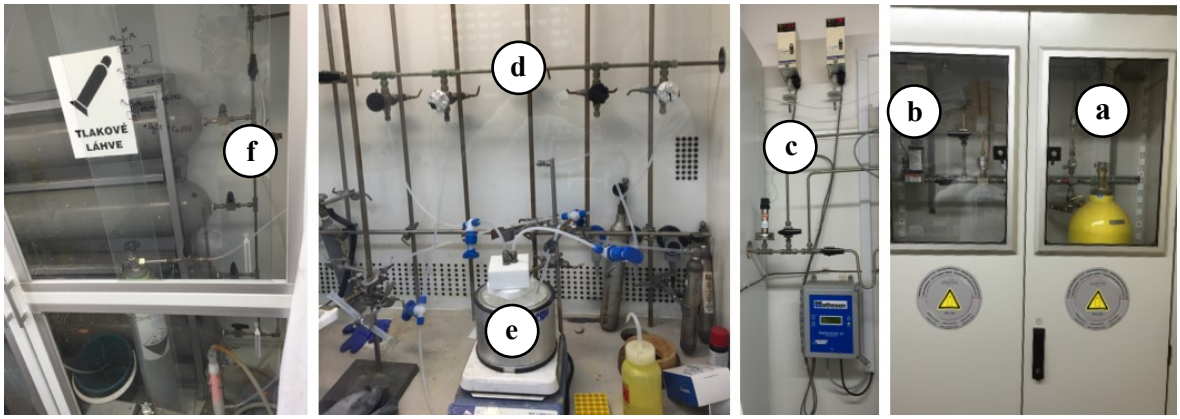
For the purpose, similar conditions to those described in the literature for the synthesis of 3- and 4-nitro-1-(pentafluorosulfanyl)benzene were employed during the fluorination reactions.[79] The corresponding disulfide **14** or thiol **15** was treated with an excess of F_2 to furnish the SF_5-derivative **16** (Scheme 22). In addition, mono- and difluoro-arylsulfur pentafluorides were detected as by-products of the reaction according to GC-MS and ^{19}F NMR. For simplicity, all these over-fluorinated species $(F)_nAr\text{-}SF_5$ (n = 1, 2) were regarded as **17** and the selectivity of the reaction has been addressed according to **16**:**17** isomer ratio.



Scheme 22. General scheme for the fluorination of thiols and disulfides

Most of the syntheses by the direct fluorination described in this work have been carried out at the fluorination facilities of IOCB (Prague, Czech Republic). The fluorine gas pipe-

line was equipped with Monel® piping and polytetrafluoroethylene tubing (PTFE) (Figure 5). Monel® is the commercial name given to a group of binary alloys composed of nickel (minimum 63%) and copper, containing iron, manganese, carbon and silicon in small amounts.[136] PTFE is a synthetic fluoropolymer, commercially known as Teflon™, formed by $–(CF_2CF_2)_n–$ units.[137] Both materials are used in the construction of laboratory pipelines for handling of corrosive agents, such as elemental fluorine, due to their high chemical resistance.



a: F_2/N_2 cylinder (20% F_2 in N_2, v/v)
b: Flowmeter
c: N_2 inlet
d: Monel pipes and PTFE tubing
e: PFA reaction vessel
f: Residual gas storage

Figure 5. Fluorination line at IOCB (Prague)

Previous research on the topic revealed that arylsulfenyl fluorides (Ar-S-F) and arylsulfur trifluorides (Ar-SF_3) are intermediates in the reaction of disulfides **14** and aromatic thiols **15** with fluorinating agents, such as KF, AgF_2 or F_2 during the synthesis of **16**.[16,17,79] Some of these species were visible in ^{19}F NMR spectroscopy and therefore, this technique served as a suitable method for the routine monitoring of the reaction (Figure 7). For the purpose, a sample of neat crude mixture was periodically taken from the reaction vessel and injected into a small inner diameter PTFE NMR tube (ca 3.5 mm), which was subsequently inserted into an ordinary NMR tube containing ca 0.2 mL of deuterated solvent (Figure 6). In order to have a proper locking in the NMR spectrometer, the use of acetone-d_6 as deuterated solvent was necessary.

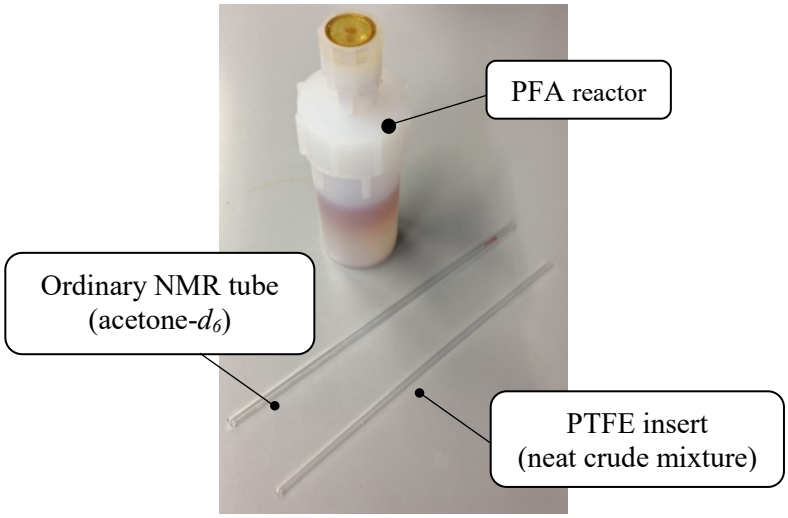


Figure 6. NMR monitoring system and PFA reactor vessel

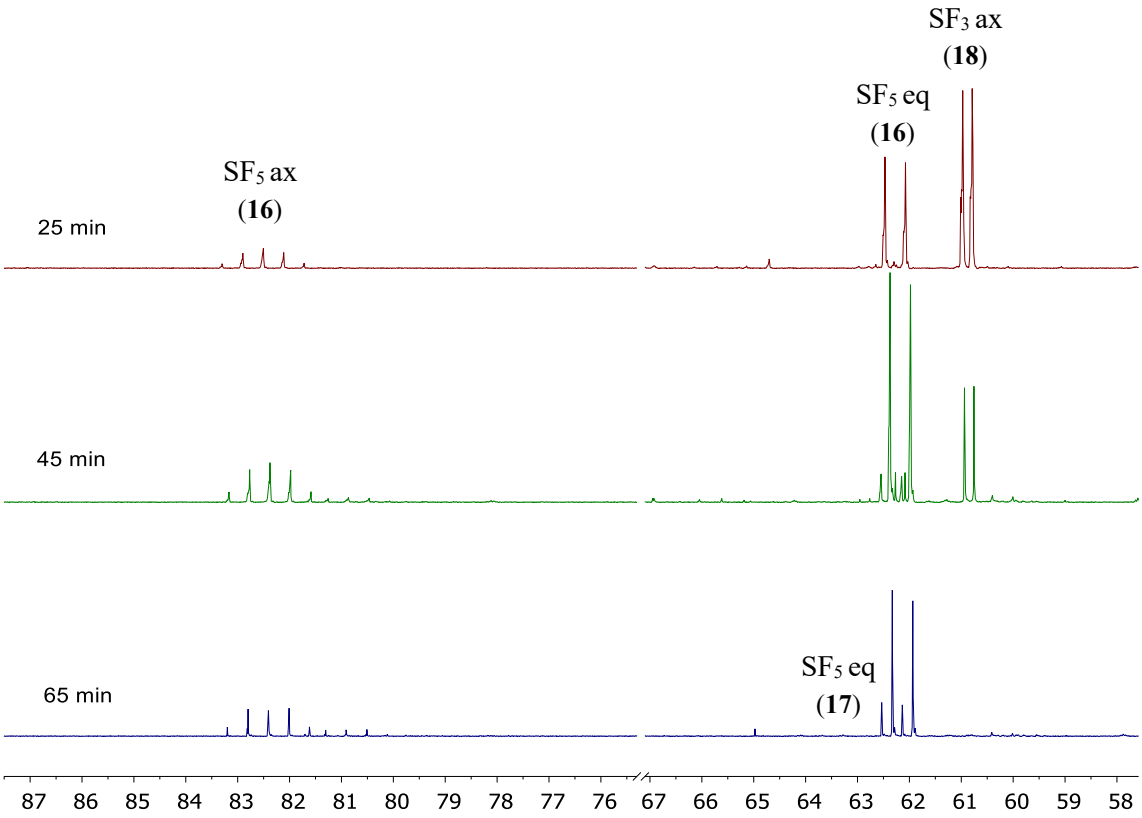
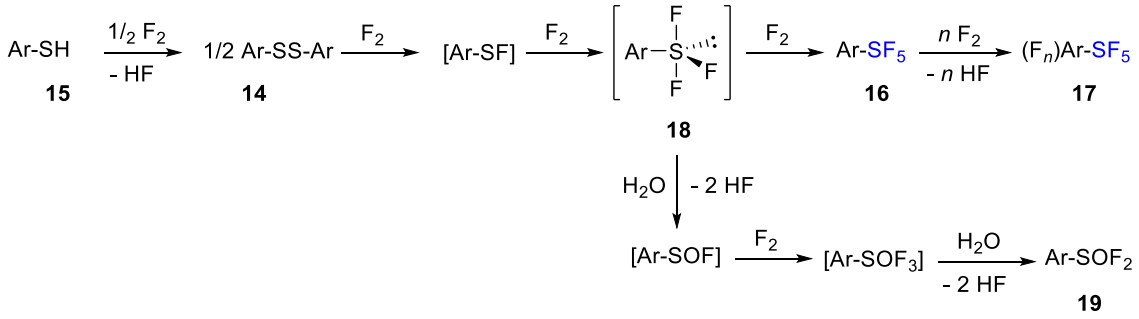


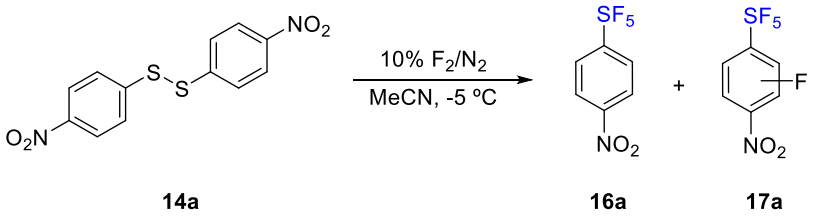
Figure 7. Example of ^{19}F NMR monitoring of crude reaction mixture for the fluorination of **14b**



Scheme 23. Proposed mechanism for direct fluorination of disulfides **(14)** and thiols **(15)**

The proposed mechanism for the fluorination of thiols and disulfides depicted in Scheme 23 is in agreement with the experimental observations in ^{19}F NMR. The first step of the reaction would be oxidation of the thiol **15** with subsequent formation of disulfide **14** and one equivalent of HF. Fluorination of **14** would lead to the formation of highly reactive sulfenyl fluoride (Ar-S-F) intermediate, which in the presence of another equivalent of F_2 would furnish the Ar-SF_3 intermediate **18**. On the other hand, Ar-S-F species were never detected spectroscopically during the monitoring of the reaction. Treatment of Ar-SF_3 **18** with another molecule of F_2 ultimately would furnish the corresponding Ar-SF_5 **16**. The use of dry solvent for the reaction is crucial since **18** is highly sensitive to moisture. The presence of aromatic sulfonyl fluorides **19** has been confirmed in preliminary results of this work upon aqueous work-up of a crude mixture containing **18**.

Due to the technical differences in the set-up of each F_2 facility, a comparison of the efficiency of our system with that of the literature was required. For the purpose, using analogous conditions, the fluorination of 1,2-bis(4-nitrophenyl)disulfane (**14a**) was carried out (Scheme 24). The reaction proceeded in good yield and high selectivity affording 4-nitro-1-(pentafluorosulfanyl)benzene (**16a**) in 45% yield and 98:2 (**16a**:**17a**) isomer ratio (entry 2, Table 2). This result correlates with that obtained by Philp (entry 1, Table 2); however, no information about the selectivity of the reaction was reported.[79]



14a **16a** **17a**

Scheme 24. Direct fluorination of **14a**

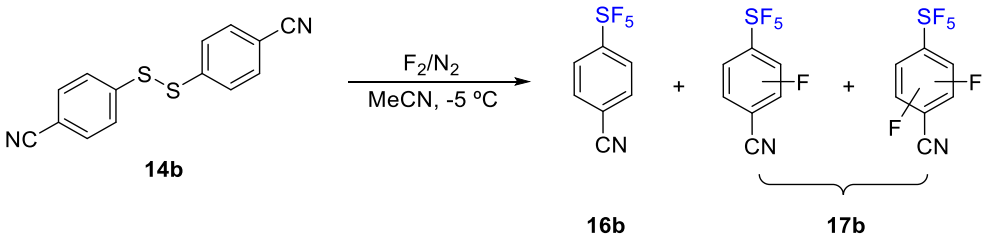
Table 2. Reaction conditions for the fluorination of **14a**

Entry	**14a** (mmol)	Conc. of **14a** (mM)	F_2 (equiv)	t (h)	**16a**, Yield[a] (%)	**16a**:**17a**[b]
1	40	200	13	24	41	–
2	1.6	65	80	1	45	98:2

[a]Isolated yield. [b]Determined by GC-MS.

Although **16a** was obtained in higher yield, our system is less efficient in terms of mass-transfer as derived from the results presented in Table 2. Fluorination of less concentrated solutions of **14a** required a higher excess of fluorine for the completion of the reaction (entry 1, Table 2). This result reflects the limitations of our system in terms of reactor size and inlet gas-mixture flow rate. For this reason, a compromise between minimum reaction time and maximal substrate concentration had to be reached; therefore, less concentrated substrate solutions of **14** were found to be more suitable for a preparative scale process.

In the same context, attempts of optimisation of fluorine dilution and solvent choice were carried out. With this aim, **14b** was treated with gas mixtures of different concentration of fluorine ranging from 2.5–10 vol. % F_2 in N_2 (Scheme 25 & Table 3). The reactions proceeded with higher selectivity when more diluted mixtures of fluorine gas were used (entries 1 and 2, Table 3); however, in a preparative scale reaction, the most practical dilution was found to be 10% F_2/N_2 (entry 3, Table 3). The use of either anhydrous HF or sulfuric acid as solvents for the fluorination of **14b** was not successful. In both cases, not even traces of any arylsulfur pentafluoride were found and only the starting material was recovered when sulfuric acid was used as the solvent.



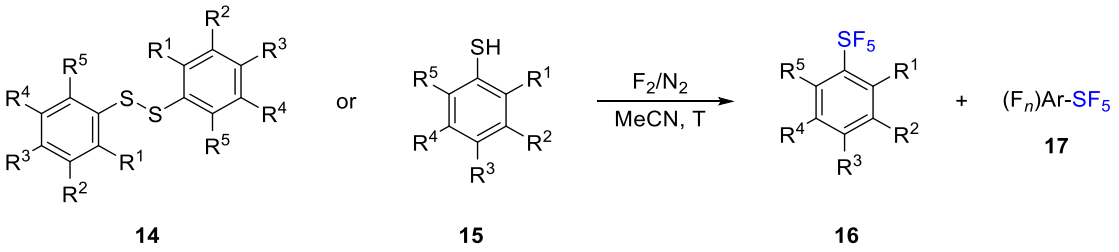
Scheme 25. Direct fluorination of **14b**

Table 3. Optimization of fluorine gas dilution for the fluorination of **14b**

Entry	F_2 in F_2/N_2 (v/v, %)	t (h)	**16b**, Yield (%)[a]	**16b**:**17b**[b]
1	2.5	4.8	33	87:13
2	5	2.3	30	85:15
3	10	1.1	28	78:22

[a]Isolated yield. [b]Determined by GC-MS.

Using optimized conditions, the scope of direct fluorination of substrates **14** and **15** was investigated (Scheme 26 & Table 4). Fluorination of substrates bearing NO_2, CN, CF_3, SF_5, SO_2Cl, SO_2F and COF groups in the *para*-position (entries 1–7, Table 4) furnished **16a-f** in moderate to good yields (in the context of direct fluorination chemistry). In contrast, fluorination of halo disulfides (entries 9–10, Table 4) afforded **16i** and **16j** in poor yields. Attempts of isolation of **16c**, **16i**, **16j** and **16m** were unsuccessful due to product volatility. In addition, isolation of **16g** by conventional workup was not possible since the compound readily hydrolyzed to benzoic acid **16h**. For these reasons, the yields of **16c**, **16g**, **16i**, **16j** and **16m** were determined by ^{19}F NMR spectroscopy using **16a** as internal standard.



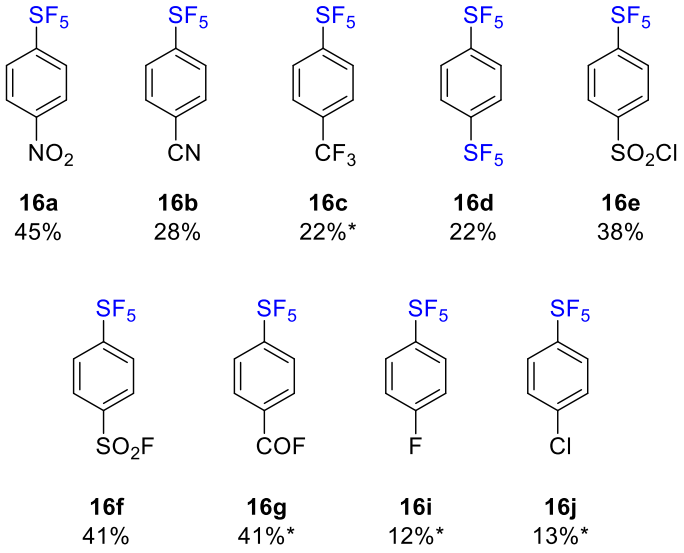
Scheme 26. Direct fluorination of **14** or **15**

Table 4. Substrate scope for the direct fluorination of **14** and **15**

Entry	**14** or **15**	R^1	R^2	R^3	R^4	R^5	**16**, Yield (%)[a]	**16**:**17**[b]
1	**14a**	H	H	NO_2	H	H	**16a**, 45	98:2
2	**14b**	H	H	CN	H	H	**16b**, 28	78:22
3	**15c**	H	H	CF_3	H	H	**16c**, 22[c]	72:28
4	**14d**	H	H	SF_5	H	H	**16d**, 22	93:7
5	**14e**	H	H	SO_2Cl	H	H	**16e**, 38	93:7
6	**14f**	H	H	SO_2F	H	H	**16f**, 41	95:5
7	**14g**	H	H	COF	H	H	**16g**, 41[c]	84:16
8	**14h**	H	H	COOH	H	H	**16h**, traces	–
9	**15i**	H	H	F	H	H	**16i**, 12[c]	n/a
10	**15j**	H	H	Cl	H	H	**16j**, 13[c]	n/a
11	**14k**	H	H	COOMe	H	H	**16k**, traces	–
12	**14l**	H	CN	H	H	H	**16l**, 23	84:16
13	**15m**	H	CF_3	H	H	H	**16m**, 21[c]	72:28
14	**14n**	H	SF_5	H	H	H	**16n**, 23	75:25
15	**14o**	NO_2	H	NO_2	H	H	**16o**, 0	–
16	**14p**	CN	H	H	H	H	**16p**, 16	60:40
17	**15q**	CN	H	NO_2	H	H	**16q**, 35	97:3
18	**15r**	CF_3	H	NO_2	H	H	**16r**, 43	98:2
19	**14s**	Cl	H	NO_2	H	H	**16s**, 8	80:20
20	**15t**	F	F	F	F	F	**16t**, traces	–

21	**15u**	OMe	NO_2	H	Cl	H	**16u**, 8	>99:1
22	**15v**	SH	H	H	H	H	**16v**, traces	–
23	**15w**	H	SH	H	H	H	**16n**, 22	83:17
24	**15x**	H	SH	H	Br	H	**16x**, 25	95:5
25	**15y**	H	H	SH	H	H	**16d**, 12	83:17
26	**15z**	H	SH	H	SH	H	**16z**, traces	–

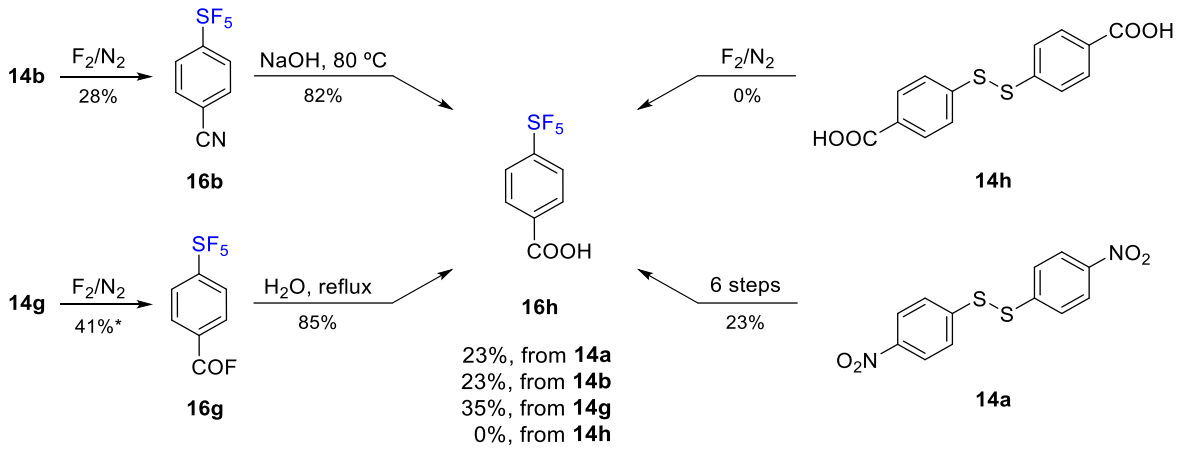
Reaction conditions: **14** or **15** (1–3 mmol), 10% F_2 in nitrogen (30 L/h), dry MeCN (25–30 mL), -5 ºC or 0 ºC, 1–4.5 h. [a]Isolated yields of **16** (unless otherwise noted). [b]Determined by GC-MS or ^{19}F NMR. [c]^{19}F NMR yield using **16a** as internal standard.



*Determined by ^{19}F NMR using **16a** as internal standard.

Scheme 27. Synthesised *para*-substituted SF_5-products

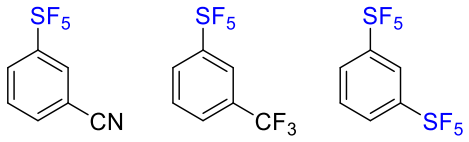
On the other hand, fluorination of thiosalicylic acid and methoxycarbonyl disulfides (entries 8 and 11, Table 4) afforded traces of **16h** and **16k**, respectively. These results could be explained by the high sensitivity of corresponding SF_3-intermediates **18h** and **18k** to hydrolysis in agreement with the presence of signals in ^{19}F NMR likely belonging to (fluorosulfonyl)benzoyl fluorides. Nevertheless, straightforward access to 4-(pentafluorosulfanyl)benzoic acid **16h** can be achieved by hydrolysis of **16g** or **16b**. Up to date, the traditional approach towards the synthesis of **16h** involves a six-step synthesis starting fromcommercially available **16a**, synthesised from **14a**.[138]



*Determined by ^{19}F NMR using **16a** as internal standard.

Scheme 28. Access to 4-(pentafluorosulfanyl)benzoic acid **16h**

The fluorination of *meta*-substituted substrates (entries 12-14, Table 4) proceeded in a similar fashion to the parent *para*-substituted analogues and **16** were obtained in moderate yields (Scheme 29). The formation of overfluorinated side-product **17** by fluorination in *meta*-position was very significant due to the *meta*-directing effect of SF_5 and EWGs present in **16l-n**.



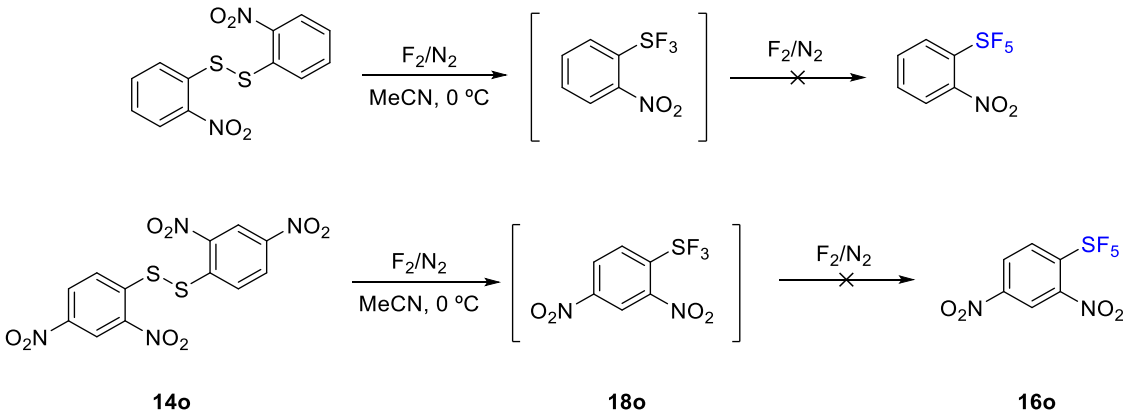
16l 28% **16m** 22%* **16n** 22%

*Determined by ^{19}F NMR using **16a** as internal standard.

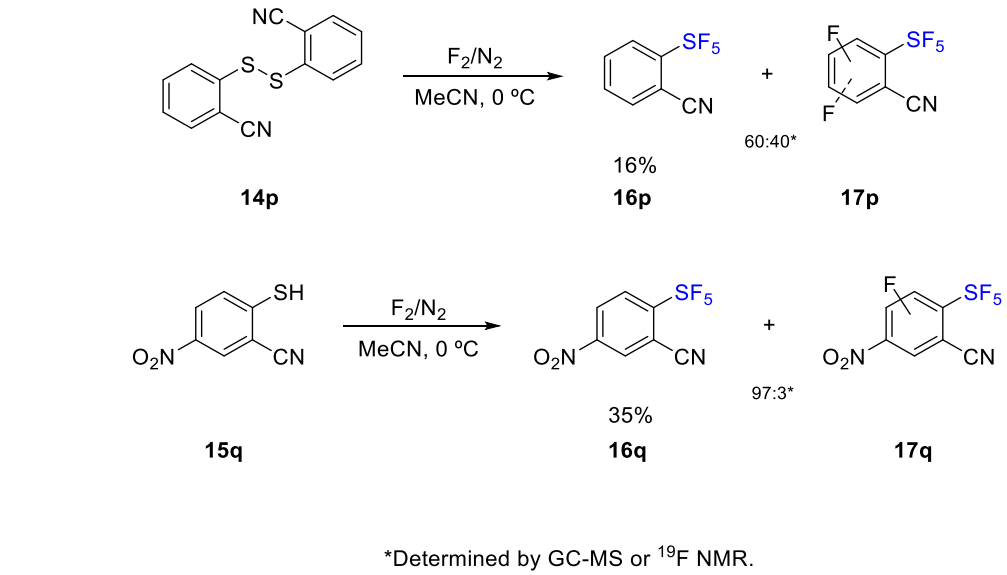
Scheme 29. Synthesised *meta*-substituted SF_5-building blocks

Fluorination of *ortho*-substituted disulfides has been scarcely described in the literature. Only a few examples affording the corresponding SF_5 product **16** in poor yield have been reported.[67] According to literature, fluorination of bis(2-nitrophenyl) disulfide resulted in the clean formation of the SF_3 intermediate and no traces of SF_5 product were found

(Scheme 30).[74] This unsuccessful result has been explained by the steric hindrance of the substituent in *ortho* position, which might constrain the last step of the reaction. Analogously, in this work, attempts of fluorination of **14o** with an excess of fluorine afforded similar result.



Scheme 30. Direct fluorination of *ortho*-nitrophenyl disulfides

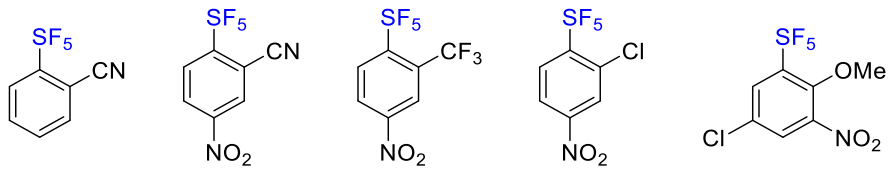


*Determined by GC-MS or ^{19}F NMR.

Scheme 31. Direct fluorination of substituted *ortho*-cyanophenyl disulfides and thiols

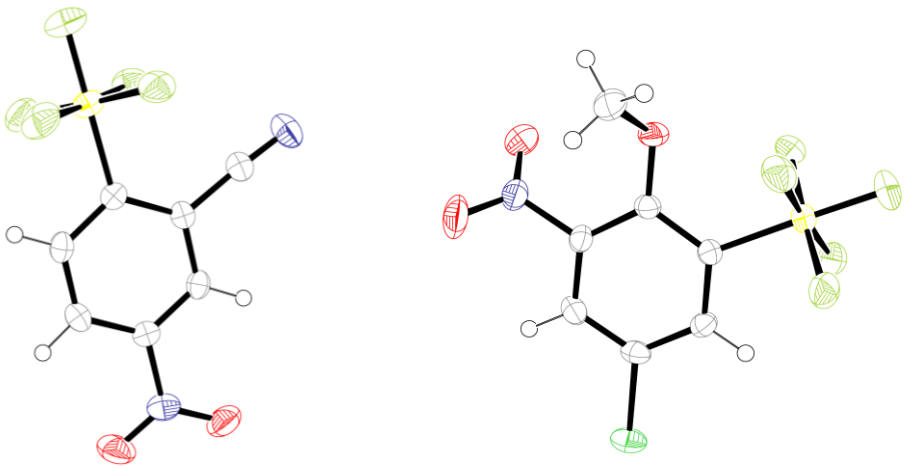
Nevertheless, the fluorination of *ortho*-substituted disulfides and thiols has been successfully carried out in this work. **14p** underwent fluorination affording **16p** in fair yield (entry 16, Table 4); however, a significant amount of over-fluorinated impurities **17p** were

formed during the process causing a detrimental impact on the regioselectivity of the reaction. To overcome this issue, the presence of an additional EWG in the starting material was crucial. Fluorination of **15q** resulted in clean formation of **16q** in good yield and high regioselectivity (entry 17, Table 4). The presence of an additional nitro group in **15q** deactivated the aromatic ring in **16q** towards fluorination and consequently, the formation of **17q** was marginal (Scheme 31). Similarly, fluorination of **15r** afforded **16r** in good yield with high regioselectivity (entry 18, Table 4). The use of aromatic thiols **15** instead of disulfides **14** as starting materials gave compatible results.



16p 16% **16q** 35% **16r** 43% **16s** 8% **16u** 8%

Scheme 32. Synthesised *ortho*-substituted SF_5-derivatives

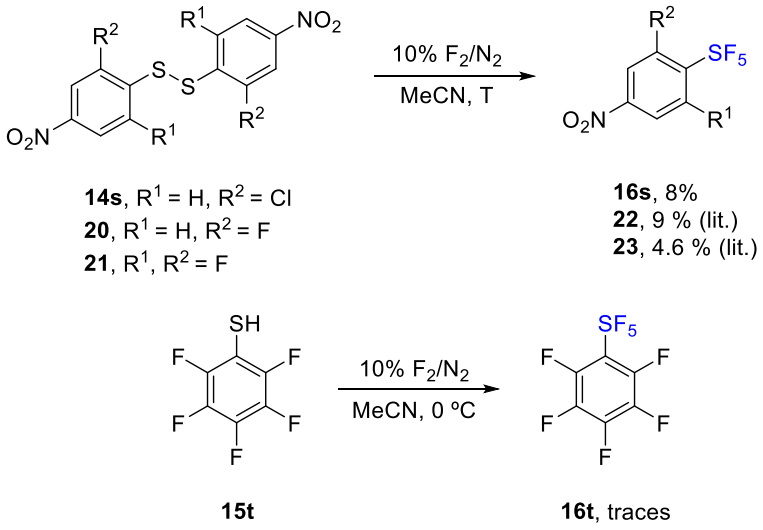


16q **16u**

Figure 8. An ORTEP view of **16q** and **16u**, displacement ellipsoids are shown with 50% probability

Interestingly, the crystal structure of **16q** (Figure 8) revealed no distortion of the octahedral geometry of the SF_5 group; however, the linearity of the cyano group is slightly distorted and displays a C-C-N bond angle of 176.86º (Calculated using Mercury 4.0.0). A higher excess of fluorine was required for the synthesis of **16p**, **16q**, **16r**, **16s** and **16u** compared to fluorination of *meta*- and *para*-substituted disulfides or thiols. This fact reflects a more difficult conversion of the *ortho*-substituted-SF_3 intermediates **18** into the corresponding SF_5-derivatives **16** probably due to steric factors.

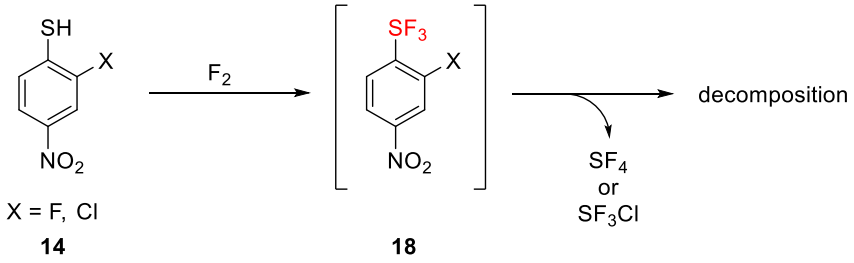
The fluorination of substituted *ortho*-halo-disulfides or thiols was problematic. The presence of halogen atoms in the *ortho* position in disulfides **14** or thiols **15** seemed to be critical for the formation of **16**. According to Kirsch, fluorination of 1,2-bis(2-fluoro-4-nitrophenyl)disulfane **20** afforded the corresponding SF_5-derivative **22** in 9% yield.[67] Analogously, the fluorination of 1,2-bis(2,6-difluoro-4-nitrophenyl)disulfane **21** afforded **23** in 4.6% yield. These results correlate with those obtained during the course of this work (Scheme 33). Fluorination of **14s** afforded **16s** in poor yield (entry 19, Table 4). In addition, only traces of **16t** where detected upon fluorination of **15t** (entry 20, Table 4).



Scheme 33. Direct fluorination of *ortho*-halo disulfides

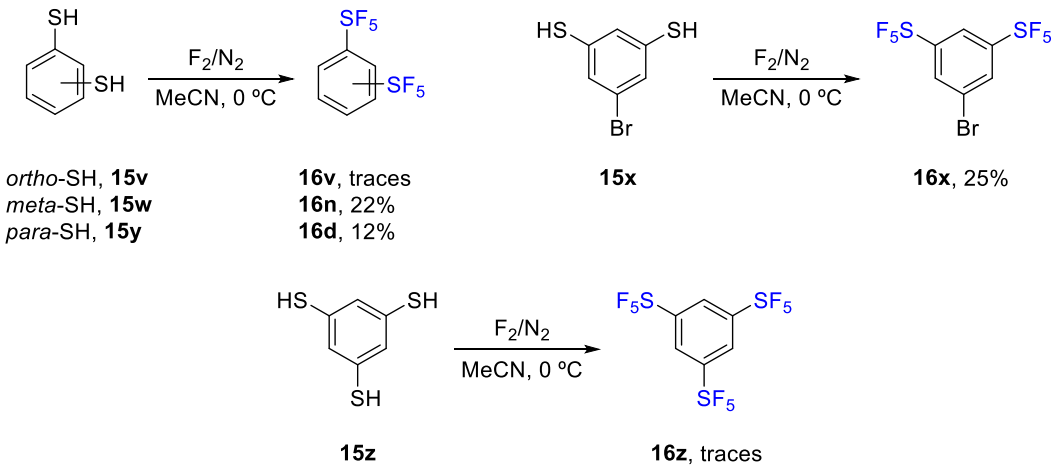
A plausible explanation of these results might be a potential release of SF_4 or SF_3Cl species from Ar-SF_3 intermediates **18** (Scheme 34). No spectroscopic evidence of this process was found; however, the fact that during the screening of the reaction by ^{19}F NMR

the intensity of the signals belonging to **18** were diminished without adequate formation of **16**, might constitute and indirect evidence of this process. At the time of submission of this dissertation, a collaboration with computational chemists to elucidate potential mechanistic pathways that would correlate with this hypothesis was in progress.

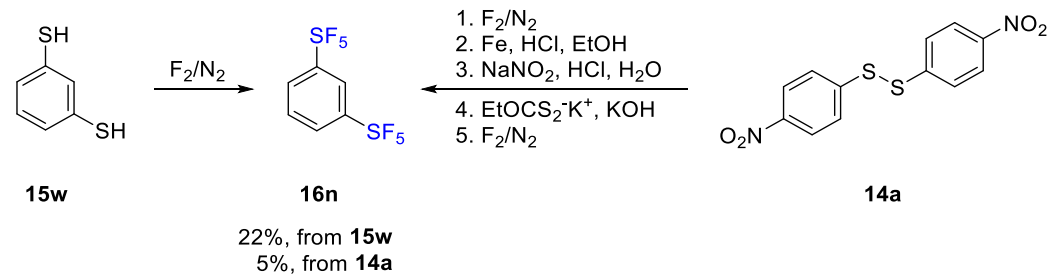


Scheme 34. Potential decomposition of Ar-SF_3 intermediates

In order to explore the possibility of forming two SF_5 fragments simultaneously, fluorination of aromatic polythiols was investigated (Scheme 35). Treatment of **15w**, **15x** and **15y** with an excess of fluorine resulted in the formation of the corresponding bis(SF_5)benzenes **16** from low to moderate yields (entries 23-25, Table 4). This strategy gave a straightforward access to 1,3-bis(pentafluorosulfanyl)benzenes **16n** and **16x** in one step and in moderate yield. Alternatively, the synthesis of **16n** has been previously described in this work by the fluorination **14n** (entry 23, Table 4); however, the overall yield for the five-step process taking into account the synthesis of **14n**, traditionally carried out from **14a**, is only 5% (Scheme 36). On the other hand, fluorination of **15v** and **15z** was unsuccessful and only afforded traces of **16v** and **16z** respectively (entries 22 and 26, Table 4).



Scheme 35. Direct fluorination of polythiols

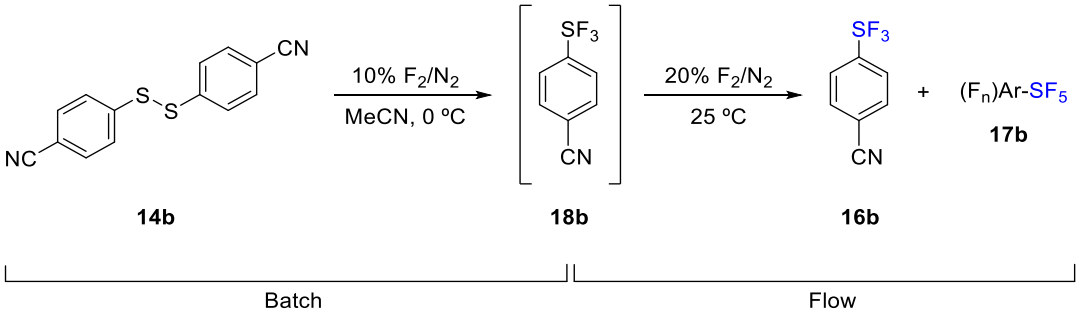


Scheme 36. Routes towards the synthesis of 1,3-bis(pentafluorosulfanyl)benzene (**16n**)

In conclusion, we have explored the scope and limitation of direct fluorination of disulfides and thiols for the synthesis of (pentafluorosulfanyl)-containing aromatics using elemental fluorine. The method is suitable for a wide variety of modified substrates bearing very different functionalities in different positions, affording SF_5-substituted benzonitriles, benzenesulfonyl chlorides and fluorides, and benzoyl fluorides in good yields. In contrast, the fluorination of dithiobenzoic acid or dimethyl dithiobisbenzoate was not successful. This result could be explained by the hydrolysis of the carbonyl function in both substrates leading to hydrolysis of the arylsulftur trifluoride intermediates. In addition, the direct fluorination of polythiols afforded bis(pentafluorosulfanyl)benzenes in moderate yields; however, the method was not suitable for 1,2-dimercaptobenzene probably due to oligomerization of Ar-S-F intermediates during the reaction preventing the formation of the arylsulftur trifluoride intermediate. The reactions proceeded in a single step, the use of metal fluorides is not required and the process has a potential for industrial scale-up. On the other hand, special facility and safety requirements for the use and handling of fluorine gas are needed.

3.1.2 Direct fluorination of disulfides applying flow-process technology

The use of flow process techniques to perform chemical reactions has received increasing attention over the last years.[139] The main advantages of the use of this technology are better mixing of the reagents, better heat transfer and simple scale-up. Better control over these parameters is translated into better control over organic reactions. In this context, the fluorination in flow of **14b** was investigated.



Scheme 37. Batch-flow synthesis of **16b**

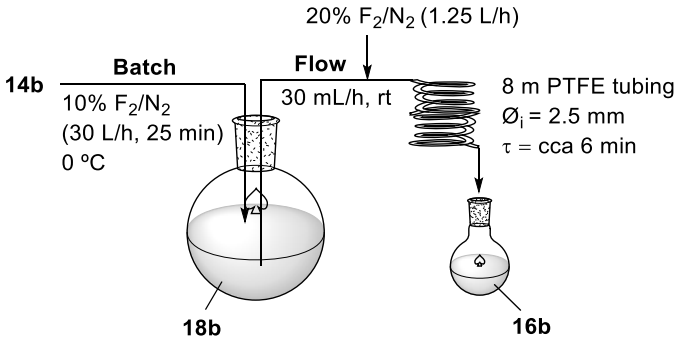


Figure 9. Hybrid batch-flow system for the fluorination of **14b**

The main limitation of the method was poor solubility of the disulfides **14** in MeCN. Attempts of carrying out the fluorination in flow-process resulted in a poor conversion of **14b** into **18b**; therefore, preformation of Ar-SF_3 (**18b**) intermediates was carried out. For this purpose, a hybrid batch-flow system was built up.

Table 5. Fluorination of **14b** by batch and batch-flow processes

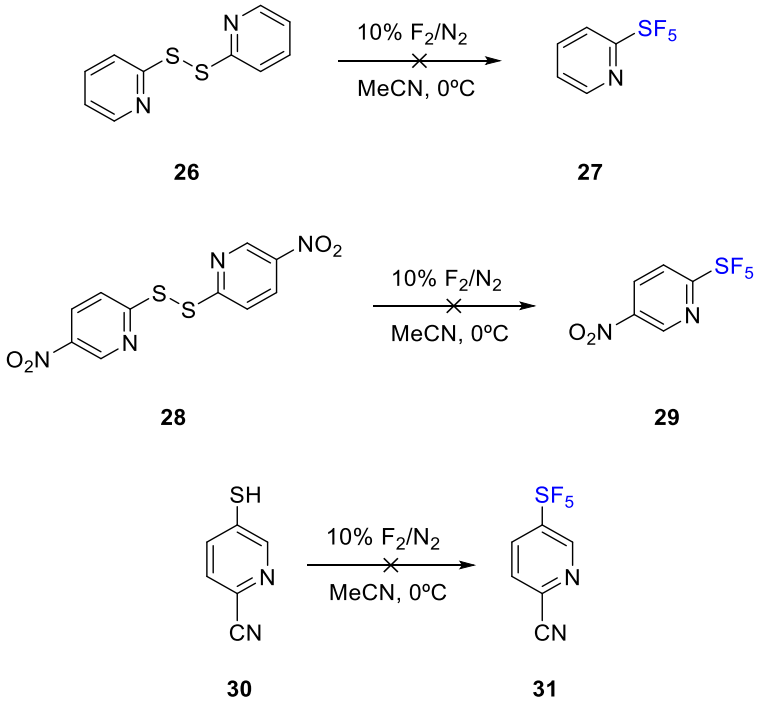
Entry	Mode	T (ºC)	**16b**, Yield (%)[a]	**16b:17b**[b]
1	Batch	-5	28	78:22
2	Batch + Flow	0 then rt	35	88:12

Reaction conditions: **14b** (1.9 mmol), dry MeCN (25–30 mL). [a]Isolated yields of **16b**. [b]Determined by GC-MS or ^{19}F NMR.

A solution of **14b** in MeCN was treated with an excess of fluorine until full conversion into **18b**. The homogeneous Ar-SF_3 solution of **18b** was then pumped into a PTFE flow reactor where the reaction with F_2 took place. **16b** was obtained in significantly higher yield and better selectivity (entry 2, Table 5) compared to the batch fluorination process (entry 1, Table 5). This result could be explained by a shorter exposure of **16b** and **18b** to F_2 during the process, which lead to a lower formation of **17b**. Although the application of this technique in this context requires further improvement, the method could be a promising alternative for the synthesis of Ar-SF_5 with enhanced efficiency, selectivity and safer handling of the fluorine gas.

3.1.3 Attempts of direct fluorination of pyridyl disulfides

Up to date, the synthesis of heteroaromatic pentafluorosulfanyl compounds is very limited.[96–98] In order to improve the availability of these important building blocks, the direct fluorination of pyridyl disulfides was investigated. With this aim, fluorination of **26**, **28** and **30** using similar conditions to those used for the synthesis of Ar-SF_5 in Section 5.3.1 was carried out.



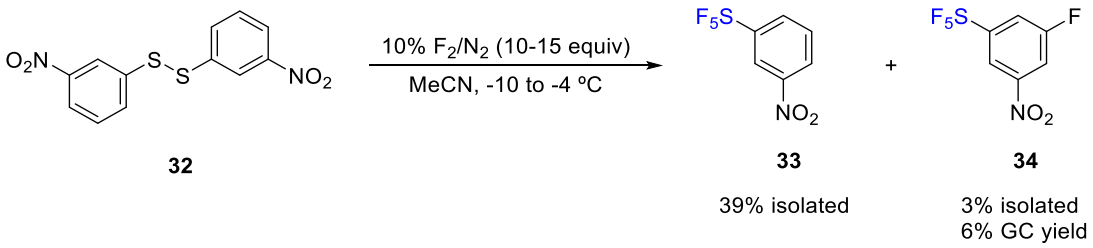
Scheme 38. Attempts of fluorination of pyridyl disulfides

During the fluorination of **26**, **28** and **30** no evidence of Py-SF_3 intermediates either of Py-SF_5 **27**, **29** or **31** were found. Possibly, the initial substrates **26-28** were converted into tar (non-volatile residue) due to the high reactivity of F_2. In conclusion, the synthesis of heteroaromatic pentafluorosulfanyl compounds by direct fluorination using F_2 was not achieved.

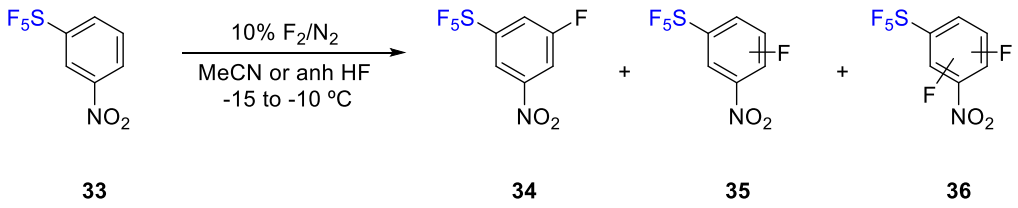
3.2 Derivatization of SF_5-containing building blocks

3.2.1 Synthesis of pentafluoro(3-fluoro-5-nitrophenyl)-λ^6-sulfane (**34**)

During the fluorination of aromatic disulfides, (poly)fluorinated arylsulfur pentafluorides $(F)_nAr\text{-}SF_5$ (n = 1, 2) were obtained as by-products of the reaction. Compound **34** was obtained almost selectively as a side-product in the reaction of **32** with F_2 due to the *meta*-directing effect of the strong electron withdrawing NO_2 and SF_5 groups, which predominantly promoted fluorination in position-5 in the ring (Scheme 39). Nevertheless, it was possible to take advantage of this side reaction as a viable method for the derivatization of SF_5-building blocks. With this aim, the direct fluorination of commercially available **33** was carried out in multi-gram scale in collaboration with Dr Greenhall and Dr Zarantonello at F2 Chemicals Ltd (Scheme 40).



Scheme 39. Direct fluorination of **32**



Scheme 40. Direct fluorination of **33**

The reactions were performed in anhydrous MeCN (Figure 10) or HF (Figure 11) as solvents and monitored by GC-MS. In both cases, the substrate **33** was fluorinated until maximal conversion (60%) of **34** was reached. The use of a higher excess of F_2 was disadvantageous since the amount of (poly)fluorinated by-products **35** and **36** were significantly higher. On the other hand, when the reaction was performed in MeCN, around 4-

fold excess of fluorine was required to reach similar conversion of **34** in comparison to the reaction using anhydrous HF. This result can be explained by fluorination of MeCN that consequently diminished efficiency of the process. The formation of non-volatile residue (tar) during the process was notably higher (28% by weight) in comparison to reaction in HF (5% by weight). Attempts of purification of **34** from **35** and **36** by column chromatography or distillation were unsuccessful.

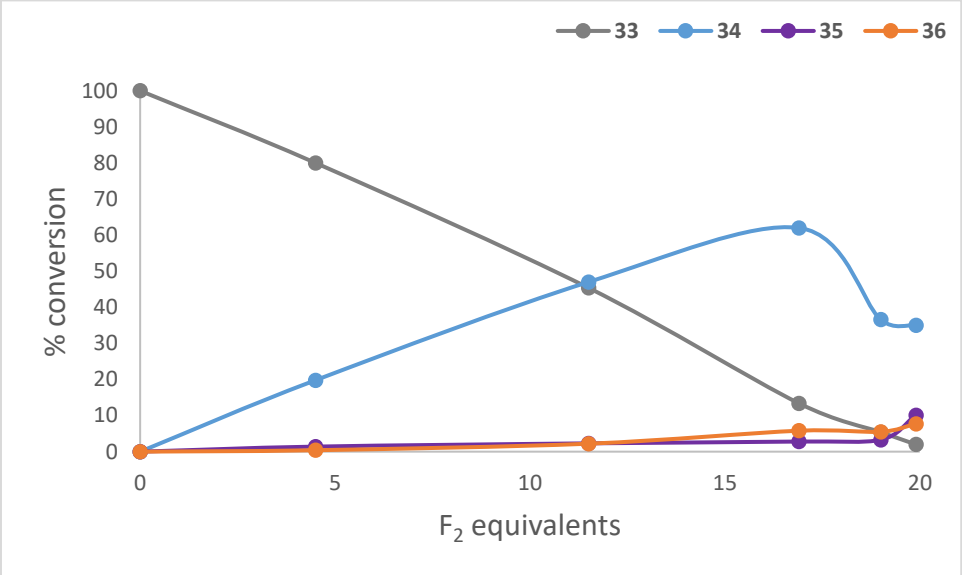


Figure 10. Reaction screening for the fluorination of **33** in dry MeCN

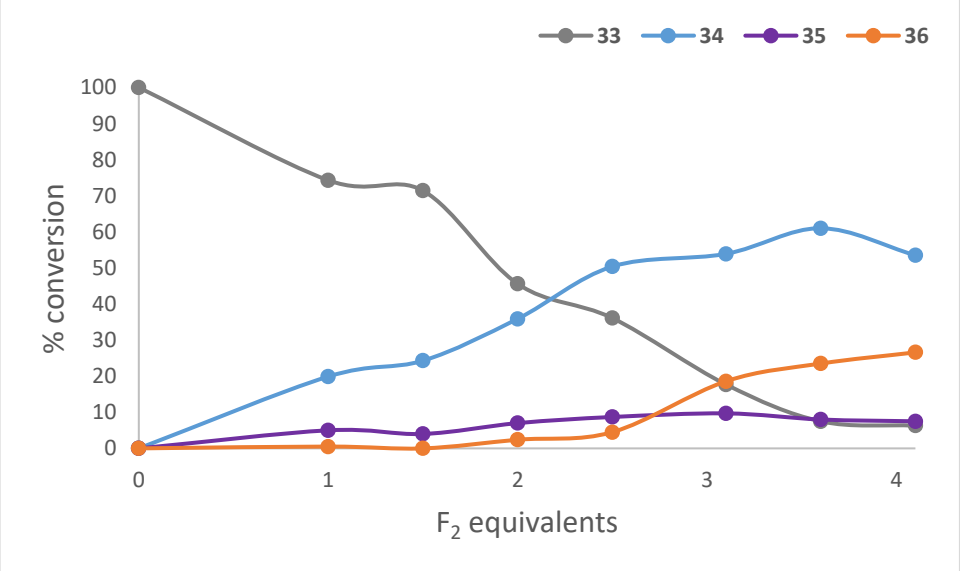
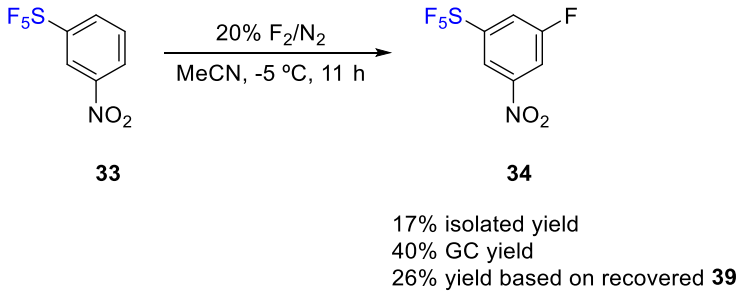


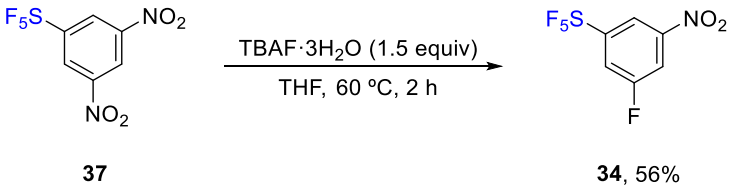
Figure 11. Reaction screening for the fluorination of **33** in anh HF

Analogously, fluorination of **33** in preparative scale was investigated. The most suitable conditions were the use of MeCN as the solvent and maximum 46% conversion of **34** (GC-MS). In this way, the amounts of **35** and **36** were significantly reduced and purification of the crude mixture by column chromatography afforded **34** in 17% isolated yield.

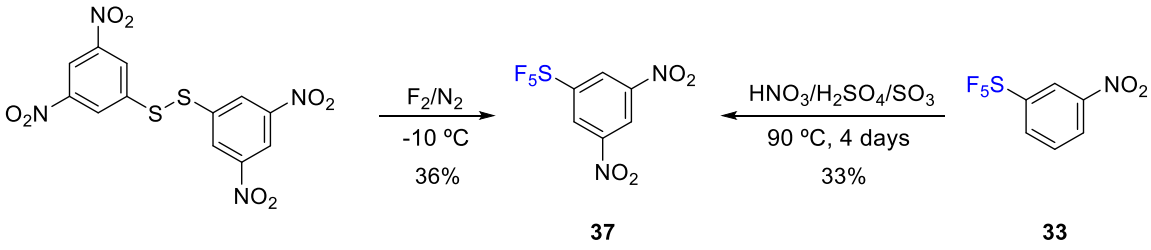


Scheme 41. Fluorination of **33** in preparative scale

Alternatively, a synthetic pathway that does not involve the use of elemental fluorine for the synthesis of **34** was investigated. Fluorodenitration of **37** with TBAF afforded **34** in 56% yield (Scheme 42). During the process, only the substitution of one nitro group by S_NAr was accomplished. The synthesis of **37** has been reported by fluorination[92] of bis(3,5-dinitrophenyl)disulfide or by nitration[116] of commercially available **33** (Scheme 43).



Scheme 42. Synthesis of **34** by fluorodenitration of **37**



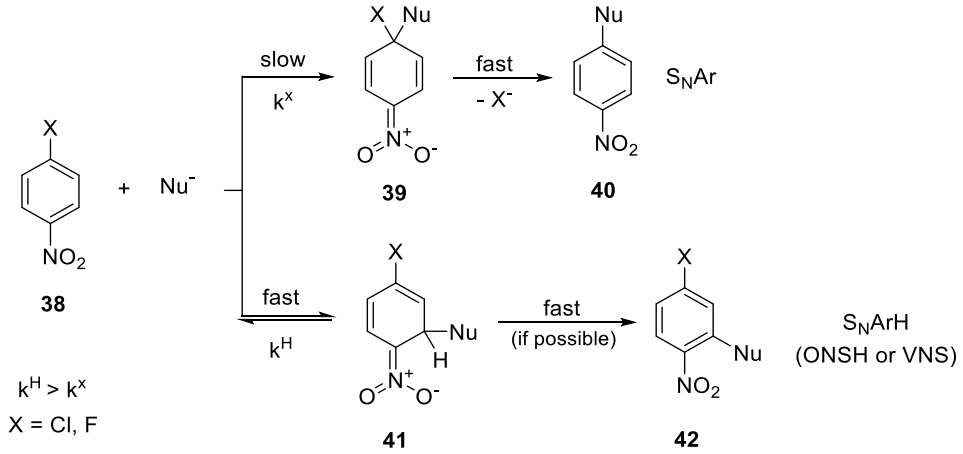
Scheme 43. Literature preparations of **37**

3.2.2 Nucleophilic substitution reactions of pentafluoro(3-fluoro-5-nitrophenyl)-λ^6-sulfane (**34**)

Derivatization of 3-fluoro-5-nitro-1-(pentafluorosulfanyl)benzene **34** was carried out by nucleophilic substitution reactions. These processes have been extensively investigated and constitute a powerful method for the derivatization of organic compounds.[140] There are six different reaction mechanisms in which the nucleophile is able to displace a leaving group.[140,141] In this work, nucleophilic aromatic substitution of fluorine (S_NAr) and vicarious nucleophilic substitution of hydrogen (VNS) were investigated.

3.2.2.1 Nucleophilic Aromatic Substitution (S_NAr) reactions of **34**

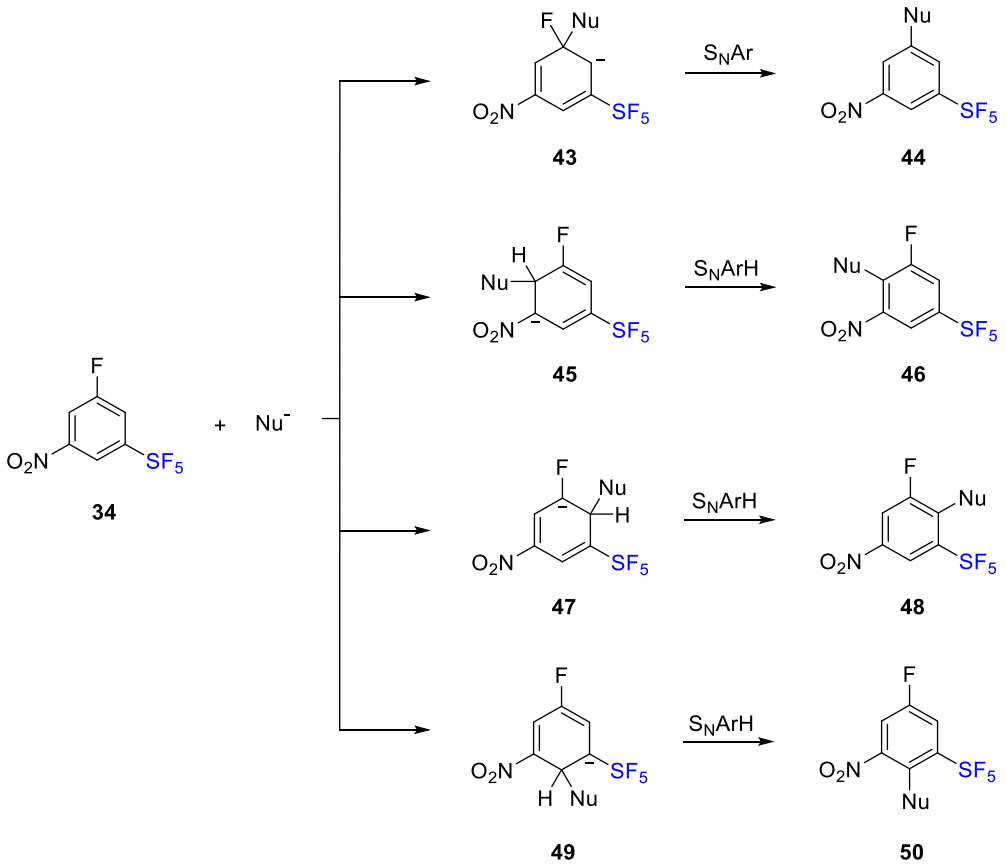
Halonitroarenes are common substrates suitable for nucleophilic aromatic substitution processes. The reaction proceeds via an addition-elimination mechanism initially postulated by Bunnett and experimentally confirmed throughout further studies. In addition, Mąkosza[142] gave a better insight into the mechanism based on computational studies and experimental observations.



Scheme 44. General mechanism for nucleophilic substitution reactions in halonitroarenes

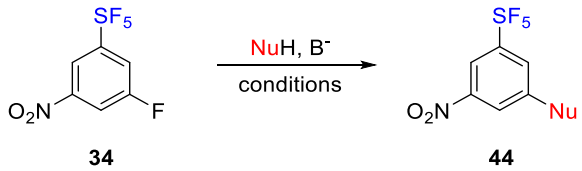
The process involves nucleophilic attack at the *ortho*- and *para*-positions to the NO_2 group in the ring, occupied by hydrogen or a halogen atom. The attack of the nucleophile

results in the formation of σ-adducts **39** and **41** with loss of aromaticity; thus is considered the rate-limiting step of the reaction. The formation of **39** is slow and subsequent spontaneous departure of X^- leads to the formation of the S_NAr product **40**. In contrast, the formation of adduct **41** is fast and reversible due to the poor leaving capability of the hydride anion leading to the kinetically favoured S_NArH product **42**. The pathway of the reaction is strongly dependent on the possibility of adduct **41** being converted into **42**, meaning that, only when **42** cannot be formed the reaction proceeds through the S_NAr pathway and therefore the thermodynamic product **40** is obtained. The conversion of adducts **41** into **42** might take place under oxidative nucleophilic substitution conditions (ONSH) or vicarious nucleophilic substitution (VNS) conditions. Alternatively, the conversion of adduct **41** into nitrosoarenes upon protonation or reaction with Lewis acids has been reported.[142]



Scheme 45. Plausible nucleophilic substitution reaction pathways in **34**

In correlation with these observations, potential nucleophilic substitution pathways in **34** are depicted in Scheme 45. Under thermodynamic conditions, the conversion of adduct **43** into the product **44** took place. The reaction of **34** with alcohol nucleophiles, such as MeOH or EtOH in the presence of a KOH upon heating resulted in the formation of the corresponding **44a-b** in very good yields (entries 1-2, Table 6). However, reactions with higher-boiling point alcohols, such as *i*-PrOH or propargyl alcohol, required the preformation of the nucleophile with NaH. In this case, the reactions were carried at room temperature and **44c-d** were obtained in good yields (entries 3-4, Table 6). The reactions with phenol, thiophenol and secondary alkyl amines (morpholine, piperidine and pyrrolidine) were carried out upon heating in the presence of K_2CO_3 (entries 5-9, Table 6). In contrast, amination and hydroxylation reactions were sluggish and required of a higher temperature for the completion of the reaction (entries 10-11, Table 6).



34 **44**

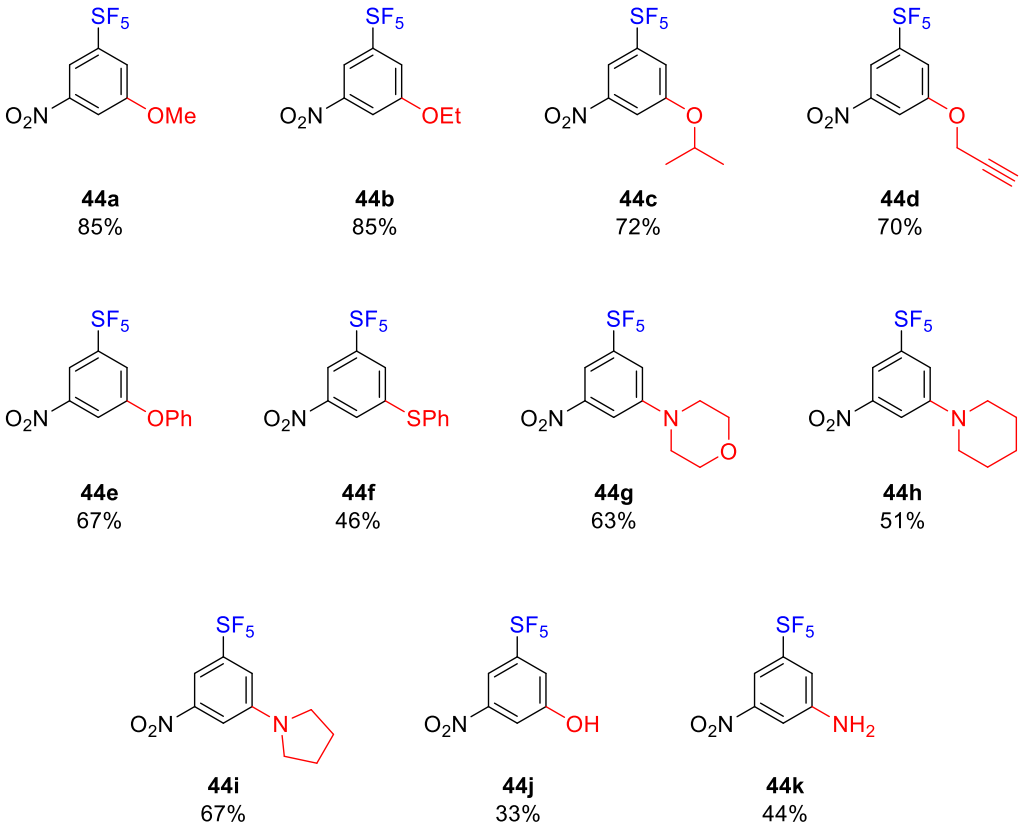
Scheme 46. General scheme for the nucleophilic substitution of fluorine in **34**

Table 6. Nucleophilic aromatic substitution reactions of **34**

Entry	NuH (equiv)	Base (equiv)	Solvent	T (ºC)	t (h)	**44**,Yield(%)[a]
1	MeOH (excess)	KOH (5)	MeOH	80	0.5	**44a**, 85
2	EtOH (excess)	KOH (3)	EtOH	80	0.6	**44b**, 85
3	*i*-PrOH (1.5)	NaH (3)	THF	rt	6	**44c**, 72
4	HC≡C-CH_2OH (1.5)	NaH (3)	THF	rt	2	**44d**, 70
5	PhOH (1.5)	K_2CO_3 (3)	DMF	80	3	**44e**, 67
6	PhSH (1.2)	K_2CO_3 (3)	DMF	90	3	**44f**, 46
7	Morpholine (3)	K_2CO_3 (3)	DMF	85	7	**44g**, 63

8	Piperidine (3)	K_2CO_3 (3)	DMF	85	3	**44h**, 51
9	Pyrrolidine (3)	K_2CO_3 (3)	DMF	85	2	**44i**, 67
10	'OH'	KOH (5)	DMSO[b]	135	6	**44j**, 33
11	'NH_2'	NH_4OH[c] (excess)	DMSO	135	5	**44k**, 44

[a]Isolated yield. [b]DMSO/H_2O (2:1, v/v). [c]28% aqueous ammonia solution.

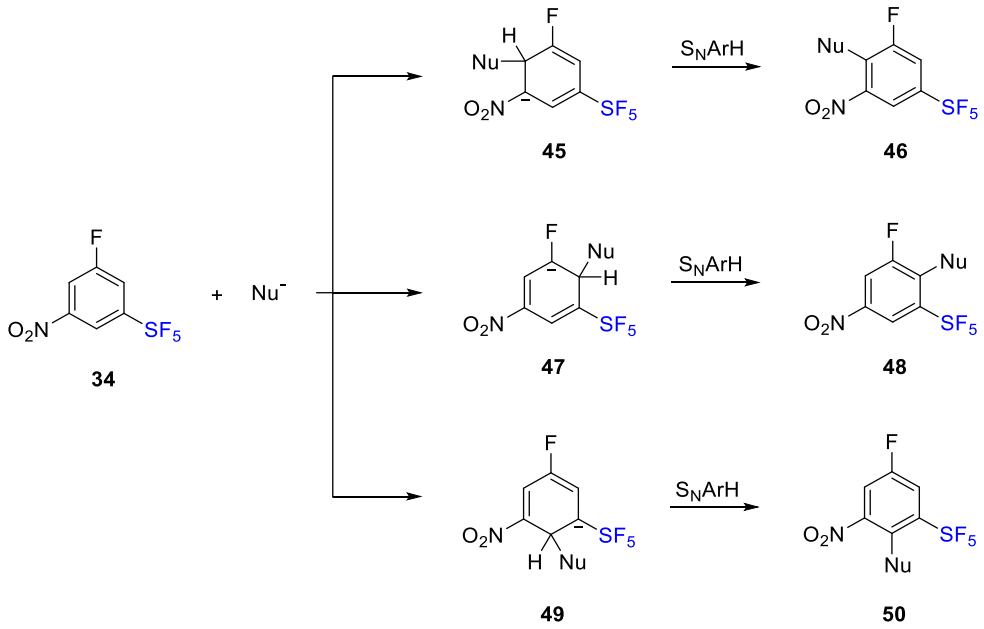


Scheme 47. S_NAr products from **34**

In conclusion, nucleophilic aromatic substitution of fluorine was proven to be versatile method for the introduction of oxygen-, nitrogen- and sulfur-functionalities by substitution of fluorine in **34**.[143]

3.2.2.2 Vicarious nucleophilic substitution (VNS) reactions of **34**

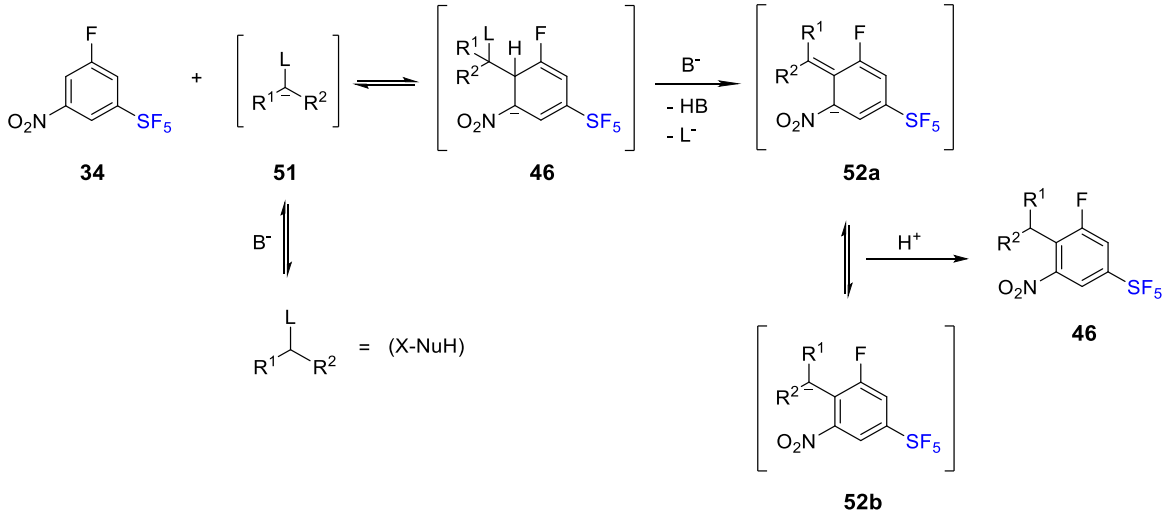
In vicarious nucleophilic substitution processes, a specific type of nucleophile, which contains a suitable leaving group, replaces a hydrogen atom in the ring of aromatic ring.[144] Mechanistically, VNS reactions differs from nucleophilic aromatic substitution processes in which, traditionally, a halogen atom is substituted by the nucleophile. General conditions for a vicarious nucleophilic substitution process are an equimolar amount of the nucleophile, short reaction times and low temperatures. Under kinetic conditions, the formation of adducts **45**, **47** and **49** took place, and therefore **46**, **48** and **50** might potentially be furnished (Scheme 48).[142,145]



Scheme 48. Reaction scheme for VNS (S_NArH) reactions of **34**

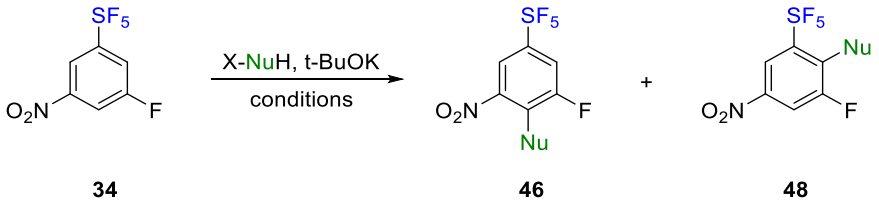
The proposed mechanism of the reaction, regarding the formation of **46** is given in Scheme 49. The first step of the reaction involves the attack of carbanion **51** to the *ortho*- and *para*- positions relative to the NO_2 group in **34**. However, the high bulkiness of the SF_5 scaffold in addition to that of the NO_2, which is planar to the ring, precludes the attack at position-6 and to a lesser extent in position-2. For this reason, **46** was the main product of the reaction and **50** was never observed in any of the reactions carried out in this work.

For this reason, the regioselectivity of the reaction was addressed as **46**:**48** isomer ratio and determined according to GC-MS peak average ratios.



Scheme 49. Detailed VNS mechanism for the formation of major isomer **46**

The second step of the reaction would involve the base-promoted β-elimination of HL with subsequent formation of intermediate **52a**, which would be in equilibrium with **52b**. Ultimately, the formation of **46** would be accomplished by acidic work-up. In addition, the chemistry of **52a** can be further exploited by the addition of an electrophile leading to VNS-alkylation products.[115]



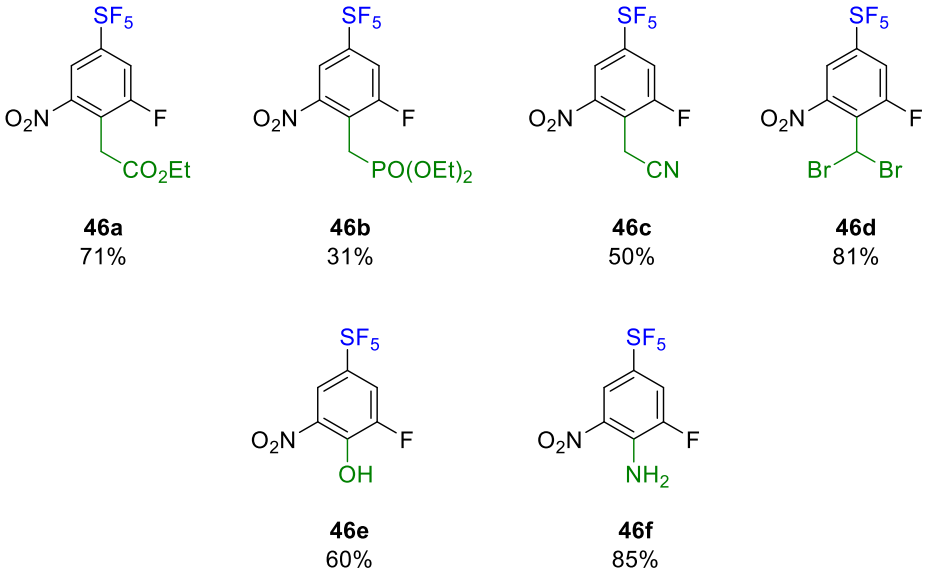
Scheme 50. General scheme for VNS reactions of **34**

The reaction of **34** with carbon nucleophiles (entries 1-4, Table 7) to furnish **46a-d** proceeded, generally, in good yields. An exception is **46b** obtained in poor yield (entry 2, Table 7). This result might be explained by the high steric demand of the carbanion formed in the reaction which might constrain the formation of the corresponding σ-adduct **45**.

Table 7. VNS reaction conditions of **34**

Entry	X-NuH (equiv)	Solvent	T (ºC)	t (min)	**46**, Yield(%)[a]	**46**:**48**[b]
1	Cl-CH_2CO_2Et (1)	DMF	-30	10	**46a**, 71	97:3
2	Cl-$CH_2PO_3Et_2$ (1)	DMF	-60	10	**46b**, 31	97:3[c]
3	PhO-CH_2CN (1)	DMF	-30	10	**46c**, 50	87:13
4	Br-$CHBr_2$ (1.1)	DMF/THF[d]	-70	2	**46d**, 81	>98:2[c]
5	$PhC(CH_3)_2O$-OH (1)	NH_3/THF[e]	-50	15	**46e**, 60	96:4
6	$I^-Me_3N^+$-NH_2 (1.8)	DMSO	rt	5	**46f**, 85	>98:2

Base: *t*-BuOK (3 equiv). [a]Isolated yields. [b]Determined by GCMS of the crude reaction mixture. [c]Determined by ^{19}F NMR of the crude reaction mixture. [d]DMF/THF (7:2, v/v). [e]NH_3/THF (4:1, v/v).



Scheme 51. VNS products from **34**

One-pot synthesis of **46f** was carried out upon treatment of **34** with 1,1,1-trimethylhydrazinium iodide (TMHI) as carbanion precursor with ultimate departure of trimethylamine (Me_3N) (entry 6, Table 7). The efficiency of TMHI as a VNS aminating agent in nitroarenes was previously reported by Pagoria.[146] In the same context, hydroxylation of

34 to afford phenol **46e** was achieved by the use of cumene hydroperoxide and liquid ammonia (NH_3) as co-solvent (entry 5, Table 7). All the reactions proceeded with high regioselectivity except when phenoxyacetonitrile was used as carbanion precursor **51** (entry 3, Table 7).

In conclusion, VNS is a powerful and mild method for the introduction of carbon, nitrogen and oxygen functionalities in electron-deficient arenes such as aromatic pentafluorosulfanyl derivatives. The presence of the SF_5 scaffold has a strong influence in the regioselectivity of the reaction mainly due to the steric factor, leading predominantly to *ortho*-functionalized nitro-SF_5-derivatives as major products. The fact that the fluorine atom of **46** remains intact during the process even in the presence of strong nucleophiles such as *t*-BuOK can be translated into a potential further exploitation of these derivatives by nucleophilic substitution processes.[143]

4 General conclusions and perspectives

Aromatic pentafluorosulfanyl derivatives have received an increasing interest over the last years due to the discovery of synthetic practical methods and potential applications in pharmaceutical, agrochemical and materials science. The main purpose of this work was to improve current low availability and accessibility of primary SF_5-building blocks, which limits the development of this chemistry.

Direct fluorination of disulfides is one of the main strategies used for the synthesis of Ar-SF_5, carried out by industry in kilogram-scale; however, the method was only limited to the fluorination of *para*- and *meta*-nitrophenyl disulfides to afford 4-nitro(pentafluorosulfanyl)benzene (**16a**) and 3-nitro(pentafluorosulfanyl)benzene (**39**). In this work, we showed that the direct fluorination strategy tolerates a wide range of substituted disulfides bearing very different functionalities. Furthermore, we have described feasible and convenient access to an ample variety of non-commercial novel substituted disulfides, ultimately submitted to fluorination using elemental fluorine.

Fluorination of *para*-substituted disulfides afforded important Ar-SF_5 building blocks such as, 4-(pentafluorosulfanyl)benzonitrile (**16b**), 4-(pentafluorosulfanyl)benzene-1-sulfonyl chloride (**16e**), 4-(pentafluorosulfanyl)benzene-1-sulfonyl fluoride (**16f**) and 4-(pentafluorosulfanyl)benzoyl fluoride (**16g**). Convenient and straightforward access to 4-(pentafluorosulfanyl)benzoic acid (**16h**) has been described in a single-step synthesis by hydrolysis of 4-(pentafluorosulfanyl)benzonitrile or 4-(pentafluorosulfanyl)benzoyl fluoride.

Importantly, the fluorination of *ortho*-substituted disulfides was successfully achieved. Nevertheless, the presence of additional EWG substituents in the ring is desirable to supress the formation of over-fluorinated arylsulfur pentafluoride derivatives (**17**). In this fashion, 3-nitro-6-(pentafluorosulfanyl)benzonitrile (**16q**) and 4-nitro-2-(trifluoromethyl)arylsulfur pentafluoride (**16r**) were obtained in good yield and regioselectivity. In contrast, the fluorination of *ortho*-halo-substituted disulfides, such as 1,2-bis(2-chloro-4-nitrophenyl)disulfane (**14s**) and 2,3,4,5,6-pentafluorothiophenol (**15t**) was problematic.

We speculated that a hypothetical sulfur fluoride elimination, taking place during the formation of the arylsulftur trifluoride intermediate (**18**), might occur. In addition, the fluorination of dimercaptobenzenes **15w** and **15x** gave straightforward access to bis(pentafluorosulfanyl)benzenes **16n** and **16x**, respectively in one step in moderate yield.

The derivatization of primary SF_5-building blocks has been carried out by fluorination and subsequent nucleophilic substitution processes. Fluorination of commercially available 3-nitro(pentafluorosulfanyl)benzene using elemental fluorine to afford 3-fluoro-5-nitro-1-(pentafluorosulfanyl)benzene (**34**) was carried out. The latter was submitted to nucleophilic substitution processes. Nucleophilic aromatic substitution (S_NAr) of fluorine of **34** allowed the introduction of nitrogen, oxygen and sulfur nucleophiles leading to novel substituted nitro(pentafluorosulfanyl)benzene derivatives **44** in moderate to very good yields. Analogously, vicarious nucleophilic substitution (VNS) of hydrogen in 3-fluoro-5-nitro-1-(pentafluorosulfanyl)benzene, allowed the introduction of carbon, nitrogen and oxygen functionalities affording substituted fluoro-nitro(pentafluorosulfanyl)benzene derivatives **46** in good yields and high selectivities. The presence of the nitro and SF_5 groups in the initial substrate, predominantly led to the formation of adduct **45** and thus **46** was the main product of the reaction. Derivatives **46** have the potential of being further exploited by S_NAr of fluorine, which remained intact during the VNS reactions of 3-fluoro-5-nitro-1-(pentafluorosulfanyl)benzene.

The processes shown in this work are ready to be scaled-up by the industry to provide a more economical and easier access to basic SF_5-building blocks. We believe that this work will contribute to the dissemination of the SF_5-chemistry to unleash all the potential of these derivatives in many scientific fields.

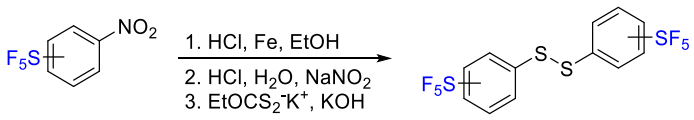
5 Experimental part

5.1 General remarks – instrumentation and methods

NMR spectra were recorded at 25 ºC in $CDCl_3$, acetone-*d*$_6$ or DMSO-*d*$_6$. Chemical shifts (δ) are reported in ppm and referenced to residual signals of solvents or internal standards: $CHCl_3$ $\delta_H = 7.26$, $\delta_C = 77.16$; acetone-*d*$_6$ $\delta_H = 2.05$, $\delta_C = 29.84$; DMSO-*d*$_6$ $\delta_H = 2.50$, $\delta_C = 39.52$; Me_4Si $\delta_H = 0.00$; $CFCl_3$ $\delta_F = 0.0$. Coupling constants (*J*) are given in Hertz. ^{13}C and ^{19}F NMR spectra were ^{1}H decoupled. GC-MS spectra were recorded on an Agilent 7890A gas chromatograph coupled with a 5975C quadrupole mass-selective electron impact (EI) detector (70 eV). High-resolution mass spectra (HRMS) were recorded on an Agilent 7890A gas chromatograph coupled with a Waters GCT Premier orthogonal acceleration time-of-flight detector using electron impact (EI) or chemical (CI) ionizations, or on an LTQ Orbitrap XL using electrospray ionization (ESI). Elemental analyses were obtained using a Perkin–Elmer PE 2400 Series II CHNS. Purification of the products was performed by flash chromatography using silica gel 60 or silica gel 100 C_{18}-reversed phase. Dry solvents were obtained the following way: THF was freshly distilled over Na/benzophenone. HiPerSolv CHROMANORM Acetonitrile was purchased from VWR Chemicals (exp. < 5 ppm H_2O). **14a**, **14h**, **15i**, **15j**, **15t**, **15y**, **26**, **28**, 1,2-dichloro-4-nitrobenzene, 3-cyanobenzenesulfonyl chloride, 1-chloro-4-methoxybenzene and sodium sulfide (Na_2S) were purchased from Sigma Aldrich. **14o** was purchased from TCI Chemicals. **15c**, **15m**, 2-fluoro-5-nitrobenzotrifluoride and 2-fluorobenzonitrile were purchased from Apollo Chemicals Ltd. Isolated products had ≥95% purity as determined by ^{1}H, ^{19}F NMR or GC-MS.

5.2 Synthesis of disulfides (**14**) and thiols (**15**)

5.2.1 General Method I: Synthesis of (pentafluorosulfanyl)phenyl disulfides



Classical xanthate method[147] was found to be suitable for the synthesis of SF_5-disulfides starting from commercially available *meta*- and *para*-SF_5-nitrobenzene.

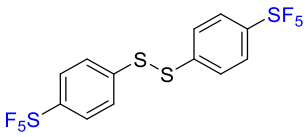
1. To a solution of the corresponding SF_5-nitrobenzene (1 equiv, 10 g, 40.2 mmol) in EtOH (150 mL) concentrated HCl (2.0 equiv, 6.8 mL, 80.4 mmol) and Fe powder (6 equiv, 13.5 g, 241.2 mmol) were added. The solution was stirred for 1.5 h at room temperature and then, the crude mixture was passed through a celite plug (2.5 cm) to remove the metal residue. The filtrate was neutralized with Na_2CO_3 until alkaline and ultimately extracted with EtOAc (4 × 20 mL). The combined organic phase was washed (brine), dried ($MgSO_4$) and the solvent was removed under reduced pressure. The corresponding anilines were obtained in almost quantitative yield and were used without any further purification for the next step.

2. To a stirred mixture of ice (30 g) and concentrated HCl (3.8 mL, 45.6 mmol, 2.5 equiv) the corresponding aniline (1 equiv, 5.0 g, 22.8 mmol) obtained in the previous step was added. The mixture was cooled to 0 ºC and an ice-cooled solution of $NaNO_2$ (1.78 g, 25.1 mmol, 1.1 equiv) in water (8 mL) was dropwise added. The diazonium salt solution was stirred for another 15 minutes and kept at 0 ºC for the next step.

3. In a two-necked 250 mL round bottom flask, equipped with a thermometer, potassium ethyl xanthate (8.48 g, 52.3 mmol, 1.14 equiv) was dissolved in H_2O/CH_3CN (9:1, 50 mL) while stirring. The temperature of the solution was kept at 45 ºC and the diazonium salt solution was added dropwise to the xanthate solution over a period of 30 min. The reaction was stirred for 1 h and then allowed to cool to room temperature. The crude mixture was extracted with EtOAc (3 × 20 mL) and the organic extracts were washed

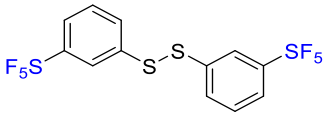
with 10% aq. NaOH (20 mL), brine (20 mL), dried ($MgSO_4$) and the solvent was removed under reduced pressure affording a red oil (ca 7 g). The oil was dissolved in EtOH (30 mL), KOH pellets (10.5 g, 187 mmol, 4 equiv) were added and the stirred mixture was refluxed for 3 h. The crude was concentrated and the residue was dissolved in water (50 mL), extracted with Et_2O (3 × 15 mL) and the organic phase was discarded. After the water phase was cooled and acidified with H_2SO_4 (20%, 25 mL) until pH = 3, gas evolution (COS) was observed. The crude mixture was extracted with EtOAc (4 × 25 mL), washed with water (3 × 20 mL), brine (50 mL), and dried ($MgSO_4$). The combined organic phase was concentrated under reduced pressure obtaining a red oil which contained SF_5-thiophenol (sensitive to air oxidation) and SF_5-disulfide (ca 6.6 g). Column chromatography of the residue afforded pure fractions of disulfide **14d** and **14n**, respectively. The corresponding thiophenols can be fully converted into disulfides by oxidation following literature procedures.[148]

1,2-Bis(4-(pentafluoro-λ^6-sulfanyl)phenyl)disulfane (14d)



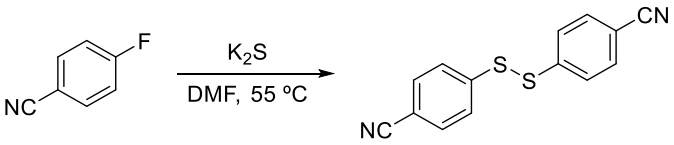
Prepared according to General Method I. Column chromatography (silica gel, hexane/EtOAc, 10:90) afforded **14d** as a pale yellowish solid (2.95 g, 55% yield); m.p. 88–90 ºC; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.73–7.68 (m, 4H), 7.54 (d, $^3J_{HH}$ = 8.8 Hz, 4H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 152.78 (p, $^2J_{CF}$ = 17.2 Hz), 140.60, 127.01 (p, $^3J_{CF}$ = 4.8 Hz), 126.32; **^{19}F NMR** (377 MHz, $CDCl_3$) δ 84.42–82.34 (m, 2F), 62.65 (d, $^2J_{FF}$ = 149.9 Hz, 8F); **HRMS** (EI) *m/z* calcd for $C_{12}H_8F_{10}S_4$ $[M]^+$ 469.9349, found 469.9348.

1,2-Bis(3-(pentafluoro-λ^6-sulfanyl)phenyl)disulfane (14n)



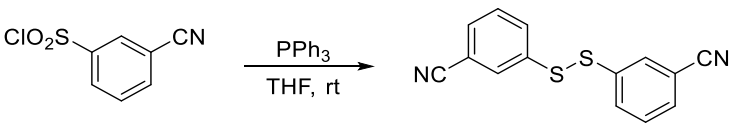
Prepared according to General Method I. Column chromatography (silica gel, hexane/EtOAc, 5:95) afforded **14n** as a pale yellowish oil (2.81 g, 53% yield; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.88 (t, $^4J_{HH}$ = 1.9 Hz, 2H), 7.69–7.58 (m, 4H), 7.43 (t, $^3J_{HH}$ = 8.1 Hz, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 155.09–154.17 (m), 137.87, 133.42, 130.95, 129.78, 125.69–125.22 (m); **^{19}F NMR** (377 MHz, $CDCl_3$) δ 84.49–80.51 (m, 2F), 62.15 (d, $^2J_{FF}$ = 150.3 Hz, 8F).

4-((4-Isocyanophenyl)disulfanyl)benzonitrile (14b)



Prepared according to literature procedure reported by Tickner.[149] Beige solid, m.p. 172–173 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.62–7.58 (m, 4H), 7.57–7.53 (m, 4H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 142.20, 132.89, 126.62, 118.27, 111.02.

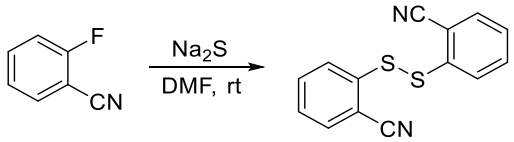
3-((3-Isocyanophenyl)disulfanyl)benzonitrile (14l)



Prepared according to literature procedure[150] from commercially available 3-cyanobenzenesulfonyl chloride; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.75 (ddd, $^4J_{HH}$ = 2.1, $^4J_{HH}$ = 1.5, $^4J_{HH}$ = 0.6 Hz, 2H), 7.69 (ddd, $^3J_{HH}$ = 8.0, $^4J_{HH}$ = 2.0, $^4J_{HH}$ = 1.1 Hz, 2H), 7.55 (ddd, $^3J_{HH}$

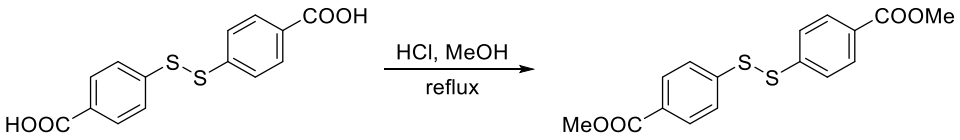
= 7.7, $^{4}J_{HH}$ = 1.2 Hz, 1H), 7.48–7.43 (m, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 138.04, 131.29, 131.12, 130.14, 130.11, 118.00, 113.89.

2-((2-Isocyanophenyl)disulfanyl)benzonitrile (14p)



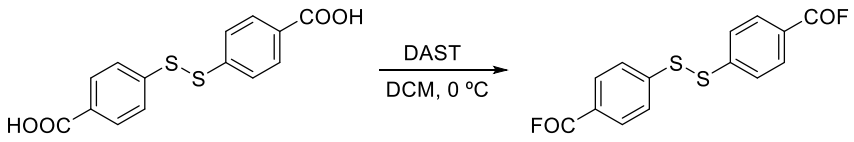
Prepared according to literature procedure reported by Taldone;[151] pale yellowish solid; m.p. 103–104 ºC; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.78 (ddd, $^{3}J_{HH}$ = 8.2, $^{4}J_{HH}$ = 1.2, $^{5}J_{HH}$ = 0.6 Hz, 2H), 7.65 (ddd, $^{3}J_{HH}$ = 7.6, $^{4}J_{HH}$ = 1.5, $^{5}J_{HH}$ = 0.5 Hz, 2H), 7.59 (ddd, $^{3}J_{HH}$ = 8.1, $^{3}J_{HH}$ = 7.5, $^{4}J_{HH}$ = 1.5 Hz, 2H), 7.39 (td, $^{3}J_{HH}$ = 7.6, $^{4}J_{HH}$ = 1.2 Hz, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 139.93, 133.77, 133.58, 129.94, 128.39, 116.21, 113.18.

Dimethyl 4,4'-disulfanediyldibenzoate (14k)



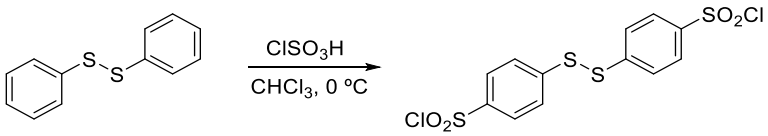
To a solution of commercially available 4,4'-disulfanediyldibenzoic acid (1 equiv, 1.00 g, 3.26 mmol) in MeOH (50 mL), concentrated HCl (2 mL) was added and the reaction mixture was refluxed for 20 h. Then, the crude mixture was filtered and the resultant solid was dried under reduced pressure. The product was recovered as a beige powder (1.04 g, 95%) and was used for direct fluorination without any further purification; m.p. 130–132 ºC; **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.03–7.84 (m, 4H), 7.75–7.54 (m, 4H), 3.83 (s, 6H); **^{13}C NMR** (101 MHz, DMSO-d_6) δ 165.55, 141.26, 130.15, 128.45, 126.16, 52.23.

4,4'-Disulfanediyldibenzoyl fluoride (14g)



To an ice cooled solution of commercially available 4,4'-disulfanediyldibenzoic acid (1 equiv, 1 g, 3.26 mmol) in DCM (50 mL), DAST (2.5 equiv, 1.31 g, 8.15 mmol) was added dropwise. The reaction mixture was kept at the same temperature and stirred for 1 h. After completion, the crude mixture was concentrated under reduced pressure. The solid was washed with *n*-pentane (2 × 10 mL) and dried under high vacuum. The product was obtained as a beige solid (0.91 g, 93%) and was used for direct fluorination without any further purification; **^{1}H NMR** (400 MHz, DMSO-*d*$_6$) δ 8.05–8.01 (m, 4H), 7.77 (d, $^{3}J_{HH}$ = 8.4 Hz, 4H); **^{13}C NMR** (101 MHz, DMSO-*d*$_6$) δ 158.15, 154.75, 144.32, 132.21 (d, $^{3}J_{CF}$ = 3.5 Hz), 128.84, 126.35, 122.79 (d, $^{1}J_{CF}$ = 61.8 Hz); **^{19}F NMR** (377 MHz, DMSO-*d*$_6$) δ 19.12 (s, 2F).

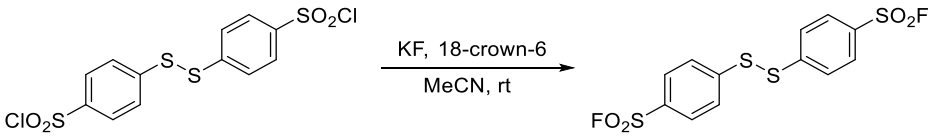
4,4'-Disulfanediyldibenzenesulfonyl chloride (14e)



To an ice-cooled solution of commercially available diphenyl disulfide (1 equiv, 2.00 g, 9.16 mmol) in $CHCl_3$ (50 mL), $ClSO_3H$ (6 equiv, 6.40 g, 54.96 mmol) was added dropwise over 20 minutes. The solution was stirred for another 5 min at 0 ºC, then allowed to warm up to room temperature and ultimately stirred for additional 3 h. Then, the crude mixture was slowly poured onto ice/water and a sticky yellow solid precipitated. The mixture was filtered and the yellow solid was discarded. The filtrate was extracted with $CHCl_3$ (3 × 10 mL), the combined organic extracts were washed with brine (50 mL), dried ($MgSO_4$) and the solvent was removed under reduced pressure. The product was recovered as a beige solid (1.33 g, 90%) and was submitted to direct fluorination without any

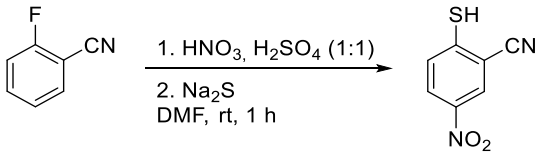
further purification; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.02–7.96 (m, 4H), 7.74–7.66 (m, 4H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 145.00, 143.04, 128.04, 126.61.

4,4'-Disulfanediyldibenzenesulfonyl fluoride (14f)



To a solution of 4,4'-disulfanediyldibenzenesulfonyl chloride (1 equiv, 1.6 g, 3.85 mmol.) in MeCN (50 mL), KF (4 equiv, 0.9 g, 15.4 mmol) and 18-crown-6 (20% mol, 0.203 g) were added. The solution was stirred overnight at room temperature. After completion of the reaction, water (100 mL) was added and the crude mixture was extracted with EtOAc (3 × 20 mL). The combined organic phase was washed with brine (50 mL), dried ($MgSO_4$) and the solvent was removed under reduced pressure. The product was recovered as a beige solid (1.33 g, 90%) and was used without further purification for direct fluorination; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.98–7.94 (m, 4H), 7.73–7.67 (m, 4H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 145.41, 131.77 (d, $^{3}J_{CF}$ = 25.6 Hz), 122.44, 126.65; **^{19}F NMR** (377 MHz, $CDCl_3$) δ 66.02 (s, 2F) ; **HRMS** (EI) *m/z* calcd for $C_{12}H_8F_2O_4S_4$ $[M]^+$ 381.9274, found 381.9277.

2-Mercapto-5-nitrobenzonitrile (15q)

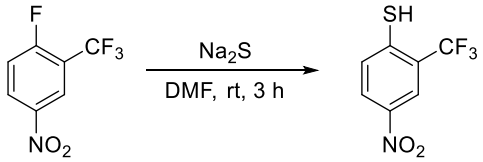


1. 2-Fluoro-5-nitrobenzonitrile was prepared starting from commercially available 2-fluorobenzonitrile according to the literature procedure reported by Bridges;[152] **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.58 (dd, $^{4}J_{HH}$ = 5.4, $^{5}J_{HH}$ = 2.8, 1H), 8.52 (ddd, $^{3}J_{HH}$ = 9.2, $^{3}J_{HH}$ = 4.4, $^{4}J_{HH}$ = 2.8 Hz, 1H), 7.45 (ddd, $^{3}J_{HH}$ = 9.2, $^{3}J_{HH}$ = 7.7, $^{5}J_{HH}$ = 1.5 Hz, 2H),

7.39 (td, $^{3}J_{HH}$ = 7.6, $^{4}J_{HH}$ = 1.2 Hz, 2H); **^{19}F NMR** (376 MHz, $CDCl_3$) δ -96.31 (s, 1F). The titled compound was used for the synthesis of 2-mercapto-5-nitrobenzonitrile without any further purification.

2. To a solution of 2-fluoro-5-nitrobenzonitrile (1 equiv, 2.05 g) in DMF (50 mL), Na_2S (1.1 equiv, 1.73 g, 60%) was added. The mixture was stirred for 1 h at room temperature. After completion, the crude was poured into water/ice (200 mL), acidified to pH = 1–3 with HCl (1M), extracted with Et_2O (4 × 20 mL) and the combined organic extracts were washed with LiCl (1M, 50 mL), brine, dried ($MgSO_4$). After removal of the solvent under reduced pressure, the product was recovered as an orange solid (1.73 g, 78%) and was used for direct fluorination without any further purification; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.46 (d, $^{4}J_{HH}$ = 2.8, 1H), 8.27 (dd, $^{3}J_{HH}$ = 8.8, $^{4}J_{HH}$ = 2.5 Hz, 1H), 7.57 (d, $^{3}J_{HH}$ = 8.8 Hz, 1H), 4.51 (s, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$) 147.32, 145.14, 129.38, 128.60, 127.41, 115.59, 111.85; **HRMS** (EI) *m/z* calcd for $C_7H_4N_2O_2S$ $[M]^+$ 179.9993, found 179.9997.

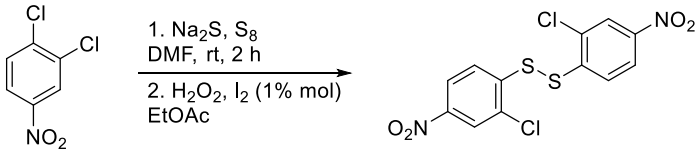
4-Nitro-2-(trifluoromethyl)benzenethiol (15r)



To a solution of 2-fluoro-5-nitrobenzotrifluoride (1 equiv, 2.50 g) in DMF (50 mL), Na_2S (1.1 equiv, 1.70 g, 60%) was added. The mixture was stirred for 3 h at room temperature. After completion, the crude mixture was poured onto water (100 mL), acidified to pH = 1–3 and extracted with Et_2O (4 × 20 mL). The combined organic extracts were washed with LiCl (1M, 50 mL), brine, dried ($MgSO_4$) and the solvent was removed under reduced pressure. The product was recovered as an orange solid (2.05 g, 77%) and was used for direct fluorination without any further purification; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.49 (d, $^{4}J_{HH}$ = 2.5 Hz, 1H), 8.21 (dd, $^{3}J_{HH}$ = 8.7 Hz, $^{4}J_{HH}$ = 2.5 Hz, 1H), 7.54 (d, $^{3}J_{HH}$ = 8.7 Hz, 1H), 4.13 (q, $^{4}J_{HH}$ = 3.4 Hz, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$) 145.24, 141.95–

141.86 (m), 132.17, 128.24 (q, $^{2}J_{CF}$ = 32.7 Hz), 126.52, 123.06–122.74 (m), 122.71 (q, $^{1}J_{CF}$ = 274.1 Hz); **^{19}F NMR** (376 MHz, $CDCl_3$) δ -63.88 (s, 3F). **HRMS** (EI) *m/z* calcd for $C_7H_4F_3NO_2S$ $[M]^+$ 222.9915, found 222.9914.

1,2-Bis(2-chloro-4-nitrophenyl)disulfane (14s)



1. To a solution of commercially available 1,2-dichloro-4-nitrobenzene (1 equiv, 1.00 g, 5.21 mmol) in DMF (40 mL), Na_2S (1.1 equiv, 0.67 g) and S_8 (1.1 equiv, 0.17 g) were added. The mixture was stirred for 2 h at room temperature and then, the crude mixture was slowly poured into ice/water (200 mL) and acidified to pH = 1–3. The crude mixture was subsequently extracted with Et_2O (4 × 20 mL) and the combined organic extracts were washed with LiCl (1M, 50 mL), brine and dried ($MgSO_4$). The volume of the solvent was reduced to about a third and the solution was passed through a silica plug.

2. The filtrate obtained in the previous step was concentrated under reduced pressure, dissolved in EtOAc (40 mL) and H_2O_2 (1.1 equiv, 0.15 mL) and I_2 (1% mol, 7 mg) were added. The mixture was stirred at room temperature for 30 minutes. It is highly advised to carry out full oxidation of the crude due to the extremely unpleasant odour of the thiol. Column chromatography (silica gel, hexane/EtOAc, 0–10%) of the precipitate obtained in the oxidation step was carried out, affording the product as a pale yellow solid (0.48 g, 49%); m.p. 162–164 ºC; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.30 (d, $^{4}J_{HH}$ = 2.3 Hz, 1H), 8.10 (dd, $^{3}J_{HH}$ = 8.8 Hz, $^{4}J_{HH}$ = 2.3 Hz, 1H), 7.64 (d, $^{3}J_{HH}$ = 8.8 Hz, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 147.18, 142.05, 132.11, 126.59, 125.13, 122.70.

5-Chloro-2-methoxy-3-nitrobenzenethiol (15u)

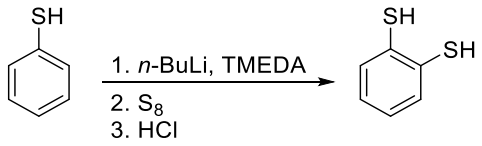
1. To an ice-cooled solution of commercially available 1-chloro-4-methoxybenzene (1 equiv, 5.0 g, 35.1 mmol) in DCM, chlorosulfonic acid (5 equiv, 11.7 mL, 175.34 mmol) was dropwise added. The mixture was stirred and allowed to warm to room temperature overnight. After the reaction is complete, the crude mixture was poured slowly onto ice/water (400 mL) and extracted with DCM (4 × 40 mL). The combined organic extracts were washed with saturated $NaHCO_3$ solution, washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure to afford 5-chloro-2-methoxybenzenesulfonyl chloride (13.1 g, 77%) as a colourless oil essentially pure by NMR; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.95 (d, $^4J_{HH}$ = 2.6 Hz, 1H), 7.63 (dd, $^3J_{HH}$ = 8.9, $^4J_{HH}$ = 2.6 Hz, 1H), 7.08 (d, $^3J_{HH}$ = 8.9, 1H), 4.06 (s, 3H).

2. In a 100 mL round-bottom flask, 5-chloro-2-methoxybenzenesulfonyl chloride (1 equiv, 3.5 g, 14.52 mmol) obtained in the previous step, was added in portions to a mixture of concentrated HNO_3/H_2SO_4 (1:1, 25 mL) cooled to -5 ºC. The mixture was allowed to warm to 0 ºC and stirred for additional 6 h. After the reaction is complete, the crude mixture was poured slowly onto ice/water (400 mL) and extracted with DCM (4 × 40 mL). The combined organic extracts were washed with aqueous saturated $NaHCO_3$ solution, washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure to afford 5-chloro-2-methoxy-3-nitrobenzenesulfonyl chloride (4.02 g, 97%) as a yellow solid essentially pure by NMR; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.22–8.19 (m, 2H), 4.13 (s, 3H).

3. In a 250 mL round-bottom flask, 5-chloro-2-methoxy-3-nitrobenzenesulfonyl chloride (1 equiv, 2.5 g, 8.74 mmol) obtained in the previous step, was dissolved in anhydrous THF (75 mL). The mixture was cooled to 0 ºC and PPh_3 (3 equiv, 6.9 g, 26.21 mmol) was slowly added in portions and stirred for additional 15 minutes. Then, the solvent was evaporated, the residue was dissolved in DCM (40 mL), H_2O was added (20 mL) and the product was extracted into the aqueous phase with NaOH (1M, 3 × 15 mL). The organic

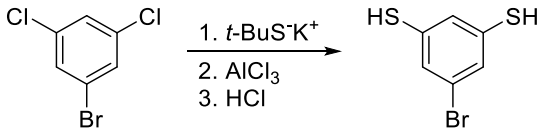
phase was discarded, the combined aqueous extracts were acidified with HCl (1M) to pH = 1−3 and the product was extracted into the organic phase with DCM (4 × 15 mL). The combined organic extracts were washed (brine), dried ($MgSO_4$) and concentration under reduced pressure to afford 5-chloro-2-methoxy-3-nitrobenzenethiol (1.61 g, 84%) as a pale yellow solid, essentially pure by NMR; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.59 (d, $^4J_{HH}$ = 2.5 Hz, 1H), 7.49 (d, $^4J_{HH}$ = 2.5 Hz, 1H), 4.00 (s, 1H), 3.95 (s,3H); **^{13}C NMR** (101 MHz, $CDCl_3$) 147.83, 132.98, 132.84, 129.64, 122.23, 61.85; **HRMS** (EI) *m/z* calcd for $C_7H_6ClNO_3S$ $[M]^+$ 128.9757, found 128.9755.

Benzene-1,2-dithiol (15v)



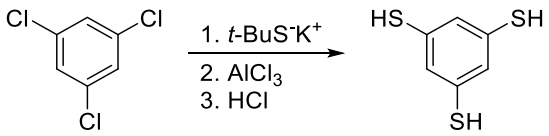
Prepared according to literature procedure;[153] **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.37 (dd, $^3J_{HH}$ = 5.7 Hz, $^4J_{HH}$ = 3.4 Hz, 2H), 7.07 (dd, $^3J_{HH}$ = 5.7 Hz, $^4J_{HH}$ = 3.4 Hz, 2H), 3.67 (s, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 130.88, 130.80, 126.48.

5-Bromobenzene-1,3-dithiol (15x)



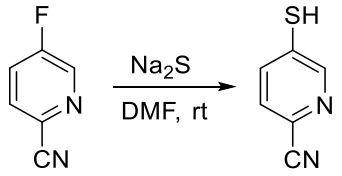
Prepared according to literature procedure;[16] **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.20 (d, $^4J_{HH}$ = 1.6 Hz, 2H), 7.09 (t, $^4J_{HH}$ = 1.6, 1H), 3.47 (s, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 144.58, 139.97, 135.00, 121.52.

Benzene-1,3,5-trithiol (15z)



Prepared according to literature procedure;[16] **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.95 (s, 3H), 3.41 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 133.13, 126.58.

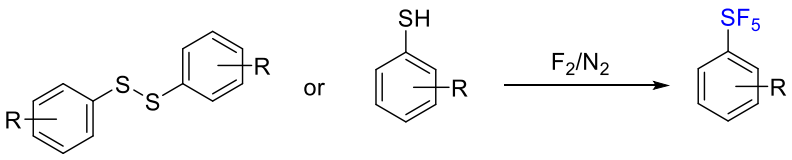
5-Mercaptopicolinonitrile (30)



Prepared according to literature procedure;[151] **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.53 (d, $^{4}J_{HH}$ = 2.4 Hz, 1H), 7.67 (dd, $^{3}J_{HH}$ = 8.1, $^{4}J_{HH}$ = 2.4 Hz, 1H), 7.53 (d, $^{3}J_{HH}$ = 8.1 Hz, 1H), 3.72 (br s, 1H).

5.3 Synthesis of SF_5-substituted aromatic compounds (**16**) by direct fluorination of disulfides (**14**) or thiols (**15**)

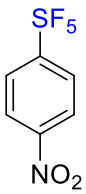
5.3.1 General method II: Direct fluorination of compounds **14** and **15**



14 **15** **16**

Compound **14** or **15** was introduced in a PFA reactor (100 mL) equipped with a stirring bar. The reactor was evacuated, purged with N_2 and anhydrous MeCN (30 mL) was added. The stirred mixture was flushed with N_2 (20 L/h) for 5 minutes and cooled to -5 °C (*meta*- and *para*-substituted substrates) or 0 °C (*ortho*-substituted substrates). Then, a mixture of F_2/N_2 (1:9, v/v; 30 L/h) is passed through the solution until the reaction is complete according to ^{19}F NMR. After completion, the reaction mixture is flushed with N_2 for additional 5 minutes, poured into a solution of saturated $NaHCO_3$ (50 mL) and extracted with Et_2O (3 × 20 mL). The combined organic extracts were washed with brine, dried under $MgSO_4$ and the solvent was removed under reduced pressure. Column chromatography and/or other purification methods afforded pure **16**.

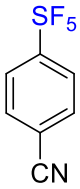
Pentafluoro(4-nitrophenyl)-λ^6-sulfane (**16a**)



Prepared according to General Method II: To a solution of **14a** (500 mg, 1.62 mmol) in dry MeCN a mixture of F_2/N_2 (1:9, v/v; 30 L/h) was passed through for 60 minutes. Extraction and purification of the product by column chromatography (silica gel, Et_2O/*n*-pentane, 0–15%) afforded **16a** (363 mg, 45% yield) as a pale yellowish solid; m.p. 37–39 °C; ^{1}**H NMR** (400 MHz, $CDCl_3$) δ 8.34 (d, $^3J_{HH}$ = 9.1 Hz, 2H), 8.01–7.95 (m, 2H);

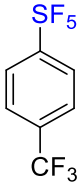
^{13}C NMR (101 MHz, $CDCl_3$) δ 158.30–157.45 (m), 149.24, 127.74 (p, $^3J_{CF}$ = 4.7 Hz), 124.25; **^{19}F NMR** (377 MHz, $CDCl_3$) δ 81.44–79.78 (m, 1F), 62.14 (d, $^2J_{FF}$ = 150.8 Hz, 4F); **MS** (EI): *m/z* (%) 249 $[M]^+$ (100).

4-(Pentafluoro)-λ^6-sulfanyl)benzonitrile (16b)



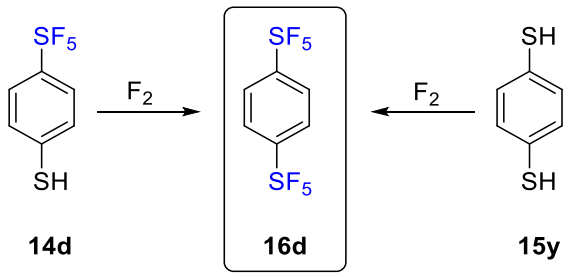
Prepared according to General Method II: To a solution of **14b** (500 mg, 1.86 mmol) in dry MeCN a mixture of F_2/N_2 (1:9, v/v; 30 L/h) was passed through for 65 minutes. Extraction and purification of the product by column chromatography (silica gel, Et_2O/*n*-pentane, 0–15%) afforded **16b** (238 mg, 28%) as a low melting white solid; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.92–7.88 (m, 2H), 7.82–7.77 (m, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 157.30–156.11 (m), 132.86, 127.19 (p, $^3J_{CF}$ = 4.7 Hz), 117.04, 116.01; **^{19}F NMR** (377 MHz, $CDCl_3$) δ 82.04–79.58 (m, 1F), 61.53 (d, $^2J_{FF}$ = 150.6 Hz, 4F); **MS** (EI): *m/z* (%) 229 $[M]^+$ (62).

Pentafluoro(4-(trifluoromethyl)phenyl)-λ^6-sulfane (16c)



Prepared according to General Method II: To a solution of **15c** (500 mg, 2.81 mmol) in dry MeCN a mixture of F_2/N_2 (1:9, v/v; 30 L/h) was passed through for 50 minutes. Attempts of isolation were unsuccessful (22%, ^{19}F NMR Yield); **^{19}F NMR** (377 MHz, $CDCl_3$) δ -62.94 (s, 3F), 62.51 (d, $^2J_{FF}$ = 148.4 Hz, 4F), 83.77–82.07 (m, 1F); **MS** (EI): *m/z* (%) 272 (44) $[M]^+$, 253 $[M\text{-}F]^+$ (22), 164 (53), 145(100), 114 (26), 95 (19).

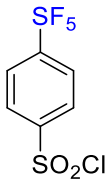
1,4-Bis(pentafluoro-λ^6-sulfanyl)benzene (16d)



Prepared according to General Method II starting from **14d**: To a solution of **14d** (500 mg, 1.06 mmol) in dry MeCN a mixture of F_2/N_2 (1:9, v/v; 30 L/h) was passed through for 40 minutes. Extraction and purification of the product by column chromatography (silica gel, Et_2O/*n*-pentane, 0–5%) afforded **16d** (154 mg, 22% yield) as a white solid; m.p. 108–110 °C.

Prepared according to General Method II starting from **15y**: To a solution of **15y** (500 mg, 3.51 mmol) in dry MeCN a mixture of F_2/N_2 (1:9, v/v; 30 L/h) was passed through for 130 minutes. Extraction and purification of the product by column chromatography (silica gel, Et_2O/*n*-pentane, 0–5%) afforded **16d** (154 mg, 12% yield); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.89 (s, 4H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 155.94–155.29 (m), 126.99 (p, $^3J_{CF}$ = 4.1 Hz). **^{19}F NMR** (377 MHz, $CDCl_3$) δ 82.31–79.92 (m, 2F), 61.96 (d, $^2J_{FF}$ = 150.5 Hz, 8F).

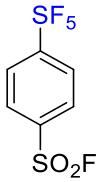
4-(Pentafluoro-λ^6-sulfanyl)benzenesulfonyl chloride (16e)



Prepared according to General Method II: To a solution of **14e** (500 mg, 1.20 mmol) in dry MeCN a mixture of F_2/N_2 (1:9, v/v; 30 L/h) was passed through for 45 minutes. Extraction and purification of the product by flash chromatography (C18 silica,

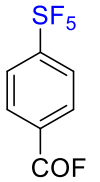
EtOAc/CH_3CN 0–10%) afforded **16e** (275 mg, 38% yield) as a white solid; m.p. 77–79 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.18 (d, $^3J_{HH}$ = 8.9 Hz, 2H), 8.08–7.99 (m, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 158.45, 146.67, 127.97 (m), 127.88; **^{19}F NMR** (377 MHz, CDCl3) δ 81.15–79.13 (m, 1F), 61.85 (d, $^2J_{FF}$ = 150.8 Hz, 4F); **HRMS** (EI) *m/z* calcd for $C_6H_4ClF_5O_2S_2$ $[M]^+$ 301.9261, found 301.9257.

4-(Pentafluoro-λ^6-sulfanyl)benzenesulfonyl fluoride (16f)



Prepared according to General Method II: To a solution of **14f** (500 mg, 1.31 mmol) in dry MeCN a mixture of F_2/N_2 (1:9, v/v; 30 L/h) was passed through for 50 minutes. Extraction and purification of the product by column chromatography (silica gel, Et_2O/*n*-pentane, 0–5%) afforded **16f** (307 mg, 41% yield) as a white solid; m.p. 90–92 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.16 (d, $^3J_{HH}$ = 8.9 Hz, 2H), 8.05 (dd, $^3J_{HH}$ = 9.1, $^4J_{HH}$ = 0.9 Hz, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 129.38, 127.88 (p, $^2J_{CF}$ = 4.6 Hz); **^{19}F NMR** (377 MHz, $CDCl_3$) δ 81.42–78.37 (m, 1F), 65.52 (s, 1F), 61.73 (d, $^2J_{FF}$ = 150.5 Hz, 4F); **HRMS** (EI) *m/z* calcd for $C_6H_4F_6O_2S_2$ $[M]^+$ 285.9557, found 285.9554.

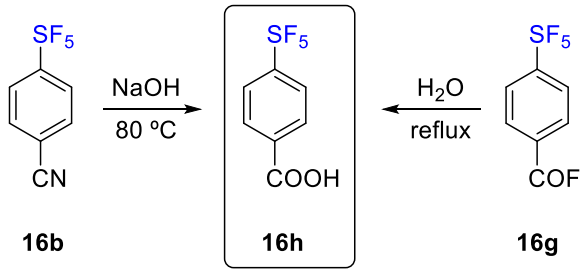
4-(Pentafluoro-λ^6-sulfanyl)benzoyl fluoride (16g)



Prepared according to General Method II: To a solution of **14g** (500 mg, 1.61 mmol) in dry MeCN a mixture of F_2/N_2 (1:9, v/v; 30 L/h) was passed through for 60 minutes. Isolation of the compound was not possible due to hydrolysis. (41% ^{19}F NMR Yield);

^{19}F NMR (377 MHz, CDCl3) δ 83.34–79.69 (m, 1F), 61.73 (d, $^{2}J_{FF}$ = 149.8 Hz, 4F), 20.01 (s, 1F).

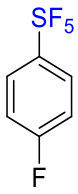
4-(Pentafluoro-λ^{6}-sulfanyl)benzoic acid (16h)



Preparation from **16b**: A solution of **16b** (100 mg, 0.44 mmol) in 25 mL of aqueous NaOH (4M), was heated up to 80 ºC and stirred for 4 h. After completion, the reaction mixture was cooled to room temperature and extracted with Et_2O (2 × 5 mL). The combined organic extracts are discarded. The aqueous phase is acidified with HCl (1M) to pH = 3 and extracted with Et_2O (3 × 10 mL). The combined organic phase was washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure affording **16h** (99 mg, 82% yield) as a white solid.

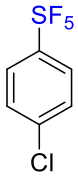
Preparation from **16g**: To the crude mixture obtained during the preparation of **16g** by General Method II, 50 mL of distilled H_2O were added and the mixture was refluxed for 2h. The solution was cooled to room temperature and extracted with Et_2O (3 × 10 mL). The organic extracts were extracted with NaOH (1M, 2 × 10 mL) and the combined aqueous phase was acidified with HCl (1M) to pH = 3 and extracted with Et_2O (3 × 10 mL). The resultant organic phase was washed (brine), dried ($MgSO_4$) and concentrated under reduced pressure. Sublimation of the solid residue (100–110 ºC, ca 5 Torr) afforded pure **16h** (280 mg, 35% yield) as a white solid; m.p. 191–193 ºC; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.22 (d, $^{3}J_{HH}$ = 8.9 Hz, 2H), 7.92–7.86 (m, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 170.03, 163.08–154.31 (m), 132.10, 130.88, 128.24–122.98 (m); **^{19}F NMR** (377 MHz, $CDCl_3$) δ 82.95–80.99 (m, 1F), 61.76 (d, $^{2}J_{FF}$ = 150.1 Hz, 4F).

Pentafluoro(4-fluorophenyl)-λ^6-sulfane (16i)



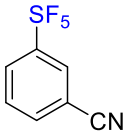
Prepared according to General Method II: To a solution of **15i** (250 mg, 1.95 mmol) in dry MeCN a mixture of F_2/N_2 (1:9, v/v; 30 L/h) was passed through for 70 minutes. Attempts of isolation were unsuccessful (12% ^{19}F NMR Yield); **^{19}F NMR** (377 MHz, $CDCl_3$) δ -107.59 (s, 1F), 63.26 (d, $^2J_{FF}$ = 151.6 Hz, 4F), 85.15–82.29 (m, 1F). Characterization by ^{19}F NMR was in agreement with literature.[154]

Pentafluoro(4-chlorophenyl)-λ^6-sulfane (16j)



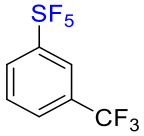
Prepared according to General Method II: To a solution of **15j** (250 mg, 1.7 mmol) in dry MeCN a mixture of F_2/N_2 (1:9, v/v; 30 L/h) was passed through for 65 minutes. Attempts of isolation were unsuccessful (13% ^{19}F NMR Yield); **^{19}F NMR** (377 MHz, $CDCl_3$) δ 84.72–82.35 (m, 1F), 63.00 (d, $^2J_{FF}$ = 150.3 Hz, 4F). Characterization by ^{19}F NMR was in agreement with literature.[154]

3-(Pentafluoro)-λ^6-sulfanyl)benzonitrile (16l)



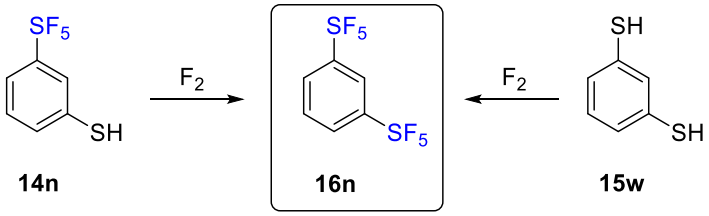
Prepared according to General Method II: To a solution of **14l** (500 mg, 1.86 mmol) in dry MeCN a mixture of F_2/N_2 (1:9, v/v; 30 L/h) was passed through for 70 minutes. Extraction and purification of the product by column chromatography (silica gel, Et_2O/*n*-pentane, 0–10%) afforded **16l** (195 mg, 23% yield) as a pale yellow solid; m.p. 66–67 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.06 (t, $^4J_{HH}$= 1.8 Hz, 1H), 8.04–7.97 (m, 1H), 7.83 (d, $^3J_{HH}$ = 7.8 Hz, 1H), 7.64 (t, $^3J_{HH}$ 8.1 Hz, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 154.17 (p, $^2J_{CF}$ = 19.6 Hz), 135.16, 130.38 (p, $^3J_{CF}$ = 4.8 Hz), 130.07, 130.22–129.83 (m), 117.05, 113.71; **^{19}F NMR** (377 MHz, $CDCl_3$) δ 85.38–76.90 (m, 1F), 62.04 (d, $^2J_{FF}$ = 150.7 Hz, 4F); **MS** (EI): *m/z* (%) 229 $[M]^+$ (57).

Pentafluoro(3-(trifluoromethyl)phenyl)-λ^6-sulfane (16m)



Prepared according to General Method II: To a solution of **15m** (500 mg, 2.81 mmol) in dry MeCN a mixture of F_2/N_2 (1:9, v/v; 30 L/h) was passed through for 65 minutes. Attempts of isolation were unsuccessful (21% ^{19}F NMR Yield); **^{19}F NMR** (377 MHz, $CDCl_3$) δ -63.09 (s, 3F), 83.25–81.33 (m, 1F), 62.35 (d, $^2J_{FF}$ = 150.1 Hz, 4F); **MS** (EI): *m/z* (%) 272 (53) $[M]^+$, 253 $[M\text{-}F]^+$ (28), 164 (60), 146 (8), 145 (100), 114 (28), 95 (20).

1,3-Bis(pentafluoro-λ^6-sulfanyl)benzene (16n)



Prepared according to General Method II starting from **14n**: To a solution of **14n** (500 mg, 1.06 mmol) in dry MeCN a mixture of F_2/N_2 (1:9, v/v; 30 L/h) was passed through for 40 minutes. Extraction and purification of the product by column chromatography (silica gel, Et_2O/*n*-pentane, 0–10%) afforded **16n** (160 mg, 23% yield) as a white solid.

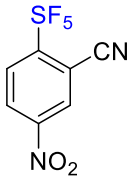
Prepared according to General Method II starting from **15w**: To a solution of **15w** (500 mg, 3.51 mmol) in dry MeCN a mixture of F_2/N_2 (1:9, v/v; 30 L/h, 130 min) was passed through until completion of the reaction. Extraction and purification of the product by column chromatography (silica gel, Et_2O/*n*-pentane, 0–10%) afforded **16n** (153 mg, 22% yield) as a white solid; m.p. 62–64 ºC; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.16 (d, $^4J_{HH}$ = 2.1 Hz, 1H) 7.94 (d, $^3J_{HH}$ = 8.3 Hz, $^4J_{HH}$ = 2.1 Hz, 2H), 7.67–7.58 (m, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 154.0–153.62 (m), 129.54, 124.66–124.19 (m), 124.54–124.31 (m); **^{19}F NMR** (377 MHz, $CDCl_3$) δ 82.12–80.32 (m, 2F), 61.96 (d, $^2J_{FF}$ = 149.9 Hz, 8F); **MS** (EI): *m/z* (%) 330 $[M]^+$ (74).

2-(Pentafluoro)-λ^6-sulfanyl)benzonitrile (16p)

Prepared according to General Method II: To a solution of **14p** (500 mg, 1.86 mmol) in dry MeCN a mixture of F_2/N_2 (1:9, v/v; 30 L/h) was passed through for 220 minutes. Extraction and purification of the product by column chromatography (silica gel, Et_2O/*n*-pentane, 0–10 %) afforded **16p** (230 mg, 16% yield) as a pale yellowish oil; **^{1}H NMR**

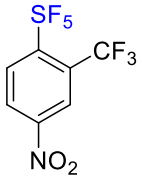
(400 MHz, $CDCl_3$) δ 7.95 (dd, $^3J_{HH}$ = 8.4 Hz, $^4J_{HH}$ = 1.1 Hz, 1H), 7.86 (d, $^3J_{HH}$ = 7.6 Hz, 1H), 7.78–7.72 (m, 1H), 7.66 (t, $^3J_{HH}$ = 7.5 Hz, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 155.43–154.52, 135.46, 133.15, 132.00, 128.68 (p, $^3J_{CF}$ = 5.0 Hz), 116.24,110.36–109.84; **^{19}F NMR** (377 MHz, $CDCl_3$) δ 80.76–79.07 (m, 1F), 65.11 (d, $^2J_{FF}$ = 151.1 Hz, 4F); **HRMS** (EI) *m/z* calcd for $C_7H_4F_5NS$ $[M]^+$ 228.9985, found 228.9987.

5-Nitro-2-(pentafluoro-λ^6-sulfanyl)benzonitrile (16q)



Prepared according to General Method II: To a solution of **15q** (500 mg, 2.78 mmol) in dry MeCN a mixture of F_2/N_2 (1:9, v/v; 30 L/h) was passed through for 4 h and 20 minutes. Extraction and purification of the product by column chromatography (silica gel, Et_2O/*n*-pentane, 0–10%) afforded **16q** (251 mg, 33% yield) as a white solid; m.p. 110–112 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.69 (d, $^4J_{HH}$ = 2.5 Hz, 1H), 8.56 (dd, $^3J_{HH}$ = 9.0, $^4J_{HH}$ = 1.9 Hz, 1H), 8.19 (d, $^3J_{HH}$ = 9.2 Hz, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 159.06–158.04, 148.74, 130.57 (p, $^3J_{CF}$ = 4.9 Hz), 130.31, 127.81, 114.28, 112.20 (p, $^3J_{CF}$ = 2.7 Hz); **^{19}F NMR** (377 MHz, $CDCl_3$) δ 77.87–76.13 (m, 1F), 65.52–65.11 (m, 4F); **HRMS** (EI) *m/z* calcd for $C_7H_3F_5N_2O_2S$ $[M]^+$ 273.9835, found 273.9837.

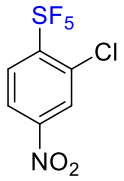
Pentafluoro(4-nitro-2-(trifluoromethyl)phenyl)-λ^6-sulfane (16r)



Prepared according to General Method II: To a solution of **15r** (500 mg, 2.24 mmol) in dry MeCN a mixture of F_2/N_2 (1:9, v/v; 30 L/h) was passed through for 5 h and 25 minutes. Extraction and purification of the product by column chromatography (silica gel,

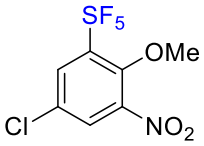
Et_2O/*n*-pentane, 0–10%) afforded **16r** (302 mg, 43% yield) as a pale yellowish oil; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.80 (d, $^4J_{HH}$ = 2.0 Hz, 1H), 8.54 (dd, $^3J_{HH}$ = 8.9, $^4J_{HH}$ = 1.9 Hz, 1H), 8.29 (d, $^3J_{HH}$ = 9.2, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 155.92–154.86 (m), 148.85, 132.64–131.89 (m), 129.94–128.55 (m), 127.40–126.98 (m), 125.09–124.59 (m), 121.36 (q, $^1J_{CF}$ = 276.1 Hz); **^{19}F NMR** (377 MHz, $CDCl_3$) δ -58.78 (p, $^5J_{FF}$ = 18.6 Hz, 3F), 78.72–76.98 (m, 1F), 68.26 (dq, $^2J_{FF}$ = 149.4 Hz, $^5J_{FF}$ = 18.5 Hz, 4F); **HRMS** (EI) *m/z* calcd for $C_7H_3F_8NO_2S$ $[M]^+$ 316.9757, found 316.9756.

(2-Chloro-4-nitrophenyl)pentafluoro-λ^6-sulfane (16s)



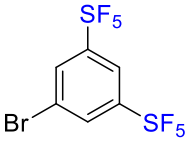
Prepared according to General Method II: To a solution of **14s** (500 mg, 1.35 mmol) in dry MeCN a mixture of F_2/N_2 (1:9, v/v; 30 L/h) was passed through for 5 h and 25 minutes. Extraction and purification of the product by column chromatography (silica gel, Et_2O/*n*-pentane, 0–10%) afforded **16s** (61 mg, 8% yield) as a colourless oil; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.41 (d, $^4J_{HH}$ = 2.5 Hz, 1H), 8.25–8.17 (m, 1H), 8.09 (d, $^3J_{HH}$ = 9.2 Hz, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 155.84–155.28 (m), 148.97, 132.15, 131.71–131.27 (m), 128.15, 121.70; **^{19}F NMR** (377 MHz, $CDCl_3$) δ 80.35–78.50 (m, 1F), 65.38 (d, $^2J_{FF}$ = 151.0 Hz, 4F); **HRMS** (EI) *m/z* calcd for $C_6H_3ClF_5NO_2S$ $[M]^+$ 282.9493, found 282.9492.

(5-Chloro-2-methoxy-3-nitrophenyl)pentafluoro-λ^6-sulfane (16u)



Prepared according to General Method II: To a solution of **15u** (500 mg, 2.28 mmol) in dry MeCN a mixture of F_2/N_2 (1:9, v/v; 30 L/h) was passed through for 85 minutes. Extraction and purification of the product by column chromatography (silica gel, Et_2O/*n*-pentane, 0–10%) afforded **16u** (60 mg, 8% yield) as a colourless solid; m.p. 65–67 ºC; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.96 (s, 2H), 3.91 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 148.70, 148.20–147.78 (m), 145.34, 133.29 (p, $^3J_{CF}$ = 4.9 Hz), 129.23, 128.73, 63.96; **^{19}F NMR** (377 MHz, $CDCl_3$) δ 80.81–78.94 (m, 1F), 68.34–67.88 (m, 4F); **HRMS** (CI) *m/z* calcd for $C_7H_5ClF_5NO_3S$ $[M]^+$ 313.9677, found 313.9676.

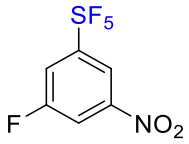
(5-Bromo-1,3-phenylene)bis(pentafluoro-λ^6-sulfane) (16x)



Prepared according to General Method II: To a solution of **15x** (250 mg, 1.13 mmol) in dry MeCN a mixture of F_2/N_2 (1:9, v/v; 30 L/h) was passed through for 40 minutes. Extraction and purification of the product by column chromatography (silica gel, Et_2O/*n*-pentane, 0–5%) afforded **16x** (230 mg, 25% yield) as a white solid; m.p. 65–67 ºC; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.09 (d, $^4J_{HH}$ = 1.9 Hz, 1H), 8.07 (d, $^3J_{HH}$ = 1.8 Hz, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 154.25 (p, $^2J_{CF}$ = 20.7 Hz), 132.49 (p, $^3J_{CF}$ = 4.9 Hz), 123.06–122.87 (m), 122.62; **^{19}F NMR** (377 MHz, $CDCl_3$) δ 81.57–78.75 (m, 2F), 62.65 (d, $^2J_{FF}$ = 149.5 Hz, 8F); **MS** (EI): *m/z* (%) 410 $[M]^+$ (80).

5.4 Derivatization SF_5-containing building blocks

5.4.1 Synthesis of pentafluoro(3-fluoro-5-nitrophenyl)-λ^6-sulfane (**34**)



The synthesis of **33** in kilogram scale and the synthesis of **34** in multigram-scale in anhydrous HF and MeCN were carried out at F2 Chemicals Ltd (Preston, UK) in collaboration with Dr. Greenhall and Dr. Zarantonello. Preparative scale synthesis of **34** and its further derivatization were carried out at IOCB (Prague, Czech Republic) by the author of this work.

By direct fluorination of 1,2-bis(3-nitrophenyl)disulfane (**32**)*:*

1,2-Bis(3-nitrophenyl)disulfane (2.50 kg, 8.1 mol) and dry MeCN (7.1 L) was charged into a 10 L reactor. The mixture was cooled to -10 ºC and 10% F_2/N_2 (v/v) was introduced to the stirred solution at a rate of 300 L/h while keeping the temperature between -10 ºC and -4 ºC. After 68–95 h (10–14 equiv of F_2), N_2 was introduced (270 L/h) for 5 min. Similar reactions were combined, carefully quenched with water, steam distilled, and extracted into CH_2Cl_2. The solvent was removed under reduced pressure affording crude **33** (12.6 kg) containing 6% of **34** (by GC) which was charged to a 10 L vacuum distillation unit equipped with a 30 plate bubble cap column and warmed offtakes. After removal of solvent residue and other volatiles, fraction **34** (445 g, 2-3% yield, 88% purity by GC) was obtained at 81–85 ºC, 3 mm Hg, and reflux ratio of 4:1. Redistillation at 66 ºC and 0.75 mm Hg afforded **34** of 99% purity by GC; Pale yellow low-melting; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.48 (d, $^4J_{HF}$ = 1.4 Hz, 1H), 8.15 (dt, $^4J_{HH}$ = 7.5 Hz, $^3J_{HF}$ = 2.3 Hz, 1H), 7.86 (dt, $^4J_{HH}$ = 7.8 Hz, $^3J_{HF}$ = 2.1 Hz, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 161.68 (d, $^1J_{CF}$ = 256.3 Hz), 154.78 (quintd, $^2J_{CF}$ = 21.3 Hz, $^3J_{CF}$ = 7.5 Hz), 148.81 (d, $^3J_{CF}$ = 7.0 Hz), 120.30 (dquint, $^2J_{CF}$ = 26.2 Hz, $^3J_{CF}$ = 4.6 Hz), 117.84 (sextet, J_{CF} = 4.9 Hz), 114.76 (d, $^2J_{CF}$ = 26.1 Hz); **^{19}F NMR** (377 MHz, $CDCl_3$) δ 80.03–78.27 (m, 1F), 62.44 (d, $^2J_{FF}$ =

151.2 Hz, 4F), -105.00 (s, 1F); **HRMS** (EI) *m/z* calcd for $C_6H_3F_6NO_2S$ $[M]^+$, 266.9789, found 266.9788.

By direct fluorination of 3-nitro-1-(pentafluorosulfanyl) benzene:

With the aim of analysing the composition of the mixture during the reaction, samples of neat crude were taken periodically and analysed by GC-MS.

1. Reaction in MeCN followed by GC: A solution of **33** (4.45 g, 17.9 mmol) in MeCN (100 mL) cooled to -15 ºC was fluorinated with 10% F_2/N_2 (v/v) at a rate of 3.6 L/h (at -15 to -10 ºC). The crude mixture was poured onto ice, extracted with CH_2Cl_2 (3 × 60 mL), the combined organic phase was dried ($MgSO_4$) and solvent was removed under reduced pressure. The amount of tar (28% by weight) was determined by Kugelrohr distillation.

2. Reaction in anhydrous HF followed by GC: A solution of **33** (4.50 g, 18.1 mmol) in anhydrous HF (100 mL) cooled to -15 ºC was fluorinated with 10% F_2/N_2 (v/v) at a rate of 3.6 L/h (at -15 to -10 ºC). The crude mixture after solvent evaporation was poured onto ice, extracted with CH_2Cl_2 (3 × 60 mL), the combined organic phase was dried ($MgSO_4$) and solvent was removed under reduced pressure. The amount of tar (5% by weight) was determined by Kugelrohr distillation.

3. Preparative reaction: A solution of **33** (2.51 g, 10.1 mmol) in MeCN (60 mL) was added to a nitrogen flushed PFA reactor with a magnetic stirring bar. A mixture of 20% F_2/N_2 (v/v) was bubbled for 11 h at a rate of 4.5 L/h while maintaining the temperature of the bath at -5 ºC. The mixture was flushed with N_2 for 10 min. and solvent was removed under reduced pressure yielding residue containing 40% of **34** (by GCMS). Purification by flash chromatography (silica gel, Et_2O/petroleum ether, 10:90) afforded **34** (466.3 mg, 17% yield, 26% yield based on recovered **33**).

4. By fluorodenitration of 3,5-dinitro-1-(pentafluorosulfanyl)benzene): To a solution of TBAF·$3H_2O$ (183 mg, 0.58 mmol, 1.5 equiv) in THF (5 mL) **37** (115 mg, 0.39 mmol, 1.0 equiv) was added. The mixture was stirred at 60 ºC for 2 h. Then water (20 mL) was

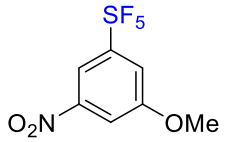
added and the product was extracted into EtOAc (3 × 15 mL). The combined organic phase was washed with water (15 mL), dried ($MgSO_4$) and solvent was removed under reduced pressure. Purification by flash chromatography (silica gel, Et_2O/hexane 4:96) afforded pure **34** as a pale yellow solid (57 mg, 56% yield).

5.4.2 Derivatization of pentafluoro(3-fluoro-5-nitrophenyl)-λ^6-sulfane

5.4.2.1 Nucleophilic Aromatic Substitution (S_NAr) reactions

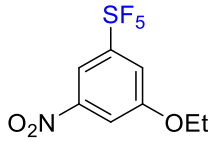
General procedure III: To a solution of KOH (138.1 mg, 2.46 mmol, 5 equiv) in the corresponding alcohol (4 mL), **34** (130.0 mg, 0.49 mmol, 1 equiv) was added. The mixture was stirred at 80 ºC for 30 min. Then, the product was extracted into Et_2O (4 × 10 mL) and the combined organic extracts were washed with water (15 mL), brine (15 mL), dried ($MgSO_4$) and the solvent was removed under reduced pressure. Purification by flash chromatography afforded pure **44**.

Pentafluoro(3-methoxy-5-nitrophenyl)-λ^6-sulfane (**44a**)



Prepared according to the General procedure III using KOH (2.46 mmol) in MeOH (4 mL) and **34** (0.49 mmol) at 80 ºC for 30 min. Purification by flash chromatography (silica gel, *n*-pentane/EtOAc, 90:10) afforded **44a** as a pale yellow solid (144 mg, 85% yield); m.p. 73–75 ºC; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.20 (t, $^4J_{HH}$ = 1.9 Hz, 1H), 7.88 (t, $^4J_{HH}$ = 2.1 Hz, 1H), 7.60 (t, $^4J_{HH}$ = 2.5 Hz, 1H), 3.96 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 160.25, 154.65 (quint, $^2J_{CF}$ = 19.7 Hz), 148.80, 119.07 (quint, $^3J_{CF}$ = 4.7 Hz), 113.79 (quint, $^3J_{CF}$ = 4.9 Hz), 111.23, 56.67; **^{19}F NMR** (377 MHz, $CDCl_3$) δ 80.73 (quint, $^2J_{FF}$ = 149.0 Hz, 1F), 62.25 (d, $^2J_{FF}$ = 150.1 Hz, 4F); **HRMS** (EI) *m/z* calcd for $C_6H_3F_5NO_3S$ $[M]^+$ 278.9989, found 278.9990.

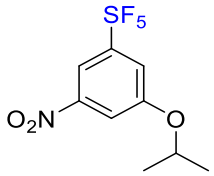
Pentafluoro(3-ethoxy-5-nitrophenyl)-λ^6-sulfane (44b)



Prepared according to the General procedure III using KOH (2.49 mmol) in EtOH (4 mL) and **34** (0.50 mmol) at 80 ºC for 35 min. Purification by flash chromatography (silica gel, *n*-pentane/EtOAc, 90:10) afforded **44b** as a yellow oil (125 mg, 83% yield); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.19 (t, $^4J_{HH}$ = 1.9 Hz, 1H), 7.86 (t, $^4J_{HH}$ = 2.1 Hz, 1H), 7.59 (t, $^4J_{HH}$ = 2.2 Hz, 1H), 4.17 (q, $^3J_{HH}$ = 7.0 Hz, 2H), 1.49 (t, $^3J_{HH}$ = 7.0 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 159.60, 154.64 (quint, $^2J_{CF}$ = 19.8 Hz), 148.77, 119.52 (quint, $^3J_{CF}$ = 4.7 Hz), 113.61 (quint, $^3J_{CF}$ = 4.8 Hz), 111.60, 65.43, 14.52; **^{19}F NMR** (377 MHz, $CDCl_3$) δ 81.69–79.99 (m, 1F), 62.24 (d, $^2J_{FF}$ = 150.7 Hz, 4F); **HRMS** (EI) *m/z* calcd for $C_8H_8F_5NO_3S$ $[M]^+$ 293.0145, found 293.0144.

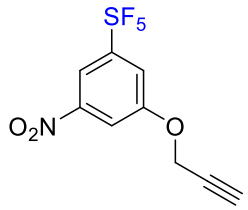
General procedure IV: To a solution of NaH (3 equiv) in the appropriate solvent the corresponding alcohol was added and stirred for 30 min at rt. Then **34** (1 equiv) was added and the mixture was stirred at room temperature for the corresponding time. Water (5 mL) and aqueous solution of NaOH (10 mL, 0.5 M) were added and the product was extracted into Et_2O (4 × 20 mL). The combined organic phase was washed with water, brine, dried ($MgSO_4$) and solvent was removed under reduced pressure. If necessary, purification by flash chromatography afforded pure **44**.

Pentafluoro(3-isopropoxy-5-nitrophenyl)-λ^6-sulfane (44c)



Prepared according to the General procedure IV from the mixture of NaH (26.0 mg, 0.65 mmol, 3 equiv) and dry *i*-PrOH (2.5 mL) stirred for 30 min. Then **34** (50.0 mg, 0.19 mmol, 1 equiv) was added and the mixture was stirred at rt for 6 h. Crude product after extraction and solvent removal was of sufficient purity. **44c** was obtained as pale brown oil (42 mg, 72% yield), essentially pure by NMR; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.17 (td, $^4J_{HH}$ = 1.9, 0.9 Hz, 1H), 7.85 (t, $^4J_{HH}$ = 2.0 Hz, 1H), 7.57 (td, $^4J_{HH}$ = 2.2, 0.8 Hz, 1H), 4.69 (heptd, $^3J_{HH}$ = 6.0 Hz, $^4J_{HH}$ = 0.6 Hz, 1H), 1.41 (dd, $^3J_{HH}$ = 6.0 Hz, $^4J_{HH}$ = 1.0 Hz, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 158.63, 154.72 (quint, $^2J_{CF}$ = 20.0 Hz), 148.82, 120.49 (quint, $^3J_{CF}$ = 4.6 Hz), 113.39 (quint, $^3J_{CF}$ = 4.8 Hz), 112.43, 72.20, 21.73; **^{19}F NMR** (377 MHz, $CDCl_3$) δ 81.95–79.77 (m, 1F), 62.18 (d, $^2J_{FF}$ = 150.9 Hz, 4F); **HRMS** (EI) *m/z* calcd for $C_9H_{10}F_5NO_3S$ $[M]^+$ 307.0302, found 307.0304.

Pentafluoro(3-nitro-5-(prop-2-yn-1-yloxy)phenyl)-λ^6-sulfane (44d)

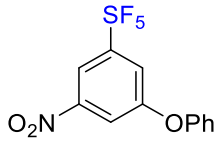


Prepared according to the General procedure IV using NaH (57.2 mg, 1.41 mmol, 3 equiv) and propargyl alcohol (42.0 mg, 0.75 mmol, 1.5 equiv) in dry THF (3.5 mL). A solution of **34** (126.0 mg, 0.47 mmol, 1 equiv) in dry THF (1 mL) was added dropwise to the solution of preformed alkoxide and the mixture was stirred at rt for 2 h. Purification of the product by flash chromatography (silica gel, hexane/EtOAc, 90:10) afforded **44d** as a pale orange oil (94.0 mg, 70% yield); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.27 (t, $^4J_{HH}$ = 1.9

Hz, 1H), 8.01 (t, $^4J_{HH}$ = 2.1 Hz, 1H), 7.70 (dd, $^4J_{HH}$ = 2.4, 1.9 Hz, 1H), 4.86 (d, $^4J_{HH}$ = 2.4 Hz, 2H), 2.64 (t, $^4J_{HH}$ = 2.4 Hz, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 157.91, 154.64 (quint, $^2J_{CF}$ = 20.0 Hz), 148.71, 120.05 (quint, $^3J_{CF}$ = 4.8 Hz), 114.68 (quint, $^3J_{CF}$ = 4.9 Hz), 112.53, 77.92, 76.31, 57.10; **^{19}F NMR** (377 MHz, $CDCl_3$) δ 81.37–79.62 (m, 1F), 62.27 (d, $^2J_{FF}$ = 150.9 Hz, 4F); **HRMS** (EI) *m/z* calcd for $C_9H_6F_5NO_3S$ $[M]^+$ 302.9989, found 302.9988.

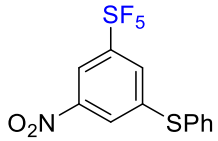
General procedure V: To a solution of K_2CO_3 (3 equiv) and the corresponding nucleophile (1.5 equiv) in DMF (3 mL), **34** (1 equiv) was added and the mixture was stirred at the appropriate temperature and time. After completion, water (25 mL) was added and the product was extracted into EtOAc or *t*-BuOMe. The combined organic phase was washed with water, brine, dried ($MgSO_4$), and solvent was removed under reduced pressure. Purification by flash chromatography afforded **44**.

Pentafluoro(3-nitro-5-phenoxyphenyl)-λ^6-sulfane (**44e**)



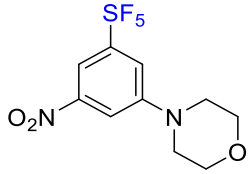
Prepared according to the General procedure V using K_2CO_3 (286.0 mg, 2.07 mmol, 3 equiv), phenol (104.6 mg, 1.11 mmol, 1.5 equiv) and **34** (162.9 mg, 0.61 mmol, 1 equiv). The mixture was stirred at 80 ºC for 3 h. Purification of the product by flash chromatography (silica gel, Et_2O/hexane, 5:95) afforded **44e** as a beige solid (139.7 mg, 67% yield); m.p. 57–59 ºC; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.31 (t, $^4J_{HH}$ = 1.9 Hz, 1H), 7.88 (t, $^4J_{HH}$ = 2.1 Hz, 1H), 7.72 (t, $^4J_{HH}$ = 2.3 Hz, 1H), 7.52–7.44 (m, 2H), 7.34–7.28 (m, 1H), 7.14–7.06 (m, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 159.04, 155.07 (quint, $^2J_{CF}$ = 20.1 Hz), 154.48, 148.86, 130.85, 126.13, 121.49 (quint, $^4J_{CF}$ = 4.5 Hz), 120.22, 115.43 (quint, $^4J_{CF}$ = 5.0 Hz), 114.86; ^{19}F NMR (377 MHz, $CDCl_3$) δ 81.30–79.30 (m, 1F), 62.32 (d, $^2J_{FF}$ = 151.0 Hz, 4F); **HRMS** (EI) *m/z* calcd for $C_{12}H_8F_5NO_3S$ $[M]^+$ 341.0145, found 341.0144.

Pentafluoro(3-nitro-5-(phenylthio)phenyl)-λ^6-sulfane (44f)



Prepared according to the General procedure V using K_2CO_3 (153.0 mg, 1.11 mmol, 3 equiv) thiophenol (63.0 mg, 0.57 mmol, 1.5 equiv) and **34** (101.0 mg, 0.38 mmol, 1 equiv). The mixture was stirred at 90 ºC for 3 h. Purification by flash chromatography (silica gel $CHCl_2$/petroleum ether, 2:98) afforded **44f** as a pale yellow oil (62.5 mg, 46% yield); **^{1}H NMR** (400 MHz,) δ 8.33 (t, $^4J_{HH}$ = 2.0 Hz, 1H), 8.03 (t, $^4J_{HH}$ = 1.8 Hz, 1H), 7.79 (t, $^4J_{HH}$ = 1.8 Hz, 1H), 7.58–7.46 (m, 5H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 154.83–153.84 (m), 148.34, 143.88, 134.59, 130.54, 130.36, 129.88, 129.72 (quint, $^3J_{CF}$ = 4.7 Hz), 124.43, 118.44 (quint, $^3J_{CF}$ = 4.9 Hz); **^{19}F NMR** (377 MHz, $CDCl_3$) δ 81.28–79.29 (m, 1F), 62.34 (d, $^2J_{FF}$ = 151.2 Hz, 4F); **HRMS** (EI) *m/z* calcd for $C_{12}H_8F_5NO_2S_2$ $[M]^+$ 356.9917, found 356.9914.

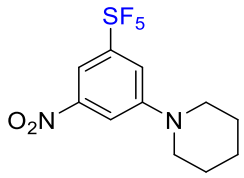
4-(3-Nitro-5-(pentafluoro-λ^6-sulfanyl)phenyl)morpholine (44g)



Prepared according to the General procedure V using K_2CO_3 (149.0 g, 1.08 mmol, 3 equiv), morpholine (49.5 g, 0.57 mmol, 1.5 equiv) and **34** (97.5 mg, 0.36 mmol, 1 equiv). The mixture was stirred at 85 ºC for 7 h. Purification by flash chromatography (silica gel, hexane) afforded **44g** as a pale yellow oil (79.0 mg, 63% yield); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.04 (t, $^4J_{HH}$ = 1.9 Hz, 1H), 7.83 (t, $^4J_{HH}$ = 2.1 Hz, 1H), 7.49 (t, $^4J_{HH}$ = 2.2 Hz, 1H), 3.95–3.85 (m, 4H), 3.93–3.85 (m, 4H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 155.48–154.73 (m), 151.90, 148.86, 117.39 (quint, $^3J_{CF}$ = 4.5 Hz), 111.73, 111.58 (quint, $^3J_{CF}$ = 4.6 Hz), 66.43, 48.22; **^{19}F NMR** (377 MHz, $CDCl_3$) δ 82.50–80.78 (m, 1F), 62.05 (d,

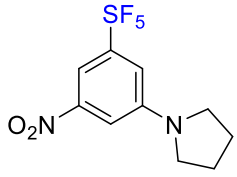
$^4J_{HH}$ = 150.5 Hz, 4F); **HRMS** (EI) *m/z* calcd for $C_6H_4F_5NO_3S$ $[M]^+$ 334.0411, found 334.0410.

1-(3-Nitro-5-(pentafluoro-λ^6-sulfanyl)phenyl)piperidine (44h)



Prepared according to the General procedure V using K_2CO_3 (145.0 g, 1.12 mmol, 3 equiv), piperidine (99.0 g, 1.12 mmol, 3 equiv) and **34** (107.0 mg, 0.36 mmol, 1 equiv). The mixture was stirred at 85 ºC for 3 h. Purification of the product, carried out by flash chromatography (silica gel, *n*-pentane), afforded **44h** as a pale yellow solid (75.0 mg, 51% yield); m.p. 79–81 ºC; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.93 (t, $^4J_{HH}$ = 1.9 Hz, 1H), 7.80 (t, $^4J_{HH}$ = 2.2 Hz, 1H), 7.47 (t, $^4J_{HH}$ = 2.2 Hz, 1H), 3.36–3.29 (m, 4H), 1.80–1.70 (m, 4H), 1.67 (dtt, $^3J_{HH}$ = 5.6, 4.3 Hz, $^4J_{HH}$ = 2.2 Hz, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 156.01–153.88 (m), 152.21, 148.88, 117.63 (t, $^3J_{CF}$ = 4.7 Hz), 111.89, 110.11 (quint, $^3J_{CF}$ = 5.1 Hz), 49.53, 25.35, 23.99; **^{19}F NMR** (377 MHz, $CDCl_3$) δ 82.96–81.32 (m, 1F), 61.96 (d, $^2J_{FF}$ = 150.4 Hz, 4F); **HRMS** (EI) *m/z* calcd for $C_{11}H_{13}F_5N_2O_2S$ $[M]^+$ 332.0618, found 332.0619.

1-(3-Nitro-5-(pentafluoro-λ^6-sulfanyl)phenyl)pyrrolidine (44i)

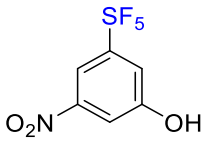


Prepared according to the General procedure V using K_2CO_3 (150.0 g, 1.12 mmol, 3 equiv), pyrrolidine (85.0 mg, 1.12 mmol, 3 equiv) and **34** (101.0 mg, 0.38 mmol, 1 equiv). The mixture was stirred at 85 ºC for 2 h. No further purification was carried out, affording **44i** as a yellow solid (82.0 mg, 67% yield); m.p. 155–157 ºC; **^{1}H NMR** (400 MHz, $CDCl_3$)

δ 7.81 (t, $^4J_{HH}$ = 1.9 Hz, 1H), 7.43 (t, $^4J_{HH}$ = 2.2 Hz, 1H), 7.10 (t, $^4J_{HH}$ = 2.1 Hz, 1H), 3.46 (ddd, $^3J_{HH}$ = 6.6, 4.3 Hz, $^4J_{HH}$ = 2.6 Hz, 4H), 2.13–2.09 (m, 4H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 155.67–155.12 (m), 149.85, 149.38, 114.31 (quint, $^3J_{CF}$ = 4.8 Hz), 109.14, 106.83 (quint, $^3J_{CF}$ = 5.0 Hz), 48.94, 26.18; **^{19}F NMR** (377 MHz, $CDCl_3$) δ 83.30–81.61 (m, 1F), 61.99 (d, $^2J_{FF}$ = 150.3 Hz, 4F); **HRMS** (EI) *m/z* calcd for $C_{10}H_{11}F_5N_2O_2S$ $[M]^+$ 318.0461, found 318.0460.

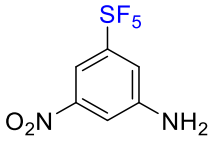
General procedure VI: A solution of **34** (1 equiv) and base in DMSO and water was heated at 135 ºC. Water (25 mL) was added and the product was extracted into EtOAc or Et_2O. The combined organic phase was washed with water (30 mL), brine (30 mL), dried ($MgSO_4$), and solvent was removed under reduced pressure. Purification by flash chromatography afforded **44j** and **44k**.

3-Nitro-5-(pentafluoro-λ^6-sulfaneyl)phenol (**44j**)



Prepared according to the General procedure VI using KOH (1.14 g, 18.7 mmol, 5 equiv) and **34** (1.00 g, 3.76 mmol, 1 equiv) in DMSO (6 mL) and water (3 mL). The mixture was stirred at 135 ºC for 6 h, cooled to rt and acidified with HCl (1M) to pH ~ 3. Purification by flash chromatography (silica gel, AcOH/EtOAc/$CHCl_3$/hexane, 1:40:40:19) afforded **44j** as a yellow solid (336.3 mg, 33% yield); m.p. 89–91 ºC; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.22 (t, $^4J_{HH}$ = 1.9 Hz, 1H), 7.88 (t, $^4J_{HH}$ = 2.1 Hz, 1H), 7.65–7.55 (m, 1H), 6.07 (s, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 156.52, 154.5–155.2 (m), 148.68, 119.84 (quint, $^3J_{CF}$ = 4.6 Hz), 114.10 (quint, $^3J_{CF}$ = 4.9 Hz), 113.76; **^{19}F NMR** (377 MHz, $CDCl_3$) δ 83.69–78.92 (m, 1F), 62.25 (d, $^2J_{FF}$ = 150.6 Hz, 4F); **HRMS** (CI) *m/z* calcd for $C_6H_4F_5NO_3S$ $[M+H]^+$ 265.9910, found 265.9908.

3-Nitro-5-(pentafluoro-λ^6-sulfanyl)aniline (44k)

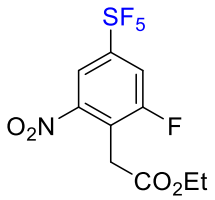


Prepared according to the General procedure VI using aqueous ammonia solution (28%, 0.1 mL, 1.31 mmol, 2.5 equiv) and **34** (149.8 mg, 0.56 mmol, 1 equiv) in DMSO (0.5 mL) introduced in a sealed vial and stirred at 135 ºC for 5 h. Purification by flash chromatography (silica gel, EtOAc/hexane, 9:1) afforded the product **44k** a yellow oil (65.3 mg, 44% yield); **^{1}H NMR** (400 MHz, acetone-d_6) δ 7.74 (d, $^4J_{HH}$ = 2.1 Hz, 2H), 7.55 (t, $^4J_{HH}$ = 2.1 Hz, 1H), 5.94 (s, 2H); **^{13}C NMR** (126 MHz, acetone-d_6) δ 155.14 (quint, $^2J_{CF}$ = 18.1 Hz), 151.51, 149.81, 116.89 (quint, $^3J_{CF}$ = 4.7 Hz), 111.58, 108.37 (quint, $^3J_{CF}$ = 5.1 Hz); **^{19}F NMR** (377 MHz, acetone-d_6) δ 85.29–82.19 (m, 1F), 62.77 (d, $^2J_{FF}$ = 148.8 Hz, 4F); **HRMS** (EI) *m/z* calcd for $C_6H_5F_5N_2O_2S$ $[M]^+$ 263.9992, found 263.9993.

5.4.2.2 Vicarious Nucleophilic Substitution (VNS) reactions

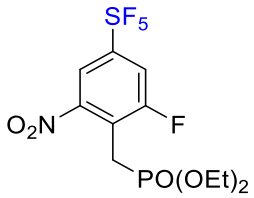
General procedure VII: To a solution of *t*-BuOK (3 equiv) in the corresponding dry solvent, a mixture of the appropriate X-NuH (1–2 equiv) and **34** (1 equiv) were added dropwise. After stirring for the indicated temperature and time, aqueous solution of HCl (1 M) was added to pH ~ 3 and the product was extracted into EtOAc (4 × 10 mL). The combined organic phase was washed with LiCl (40 mL, 1M), dried ($MgSO_4$), and the solvent was removed under reduced pressure. Purification by flash chromatography afforded pure **46**.

Ethyl 2-(2-fluoro-6-nitro-4-(pentafluoro-λ^6-sulfanyl)phenyl)acetate (46a)



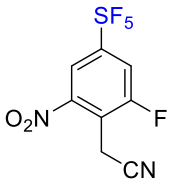
Prepared according to the General procedure VII using *t*-BuOK (77.0 mg, 0.69 mmol, 3 equiv) in DMF (3 mL) and a mixture of **34** (50.4 mg, 0.19 mmol, 1 equiv) and $ClCH_2CO_2Et$ (25.9 mg, 0.21 mmol, 1 equiv) in DMF (1.5 mL) at -30 ºC for 10 min. After extraction **46a** as a pale yellow oil (47.5 mg, 71% yield); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.32 (t, $^4J_{HH}$ = 2.0 Hz, 1H), 7.81 (dd, $^3J_{HH}$ = 8.8 Hz, $^4J_{HH}$ = 2.2 Hz, 1H), 4.21 (q, $^3J_{HH}$ = 7.1 Hz, 2H), 4.11 (d, $^4J_{HH}$ = 1.4 Hz, 2H), 1.28 (t, $^3J_{HH}$ = 7.1 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 168.16, 160.47 (d, $^1J_{CF}$ = 253.8 Hz), 152.75 (quintd, $^2J_{CF}$ = 21.7 Hz, $^3J_{CF}$ = 9.3 Hz), 149.50–149.15 (m), 122.79 (d, $^2J_{CF}$ = 18.9 Hz), 119.28–119.02 (m), 119.09–118.46 (m), 62.13, 31.08 (d, $^3J_{CF}$ = 4.5 Hz), 14.21; **^{19}F NMR** (377 MHz, $CDCl_3$) δ 80.38–78.13 (m, 1F), 62.36 (d, $^2J_{FF}$ = 151.4 Hz, 4F), -108.46 (s, 1F); **HRMS** (EI) *m/z* calcd for $C_{10}H_9F_6NO_4S$ $[M]^+$ 353.0156, found 353.0158.

Diethyl (2-fluoro-6-nitro-4-(pentafluoro-λ^6-sulfanyl)benzyl)phosphonate (46b)



Prepared according to the General procedure VII using *t*-BuOK (186.7 mg, 1.66 mmol, 3 equiv) in DMF (4 mL) and a mixture of **34** (157.3 mg, 0.59 mmol, 1 equiv) and $ClCH_2PO_3Et_2$ (105.3 mg, 0.56 mmol, 1 equiv) in DMF (1 mL) 60 ºC for 10 min. Purification by flash chromatography (silica gel, EtOAc/hexane 50:50) afforded **46b** as a beige solid (57.64 mg, 31% yield); m.p. 94–96 ºC; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.19–8.16 (m, 1H), 7.75 (ddd, $^3J_{HF}$ = 9.1 Hz, $^4J_{HH}$ = 2.3 Hz, $^4J_{HF}$ = 0.9 Hz, 1H), 4.14–4.01 (m, 4H), 3.81 (dd, $^2J_{HP}$ = 22.9 Hz, $^4J_{HF}$ = 1.7 Hz, 2H), 1.26 (td, $^3J_{HH}$ = 7.1 Hz, $^4J_{HP}$ = 0.5 Hz, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 160.10 (dd, $^1J_{CF}$ = 254.7 Hz, $^3J_{CP}$ = 6.1 Hz), 152.59–151.80 (m), 149.73–149.12 (m), 121.30 (dd, $^2J_{CF}$ = 19.5 Hz, $^2J_{CP}$ = 10.7 Hz), 119.39–119.03 (m), 118.51–117.97 (m), 62.95 (d, $^2J_{CP}$ = 6.6 Hz), 23.19 (dd, $^1J_{CP}$ = 137.3 Hz, $^3J_{CF}$ =3.6 Hz), 16.29 (d, $^3J_{CP}$ = 6.1 Hz); **^{19}F NMR** (376 MHz, $CDCl_3$) δ 80.44–78.47 (m, 1F), 62.46 (d, $^2J_{FF}$ = 151.5 Hz, 4F), -107.06 (d, $^4J_{FP}$ = 4.6 Hz, 1F); **HRMS** (ESI) *m/z* calcd for $C_{11}H_{14}F_6NO_5PS$ $[M + Na]^+$ 440.01263, found 440.01267.

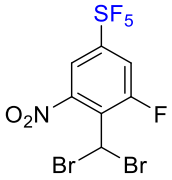
2-(2-Fluoro-6-nitro-4-(pentafluoro-λ^6-sulfanyl)phenyl)acetonitrile (46c)



Prepared according to the General procedure VII using *t*-BuOK (186.9 mg, 1.67 mmol, 3 equiv) in DMF (3.5 mL) and a mixture of **34** (149.0 mg, 0.56 mmol, 1 equiv) and $PhOCH_2CN$ (79.6 mg, 0.60 mmol, 1 equiv) in DMF (2 mL) at -30 ºC for 10 min. Purification flash chromatography (silica gel, Et_2O/hexane, 70:30) afforded **46c** as an orange oil (86.3 mg, 50% yield); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.41 (t, $^4J_{HH}$ = 2.0 Hz, 1H), 7.91

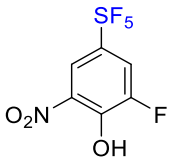
(dd, $^{3}J_{HF}$ = 8.8 Hz, $^{4}J_{HH}$ = 2.2 Hz, 1H), 4.15 (d, $^{4}J_{HF}$ = 1.4 Hz, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 160.24 (d, $^{1}J_{CF}$ = 257.0 Hz), 159.39–153.65 (m), 148.45, 120.5–119.71 (m), 119.60 (quint, $^{3}J_{CF}$ = 4.6 Hz), 118.61 (d, $^{2}J_{CF}$ =18.5 Hz), 114.11, 14.73 (d, $^{4}J_{CF}$ = 5.9 Hz); **^{19}F NMR** (377 MHz, $CDCl_3$) δ 79.25–77.19 (m, 1F), 62.30 (d, $^{2}J_{FF}$ = 150.5 Hz, 4F), -106.40 (s, 1F); **HRMS** (EI) *m/z* calcd for $C_8H_4F_6N_2O_2S$ $[M]^+$ 305.9898, found 305.9896.

(4-(Dibromomethyl)-3-fluoro-5-nitrophenyl)pentafluoro-λ^6-sulfane (46d)



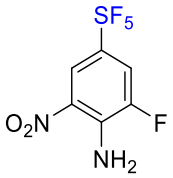
Prepared according to the General procedure VII using *t*-BuOK (133.8 mg, 1.19 mmol, 3 equiv) in DMF (3.5 mL) and a mixture of **34** (103.2 mg, 0.39 mmol, 1 equiv) and $CHBr_3$ (108.6 mg, 0.43 mmol, 1.1 equiv) in THF (1 mL) at -70 ºC for 2 min. Purification by flash chromatography (silica gel, Et_2O/hexane, 2:98) afforded **46d** as a white solid (131.0 mg, 81% yield); m.p. 87–89 ºC; **^{1}H NMR** (500.0 MHz, $CDCl_3$) δ 8.11 (dd, $^{4}J_{HH}$ = 2.3 Hz, $^{5}J_{HF}$ = 1.7 Hz, 1H), 7.87 (dd, $^{3}J_{HF}$ = 10.1 Hz, $^{4}J_{HH}$ = 2.3 Hz, 1H), 7.20 (d, $^{4}J_{HH}$ = 3.2 Hz, $^{4}J_{HF}$ = 0.5 Hz, 1H); **^{13}C NMR** (125.7 MHz, $CDCl_3$) δ 162.77–159.84 (m), 154.40–153.74 (m), 145.69–145.43 (m), 127.57 (d, $^{2}J_{CF}$ = 12.5 Hz), 120.26 (dquint, $^{2}J_{CF}$ = 26.7 Hz, $^{3}J_{CF}$ = 4.7 Hz), 118.39 (quint, $^{3}J_{CF}$ = 4.8 Hz), 22.71 (d, $^{3}J_{CF}$ = 3.8 Hz); **^{19}F NMR** (377 MHz, $CDCl_3$) δ 80.29–78.57 (m, 1F), 62.46 (d, $^{2}J_{FF}$ = 151.6 Hz, 4F), -107.06 (d, $^{4}J_{HF}$ = 4.6 Hz, 1F). **Anal. Calcd.** (%) for $C_7H_3Br_2F_6NO_2S$: C 19.15, H 0.69, Br 36.41, F 25.97, N 3.19, S 7.30, found: C 19.35, H 0.76, Br 36.29, F 23.49, N 2.90, S 7.25.

2-Fluoro-6-nitro-4-(pentafluoro-λ^6-sulfaneyl)phenol (46e)



Prepared according to the General procedure VII: To a mixture of *t*-BuOK (199.5 mg, 1.78 mmol, 3 equiv) in liquid NH_3 (4 mL) cooled to -50 ºC a mixture of **34** (158.5 mg, 0.59 mmol, 1 equiv) and cumene hydroperoxide (87.6 mg, 0.58 mmol, 1 equiv) in THF (1 mL) was added dropwise. After stirring for 15 min at -50 ºC aqueous solution of HCl (1 M) was added to pH ~ 3 and the product was extracted into EtOAc (4 × 10 mL). The combined organic phase dried ($MgSO_4$), and the solvent was removed under reduced pressure. HCl (36%, 5 mL) was added and the mixture was stirred at 60 ºC for 30 min. Water (10 mL) was added and the product was extracted into EtOAc (3 × 10 mL). The combined organic phase dried ($MgSO_4$), and the solvent was removed under reduced pressure. Purification by flash chromatography (silica gel, hexane/EtOAc/AcOH (80:15:5 to 95:0:5) afforded **46e** as yellow oil (101.6 mg, 60% yield); m.p. = 79–81 ºC; **^{1}H NMR** (500 MHz, acetone-d_6) δ 8.14 (dd, $^4J_{HH}$ = 3.1 Hz, $^4J_{HF}$ = 1.8 Hz, 1H), 7.40 (dd, $^3J_{HF}$ = 11.4 Hz, $^4J_{HH}$ = 3.1 Hz, 1H); **^{13}C NMR** (126 MHz, acetone-d_6) δ 160.60 (d, $^2J_{CF}$ = 18.2 Hz), 157.62 (d, $^1J_{CF}$ = 245.7 Hz), 135.75, 133.25–132.91 (m), 121.77, 115.42 (d, $^2J_{CF}$ = 25.5 Hz); **^{19}F NMR** (377 MHz, acetone-d_6) δ 88.43 (quint, $^2J_{FF}$ = 149.2 Hz, 1F), 65.89 (d, $^2J_{FF}$ = 148.9 Hz, 4F), -129.64 (s, 1F); **HRMS** (EI) *m/z* calcd for $C_6H_3F_6NO_3S$ $[M]^+$ 282.9738, found 282.9739.

2-Fluoro-6-nitro-4-(pentafluoro-λ^6-sulfaneyl)aniline (46f)

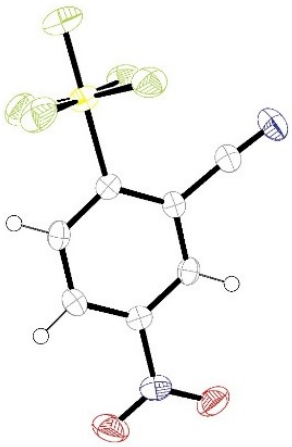


Prepared according to the General procedure VII: To a solution of *t*-BuOK (256.4 mg, 2.38 mmol, 4 equiv) in DMSO (4 mL) a mixture of **34** (159.0 mg, 0.60 mmol, 1 equiv) and I^- Me_3N^+-NH_2 (225.1 mg, 1.11 mmol, 1.8 equiv) in DMSO (1 mL) was added drop-wise at rt. After stirring for 5 minutes, NaOH (0.5 M, 20 mL) was added and the product was extracted into EtOAc (4 × 15 mL). The combined organic phase dried ($MgSO_4$), and the solvent was removed under reduced pressure. Purification by flash chromatography (silica gel, EtOAc/hexane, 10:90) afforded **46f** as yellow solid (143 mg, 85 % yield); m.p. 78–80 ºC; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.42 (t, $^4J_{HH}$ = 2.2 Hz, 1H), 7.63 (dd, $^3J_{HF}$ = 10.8 Hz, $^4J_{HH}$ = 2.5 Hz, 1H), 6.49 (s, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 150.50 (d, $^1J_{CF}$ = 247.0 Hz), 140.68–139.14 (m), 137.23 (d, $^2J_{CF}$ = 15.5 Hz), 130.90–130.85 (m), 120.65–120.36 (m), 117.46 (dquint, $^3J_{CF}$ = 23.7 Hz, $^4J_{CF}$ = 4.3 Hz); **^{19}F NMR** (377 MHz, $CDCl_3$) δ 83.26–81.62 (m, 1F), 63.70 (d, $^2J_{FF}$ = 151.3 Hz, 4F), -129.50 (s, 1F); **HRMS** (EI) *m/z* calcd for $C_6H_4F_6N_2O_2S$ $[M]^+$ 281.9898, found 281.9899.

5.5 Crystallographic Data

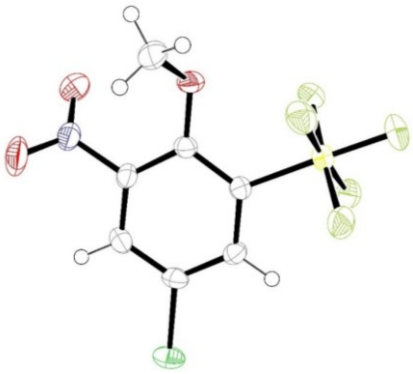
Crystallographic data for **16q** and **16u** were obtained from Xcalibur X-ray diffractometer by monochromatized Cu($K\alpha$) radiation (λ = 1.54180 Å) at 180 K. CrysAlisProCCD[155] was used for data collection, cell refinement and data reduction. The structures were solved by direct methods with SIR92[156] and refined by full-matrix least-squares on F with CRYSTALS[157]. All non-hydrogen atoms were refined with anisotropic displacement parameters. Hydrogen atoms were located in a Fourier difference map, recalculated into idealized positions and then refined with riding constraints.

5-nitro-2-(pentafluoro-λ^6-sulfanyl)benzonitrile (16q)



Empirical formula	$C_7H_3F_5N_2O_2S_1$
Formula weight	274.17
Temperature (K)	180
Wavelength (Å)	1.54180
Crystal system	orthorhombic
Space group	*Pbca*
Unit cell dimensions	
a (Å)	12.7356(5)
b (Å)	10.1080(4)
c (Å)	15.0713(6)
V (Å^3)	1940.15(13)
Z	8
Crystal size (mm)	0.12 × 0.20 × 0.74
Reflections measured	15970
Independent reflections	1775
Data / parameters	1770 / 155
Goodness-on-fit	1.050
Final R índices [I>2σ(I)]	R = 0.030 , wR = 0.035
CCDC	1875085

(5-chloro-2-methoxy-3-nitrophenyl)pentafluoro-λ^6-sulfane (16u)



Empirical formula	$C_7H_5Cl_1F_5N_1O_3S_1$
Formula weight	313.63
Temperature (K)	180
Wavelength (Å)	1.54180
Crystal system	monoclinic
Space group	$P2_1/c$
Unit cell dimensions	
a (Å)	8.3114(5)
b (Å)	16.1280(10)
c (Å)	8.8272(5)
β (º)	114.2148(12)
V (Å^3)	1079.14(11)
Z	4
Crystal size (mm)	0.12 × 0.32 × 0.37
Reflections measured	21892
Independent reflections	1901
Data / parameters	1899 / 164
Goodness-on-fit	0.991
Final R índices [I>2σ(I)]	R = 0.034 , wR = 0.033
CCDC	1875086

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Annex I

Publications

Part of the work described in this dissertation has been published or is in preparation.

Synthesis and nucleophilic aromatic substitution of 3-fluoro-5-nitro-1-(pentafluorosulfanyl)benzene. J. Ajenjo, M. Greenhall, C. Zarantonello, P. Beier, *Beilstein J. Org. Chem.* **2016**, *12*, 192–197. (doi:10.3762/bjoc.12.21)

Synthesis of substituted (pentafluorosulfanyl)benzenes by direct fluorination of diaryldisulfides. J. Ajenjo, L. Rulíšek, B. Klepetářová, M. Greenhall, P. Beier, *Chem. Eur. J.* **2019**, in preparation.

Oral communications

Synthesis of substituted (pentafluorosulfanyl)benzenes by direct fluorination of diaryldisulfides. 53rd Advances in Organic, Bioorganic and Pharmaceutical Chemistry (Liblice 2018), Lázně Bělohrad, Czech Republic, November 2018.

Posters

Improving access to aromatic sulfur pentafluorides by direct fluorination of disulfides. 23rd Winter Fluorine Conference, Clearwater Beach, Florida, USA, January 15th–20th, 2017. (Poster award)

Synthesis and nucleophilic aromatic substitution of 3-fluoro-5-nitro-1-(pentafluorosulfanyl)benzene. 5th International Symposium on Organofluorine Compounds in Biomedical, Materials and Agriculture Sciences ("Bremen Fluorine Days"), Bremen, Germany, July 3–7th, 2016.

Nucleophilic aromatic substitution of 3-fluoro-5-nitro-1-(pentafluorosulfanyl) benzene. 15th Annual RSC Fluorine Subject Group Postgraduate Meeting, Durham, United Kingdom, April 16–17th, 2015.