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Abstract: The pentafluorosulfanyl group (SF₅) is a highly stable chemical function which has been attracting a great deal of interest owing to its peculiar chemical, structural, physicochemical and biological properties. Progress in the area of SF₅-compounds has been somewhat hindered by the lack of straightforward lab-scale synthetic methods for introducing the SF₅-group into organic molecules. However, recent synthetic progress, the availability of some SF₅-building blocks from commercial suppliers and the discovery of interesting properties of SF₅-substituted molecules in materials science, biology and drug discovery are giving new momentum to research in this fascinating area of fluorine chemistry. Synthesis, reactivity and biological properties of SF₅-substituted organic molecules are herein reviewed with an emphasis on the work published after year 2000.



Object: revision of Ms. Ref. No.: FLUOR-D-12-00140

Aberdeen, 19/06/2012

Dear Professor Dolbier,

Please find attached our revised review article for the special issue of JFC honoring Professor David O'Hagan, entitled "**Synthetic Chemistry and Biological Activity of Pentafluorosulfanyl (SF₅) Organic Molecules**" by Stefano Altomonte and Matteo Zanda.

We would like to thank the referees for their extremely helpful feedback.

Sincerely yours,

Professor Matteo Zanda

A handwritten signature in blue ink that reads 'Matteo Zanda'.

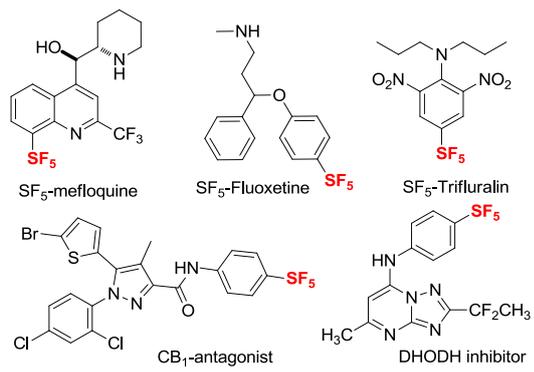
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All of the referees' suggestions have been accepted, with the only exception of Referee's 2 point 5 "Reactions of ArylSF5 systems should be divided into sections ...electrophilic substitutions, nucleophilic substitutions, reactions of diazo systems,..." because in that section the chemistry is inherently heterogeneous and we feel that such a sub-classification would be very challenging to achieve and would make less homogeneous the discussion of the topic.

*Graphical Abstract - Pictogram



Graphical Abstract

Synthetic Chemistry and Biological Activity of Pentafluorosulfanyl (SF₅) Organic Molecules

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Synthesis, reactivity and biological properties of SF₅-substituted organic molecules are reviewed in this article, with an emphasis on the work published in the last decade.

Highlights

- We review the synthesis of SF₅-compounds, with an emphasis on work published after year 2000.
- We review the reactivity of SF₅-substituted organic molecules.
- We review the biological properties of SF₅-substituted drug candidates.

Synthetic Chemistry and Biological Activity of Pentafluorosulfanyl (SF₅) Organic Molecules

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Abstract

The pentafluorosulfanyl group (SF₅) is a highly stable chemical function which has been attracting a great deal of interest owing to its peculiar chemical, structural, physicochemical and biological properties. Progress in the area of SF₅-compounds has been somewhat hindered by the lack of straightforward lab-scale synthetic methods for introducing the SF₅-group into organic molecules. However, recent synthetic progress, the availability of some SF₅-building blocks from commercial suppliers and the discovery of interesting properties of SF₅-substituted molecules in materials science, biology and drug discovery are giving new momentum to research in this fascinating area of fluorine chemistry. Synthesis, reactivity and biological properties of SF₅-substituted organic molecules are herein reviewed with an emphasis on the work published after year 2000.

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1. INTRODUCTION

Pentafluorosulfanyl (SF_5) compounds are considered to be organic derivatives of sulfur hexafluoride SF_6 . Both in SF_6 and in SF_5 -compounds the sulfur atom is in hypervalent hexacoordinated state with an octahedral geometry of the ligands. The pentafluorosulfanyl group has remarkable chemical stability and compounds incorporating this group often possess advantageous and interesting properties, including high thermal, hydrolytic and chemical stability, high density, high lipophilicity and biological activity [1, 2]. Some of these properties are also to some extent typical of the trifluoromethyl group, to which the SF_5 has been often compared. However, the SF_5 is not just an exotic and “larger” version of the trifluoromethyl group, i.e. a “super-trifluoromethyl group” as it was dubbed recently [3].

The SF_5 group properties are fascinating, peculiar and to a large extent largely unexplored, particularly in the biomedical field and in drug discovery. This review article is focused on small organic molecules having an SF_5 -carbon bond, i.e. inorganic SF_5 -chemistry and SF_5 -substituted polymers will not be discussed. The review is structured in three main sections: (1) Synthesis of SF_5 -containing molecules (primary reactivity); (2) Reactions of SF_5 -containing molecules (secondary reactivity); (3) Biological properties. Different aspects of the chemistry and properties of SF_5 -compounds have been reviewed, mainly in book chapters [4–9]. To our knowledge the most recent general review covering SF_5 -compounds dates back to 2005 [10] and comprehensively covers the literature until 2000, with scattered references to articles published in the following two years. This review will therefore cover the literature published after 2000, but important previous work will be reviewed too, especially on the preparation of SF_5 -compounds, which remains the “Achille’s heel” of this chemistry.

2. SYNTHESIS OF SF_5 -COMPOUNDS (PRIMARY REACTIVITY)

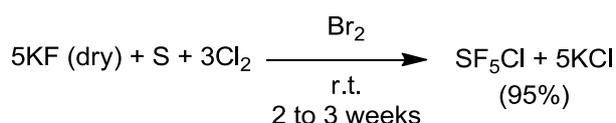
This section will review the “primary reactivity” of SF_5 -compounds, i.e. the *ex-novo* synthesis of different classes of SF_5 -compounds *via* (1) pentafluorosulfanyllating agents or (2) fluorination of suitable precursors. Sulfur hexafluoride (SF_6) is generally not useful for the preparation of SF_5 -compounds. Therefore, the two main strategies for installing an SF_5 group into organic molecules are (1) straight introduction of an SF_5 group using a pentafluorosulfanyllating agent on suitably functionalised substrates, such as alkenes, alkynes or an aromatic moieties, generally through radical chemistry, and (2) fluorination of a thiol, sulphide or disulfide function.

2.1. Pentafluorosulfanyllating agents

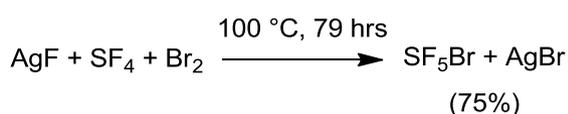
The most important reagents for introducing an SF_5 group into organic molecules are the two SF_5 -X halides: SF_5 -Cl, first prepared in 1959 [11], and the more reactive SF_5 -Br, obtained for the first time in 1965 [12]. The least reactive and highly toxic dimer $\text{F}_5\text{S-SF}_5$ has been also occasionally reported as a pentafluorosulfanyllating agent [13–15]. SF_5Cl is thermally stable up to 400 °C in inert vessels, and is not hydrolysed by water or aqueous acids, but undergoes decomposition at lower temperatures in the presence of ultraviolet light and in alkaline solutions. SF_5Br is less thermally stable and decomposition starts at 150 °C.

One of the most recent improvements of the preparation of SF_5Br was developed by Gard et al. who reported that a slow reaction (6-11 days at r.t.) between molecular bromine and BrF_3 in the presence of cesium fluoride, followed by an even slower reaction of the resulting BrF with SF_4 (36 days at r.t.

or 20 days with moderate heating) afforded high yields (99.6% and 88.2%, respectively) of SF₅Br [16]. Replacement of CsF with dry and carefully powdered KF was reported to be a key factor in the improvement of the preparation of SF₅Cl, using the reaction between SF₄ and Cl₂ (Scheme 2) [17]. However, recently a more convenient synthetic method for the preparation of both SF₅Cl and SF₅Br was reported in the patent literature [18]. According to this protocol, dry KF, sulphur powder and Cl₂ were mixed in a reactor in the presence of Br₂ which apparently acted as a catalyst (no reaction took place in the absence of Br₂), affording excellent yields of SF₅Cl after two to three weeks at r.t. The reaction was found to take place through the formation of SF₄ as an intermediate (Scheme 1). Analogously, SF₅Br was prepared in good yields by reaction of AgF, SF₄ and Br₂, but the latter in this case was a true reagent and was consumed in the process (Scheme 2).

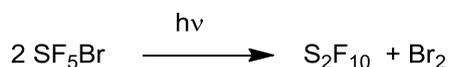


Scheme 1



Scheme 2

The dimer (SF₅)₂ can be efficiently prepared (99% yield) by photochemical decomposition of SF₅Br in a quartz vessel (Scheme 3) [19].



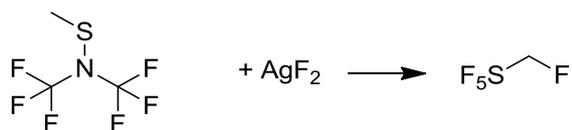
Scheme 3

The chemistry of SF₅-X compounds above is dominated by the proclivity to form the SF₅· radical. In particular, the pentafluorosulfanyl radical can be generated from (SF₅)₂ under thermal conditions (heating to 125-140 °C), from SF₅Cl using photo-irradiation or heating in the presence of a peroxide catalyst, and from the more reactive SF₅Br by action of light or heating even without a catalyst. Less practically from the synthetic angle, it is also possible to generate this radical by microwave heating or electrical discharge from SF₆ [10].

2.2. Synthesis of alkyl and fluoroalkyl SF₅-compounds

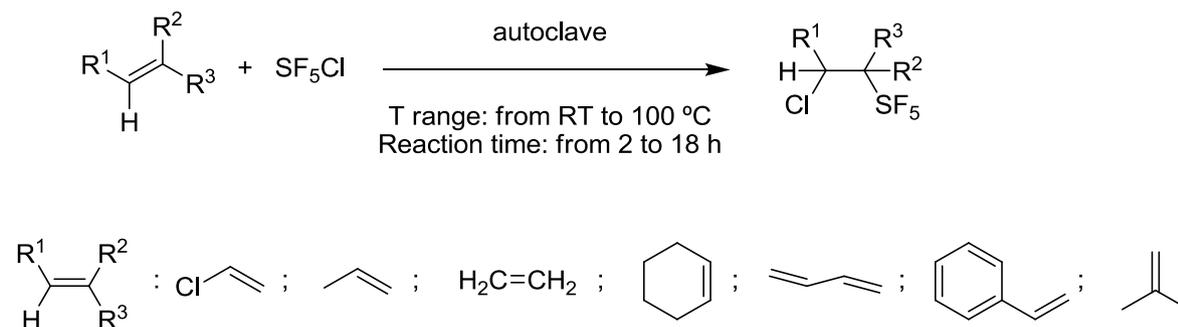
This chapter reviews the preparation of compounds having an SF₅-C(sp³) bond. The first efforts directed at the synthesis of simple fluoroalkyl-SF₅ compounds dates back to the 1950s when CF₃SF₅ was obtained from both CH₃SH and CS₂ by reaction with CoF₃ in yields up to 40% [20]. In the following years, several electrochemical fluorination versions of the same process were also published [21–23].

The fluoromethyl analogue was prepared in very good yields (86%) by AgF₂ promoted fluorination of a N,N-bistrifluoromethyl sulfenamide (Scheme 4) [24].



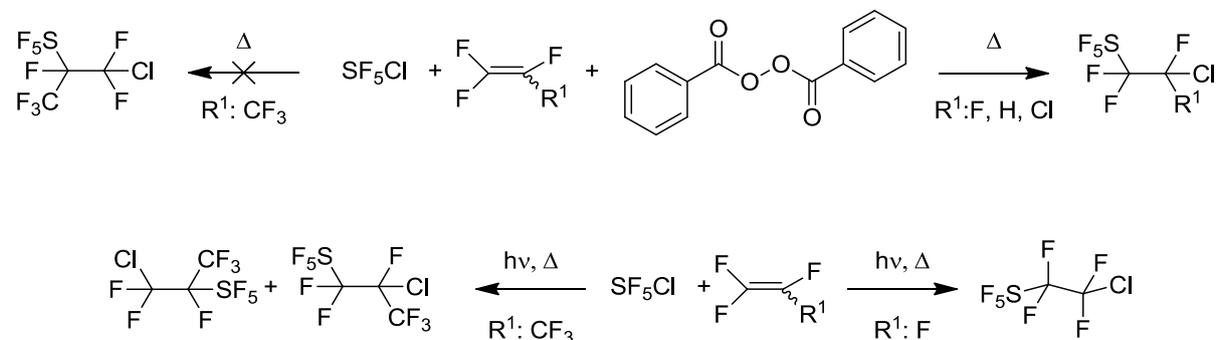
Scheme 4

In a seminal contribution to the chemistry of SF₅-compounds, Case et al. reported that SF₅Cl is able to add thermally to a wide range of olefins, affording the corresponding SF₅-alkanes incorporating a β-chlorine atom (Scheme 5) [25].



Scheme 5

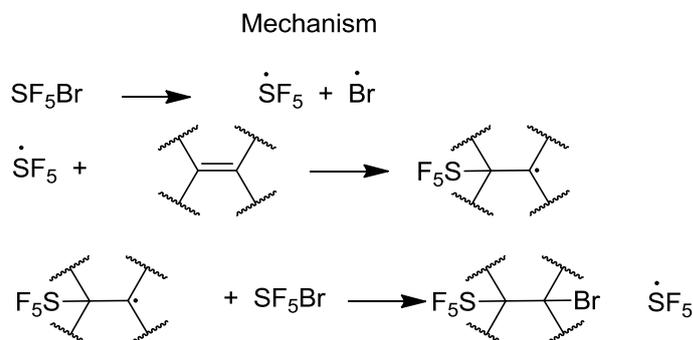
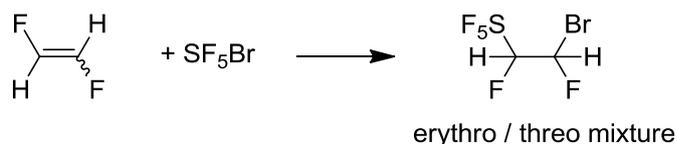
Although SF₅Cl has been reported to react with tri- or tetra-fluoroethylenes in the presence of a radical initiator to provide the corresponding saturated addition products, no reaction was observed with hexafluoropropylene. To accomplish this chloro-pentafluorosulfanylation reaction, the reactants were submitted to photochemical irradiation (Scheme 6) [26] (for related chemistry see: [27]).



Scheme 6

Addition of SF₅Br to tetrafluoroethylene and other fluoroethylenes was also reported to take place [28] and later on was used to prepare SF₅-fluoropolymers [29].

SF₅Br was found to react with 1,2-difluoroethylene through a radical non-stereospecific addition, resulting from a homolytic cleavage of the F₅S–Br bond, as demonstrated by the fact that both *trans* and *cis* olefins afforded a mixture of *erythro* and *threo* diastereomeric products, in similar ratio (Scheme 7) [30].

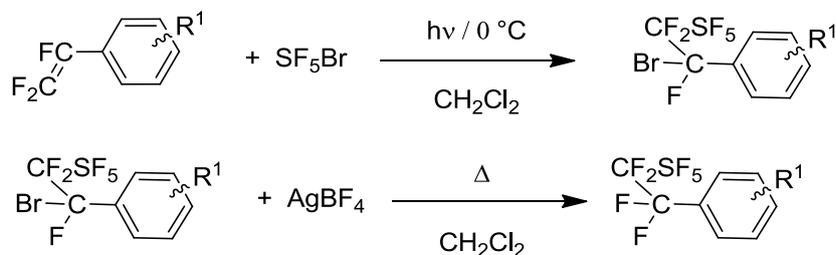


Scheme 7

Other fluoroolefins, such as 3,3,3-trifluoropropene and chlorofluoroethylenes, were also shown to react with SF_5Br leading to the corresponding addition products [31]. Bromo- and bromofluoroethylenes were also found to undergo addition of SF_5Br [32].

$\text{SF}_5\text{-CF}_2\text{CF}_2\text{-Ph}$ was synthesised by means of SF_5Br addition to $\text{CF}_2=\text{CF-Ph}$ followed AgBF_4 promoted displacement of the secondary bromine atom by fluoride [33].

The scope of the methodology was subsequently expanded to a series of *ortho*-, *meta*- and *para*-(SF_5 -perfluoroethyl)benzene derivatives. In fact, regioselective photochemical addition of SF_5Br to the corresponding $\text{CF}_2=\text{CF-Aryl}$ substrates, followed by AgBF_4 treatment afforded the target compounds in moderate to good yields (Scheme 8 and Table 1) [34].



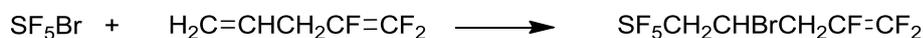
Scheme 8

Table 1

Entry	R ¹	Reaction time	% Yield of $\text{SF}_5(\text{CF}_2)_2\text{C}_6\text{H}_4\text{-R}^1$
1	<i>m</i> -Br	18 h	53
2	<i>p</i> -Br	25 h	53
3	<i>p</i> -Cl	20 h	52
4	<i>p</i> -CH ₃	48 h	41
5	<i>p</i> -CF ₃	20 h	22 ^a
6	<i>p</i> -NO ₂	51 h	80
7	<i>o</i> -F	17 h	82
8	<i>o</i> -CF ₃	18 h	74

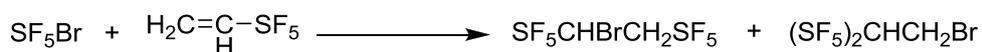
^a Low yield due to volatility of product

In the presence of two different terminal C=C bonds, one hydrogenated and one perfluorinated, SF₅Br added to the former through a thermally induced radical process (Scheme 9) [35].



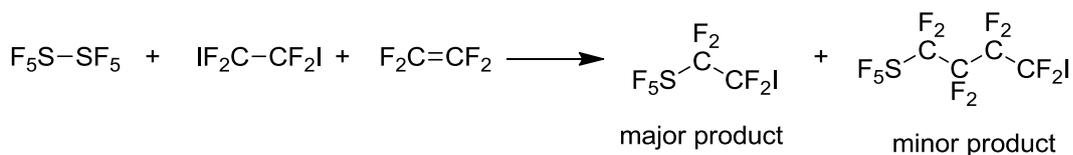
Scheme 9

Bis-SF₅-ethenes were obtained by SF₅Br addition to the mono-SF₅ precursor upon heating to 70 °C. No reaction was observed with fluorinated analogues like SF₅-CF=CF₂ (Scheme 10) [36].



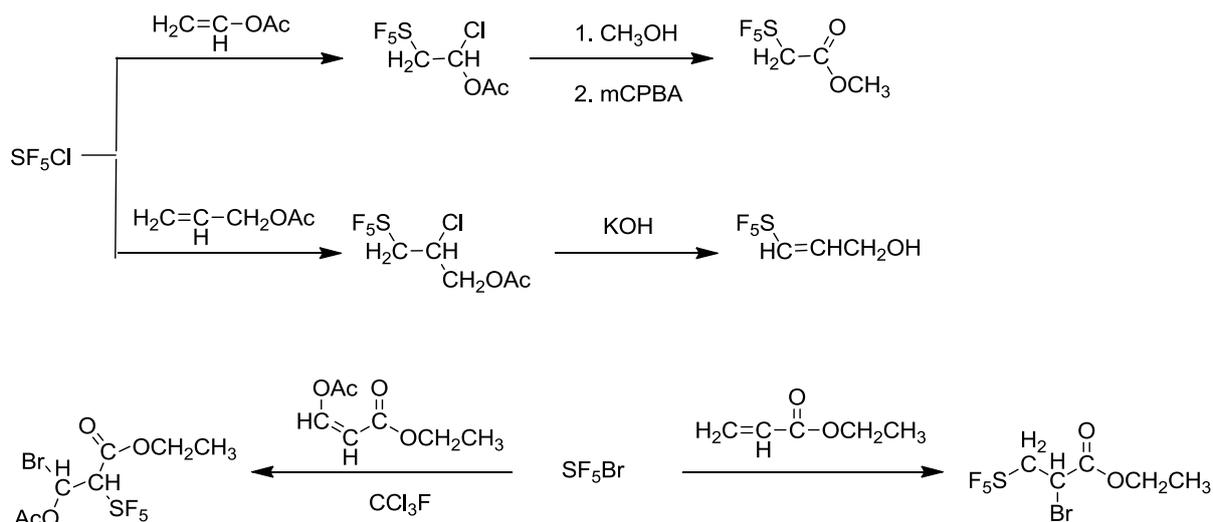
Scheme 10

Since SF₅-I was unknown, SF₅-iodoperfluoroalkanes were obtained by reaction of (SF₅)₂ (1.1 equiv) with (ICF₂)₂ (1.1 equiv) and tetrafluoroethylene (1 equiv) in a stainless steel vessel at 155 °C. The reaction occurred through a radical process and produced minor amounts of 4-iodo-perfluorobutyl-SF₅ as a co-product (Scheme 11) [15]. A related process was previously used for the preparation of SF₅-telomers [14].



Scheme 11

SF₅Cl was found to add to electron-rich and very reactive vinyl acetate and also with allyl acetate affording good yields of the corresponding primary SF₅-adducts, which were then subjected either to oxidation to yield SF₅-acetate or to elimination of hydrochloric acid to give γ-SF₅-allyl alcohol (no epoxide formation was observed). More reactive SF₅-Br gave lower yields in the reaction with vinyl acetate under the same conditions above, owing to partial decomposition, but was found to react efficiently under photochemical irradiation using CCl₃F as solvent. Rewardingly, SF₅-Br was found to add to less reactive acrylate affording β-SF₅-α-Br-acrylate (Scheme 12) [37].



Scheme 12

Addition of SF_5Br to acrylic and methacrylic esters was reported to occur upon heating the reaction mixture in order to achieve completeness of the process. Interestingly, more activated β,β -diethoxy ethyl acrylate did not afford the expected addition product upon reacting with SF_5Cl but produced α -chloro-malonate, SF_4 and fluoroethylene instead (Scheme 13 and Table 2) [38].

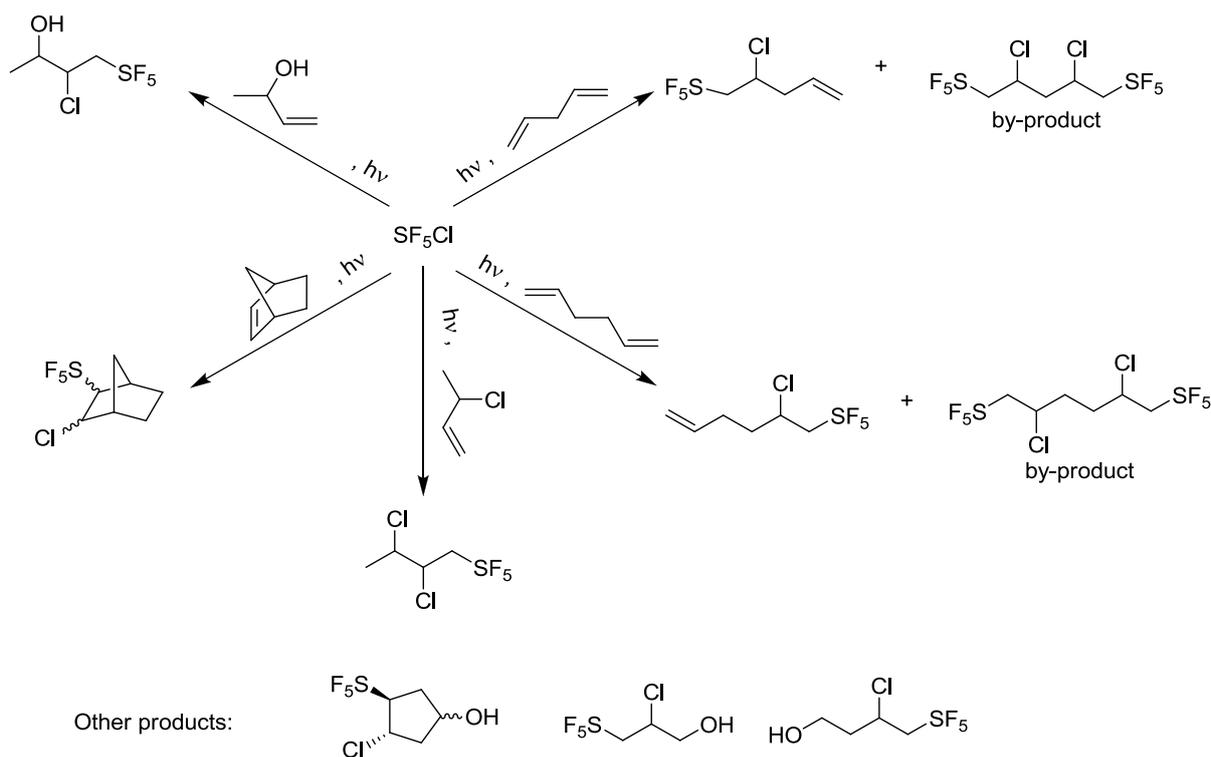


Scheme 13

Table 2

Entry	R ¹	X
1	H	<i>t</i> -Bu
2	CH ₃	CH ₃
3	CH ₂ Cl	C ₂ H ₅
4	<i>n</i> -C ₇ H ₁₅	C ₂ H ₅

SF_5Cl was described to add under photochemical irradiation conditions to a wide structural range of functionalised olefins, affording the corresponding terminal SF_5 -substituted β -chloro adducts in variable yields (Scheme 14) [39–43].



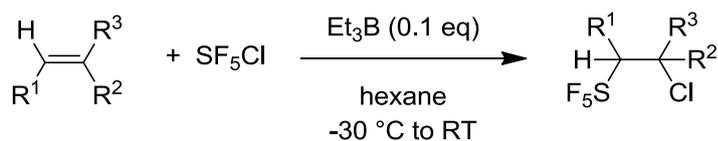
Scheme 14

A long chain aliphatic system bearing an ω -SF₅ group was obtained by SF₅Cl addition to the corresponding ω -unsaturated acetate (Scheme 15)[44].



Scheme 15

A wide range of β -chloro SF₅-alkyl compounds was obtained by Et₃B-catalysed regioselective and highly diastereoselective radical addition of SF₅Cl to alkenes, including internal ones. Yields were remarkably high (79-98%) and reaction conditions very mild, rendering this method very attractive for lab-scale preparation. Acrylates however did not afford the expected SF₅Cl addition (partly due to cross-reactivity of Et₃B with the ester moiety), whereas alkynes like phenylacetylene afforded lower yields (49%) of the corresponding SF₅- β -chloroalkene and partial dimerization (Scheme 16 and Table 3)[45].



Scheme 16

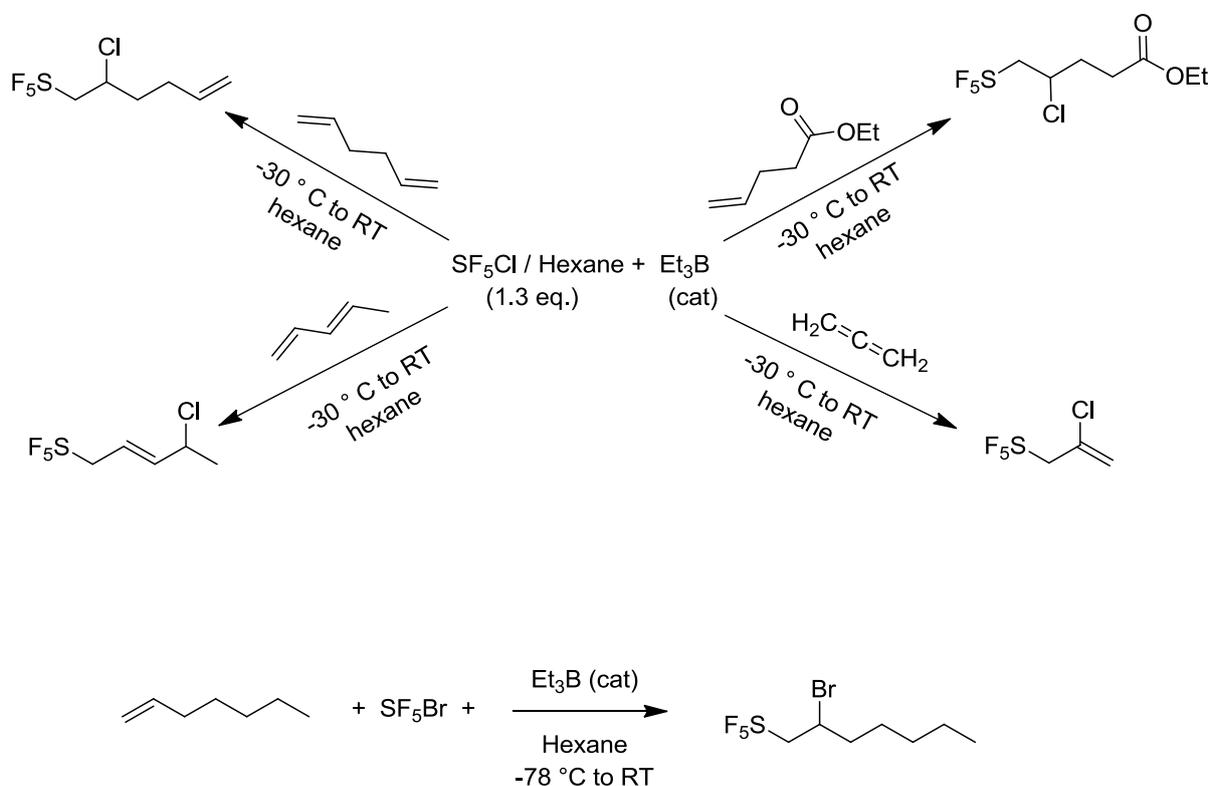
Table 3

R ¹	R ²	R ³	% Yield
H	<i>n</i> -C ₆ H ₁₃	H	95

H	<i>n</i> -C ₄ H ₉	H	98
H	<i>t</i> -C ₄ H ₉	H	96
H	C ₂ H ₅	C ₂ H ₅	89
<i>n</i> -C ₃ H ₇	H	<i>n</i> -C ₃ H ₇	95 ^b
(CH ₂) ₄	(CH ₂) ₄	H	98 ^b
H	<i>p</i> -tolyl	H	79
H	OAc	H	98

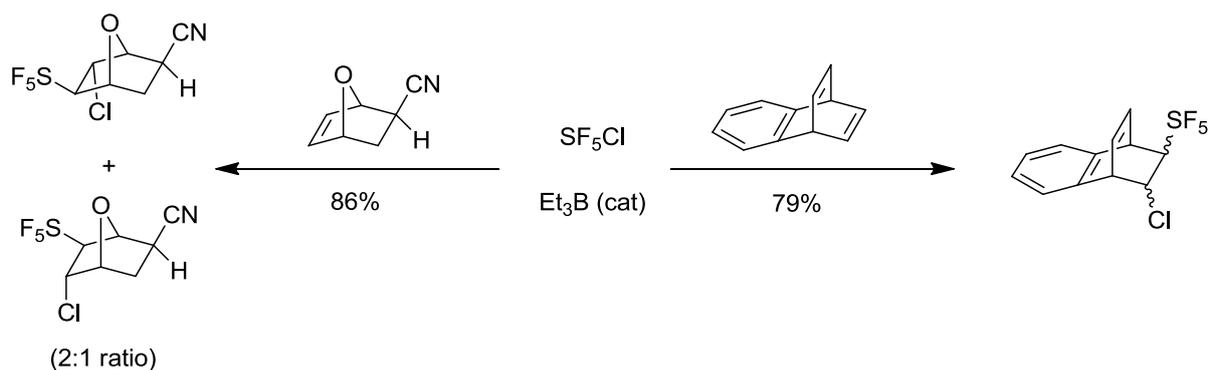
^b One major diastereomer (>90% by NMR)

Later on, the methodology was expanded to include the regioselective synthesis of functionalised SF₅-β-chloro alkyl derivatives, incorporating C=C bonds and ester moieties (Scheme 17). Allene successfully underwent the reaction producing the 2-chloroallyl-SF₅ product. The same strategy worked also when SF₅Cl was replaced by SF₅Br, and β-Br SF₅-alkanes could be obtained by this route. The use of SF₅Br seemed to be more appropriate for the reaction with electron deficient alkenes [46].



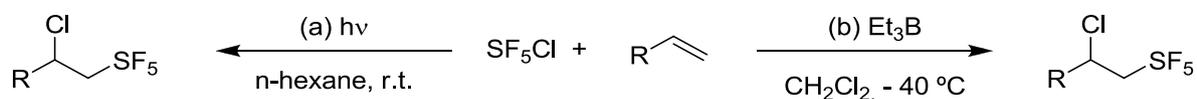
Scheme 17

Another synthetic application of this methodology eventually resulted in an efficient entry to 2-SF₅-naphthalene. One of the key steps was the Et₃B-promoted addition of SF₅Cl to benzobarralene [47]. Another substrate which underwent addition of SF₅Cl under the same conditions is a furan-acrylonitrile exo-adduct which afforded the corresponding SF₅Cl-addition product in very good yields and 2:1 diastereomeric ratio (Scheme 18) [48].



Scheme 18

The scope of the methodology was further investigated and validated by Röschenthaler et al. who showed that the BEt_3 -promoted addition of SF_5Cl is superior to the photochemical process on a range of olefins (Scheme 19 and Table 4)[49, 50].



Scheme 19

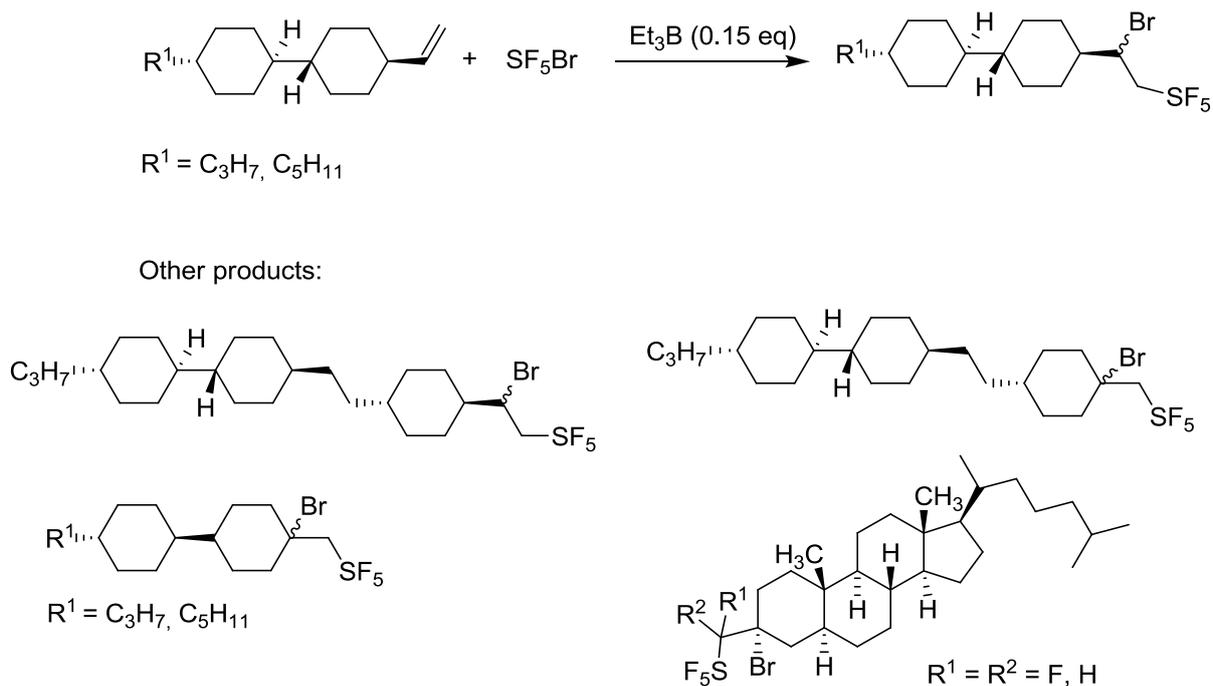
Table 4

Entry	R	Method	Reaction time ^a	Yield (%)
1		a	8	25
		b	6	48
2 ^b		a		
		b	4	92
3		a	8	56
		b	4	91
4		a	6	84
		b	2	95

^a In hour

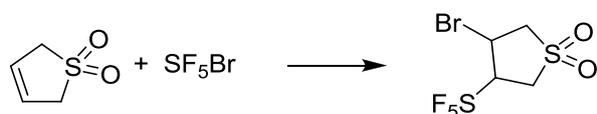
^b The volatility of olefin 2 meant that only method (b) was used

The methodology was also used for the addition of SF_5Br to different alkenes which afforded a series of compounds that showed interesting properties as liquid crystals (Scheme 20) [51].



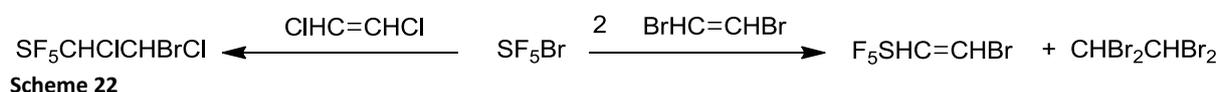
Scheme 20

3-SF₅-4-Bromo sulfolane was obtained by addition of SF₅Br to sulfol-3-ene (Scheme 21) [52]. This molecule was then used as an efficient precursor of 2-SF₅-butadiene (see Section 3.2, Scheme 75).

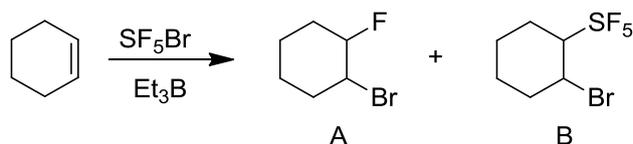


Scheme 21

Dihaloethylenes were found to react with SF₅Br through a radical mechanism, producing different reaction outcomes depending on the nature of the halogen. Indeed, ClCH=CHCl afforded the expected standard 1:1 adduct, whereas BrCH=CHBr reacted in a more complex way affording two different products, one saturated and one unsaturated, the latter incorporating the SF₅ group. Interestingly the reaction producing SF₅-CH=CHBr was stereoconvergent and starting from a mixture of *cis/trans* olefins only the *trans* product was formed (Scheme 22) [53].



An important step forward in the synthesis of SF₅-alkyl compounds was recently achieved by Welch et al. who reported that the use of CCl₃F as a solvent can strongly improve the Et₃B-catalysed addition of SF₅Br to C=C bonds, using operatively simple conditions such as normal glassware, ambient pressure and a temperature of 0 °C (Scheme 23 and Table 5) [54].



Scheme 23

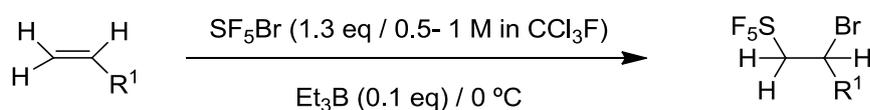
Table 5

Entry	Conditions ^a	Solvent	A ^b	B
1	KF	CH ₂ Cl ₂	9	1
2	-	CH ₂ Cl ₂	9	1
3	SF ₅ Br (sol in CH ₂ Cl ₂) and KF	CH ₂ Cl ₂	9	1
4	SF ₅ Br (sol in CH ₂ Cl ₂)	CH ₂ Cl ₂	9	1
5	KF	Pentane	7	3
6	-	CCl ₃ F	4	6

^a All reactions, 0.1 eq. Et₃B, 1.2 eq. SF₅Br, Temp: -78 °C to RT

^b Product ratio determined by ¹⁹F NMR

The use of CCl₃F as a solvent was then successfully extended to the Et₃B-catalysed addition of SF₅Br to various unsaturated esters, which produced the corresponding bromo-pentafluorosulfonylated esters in excellent yields (Scheme 24 and Table 6). The use of SF₅Cl afforded lower yields, and addition of DBU resulted in efficient dehydrobromination of the products [54]. Addition of SF₅Cl to allyl acetate was subsequently described to occur efficiently [55].



Scheme 24

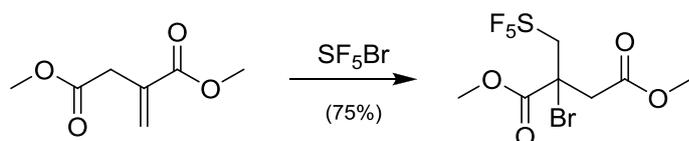
Table 6

Entry	R ¹	Reaction time ^a	Yield ^b
1	C(O)Ot-Bu	20	94
2	CH ₂ C(O)OMe	10	85
3	CH ₂ CH ₂ C(O)OEt	20	93
4	CH ₂ CH(CH ₃)C(O)OEt	10	92
5	CH ₂ OC(O)CH ₃	10	99

^a In minutes

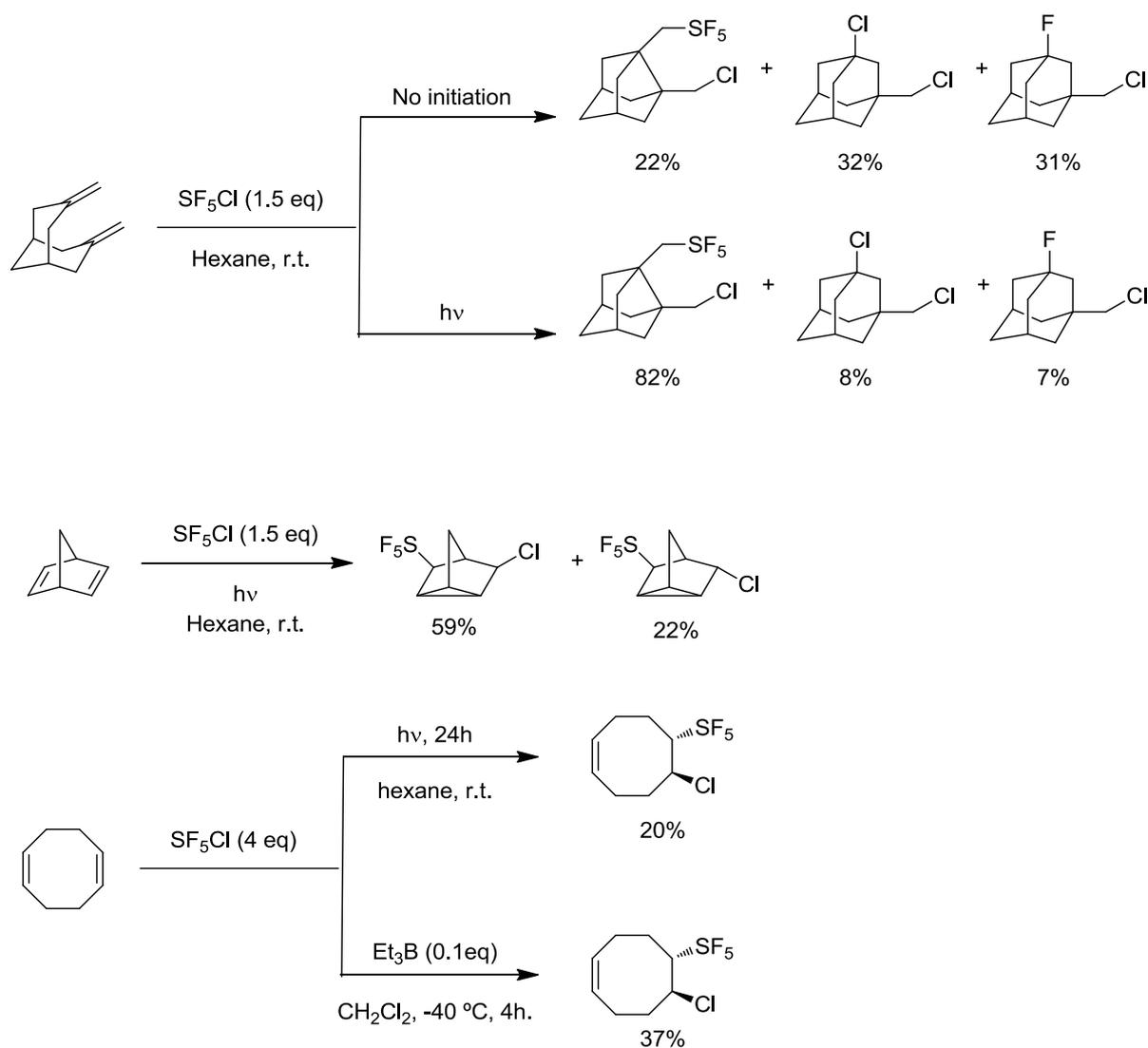
^b Isolated, purified yield

Dimethyl itaconate was also successfully reacted with SF₅Br affording the expected addition product in good yields (Scheme 25) [56].



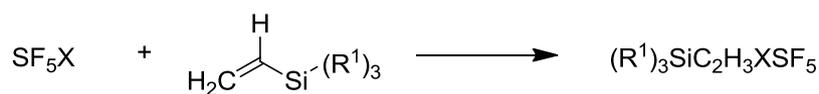
Scheme 25

An interesting addition reaction of SF₅Cl to a diene, occurring with concomitant transannular cyclization was recently reported by Röschenthaler et al. Without any radical initiation, the process affords low yields of the target SF₅-substituted adamantane-type cyclised product, with the formation of significant amounts of dichloro and chlorofluoro-substituted by-products, which may arise from the dissociation of SF₅Cl into FCl and SF₄. However, upon UV irradiation the process delivered high yields of target SF₅-compound. Under UV-irradiation also norbornadiene reacted with SF₅Cl affording two diastereoisomers of the corresponding transannulated SF₅-product, in ca. 3:1 ratio. Finally, cycloocta-1,5-diene failed to produce transannulation, affording the product arising from simple addition of SF₅Cl to one of the C=C bonds, in rather modest yields (Scheme 26) [57].



Scheme 26

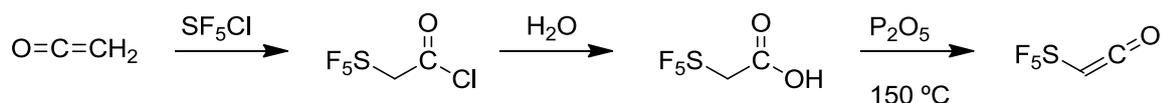
The addition of SF₅Cl and SF₅Br to vinyl silanes was reported to occur efficiently and under mild conditions. The authors were unable to assign unambiguously the regioisomery of the products on the basis of spectroscopic and analytical data (Scheme 27) [58].



X = Cl, Br
R¹ = Me, Cl

Scheme 27

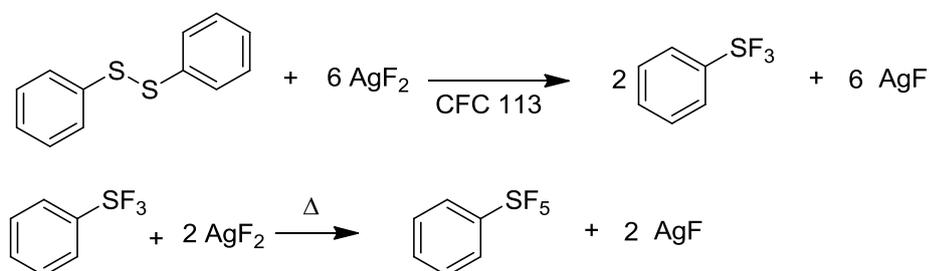
Ketene was also found to be reactive towards SF₅-Cl, affording SF₅-acetyl chloride [59]. This intermediate was then used as a starting material for the preparation of SF₅-ketene through hydrolysis followed by dehydration (Scheme 28) [60].



Scheme 28

2.3. Synthesis of aryl SF₅-compounds

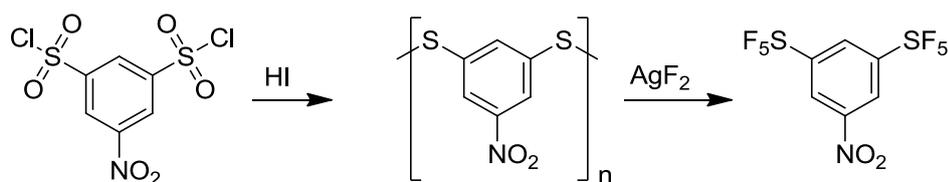
This chapter reviews the preparation of compounds having an SF₅-group attached to an aromatic residue. Following unsuccessful efforts to prepare aromatic SF₅-compounds by Emeleus et al. [61], the first aryl-pentafluoride C₆H₅-SF₅ was successfully obtained by Sheppard by action of AgF₂ on (C₆H₅S)₂ in Freon which produced the intermediate trifluoride, then converted into the target phenyl-SF₅ upon heating to 130 °C (yields 5-14%) (Scheme 29) [62].



Scheme 29

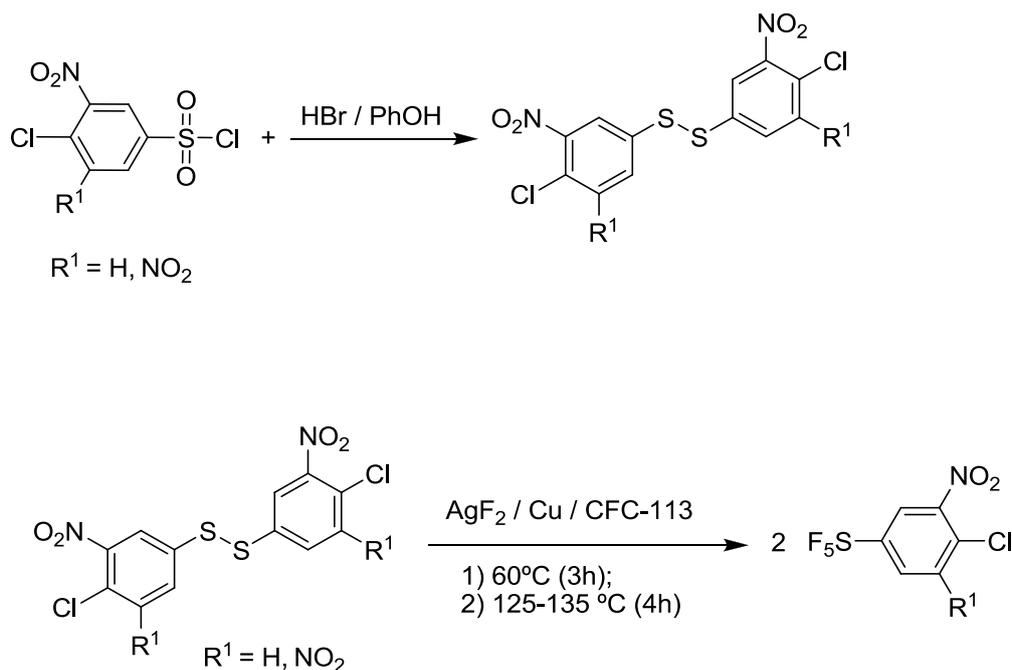
The same transformation was achieved 40 years later by using XeF₂ as fluorinating agent (up to 25% yield) [63].

The scope of the reaction was subsequently extended to *meta*- and *para*-nitrophenyl-SF₅ compounds by using a Teflon reactor (5-14% yields), whereas the use of a copper reactor increased the yields to 15-30%. Interestingly, bis-3,5-SF₅ nitrobenzene could be obtained, albeit in low yields, starting from the corresponding bis-sulfonyl chloride (Scheme 30) [64].



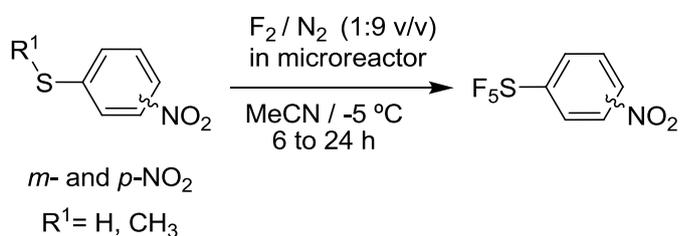
Scheme 30

A related methodology was used later on for the synthesis of two other nitro-substituted SF₅-benzenes (Yields 29-43%) (Scheme 31) [65].



Scheme 31

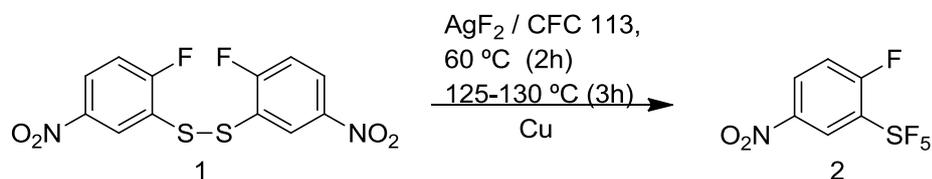
Elemental fluorine (10% F₂ in N₂), that was used to convert at room temperature aromatic nitrothiols and nitro-methylsulfides into the corresponding SF₅ compounds in moderate yields (Scheme 32) [66]. Remarkable results were achieved by employing micro-reactors for fluorinations that were used to convert bis(*m*-NO₂-phenyl)-disulfide and *p*-NO₂-phenyl-SF₃ into the corresponding SF₅ compounds at room temperature [67].



Scheme 32

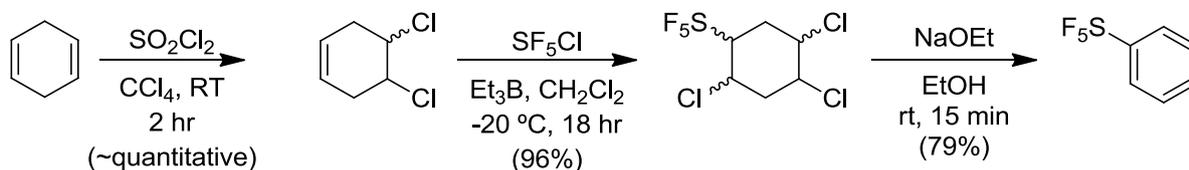
The first *ortho*-substituted SF₅-benzene was synthesised by AgF₂-promoted fluorination of the corresponding disulfide (Scheme 33), although the scope of the reaction seems to be limited because other structurally related substrates did not afford the desired SF₅-compounds [68]. A few

years later, more *ortho*-fluorinated SF₅-aryl compounds were obtained in low yields (< 10%) by treatment of a disulfide precursor with F₂/N₂ [69].



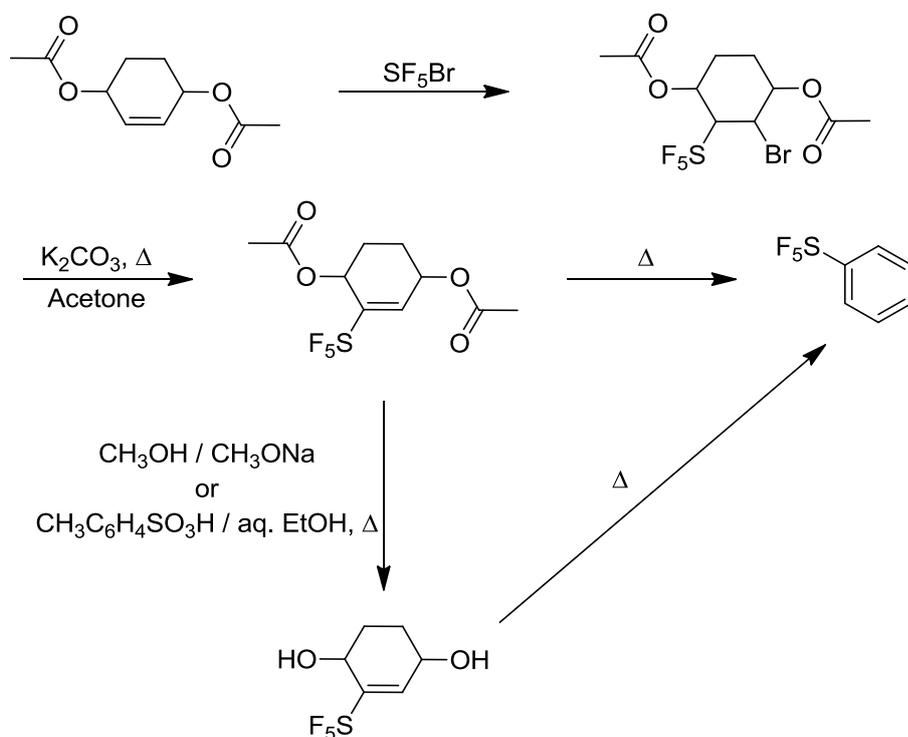
Scheme 33

A remarkably more efficient synthesis of SF₅-benzene was achieved by chlorination of cyclohexa-1,4-diene with SO₂Cl₂ followed by treatment of the resulting dichloro-intermediate with SF₅Cl and then easy aromatisation resulting from elimination of three molecules of HCl (Scheme 34) [70].



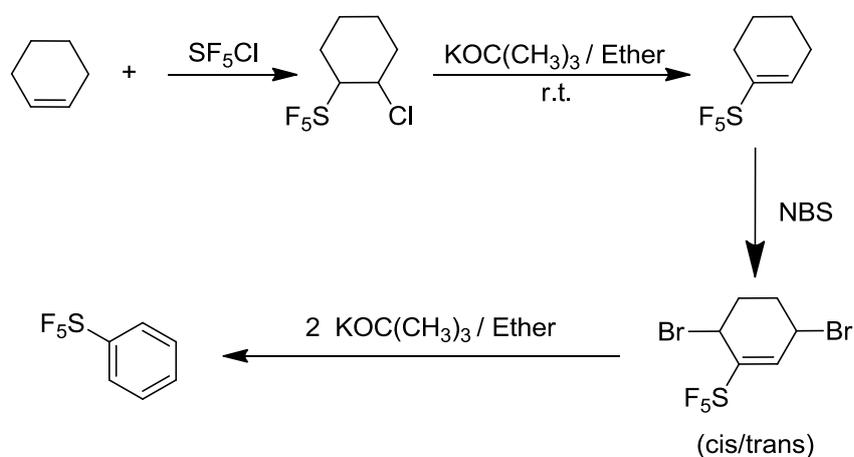
Scheme 34

A conceptually related entry to SF₅-benzene was developed starting from 3,6-diacetoxy-cyclohex-1-ene, which upon treatment with SF₅Br followed by aromatisation resulting from elimination of HBr and 2 molecules of acetic acid or water afforded the target SF₅-benzene (Scheme 35) [71].



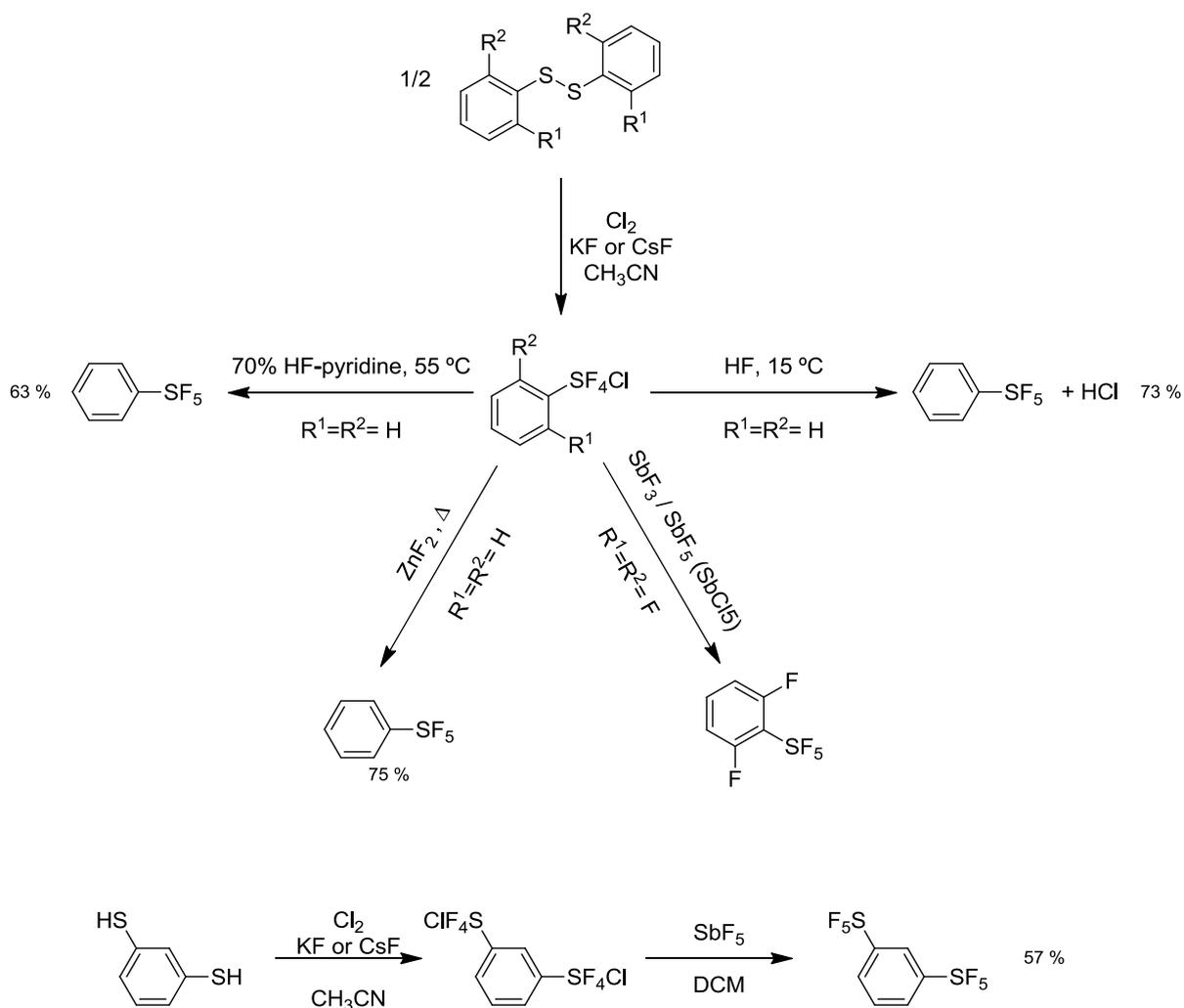
Scheme 35

The method worked also when less reactive SF₅Cl was used instead of SF₅Br; in that case, cyclohexene was used as starting material followed by NBS-promoted dibromination of the intermediate 1-SF₅-cyclohexene (Scheme 36) [71].



Scheme 36

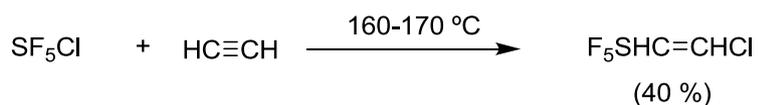
Very recently Umemoto et al. published a novel two-steps synthesis of SF₅-aromatics, which appears to be a significant improvement over previous methods. The synthesis is based on the conversion of aryl-disulfides or thiols into the corresponding SF₄Cl derivatives by action chlorine and potassium or cesium fluoride (Scheme 37). Subsequent treatment with a fluoride source such as ZnF₂ or Sb(III/V) fluorides effectively produced a displacement of the chlorine atom by fluoride affording the target SF₅-aryl compounds. Bis-SF₅-aromatics could be also prepared from the corresponding thiols [72].



Scheme 37

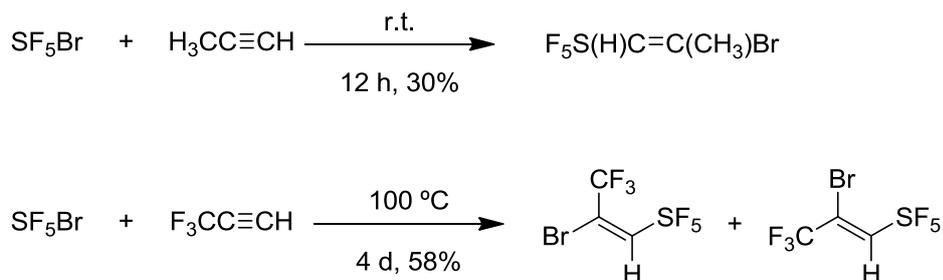
2.4. Synthesis of alkenyl, alkynyl and acyl SF₅-compounds

This section reviews the preparation of compounds having an SF₅-C(sp²) or SF₅-C(sp) bond. The first example of addition of SF₅Cl to an alkyne dates back to 1964 when Hoover and Coffman reported the formation of 1-SF₅-2-Cl-ethylene from acetylene under thermal conditions (Scheme 38) [73]. The corresponding reaction with SF₅Br was described 20 years later to afford 80% yield of F₅SCH=CHBr [74].



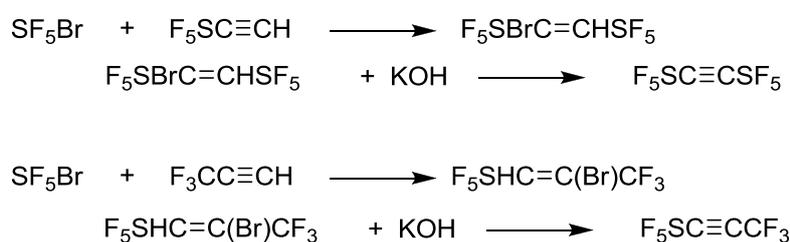
Scheme 38

Propyne and trifluoropropyne efficiently reacted with SF₅Br affording the corresponding SF₅-prop-1-enes. The former, which is more activated, underwent reaction at r.t. affording a single isomer, whereas the latter required heating to 100 °C and longer reaction times, affording a mixture of E/Z isomers (Scheme 39) [75].



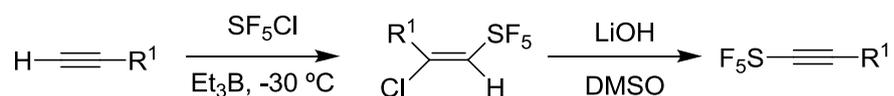
Scheme 39

The addition of SF₅Br to alkynes was also exploited as a means to prepare SF₅-alkynes, which were obtained by treating the intermediate 1-SF₅-2-Br-alkenes with KOH that resulted in an elimination reaction (Scheme 40) [76].



Scheme 40

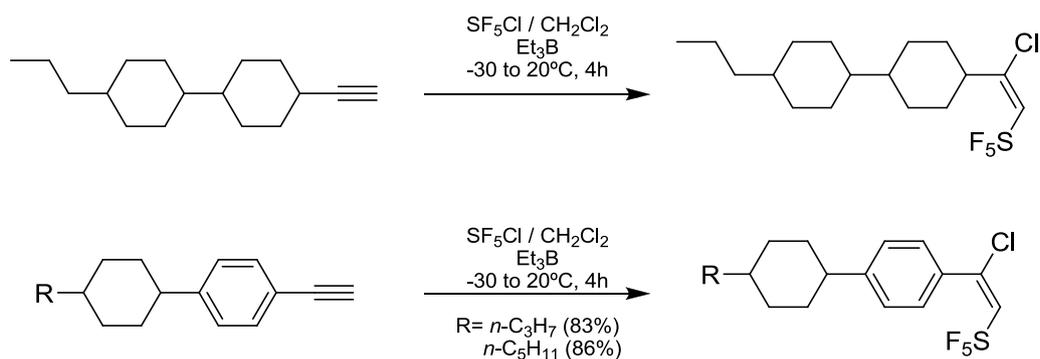
Further SF₅-acetylene derivatives were prepared by means of a conceptually related synthetic protocol based on Et₃B-catalysed addition of SF₅Cl to terminal alkynes, followed LiOH-promoted elimination (Scheme 41) [77].



R¹: CH₂CH₂Ph, Ph, *n*-Butyl, *p*-tolyl

Scheme 41

The same methodology was recently used to prepare SF₅-substituted acetylenes having liquid crystal properties (Scheme 42). The SF₅-substituted β-chloro-alkene intermediates were treated with LiOH in DMSO at 50 °C for 12 h resulting in the desired elimination of HCl which produced the target SF₅-alkenes in 65-72% yields [78].



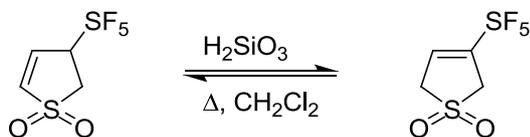
Scheme 42

β -SF₅-acrylate monomers were obtained by reaction of SF₅Br with ethyl propiolate (Scheme 43) [79].



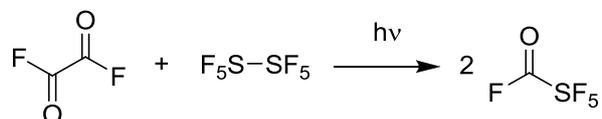
Scheme 43

A conceptually different approach to an SF₅-alkene was reported by Winter and Gard who described the silicic acid promoted isomerisation 3-SF₅-4-sulfolene to the corresponding 3-sulfolene (Scheme 44) [52].



Scheme 44

One of the few acyl-SF₅ compounds described so far was obtained by radical addition of (SF₅)₂ to oxalyl fluoride (Scheme 45). The resulting product was then used as an intermediate in the preparation SF₅OC(O)F and SF₅O₂C(O)F [80].



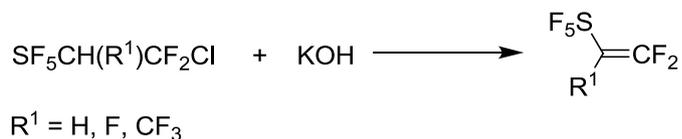
Scheme 45

3. CHEMISTRY OF SF₅-COMPOUNDS (SECONDARY REACTIVITY)

This section will review the reactivity of “primary” SF₅-building blocks, obtained as described in Section 2, for producing more complex SF₅-derivatives (secondary reactivity).

3.1. Reactions of SF₅-alkanes.

The reactivity of SF₅-alkanes, i.e. derivatives having a pentafluorosulfanyl group bound to an sp³-carbon which are generally obtained by addition of SF₅X to the parent alkenes (see Section 2.2), is dominated by the β-elimination of HX to afford the corresponding SF₅-alkenes. De Marco and Fox described the KOH-promoted elimination of HCl from α-chlorodifluoromethyl-SF₅-compounds (Scheme 46) [27].

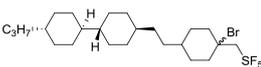
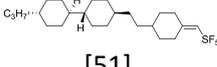
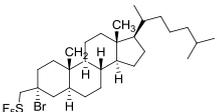
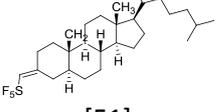
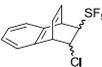
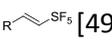


Scheme 46

This reactivity has been extensively exploited from 2000 to date for preparing a number of structurally diverse SF₅-alkenes, using a wide range of different bases and conditions, as summarised in Table 7.

Table 7

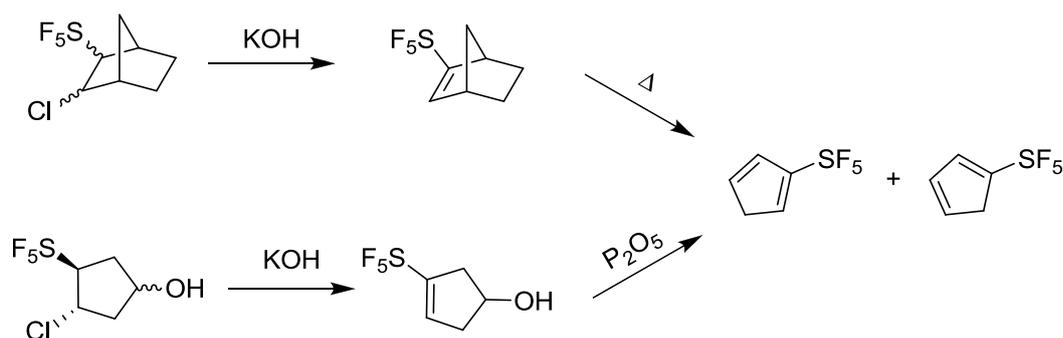
Entry	Starting material	Product [Ref]	Base / Temp	Yield ^a (%)	Comments
1			NaOMe / r.t.	91	
2			NaOCH ₃ / 0 °C	71	Two isomers in ratio: 3:97
3			NaOEt / r.t.	79	
4			K ₂ CO ₃ / 56 °C	98, 70 ^b	Heating to 265 °C:
5			KOC(CH ₃) ₃ / r.t.	71	
6			K ₂ CO ₃ / 60 °C	n=1, 79 n=2, 86	
7			K ₂ CO ₃ / 55 °C	50	Heating to 75-80 °C
8			KOH / 30 °C	67	
9			KOH / 30 °C		R= H, CH ₃
10			KOH / 30 °C		
11			K ₂ CO ₃ / 60 °C	87	
12			K ₂ CO ₃ / 60 °C	90	
13			NaOMe / r.t.	76	
14			LiOH * H ₂ O / r.t.	96	
15			KOH / 35 °C	R=C ₃ H ₇ , 74 R= C ₅ H ₁₁ , 84	
16			KOH / 35 °C	97	
17			KOH / 65 °C	R=C ₃ H ₇ , 87 R= C ₅ H ₁₁ , 89	

18			KOH / 65 °C	96	
		[51]			
19			KOH / 65 °C	81	
		[51]			
20			NaOMe / 50 °C	95	
		[47]			
21			AgOTs / 82 °C	52	By-product 
		[52]			
22			K ₂ CO ₃ / 50 °C		R= Cy, 91 R= <i>i</i> -Pr, 88 R= (CH ₂) ₂ Ph 87 R= CH ₂ Cy, 78
		[49]			

^a Total yield

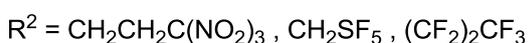
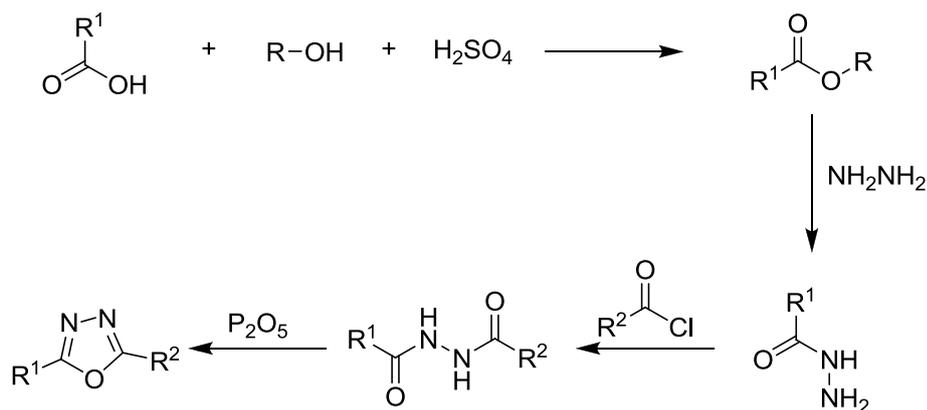
^b Starting from the *trans* isomer, 98 % of *trans* product has been obtained. Starting from the *cis*, 70% of *cis* product has been obtained

SF₅-cyclopentadiene was obtained as a mixture of two tautomeric forms from two different starting materials. In both cases elimination of HCl was the key step, followed by either a retro-Diels Alder reaction or a P₂O₅-promoted dehydration (Scheme 47) ([39]).



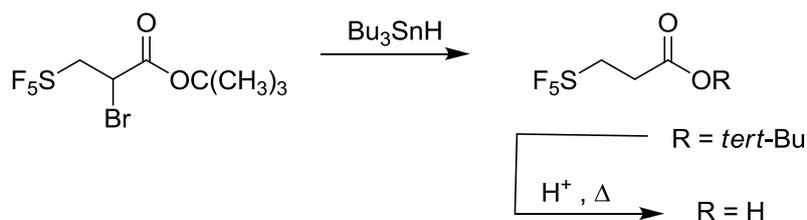
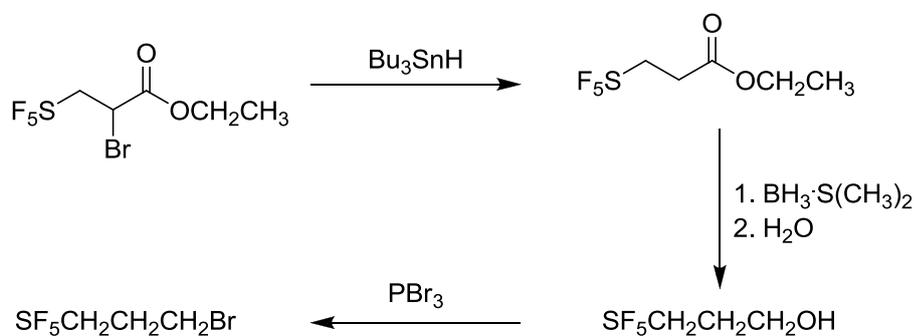
Scheme 47

1,3,4-Oxadiazoles incorporating SF₅-perfluoroalkyl/alkyl substituents were synthesised starting from the corresponding SF₅-containing carboxylic acids through the corresponding hydrazides which were coupled to a second carboxylic acid, and then submitted to intramolecular condensation (Scheme 48) [83] .



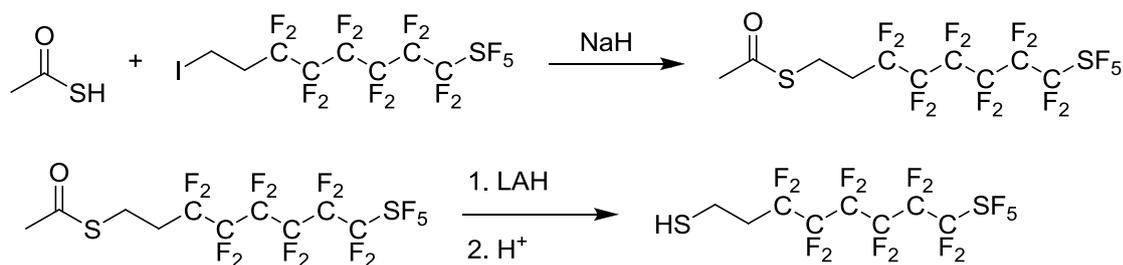
Scheme 48

Aliphatic SF_5 -substituted C-3 building blocks such as 3-Br-pentafluorosulfanyl-propane and 3- SF_5 -propionic acid were prepared by radical reduction of the parent 2-Br-propionates followed by manipulation of the carboxy function (Scheme 49) [38]. A related halide displacement was reported to occur when $\text{SF}_5\text{CF}_2\text{CFBrPh}$ was treated with AgBF_4 affording $\text{SF}_5\text{CF}_2\text{CF}_2\text{Ph}$ together with AgBr and BF_3 [33]. The scope of the method was subsequently extended to the synthesis of an array of $\text{SF}_5\text{CF}_2\text{CF}_2\text{Ar}$ compounds (Ar = substituted aryl groups) [34].



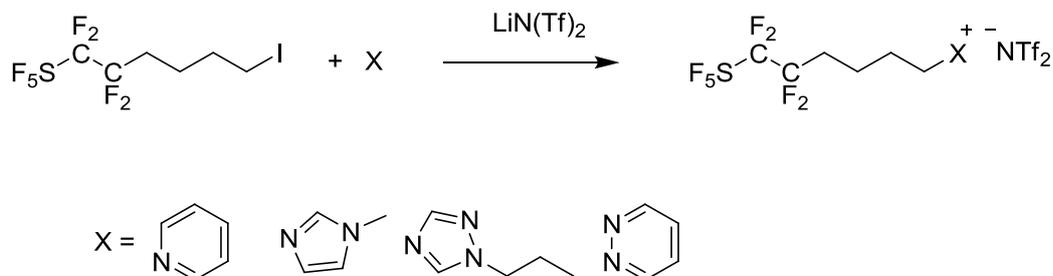
Scheme 49

An SF₅-perfluoroalkyl thiol was obtained by S_N2-reaction of thioacetic acid with an ω-iodo precursor followed by LiAlH₄ reduction (Scheme 50) [44].



Scheme 50

Similarly, a series of quaternary trifluoromethanesulfonimide salts incorporating different N-heterocyclic residues were prepared by S_N2-reaction with the parent ω-iodo derivative followed by anion exchange (Scheme 51) [84]. Similar strategy was subsequently used to prepare energetic salts incorporating SF₅-alkyl residues, heterocyclic rings and perchlorate, nitrate, and related counterions [85].

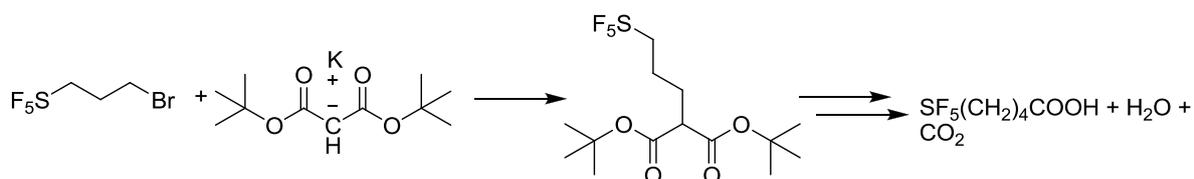
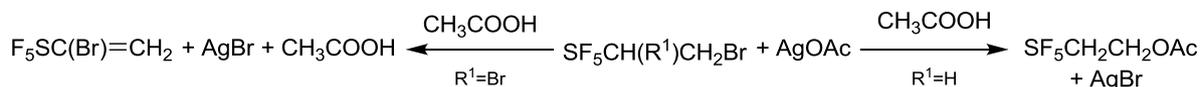


Scheme 51

A broad range of ω-SF₅-alkyl building blocks were prepared by halogen displacement with O-nucleophiles by treatment with the corresponding silver and alkali metal salts. Interestingly, treatment of 1-SF₅-2-bromoethyl derivatives with AgOAc and acetic acid resulted in either elimination or in S_N2 reaction depending on the presence or not, respectively, of a bromine atom in α-position to the SF₅. (3-SF₅-propyl)malonate was then prepared from the corresponding bromide and decarboxylated to give ω-SF₅-pentanoic acid (Scheme 52) [56].

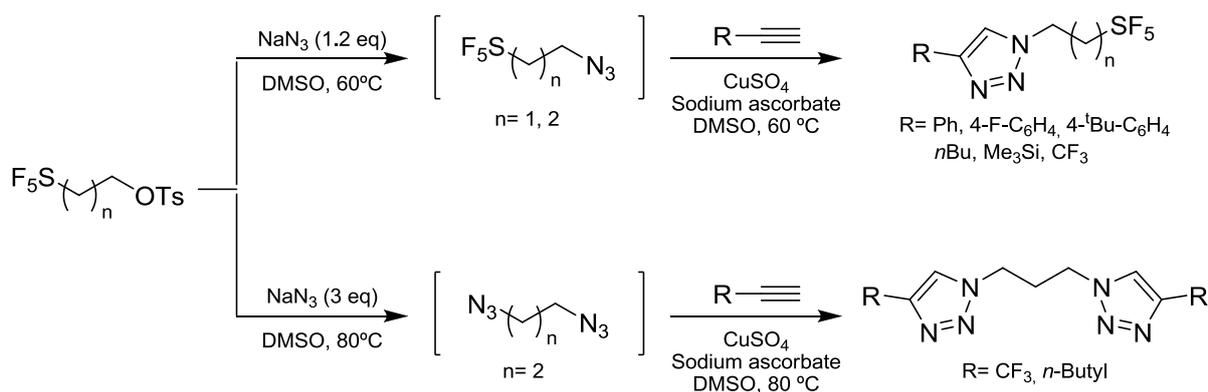


$n = 0, 4$
 $m = 2, 3$
 $X = \text{Br}, \text{I}$
 $Y = \text{OAc}, \text{OTos}, \text{OTf}, \text{ONO}_2$



Scheme 52

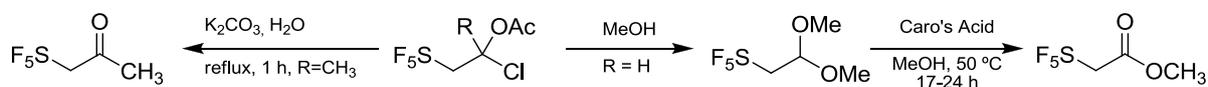
An extremely interesting development related to the preparation of SF_5 -substituted azides for click-chemistry was recently reported (Scheme 53) [86]. SF_5 -Ethyl and propyl azides were synthesized by nucleophilic substitution of the parent tosylates with 1.2 equivalents of sodium azide at 60°C , whereas an attempt to reduce the reaction time by using a larger excess of azide and higher temperatures resulted in a rather unexpected concomitant SF_5 -displacement that afforded the bis-azide derivative. The use of SF_5 -alkyl-bromides in the reaction with NaN_3 gave poor results. The azides were reacted in situ with a series of terminal alkynes under classical "click-chemistry" conditions affording the target 1,2,3-triazoles in good yields.



Scheme 53

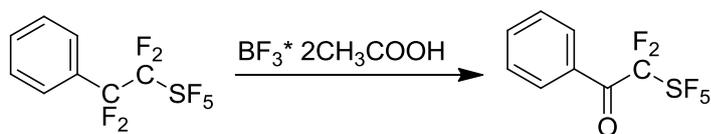
SF_5 -acetate and acetone were synthesised by hydrolysis of the α -chloro acetate precursors in the presence of, respectively, methanol and water. Interestingly attempts to alkylate the α -anion of SF_5 -acetate were unsuccessful. Control experiments with the anion of γ - SF_5 -crotonate, which could not be alkylated either, suggested that the observed lack of reactivity may be due to the stabilising

effect of the electron withdrawing SF₅ group rather than to its steric bulk (Scheme 54)[46]. SF₅-Acetate was recently utilised by Dolbier et al. in the synthesis of energetic materials [87]. SF₅-Acetyl chloride was also used as a starting material for the synthesis of high-energy SF₅-nitro compounds [59].



Scheme 54

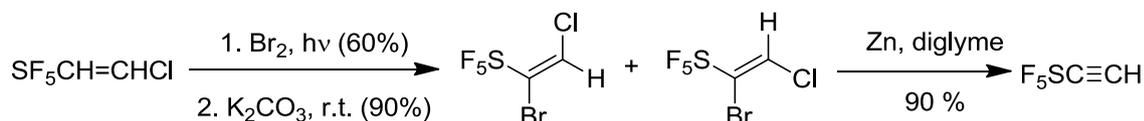
Another example of SF₅-substituted ketone was obtained by hydrolysis of SF₅-tetrafluoroethylbenzene (Scheme 55)[88].



Scheme 55

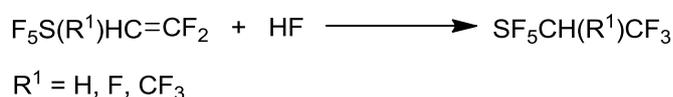
3.2. Reactions of SF₅-alkenes: addition, addition-elimination, elimination and cycloaddition

One of the first reactions involving SF₅-alkenes, specifically SF₅-CH=CHCl, was described in 1964. Photochemical addition of bromine followed by basic elimination produced a regioisomeric mixture of SF₅-CBr=CHCl that was eventually reduced by zinc to SF₅-acetylene in high yields (Scheme 56) [73].



Scheme 56

Later on, the addition of HF, indirectly generated from KF + formamide, to SF₅-difluoroethylenes was reported to produce a small array of α-CF₃-pentafluorosulfanyl compounds (Scheme 57) [27].



Scheme 57

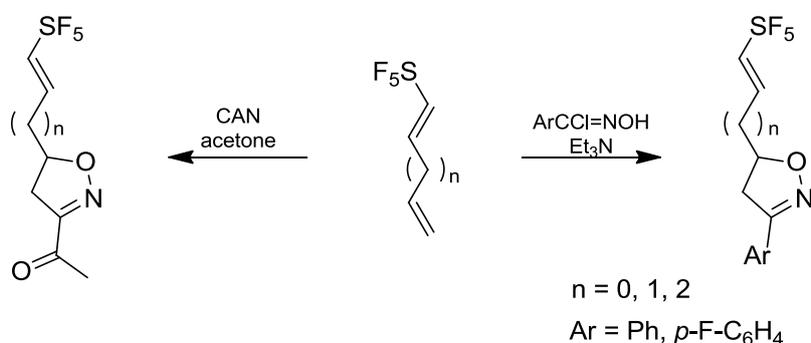
Perfluorinated β-sultone was obtained by addition of SO₃ to SF₅-trifluoroethylene, and then hydrolysed with water at 45-60 °C producing the corresponding sulfonyl fluoride and CO₂ + HF as co-products (Scheme 58) [89]. This finding built on extensive previous work dedicated to the preparation of SF₅-substituted β-sultones and their conversion into fluorosulfonyl derivatives [90] (for a review see [91]).

However, hypochlorite oxidation of SF₅-trifluoroethylene successfully produced the corresponding epoxide. As the reaction involves the formation of an anionic intermediate, the SF₅ group was found to facilitate the reaction and was more effective than a CF₃ group in terms of negative charge stabilisation (Scheme 61) [92].



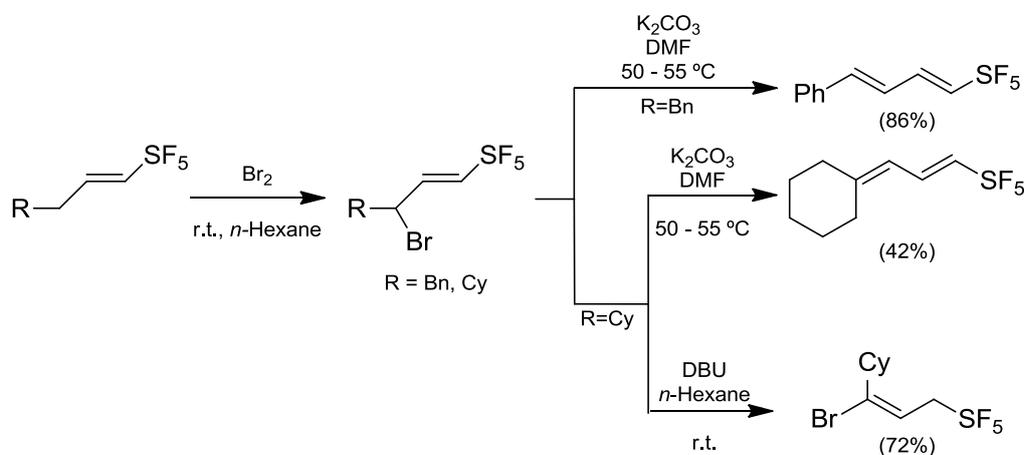
Scheme 61

Similarly, SF₅-dienes showed chemoselective reactivity towards cycloaddition reactions, affording under different conditions the corresponding 4,5-dihydroisoxazoles originated by exclusive reaction of the non-SF₅-substituted C=C bond (Scheme 62) [41].



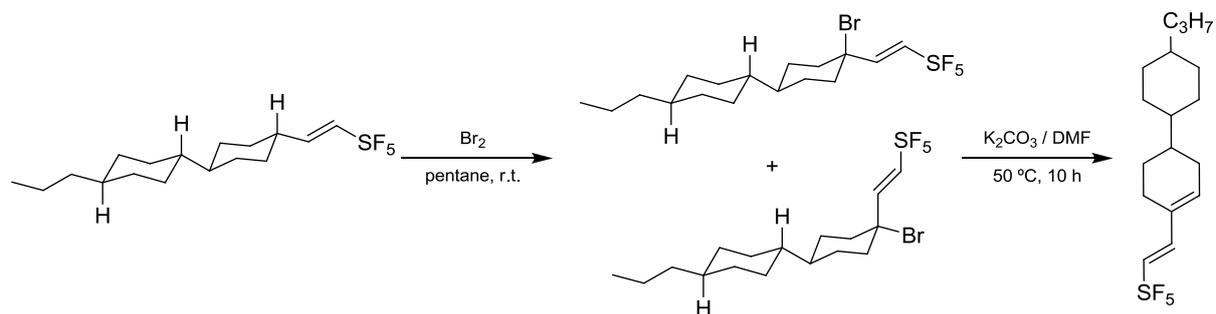
Scheme 62

Treatment of SF₅-alkenes with bromine did not result in addition across the C=C bond but rather in allylic bromination, confirming the lack of reactivity of SF₅-substituted C=C bonds. The allylic bromides were submitted to base-elimination affording a set of terminally SF₅-substituted buta-1,3-dienes (Scheme 63) [49, 50].



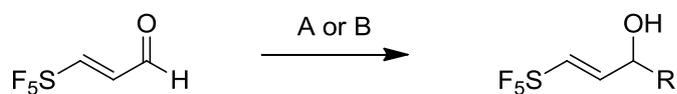
Scheme 63

The same kind of reactivity towards bromination was very recently observed in SF₅-alkene systems deemed to be used for novel liquid crystals (Scheme 64) [78].



Scheme 64

SF₅-1,3-dienes were prepared exploiting a key Wittig or Horner-Wadsworth-Emmons (HWE) reaction. The starting allylic alcohols were prepared by Grignard-reagent 1,2-addition to β-SF₅-acrolein, which occurred in low to moderate yields (Scheme 65 and Table 8).



Scheme 65

Table 8

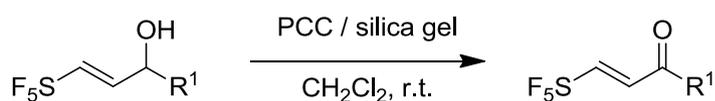
Entry	R	Yield ^a	Yield ^b
		(%) method A	(%) method B
1	C ₅ H ₁₁	65	38
2	C ₁₄ H ₂₉	62	26
3	Ph	60	30
4	C ₆ H ₁₁	30	16
5	Allyl	33	32
6	Bn	5 ^c	2 ^c
7	Vinyl	0	53

^a Method A: *In situ* Grignard preparation

^b Method B: Addition of pre-formed Grignard reagent

^c GC yields

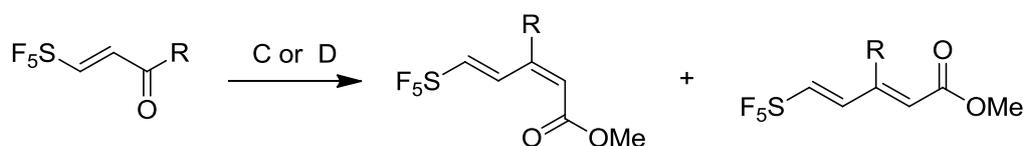
Oxidation of the SF₅-allylic alcohols to β-SF₅-oxo-compounds was achieved via PCC-oxidation in the presence of silica gel (Scheme 66).



R ¹	Yield (%)
H	95
C ₅ H ₁₁	17
C ₁₄ H ₂₉	91
Ph	98
C ₆ H ₁₁	41

Scheme 66

The target dienes were eventually obtained in generally good yields and as mixtures of regioisomers, either by Wittig or HWE reactions (Scheme 67 and Table 9).



Scheme 67

Table 9

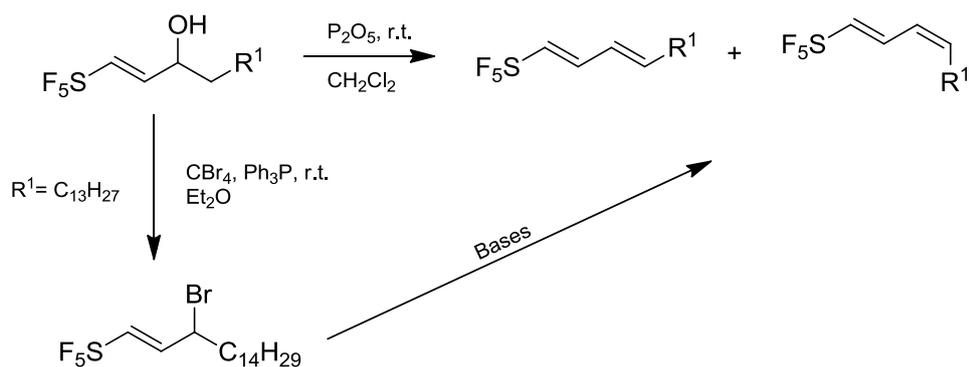
Entry	R	Method ^a	Product Isomers formed	Ratio ^b	Yield ^c (%)
1		C	(2Z,4E);(2E,4E)	16:84	72
2	H	D	(2Z,4E);(2E,4E)	2:98	46
3		C	(2Z,4E);(2E,4E)	14:86	60
4	C ₆ H ₁₁	D	(2Z,4E);(2E,4E)	0:100	46
5		C	(2Z,4E);(2E,4E)	43:57	57
6	C ₁₄ H ₂₉	D	(2Z,4E);(2E,4E)	39:61	74
7	Ph	C	(2E,4E);(2Z,4E)	-	0
8	Ph	D	(2E,4E);(2Z,4E)	62:38	41

^a Method C: Wittig reaction; Method D: Horner-Wadsworth-Emmons (HWE) reaction

^b Determined by GC and confirmed by ¹⁹F NMR

^c Combined yields

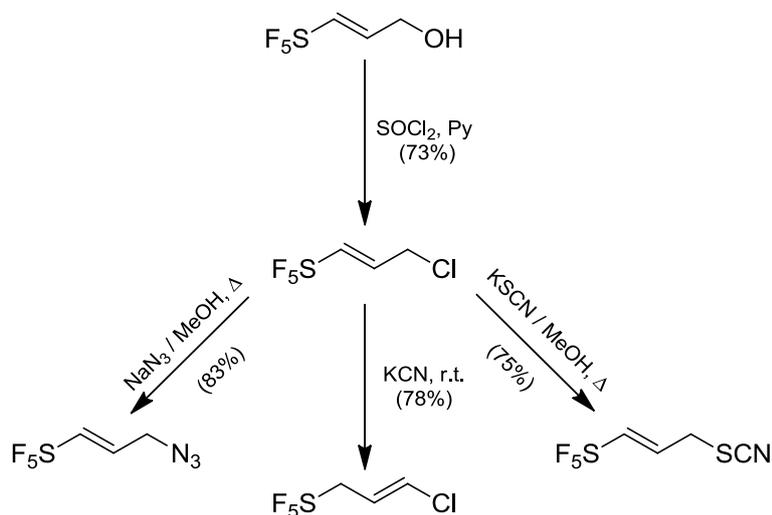
Some 1,3-dienes were alternatively obtained by direct dehydration of the intermediate allylic alcohols or alternatively by elimination of the allylic bromides produced by dehydroxy-bromination with CBr₄/triphenylphosphine (Scheme 68) [55].



Scheme 68

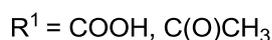
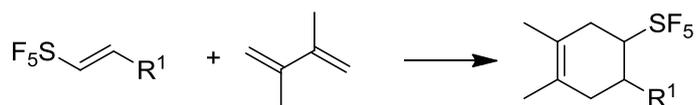
A series of useful SF₅-alkene compounds was prepared from SF₅-allyl alcohol, which was selectively oxidised to SF₅-acrolein by action of CAN and then converted into a regioisomeric mixture of oximes, which were dehydrated to SF₅-acrylonitrile (Scheme 69).

3-Chloro-1-SF₅-propene demonstrated a peculiar reactivity. In fact, following its preparation from the corresponding SF₅-allyl alcohol, the compound showed the expected S_N2-type reactivity with azide and thiocyanate anions, whereas upon reaction with cyanide at r.t. a double-bond migration was observed instead. Supported by calculations, this behaviour was interpreted in terms of CN⁻ preferentially acting as a base rather than as a nucleophile (Scheme 71) [40].



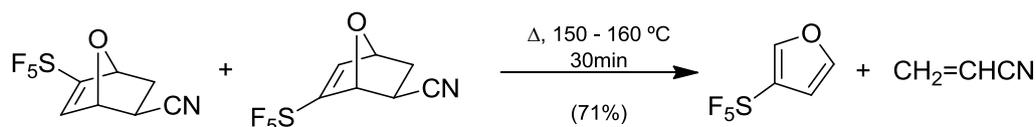
Scheme 71

SF₅-substituted C=C bonds proved to be reactive under Diels-Alder reaction conditions, and the corresponding cyclohexenes were obtained by reaction with 2,3-dimethyl-butadiene upon heating for 8-10 hr at 100-110 °C (Scheme 72) [41].



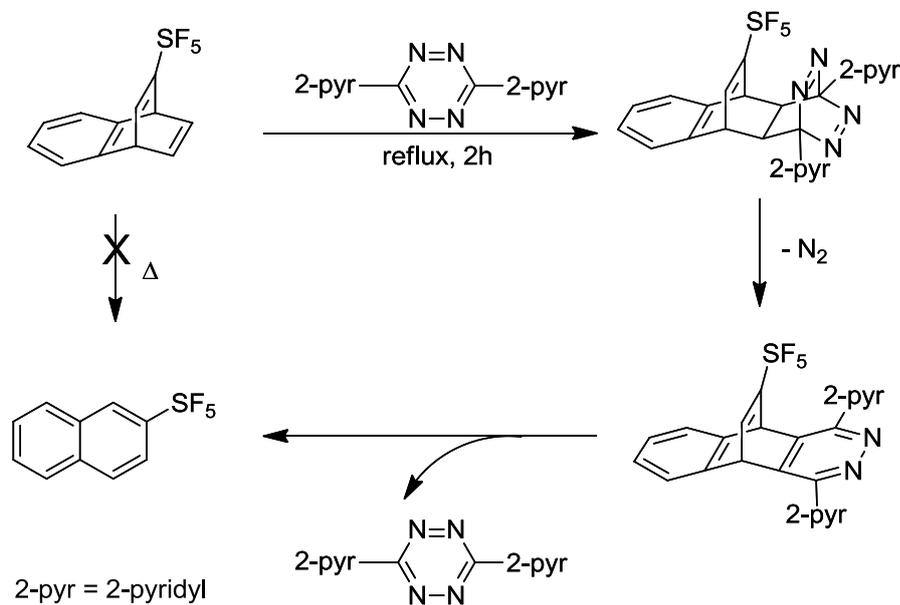
Scheme 72

A retro-Diels-Alder reaction was used to prepare 3-SF₅-furan in good yields, with the concomitant formation of acrylonitrile as a co-product. 2-Methyl-3-SF₅-furan was prepared following the same protocol (Scheme 73) [48].



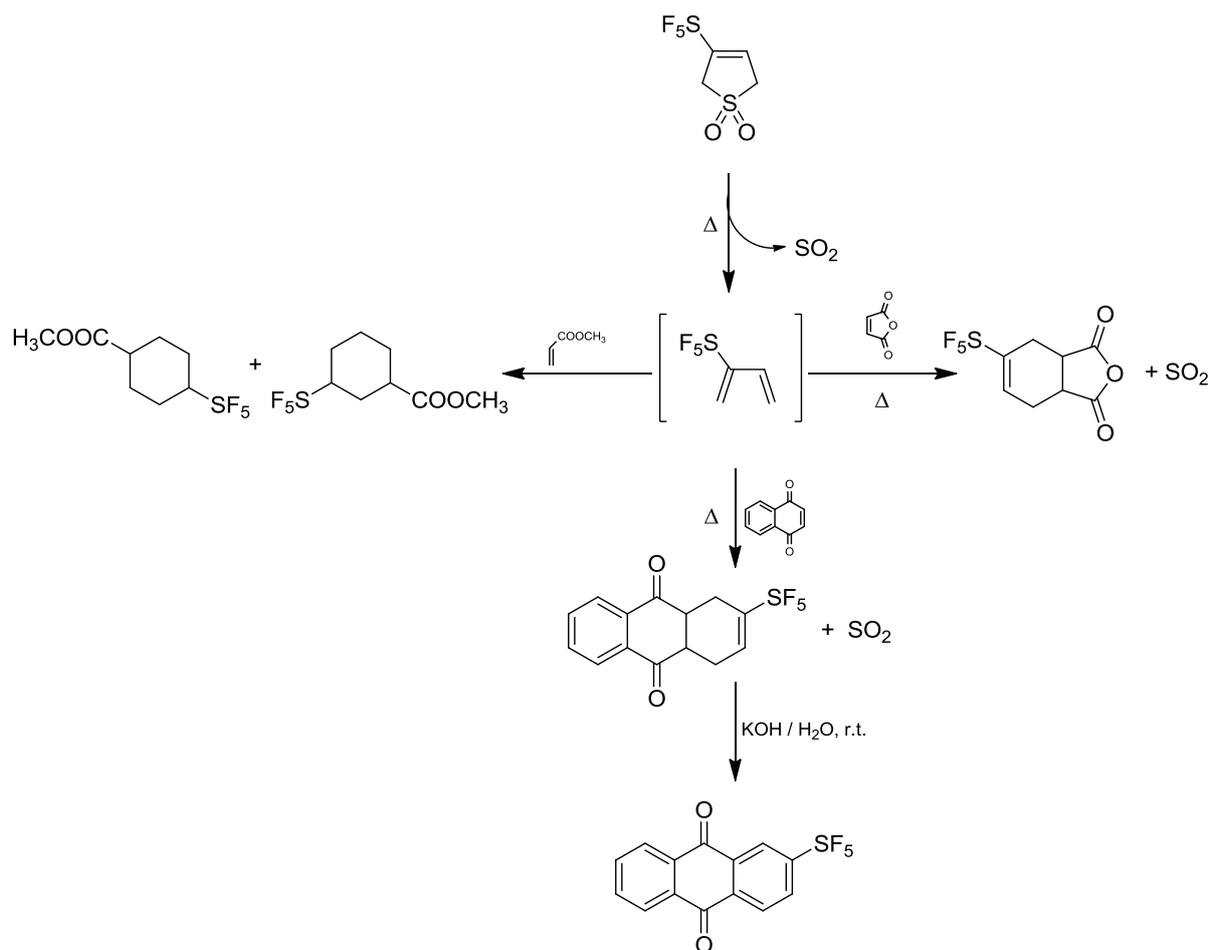
Scheme 73

In contrast, 2-SF₅-benzobarralene did not undergo the expected thermal retro-Diels-Alder reaction to 2-SF₅-naphthalene, therefore an indirect approach to the target compound was sorted out. A bis-pyridyl tetrazine was submitted to Diels-Alder reaction with 2-SF₅-benzobarralene affording the corresponding adduct, which underwent first a loss of N₂ and then a retro-Diels-Alder affording the target compound, which proved to be thermally stable up to 250 °C (Scheme 74) [47].



Scheme 74

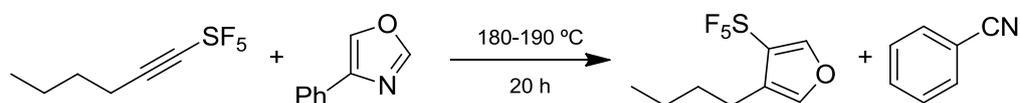
3-SF₅-sulfolane was found to be a synthetic precursor of 2-SF₅-butadiene and successfully used as a substrate in Diels-Alder reactions leading to an array of SF₅-substituted cyclic compounds (Scheme 75) [52].



Scheme 75

3.3. Reactivity of SF₅-alkynes

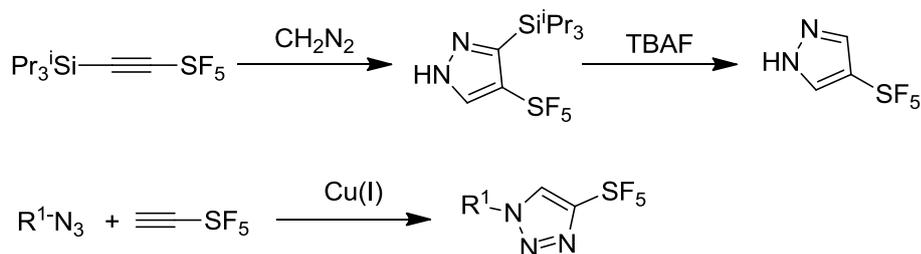
A limited number of SF₅-substituted heterocycles have been reported and many of them were obtained via dipolar cycloadditions involving SF₅-alkynes. 1-SF₅-Hex-1-yn underwent a tandem Diels-Alder/retro-Diels-Alder reaction with 4-phenyl-oxazole that afforded 3-SF₅-4-butyl-furane with the formation of cyanobenzene as a co-product (Scheme 76) [48].



Scheme 76

SF₅-Azoles, including pyrazoles and 1,2,3-triazoles, were synthesised by 1,3-dipolar cycloaddition reaction of diazomethane or azides, respectively, with different SF₅-alkynes. The resulting compounds demonstrated interesting properties as energetic materials, with detonation properties

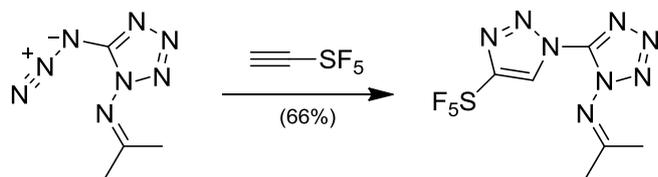
similar to those of TNT. The SF₅-group was shown to play an important role by increasing the density of these molecules and therefore their detonation performance (Scheme 77) [93].



R = H, Ph, allyl

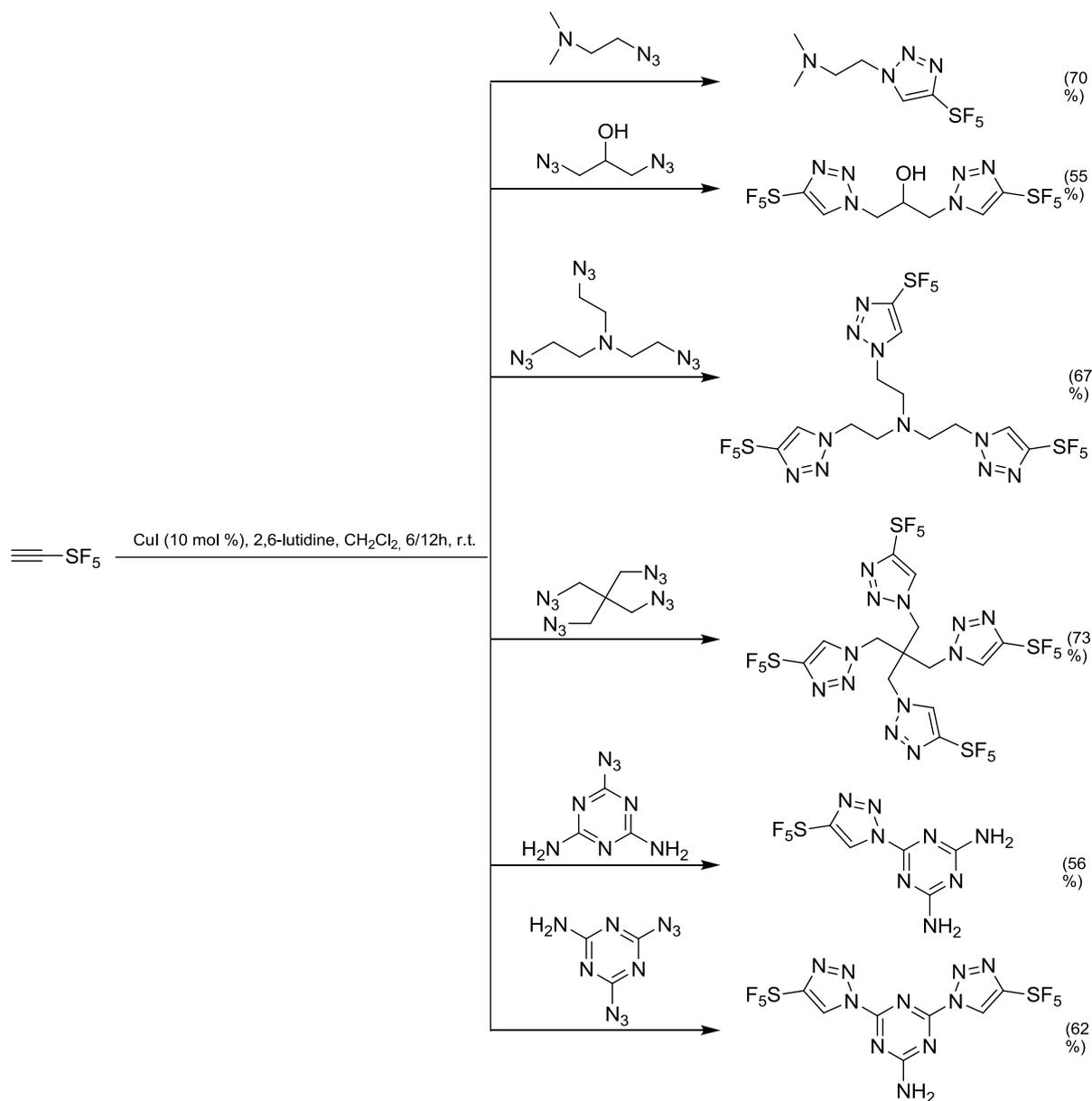
Scheme 77

An SF₅-triazole bearing a tetrazolyl substituent was analogously synthesised by cycloaddition reaction of a tetrazolyl-azide with SF₅-acetylene (Scheme 78) [94].



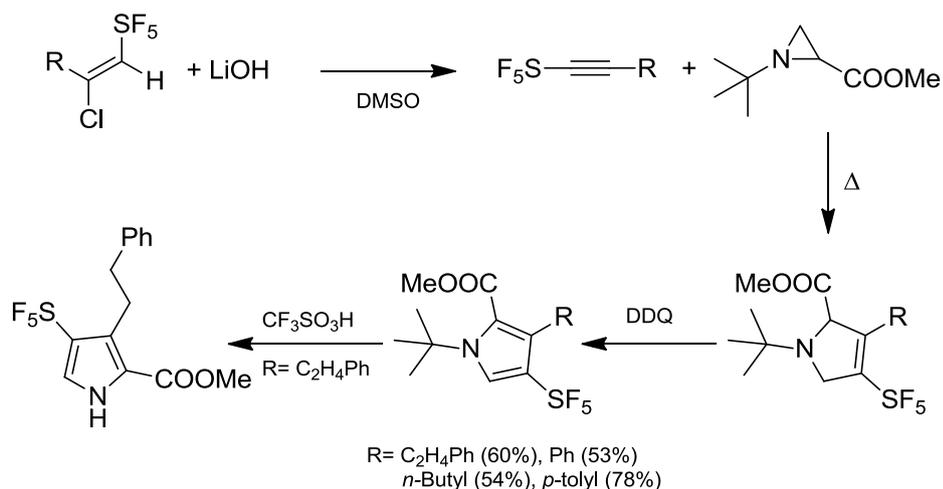
Scheme 78

A broad range of dense stable energetic materials incorporating multiple 1,2,3-triazine units was prepared by addition of azides and polyazides with SF₅-acetylene in generally good yields. The trifluoromethyl-analogues were also prepared and compared to the SF₅-counterparts, which invariably showed more negative enthalpies of formation and higher densities (Scheme 79) [95].



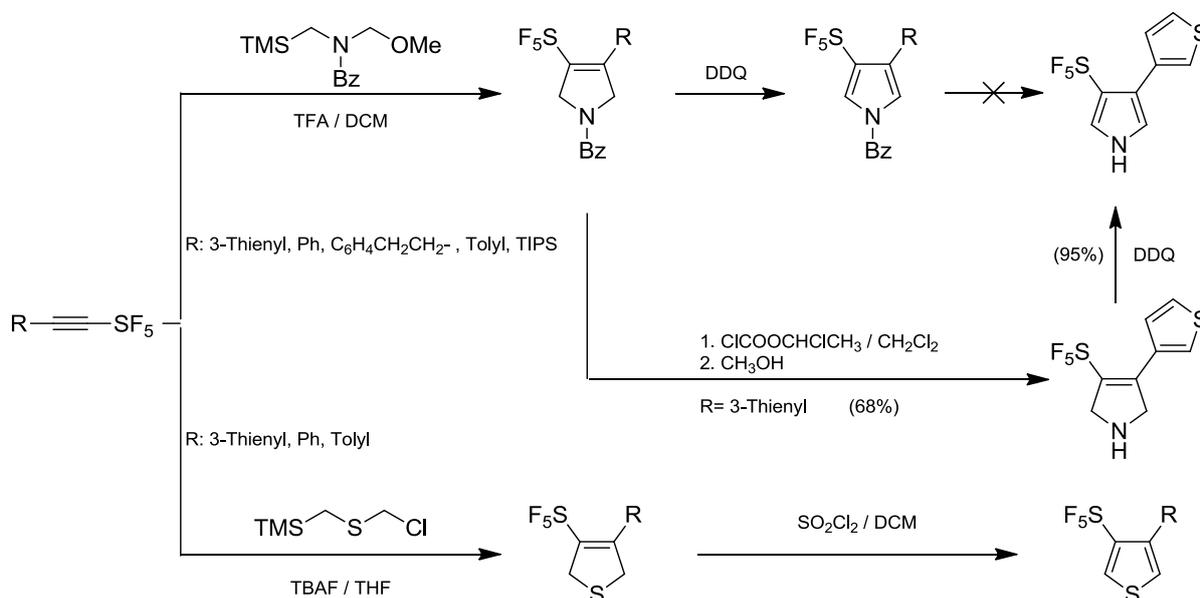
Scheme 79

A series of SF_5 -alkynes, generated by base-elimination from the corresponding β -chloro-alkenes (for another example see: [46]), were reacted with an azomethine ylide thermally obtained from *N*-tert-butyl-carbomethoxy aziridine affording the corresponding dihydropyrroles which were then oxidised by DDQ to the previously unknown 3- SF_5 -pyrroles. In some case, it was also possible to cleave the *N*-tert-butyl group by treatment with triflic acid (Scheme 80) [77].



Scheme 80

SF₅-Pyrroles were synthesised through a reaction sequence involving 1,3-dipolar cycloaddition of SF₅-alkynes with azomethine ylides, followed by DDQ-oxidation of the resulting pyrrolines. SF₅-thiophenes were also obtained by employing thiocarbonyl ylides as dipoles. In that case DDQ could not be used for the oxidation of the dihydrothiophenes to thiophenes, which was achieved by means of SO₂Cl₂ (Scheme 81) [96].

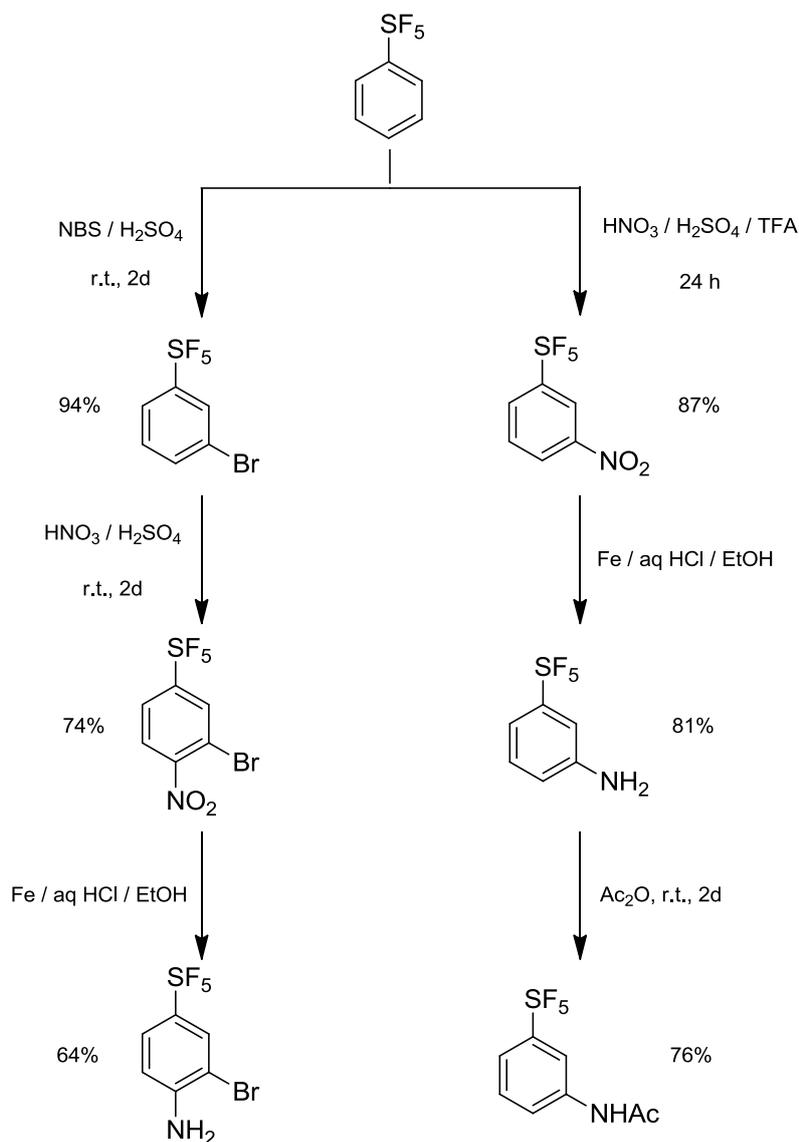


Scheme 81

3.4. Reactivity of SF₅-aromatic compounds.

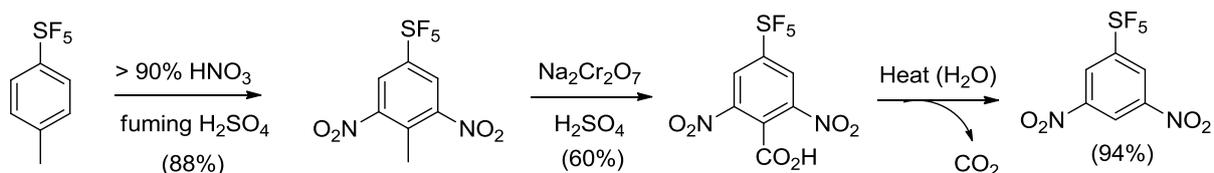
The reactivity of SF₅-substituted aromatic compounds is dominated by (1) the *meta*-directing, deactivating inductive effect that the electron-withdrawing SF₅ group displays in electrophilic substitution reactions, (2) the activating *ortho*- and *para*-effect displayed in nucleophilic substitution

reactions. SF₅-nitrobenzene is a key building block for the synthesis of aromatic pentafluorosulfonyl compounds. The original synthesis from aromatic nitrothiols and disulfides (see Section 2.3) was recently improved by Dolbier et al. who successfully achieved the nitration of SF₅-benzene in high yields and *meta*-regiocontrol (Scheme 82) [70]. *Meta*-SF₅-nitrobenzene was then reduced with Fe/HCl to the aniline, which was *N*-acetylated too. *Meta*-bromination of SF₅-benzene was also performed in high yield and the resulting *m*-SF₅-bromobenzene was *para*-nitrated in good yields. Eventually, the aniline derivative was synthesised using the same NO₂-reduction conditions.



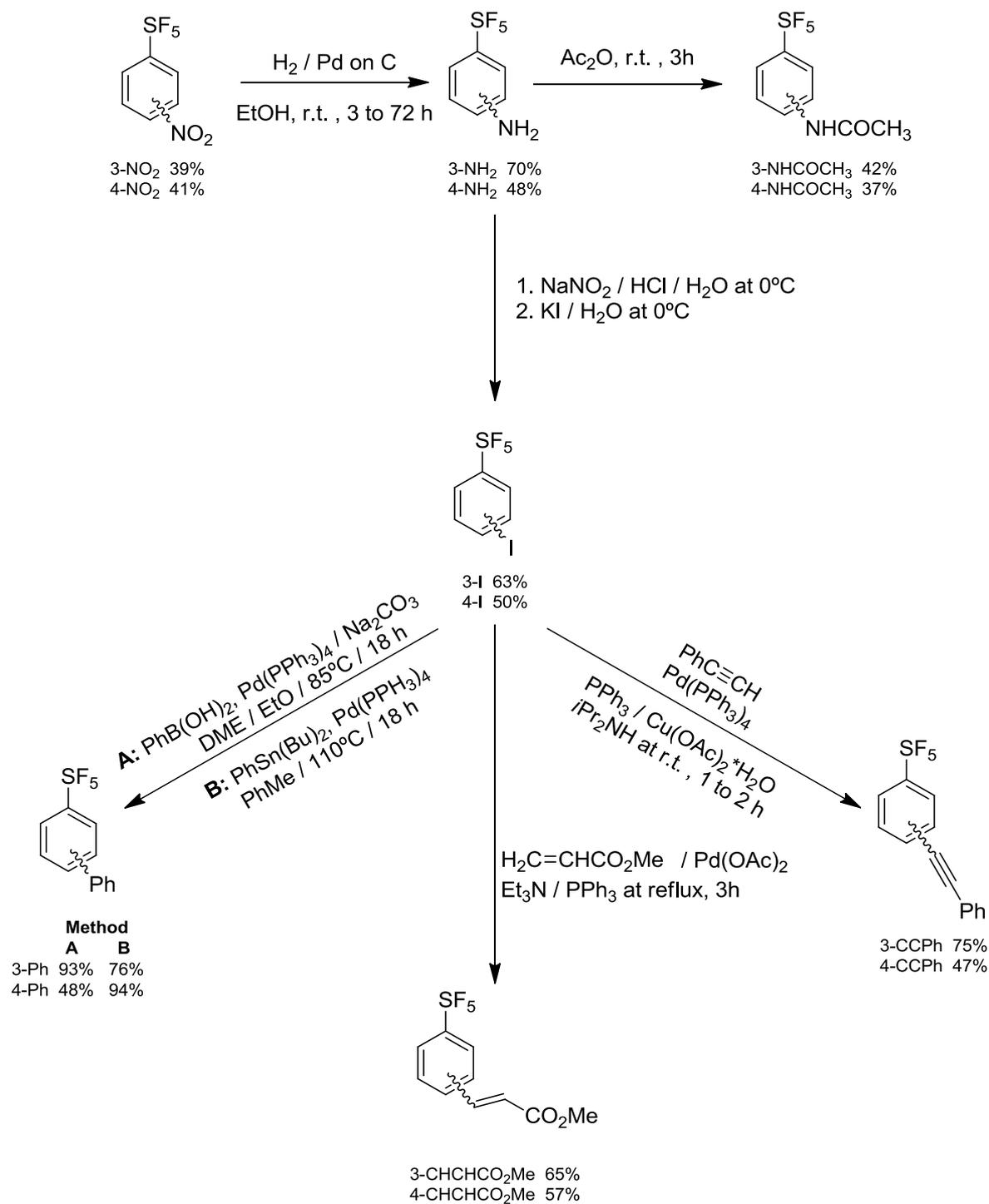
Scheme 82

Recently, a synthesis of 3,5-dinitro-SF₅-benzene was reported in the patent literature [97]. The method relies on the dinitration of *para*-SF₅-toluene, followed by oxidation of the methyl group to carboxylic function and finally thermal decarboxylation (Scheme 83).



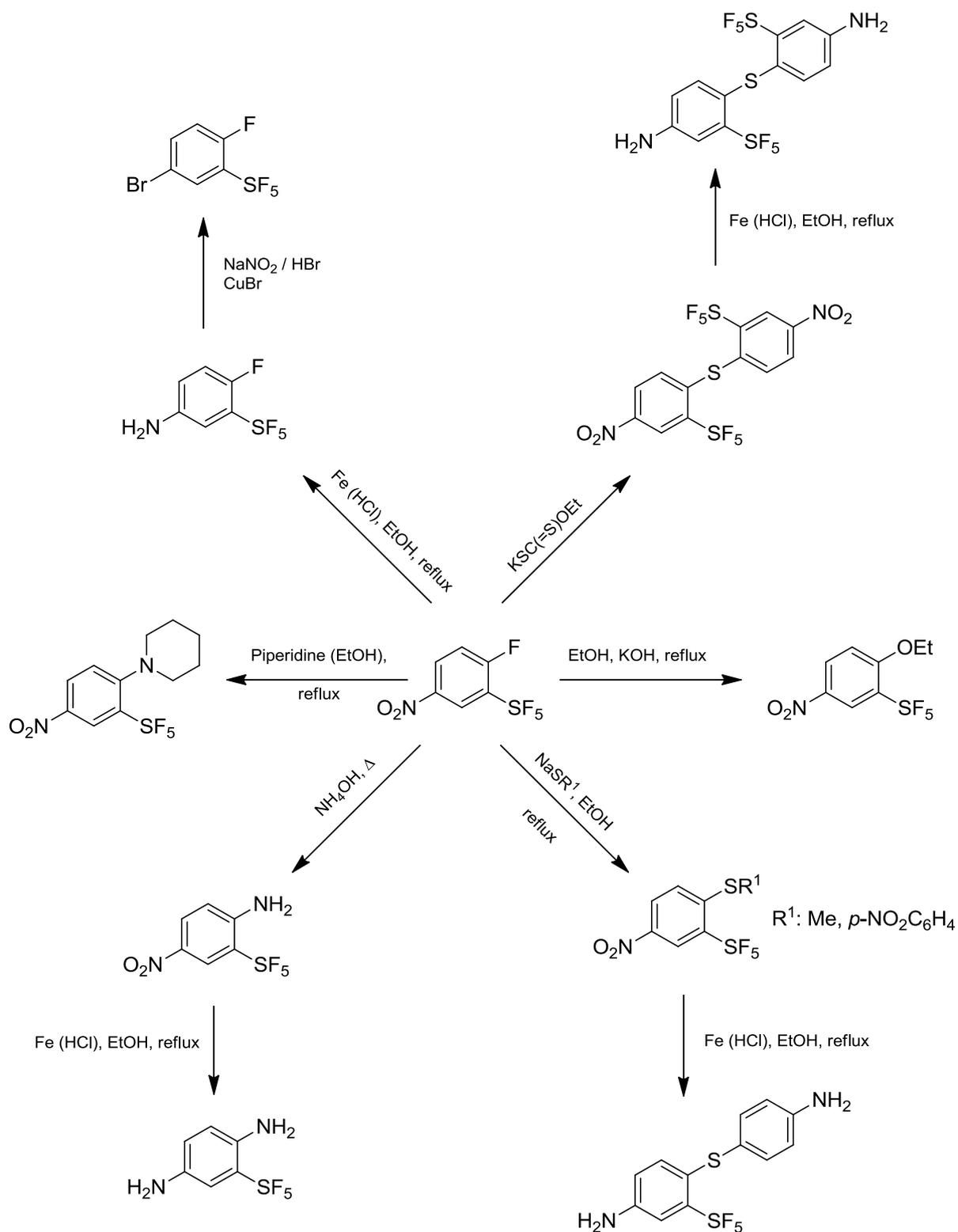
Scheme 83

A number of aromatic SF₅-compounds were synthesised starting from the *meta*- and *para*-nitro SF₅-precursors, which were initially reduced to the corresponding anilines, and then submitted to a range of different reactions including Sandmeyer iodination followed by Sonogashira alkylation, Suzuki arylation and Heck olefination (Scheme 84) [66]. Interestingly, the authors demonstrated that 4-SF₅-aniline and 4-CF₃-aniline show similar stability towards acid hydrolysis, namely treatment with concentrated sulphuric acid at 160 °C leads to hydrolysis of both CF₃ and SF₅ groups. However under basic conditions (2 N NaOH) the CF₃ group was readily hydrolysed to CO₂H whereas the SF₅ group was perfectly stable. The authors rationalised this behaviour on the basis of electronic stabilisation of the planar difluoromethylene group resulting from fluoride elimination by the deprotonated *para*-amino group. In contrast, the same stabilisation cannot occur for geometric reasons in the case of the SF₅ group, because the sulphur atom has an octahedral geometry whereas the carbon atom in the -CF₃ is tetrahedral.



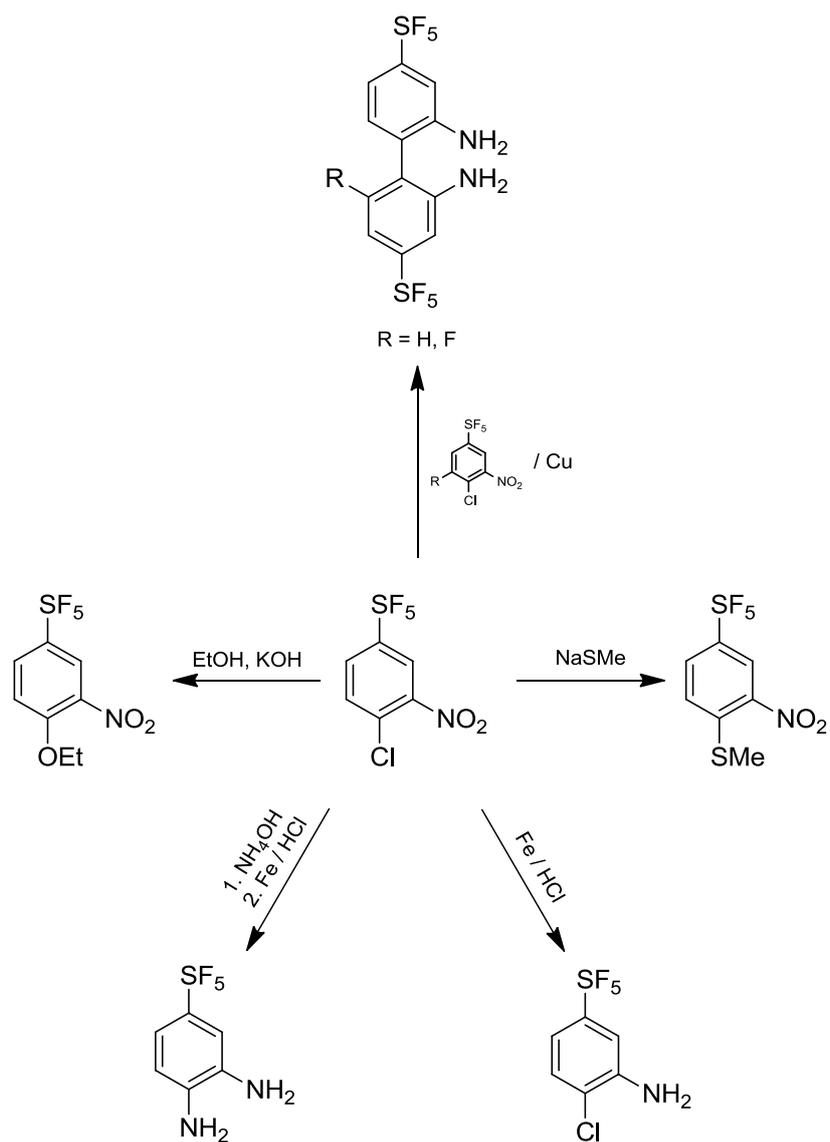
Scheme 84

A small library of *ortho*-substituted SF₅-compounds was obtained starting from 2-fluoro-5-nitro-SF₅-benzene which is highly activated towards nucleophilic aromatic substitution and was therefore submitted to a range of reactions with different nitrogen-, oxygen- and sulphur-centered nucleophiles such as piperidine, potassium ethylate, ammonia, sodium thiolate affording the corresponding fluoride-substitution products (Scheme 85) [68].



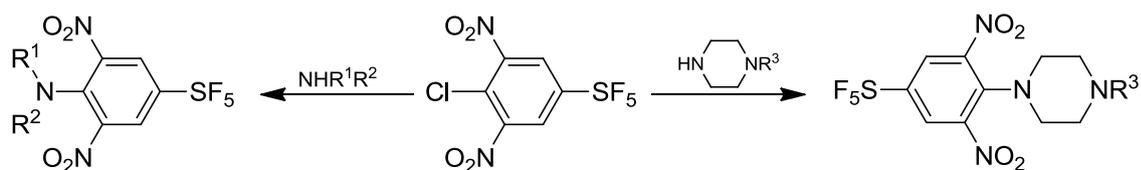
Scheme 85

Related chemistry was used by Trasher et al. for the synthesis of a small array of SF_5 -aryl compounds from 3-nitro-4-chloro-pentafluorosulfanyl benzene. The chlorine atom was shown to be very reactive towards substitution with different nucleophiles that provided good yields of the corresponding nitro-compounds, which were reduced with Fe/HCl to the anilines. An interesting bis- SF_5 -biaryl was also synthesised via Ullman-type coupling (Scheme 86) [65].



Scheme 86

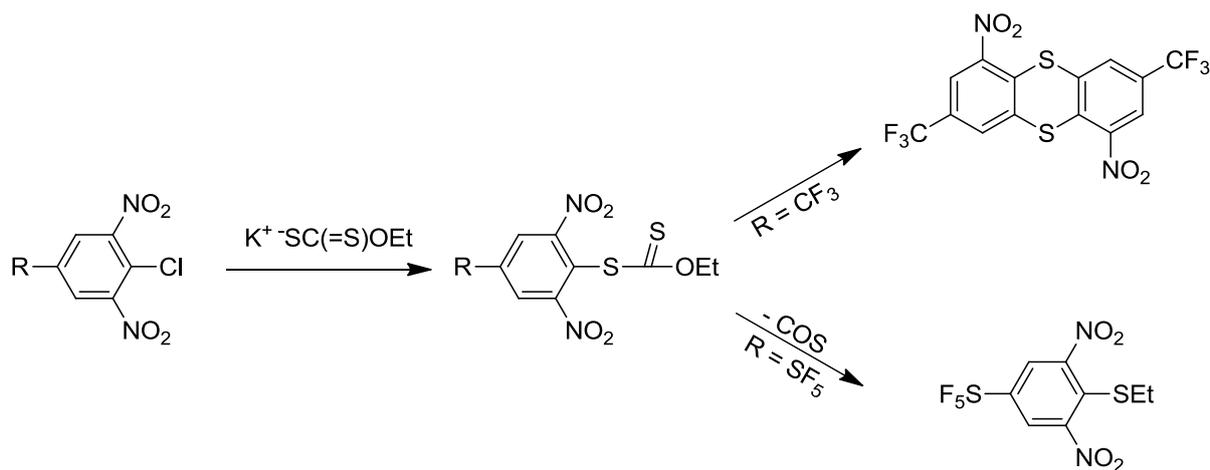
4-Chloro-3,5-dinitro SF₅-benzene was submitted as well to nucleophilic substitution reaction with secondary amines affording good yields of the resulting tertiary amines (Scheme 87) [65].



R ¹	R ²	R ³
C ₃ H ₇	C ₃ H ₇	
C ₃ H ₇	CH ₂ C ₃ H ₅	
C ₂ H ₅	<i>n</i> -C ₄ H ₉	
C ₂ H ₅	CH ₂ C(CH ₃)=CH ₂	
C ₃ H ₇	C ₄ H ₇ O	
		H
		CH ₃

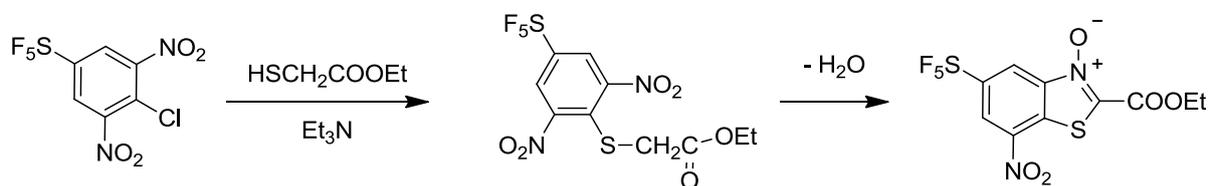
Scheme 87

An interesting observation on the reactivity difference between CF₃ and SF₅-compounds came from the reaction of the two 4-chloro-3,5-dinitrobenzene derivatives with potassium ethyl xanthate. In the CF₃-compound also the nitro moiety was found to be a good leaving group affording the thianthrene via dimerisation of the intermediate aryl xanthate, whereas the SF₅-compound underwent only loss of COS affording the monomeric ethylthio derivative (Scheme 88) [65].



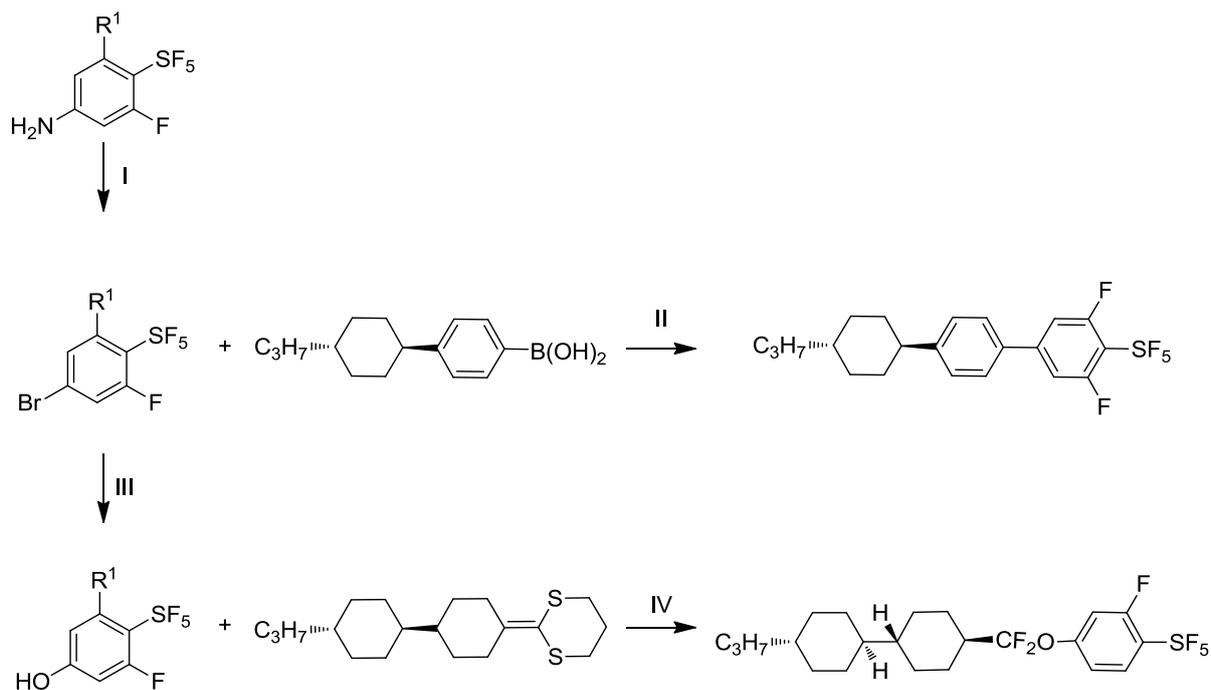
Scheme 88

Reaction of the same 4-chloro-3,5-dinitro-SF₅-benzene with another S-centered nucleophile, i.e. ethyl thiolacetate, provided the expected nucleophilic substitution product which was subjected to intramolecular condensation affording a benzothiazole N-oxide (Scheme 89) [65].



Scheme 89

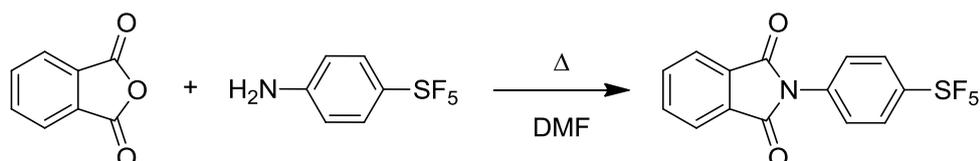
A wide range of SF₅-perfluoroethyl-benzene derivatives were synthesised starting from SF₅-perfluoroethyl-benzene which was *meta*-nitrated, reduced to the corresponding aniline, and transformed into the key diazonium salt intermediate. Sandmeyer-type chemistry was then used to functionalise the scaffold with a number of different functionalities including halogens, hydroxyl and acyloxy functions, SO₂Cl, vinyl and azide groups (Scheme 90)[98, 99]. The corresponding sulfonic acids were also obtained by treatment of the same substrate with chlorosulfonic acid [100].



Key: Synthesis of the liquid crystals; reagents and conditions: I) 1. NaNO_2 , HBr , $0-5^\circ\text{C}$; 2. CuBr , 85°C ; II) $\text{NaBO}_2 \cdot 8\text{H}_2\text{O}$, H_2O , THF , cat. $\text{Pd}(\text{PPh}_3)_4$, reflux, 18 h (16 %); III) 1. $t\text{-BuLi}$, Et_2O , -70°C ; 2. $\text{B}(\text{OMe})_3$; 3. HOAc , H_2SO_4 , 30% H_2O_2 , -20 to 35°C (crude product used for next step); IV) 1. $\text{CF}_3\text{SO}_3\text{H}$, CH_2Cl_2 , 0°C (5 min) to r.t. (30 min) to -70°C ; 2. NEt_3 , CH_2Cl_2 , -70°C ; 3. $\text{NEt}_3 \cdot 3\text{HF}$, -70°C ; 4. Br_2 , CH_2Cl_2 , -70 to -10°C (7 %)

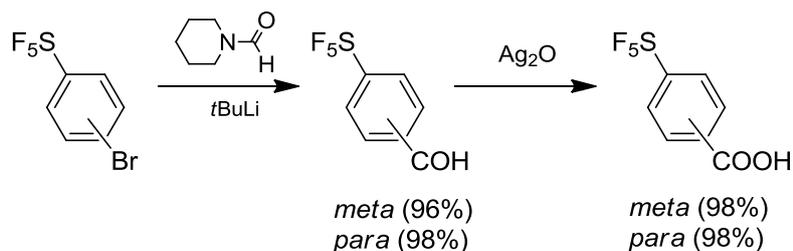
Scheme 91

A further derivative obtained from *para*- SF_5 -aniline, i.e. its phthalimide, was submitted to triboluminescence studies (Scheme 92) [101].



Scheme 92

SF_5 -substituted benzoic acids were synthesised in excellent yields from the corresponding bromo-derivatives by reaction with 1-formyl-piperidine and *tert*-BuLi, followed by oxidation of the resulting benzaldehydes (Scheme 93) [102].



Scheme 93

An interesting example of vicarious nucleophilic substitution reaction involving SF₅-nitrobenzenes and activated halides was exploited to synthesise a library of functionalised SF₅-nitroaromatic derivatives. Treatment of α -chloro or -bromo acetates, sulfones, phosphonates, acetonitriles or simple haloforms with an excess of *tert*-butoxide followed by reaction quenching either with hydrochloric acid or with another carbon electrophile afforded the corresponding mono- or di-alkylation products, respectively. The reaction with *para*-SF₅-nitrobenzene was regioselective producing exclusive meta-SF₅ reaction, whereas the *meta*-regioisomer produced a mixture of two regioisomers with large predominance of the *para*-SF₅ products (Scheme 94 and Table 10) [103].

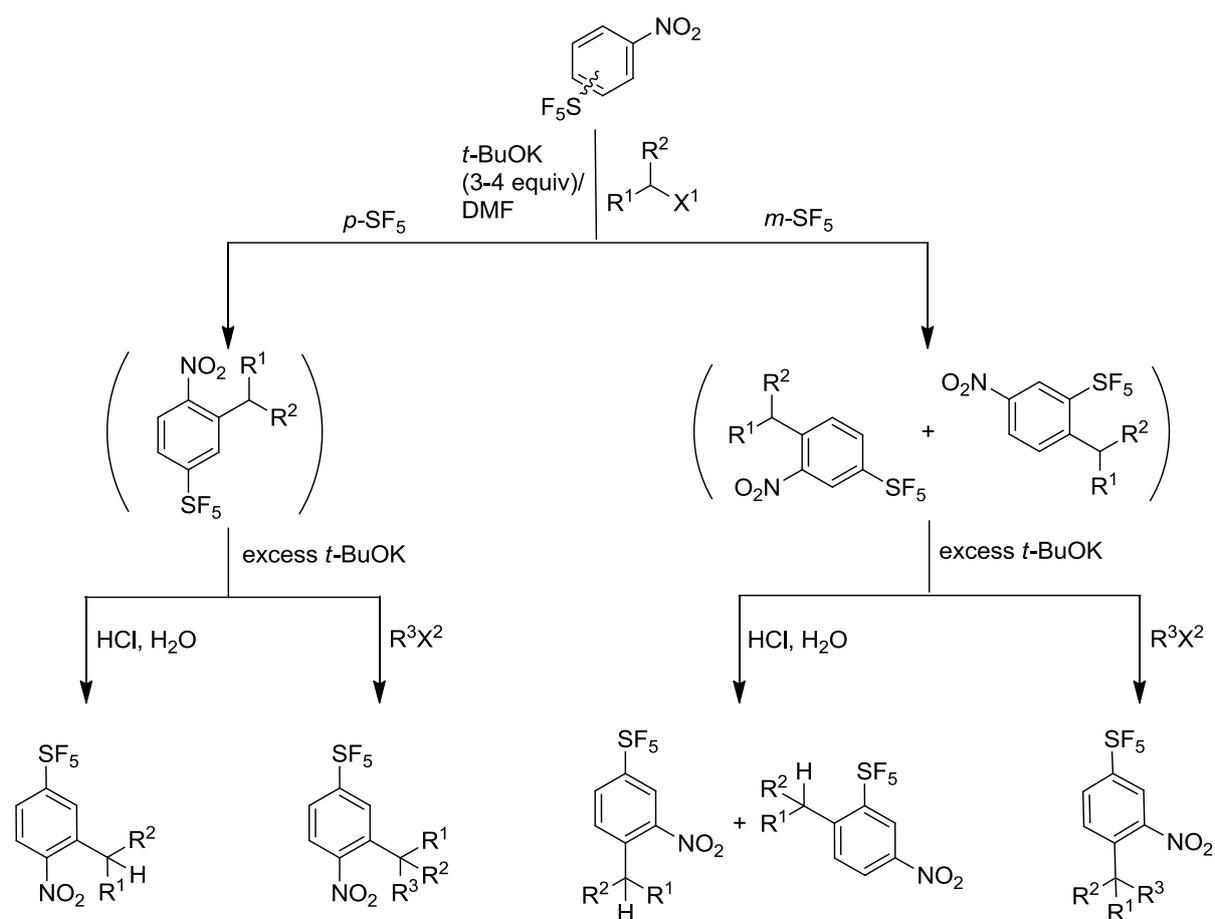
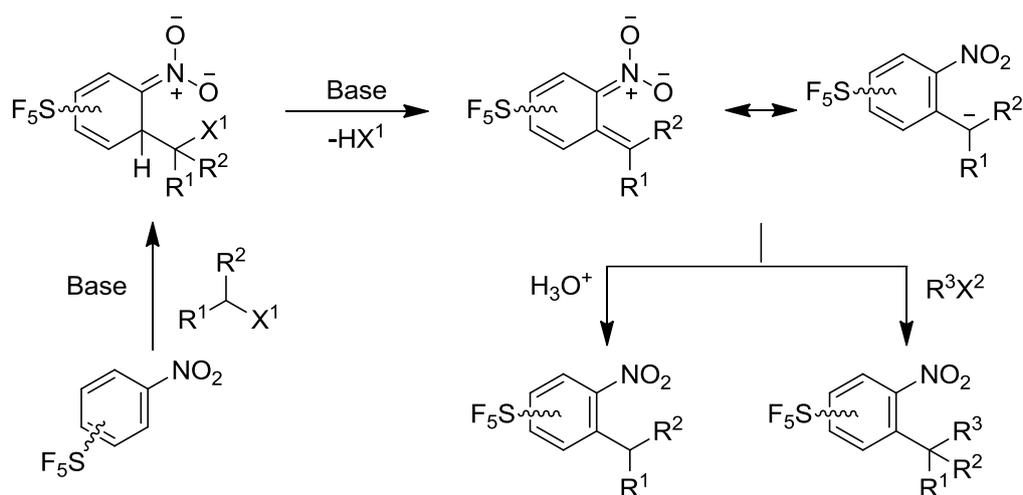


Table 10

Entry		X ¹	R ¹	R ²	R ³	X ²	Yield ^a (%)	<i>o</i> -CH(R ¹)R ² / <i>p</i> -CH(R ¹)R ² ratio (relative to NO ₂)
1	<i>p</i> -SF ₅	Cl	H	PhSO ₂			84	
2	<i>p</i> -SF ₅	Cl	H	CO ₂ Et			76	
3	<i>p</i> -SF ₅	Cl	H	CO ₂ Bu- <i>t</i>			91	
4	<i>p</i> -SF ₅	Cl	Cl	CO ₂ Me			83	
5	<i>p</i> -SF ₅	Cl	Me	CO ₂ Me			9	
6	<i>p</i> -SF ₅	Cl	H	P(O)(OEt) ₂			84	
7	<i>p</i> -SF ₅	PhO	H	CN			74	
8	<i>p</i> -SF ₅	Cl	Cl	Cl			74	
9	<i>p</i> -SF ₅	Br	Br	Br			74	
10	<i>p</i> -SF ₅	Cl	H	CO ₂ Et	PhCH ₂	Br	59	
11	<i>p</i> -SF ₅	PhO	H	CN	CH ₃	I	57	
12	<i>m</i> -SF ₅	Cl	H	PhSO ₂			94 ^c	96:4
13	<i>m</i> -SF ₅	Cl	H	CO ₂ Bu- <i>t</i>			94 ^c	94:6
14	<i>m</i> -SF ₅	Cl	Cl	CO ₂ Me			79 ^d	98:2
15	<i>m</i> -SF ₅	Cl	H	P(O)(OEt) ₂			73 ^c	95:5
16	<i>m</i> -SF ₅	PhO	H	CN			73 ^c	85:15
17 ^b	<i>m</i> -SF ₅	Cl	Cl	Cl			91 ^d	96:4
18 ^b	<i>m</i> -SF ₅	Br	Br	Br			84 ^d	98:2
19	<i>m</i> -SF ₅	Cl	H	PhSO ₂	CH ₂ =CHCH ₂	Br	84	
20	<i>m</i> -SF ₅	Cl	Cl	CO ₂ Me	<i>n</i> -Bu	I	0	

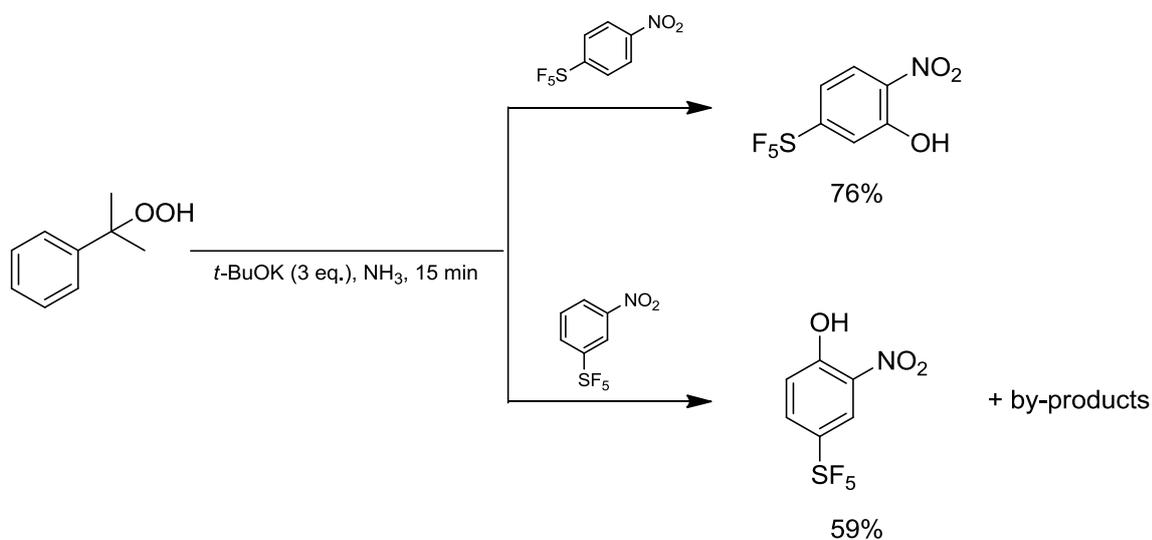
^a Isolated yields^b Determined by ¹⁹F NMR of the crude product mixture^c Relative to the sum of *o*-CH(R¹)R² and *p*-CH(R¹)R² products^d Relative just to the *o*-CH(R¹)R² product

The reaction mechanism is thought to involve deprotonation of the activated α -halogen or α -phenoxy-nucleophile which adds in *ortho*-position to the nitro group. The intermediate anion, stabilized by delocalization of the negative charge onto the nitro-group, undergoes base-promoted elimination of HCl, HBr or PhOH producing a second anion that is eventually quenched affording the final alkylated products (Scheme 95). The position of the SF₅-group determines the regioselectivity of the process.



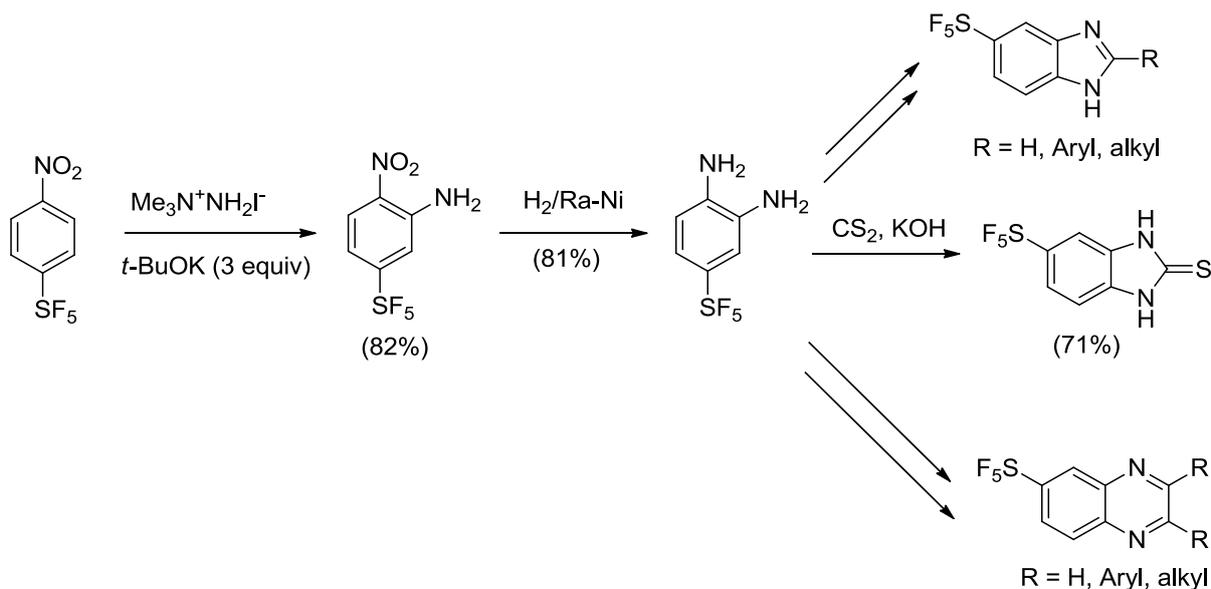
Scheme 95

SF_5 -Phenol derivatives could be also prepared by means of the same methodology, i.e. by submitting SF_5 -nitrobenzenes to vicarious nucleophilic substitution reaction with *tert*-butoxide anion and cumyl hydroperoxide (Scheme 96). Higher yield and a cleaner reaction were observed with *p*- SF_5 -nitrobenzene [104].



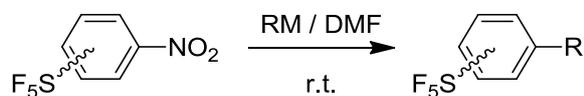
Scheme 96

Very recently, the same vicarious nucleophilic substitution strategy was used for preparing a series of heterocycles, exploiting a key reaction of 1,1,1-trimethylhydrazinium iodide in the presence of potassium *tert*-butoxide with *para*- SF_5 -nitrobenzene. The same products could be accessed from the *meta*-derivative by the same sequence (Scheme 97) [105].



Scheme 97

In another example, SF₅-nitrobenzenes were used as building blocks taking advantage of the good leaving-group nature of the nitro group activated by the pentafluorosulfanyl moiety. As expected, treatment of the more activated *para*-SF₅-nitrobenzene with a wide range of nucleophiles occurred under milder conditions and afforded higher yields of the corresponding substitution products than the *meta*-SF₅-isomers (Scheme 98 and Table 11) [106].



Scheme 98

Table 11

Entry	RM	Time / h	Yield ^a (%)	
1	<i>p</i> -SF ₅	MeONa	1	83
2	<i>m</i> -SF ₅	MeONa	5	52
3	<i>p</i> -SF ₅	<i>n</i> -PrONa	0.5	71
4	<i>m</i> -SF ₅	<i>n</i> -PrONa	1	41
5	<i>p</i> -SF ₅	PhCH ₂ OK	1	96
6	<i>m</i> -SF ₅	PhCH ₂ OK	2.5	42
7	<i>p</i> -SF ₅	PhOK	17	59
8	<i>m</i> -SF ₅	PhOK	16	Traces ^b
9	<i>p</i> -SF ₅	MeSNa	16	64
10	<i>m</i> -SF ₅	MeSNa	21	Traces ^b

^a Isolated yields

^b Detected by GCMS analysis in trace amounts

4. BIOLOGICAL ACTIVITY OF SF₅-SUBSTITUTED COMPOUNDS

The SF₅ group has been often referred to as a “super-trifluoromethyl group” [3] because as a matter of fact these two groups share many peculiar features, such as high electronegativity, steric bulk, thermal and chemical stability, lipophilicity, with the SF₅-group slightly prevailing over the CF₃ in all of these aspects. Some quantitative parameters for the two groups are summarised in the Table 12.

Table 12

	SF ₅	CF ₃	Ref
Hammett constant σ _p (electronegativity)	+0.68	+0.54	[107]
σ _R (resonance contribution)	0.11	0.12	[108] and references therein
σ _I (field effects)	0.55	0.39	
Hansch hydrophobicity constant π	1.51 ^a	1.09 ^a	[109]
Electronegativity	3.65	3.36	[110] and references therein
pK _a ^c	2.37 ^b	2.94 ^b	[111]
Volume	49.2 cm ³ /mol (calculated in liquids)	20.49 cm ³ /mol (van der Waals volume)	[83] (SF ₅); [112] (CF ₃) and references therein
^a : referred to the <i>m</i> -position of the substituent ^b : referred to the <i>p</i> -position of the substituent ^c : Determination of acidity constant of Anilinium ions from optical density measurement			

Importantly, both the SF₅ and CF₃ groups are xenobiotic and their stability is very high under physiological conditions, which make them very interesting functions for biomedicine and drug discovery/development applications. Interestingly, whereas it is becoming increasingly clear and widely accepted that the CF₃-group is a bioisosteric equivalent of an ethyl group [113], the corresponding features for the SF₅-group have not been investigated in detail yet. However, it is apparent that the volume of the SF₅ group is slightly less than that of a *tert*-butyl group, but remarkably larger than the CF₃ volume (see also Table 12) [110]. In spite of these considerations, the SF₅ group has been shown to behave often like a CF₃ group, possibly because both would appear to a receptor site as highly fluorinated surfaces having similar electrostatic properties. However, also in this case the geometries are remarkably different, because the SF₅ group will present a pyramidal electron density, whereas the CF₃ will display an inverted cone of density [114]. For all of the reasons above it is reasonable to predict that future research will show that, besides some similarities, the SF₅ and the CF₃ group can impart distinct and peculiar biological properties to molecules. This is in line with recent results obtained by our group, showing that in two series of -CF₃- and -SF₅-aniline-containing pyrazoles the SF₅ compounds consistently had lower K_i for the CB₁ receptor than the CF₃-counterparts in *in vitro* assays (Figure 1). This could be very roughly explained with a “better fit” of the SF₅ group into the corresponding pocket of the CB₁ receptor relative to the CF₃ group, which confirms that the two groups are not “biologically” equivalent. The most potent compounds in the series displayed nanomolar K_i values for CB₁, and are currently tested for their pharmacological properties [115].

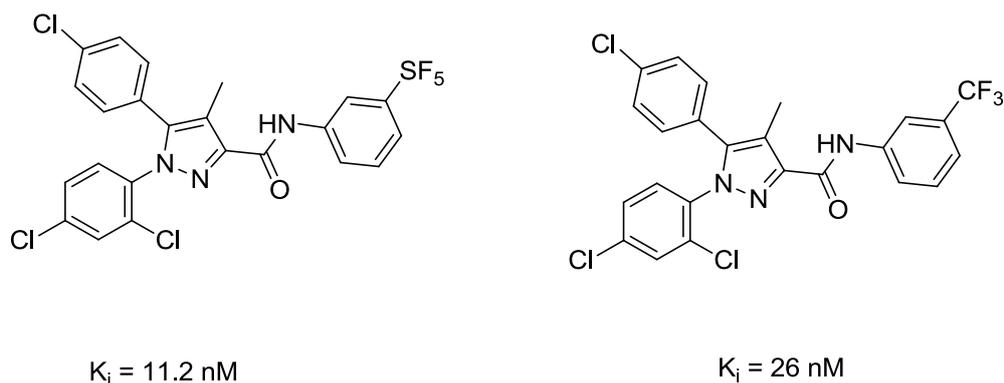
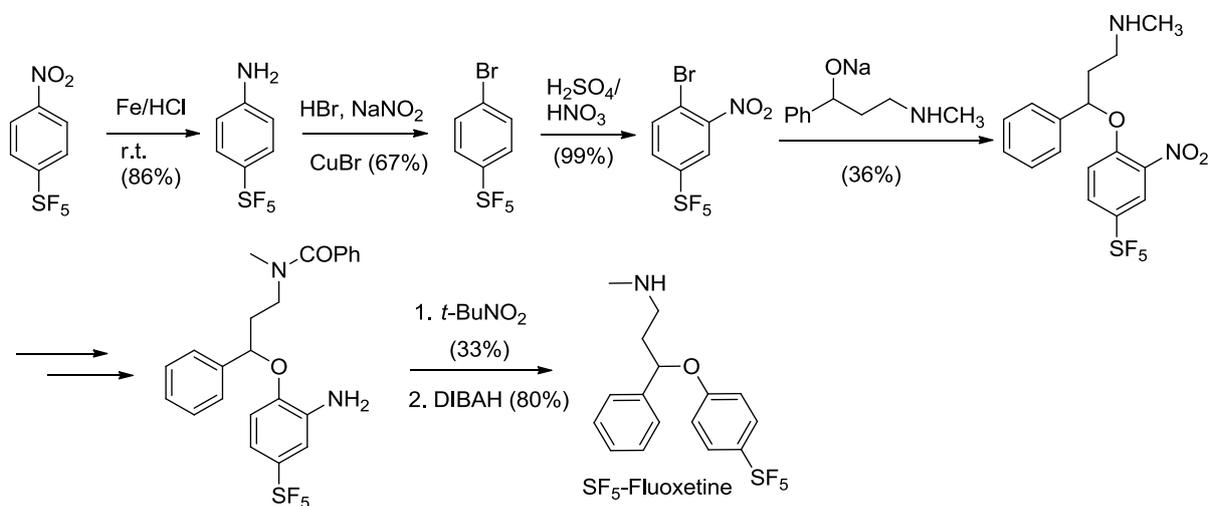


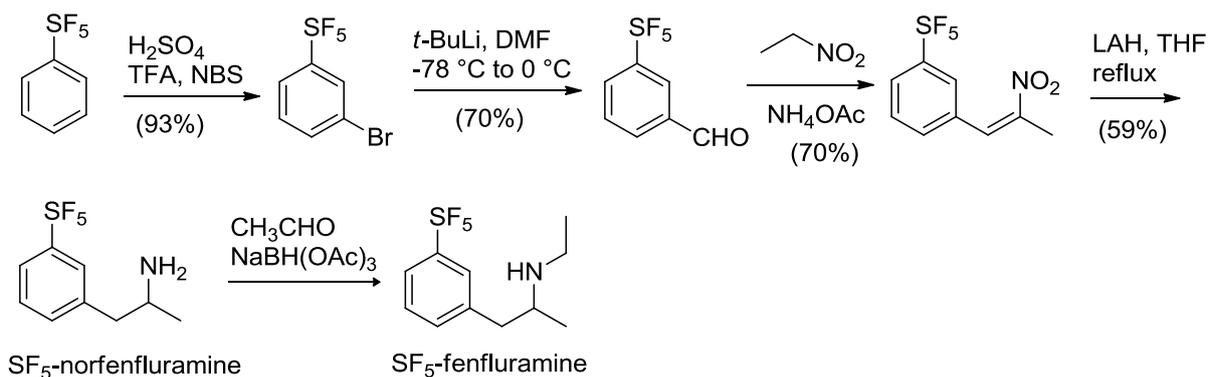
Figure 1

These findings are in line with previous work that showed that SF₅-analogues of the popular serotonin uptake inhibitors fluoxetine (Prozac), fenfluramine and norfenfluramine, which incorporate a CF₃-group, could lead to enhanced selectivity and, in the case of fluoxetine, SF₅-substitution enhanced potency vs. some of the 5-HT receptors. The synthesis of SF₅-fluoxetine started from 4-SF₅-nitrobenzene, which was submitted to the usual conversion of the NO₂ group into Br via reduction to NH₂. Nitration occurred in meta to the SF₅ affording a substrate highly activated towards nucleophilic aromatic substitution, which was reacted with the sodium alcoholate of the appropriate γ -aminoalcohol affording the desired aryl-ether, which was then converted into the target compounds (Scheme 99) [114].



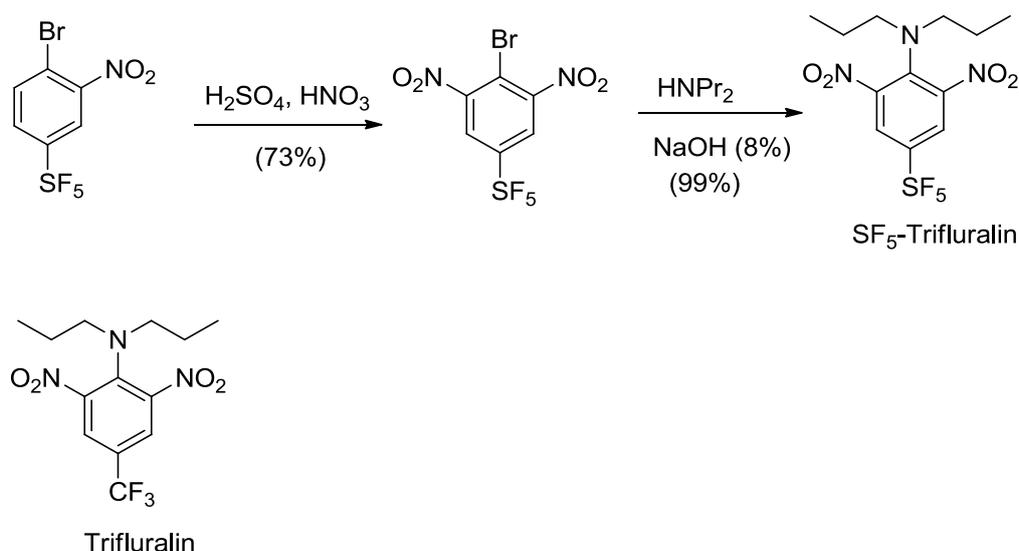
Scheme 99

The SF₅-fenfluramine and norfenfluramine were prepared by meta-bromination of pentafluorosulfanyl-benzene, which was then lithiated and formylated with DMF. The benzaldehyde was condensed with nitroethane and the resulting nitroalkene was reduced to the target products (Scheme 100).



Scheme 100

A key intermediate in the synthesis of SF₅-fluoxetine was also used for the preparation of an SF₅-analogue of the herbicide trifluralin (Scheme 101). Remarkably, the SF₅-trifluralin demonstrated 5-fold greater herbicidal potency relative to the parent CF₃-compound. This was rationalised according to a favourable interaction of the SF₅ residue with a key Thr239 residue of α -tubulin, which is associated with the electron-rich surface of this group that apparently interacts even more favourably than the CF₃ [108].

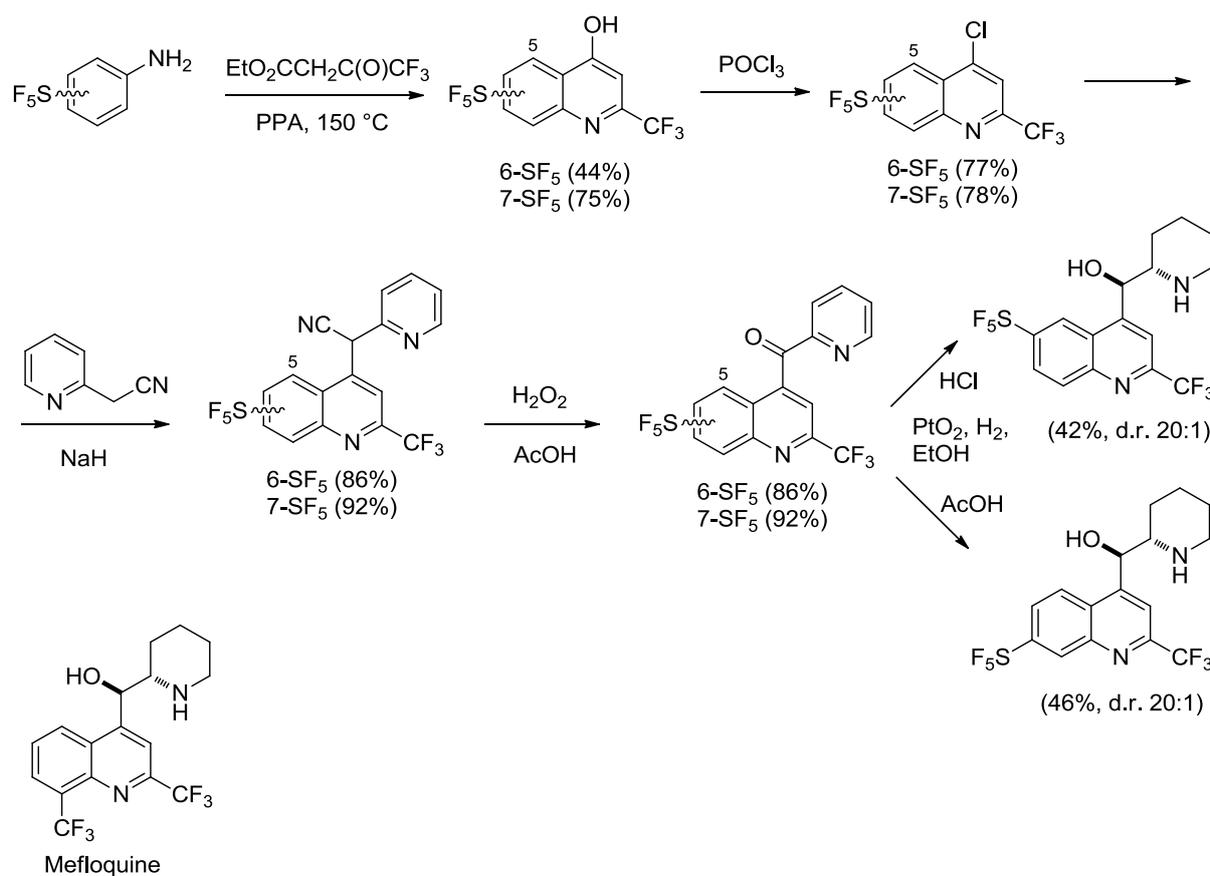


Scheme 101

Among the first reports of biological activity of SF₅-compounds one should also mention the use of SF₅-CF=CF₂ and SF₅-CFI-CF₃ as effective fumigants, and the insecticidal properties of the non-fluorinated versions of these compounds [10].

Wipf et al. reported the synthesis of 6- and 7-SF₅ analogues of Mefloquine, which is an antimalarial drug used against chloroquine-resistant *Plasmodium falciparum* strains. Mefloquine incorporates two CF₃ groups, one of them in position 8 of the quinoline heterocycle. However the authors initially

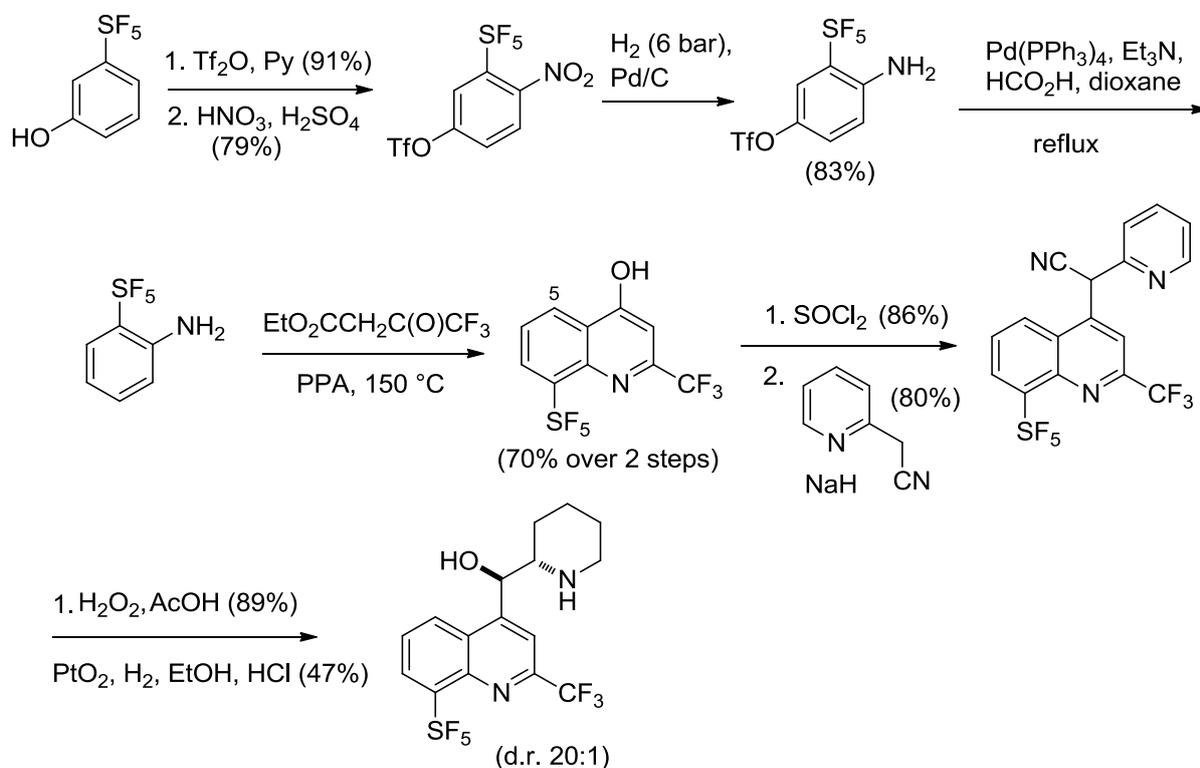
could not access to the exact 8-SF₅ mefloquine analogue because the necessary starting material, *ortho*-SF₅-nitrobenzene, was not available (Scheme 102). Therefore, *meta*- and *para*-SF₅-anilines were condensed with trifluoroacetoacetate and the resulting 4-hydroxy quinoline was dehydrochlorinated. The resulting 4-chloro-quinolines, which are activated towards nucleophilic aromatic substitution, were reacted with metalated 2-pyridyl-acetonitrile and the resulting adducts were oxidised delivering the key intermediate pyridyl-ketones, which were eventually submitted to PtO₂-catalysed hydrogenation to the target SF₅-mefloquine analogues. The two molecules were tested on different strains of the malaria parasite showing improved activity (IC₅₀s were as low as 3.3 ng/mL for both isomers) and selectivity towards a mammalian cell line relative to the parent CF₃-substituted mefloquine [110].



Scheme 102

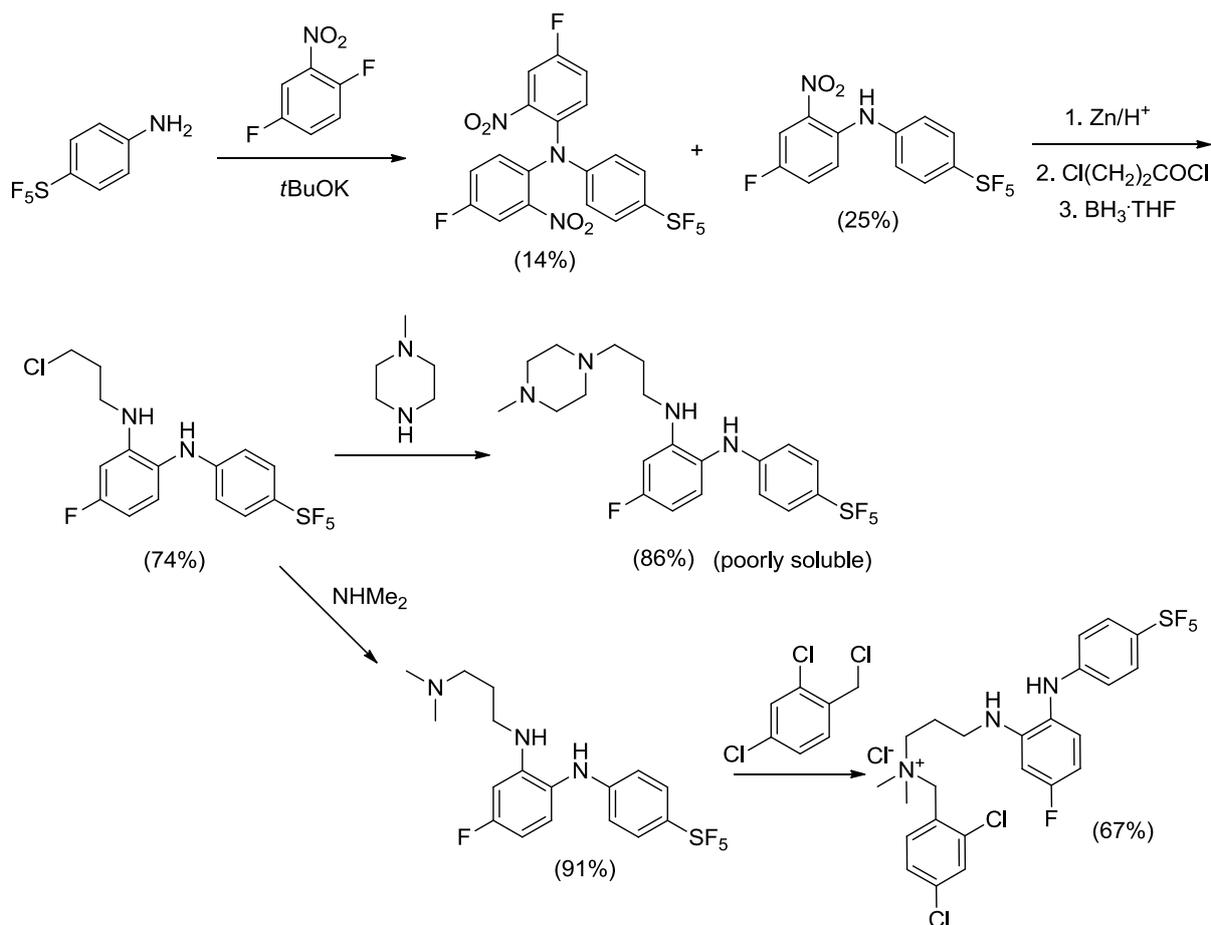
The exact 8-SF₅-mefloquine analogue was published by the same group one year later, when *ortho*-SF₅-aniline became available. Commercially available 3-SF₅-phenol was submitted to nitration but unfortunately the strong *ortho*-directing effect exerted by the hydroxyl group afforded poor *para*-regioselectivity (Scheme 103). Therefore, the OH was protected as triflate which was nitrated in very good yields under total regiocontrol affording the desired *para*-nitro derivative, which was hydrogenated to aniline. Reductive removal of the triflate function proved to be challenging and eventually the modification was achieved by treatment with Pd(0)-tetrakis in the presence of formic acid and triethylamine. With the key *ortho*-SF₅-aniline in hand the synthesis of 8-SF₅-mefloquine was

performed along the lines previously followed for the 6- and 7-SF₅ analogues [116]. This compound showed the best balance activity/permeability through blood-brain barrier among the different SF₅-mefloquines. Furthermore, administered in mice, 8-SF₅-mefloquine showed a higher activity than mefloquine itself, with a longer half-life (68 h vs 23 h)[117].



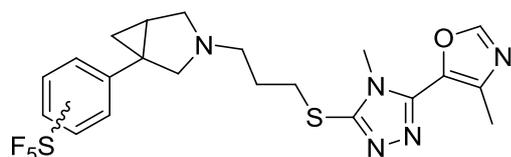
Scheme 103

Diederich et al. recently described a rationally-designed SF₅-substituted diarylamine as a potential antiprotozoal compound. The molecule was obtained from para-SF₅-aniline which was used as a nucleophile with 2,5-difluoro-nitrobenzene affording a mixture of mono- and di-*N*-arylation products (Scheme 104). The former was isolated and reduced to the corresponding diarylamine, and the primary amino group was acylated with 3-chloropropionyl chloride. S_N2 reaction with *N*-methyl-piperidine provided the target diarylamine, which unfortunately was poorly soluble and could not be appropriately tested for its inhibitory properties against the flavoenzyme trypanothione reductase, which is an interesting therapeutic target for the treatment of tripanosomatid parasites. Therefore, the 3-chloropropyl intermediate was reacted with dimethylamine and the resulting tertiary amine was reacted further with 2,4-dichlorobenzyl chloride affording a quaternary ammonium salt. This compound showed interesting inhibitory properties with an IC₅₀ = 1.5 μM, similar to that displayed by the exact analogues having CF₃- and tert-butyl groups replacing the SF₅. Furthermore, the SF₅-derivative showed the lowest cytotoxicity among all the compounds tested, showing also good membrane permeability. Interestingly, switching from CF₃ to SF₅ the mode of inhibition changed from purely competitive to competitive-uncompetitive, respectively. Molecular modelling simulations indicated that the SF₅-group can effectively occupy the hydrophobic “mepacrine binding site” of the receptor [118].



Scheme 104

A series of SF₅- and CF₃-substituted selective dopamine D₃ antagonists were recently compared both in terms of in vitro and in vivo properties (Figure 2). No specific information on the synthesis of these SF₅-compounds was provided (the CF₃-analogues were synthesised in [119]). In general, the two series of compounds showed rather similar biological properties in vitro, as well as in vivo [120].



3-SF₅ and 4-SF₅ dopamine D₃ antagonists

Figure 2

Recently, aryl amine-based triazolopyrimidine derivatives incorporating both a CF₃ and an SF₅ group were reported as *Plasmodium falciparum* dihydroorotate dehydrogenase (PfDHODH) inhibitors, showing antimalarial activity in mice [121]. The substitution of the 4-CF₃ group with a 4-SF₅ resulted in a compound with 2-3-fold better activity against PfDHODH, possibly due to the increase in hydrophobicity with SF₅ relative to CF₃. The SF₅-triazolopyrimidine displayed good metabolic stability and interesting pharmacokinetic parameters in vivo. Furthermore, it showed good suppression of

Plasmodium berghei growth in a mouse model, with an ED₅₀ of 17 mg/kg and better efficacy than the CF₃-compound (Figure 3).

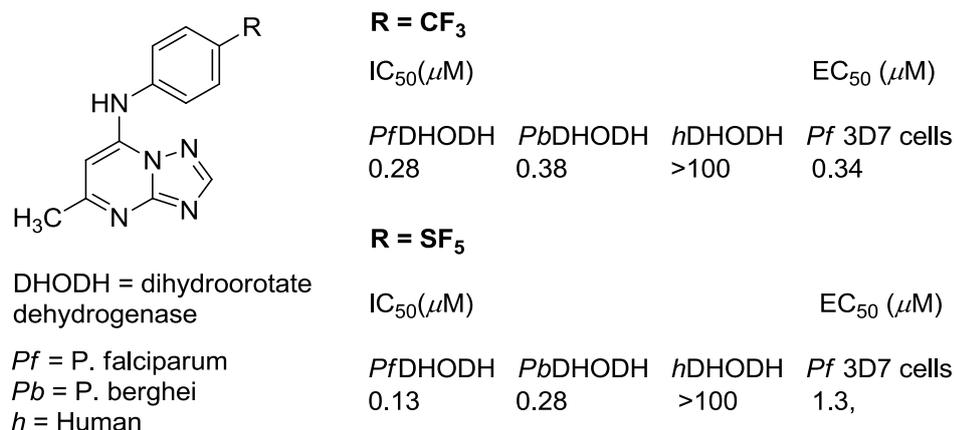


Figure 3

The compounds above were subsequently optimised and a number of novel derivatives having the structure below were synthesised and tested for their ability to inhibit *P. falciparum* and *P. berghei* DHODH [122]. The compounds having R = CF₂CH₃ were found to display the highest inhibitory potency and the DHODH/CF₃-triazolopyrimidine complex was successfully crystallised confirming that the CF₃ group (and therefore the SF₅ group too) occupy a narrow and hydrophobic pocket of the enzyme. The two lead compounds were submitted to *in vivo* tests on SCID mouse *P. falciparum* model for testing their antimalarial efficacy. The SF₅-compound was found to have the most potent *in vivo* activity showing remarkable efficacy, with long half life and excellent oral exposure. Toxicological studies were not reported, but this SF₅-triazolopyrimidine appears to be a very promising antimalarial drug candidate.

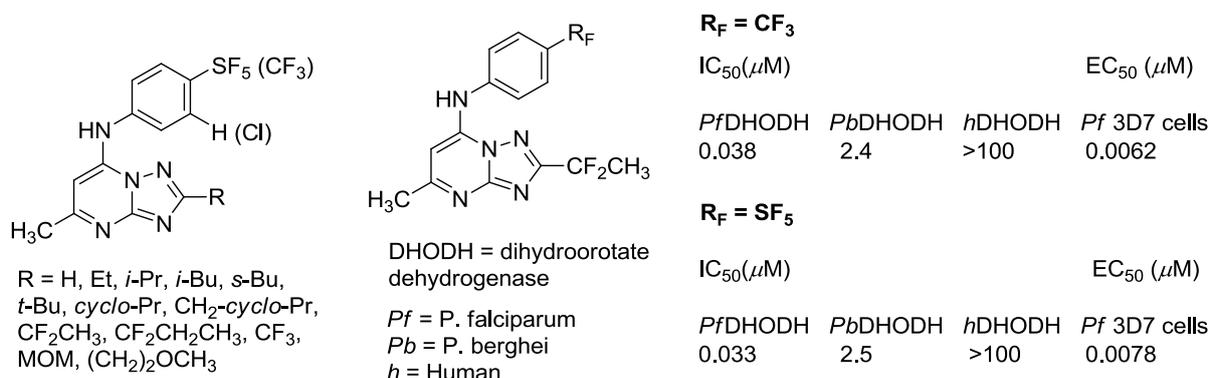


Figure 4

5. CONCLUSIONS

As demonstrated by the body of work reviewed in this article, pentafluorosulfanyl compounds are very interesting molecules featuring peculiar chemistry, which remains largely unexplored, and very interesting biological properties which go well beyond the analogies with trifluoromethyl-containing compounds. It is apparent that the area of SF₅-molecules is still in its infancy and important breakthroughs concerning both their chemistry and their applications in biomedicine and drug discovery might be just around the corner.

6. ACKNOWLEDGEMENTS

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