Journal of Fluorine Chemistry 143 (2012) 57–93

Contents lists available at SciVerse ScienceDirect

Journal of Fluorine Chemistry

journal homepage: www.elsevier.com/locate/fluor

Review

Synthetic chemistry and biological activity of pentafluorosulphanyl (SF_5) organic molecules

Stefano Altomonte [a], Matteo Zanda [a,b,*]

[a] Kosterlitz Centre for Therapeutics, Institute of Medical Sciences, and John Mallard Scottish PET Centre, University of Aberdeen, Foresterhill, Aberdeen AB25 2ZD, Scotland, UK
[b] C.N.R.-Istituto di Chimica del Riconoscimento Molecolare, via Mancinelli 7, 20131 Milano, Italy

ARTICLE INFO

Article history:
Received 29 April 2012
Received in revised form 19 June 2012
Accepted 27 June 2012
Available online 11 July 2012

Keywords:
Pentafluorosulphanyl group
Review
Synthesis
Biological properties

ABSTRACT

The pentafluorosulphanyl group (SF_5) 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 SF_5-compounds has been somewhat hindered by the lack of straightforward lab-scale synthetic methods for introducing the SF_5-group into organic molecules. However, recent synthetic progress, the availability of some SF_5-building blocks from commercial suppliers and the discovery of interesting properties of SF_5-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 SF_5-substituted organic molecules are herein reviewed with an emphasis on the work published after year 2000.

Contents

1. Introduction

Pentafluorosulphanyl (SF_5) compounds are considered to be organic derivatives of sulphur hexafluoride SF_6. Both in SF_6 and in SF_5-compounds the sulphur atom is in hypervalent hexacoordinated state with an octahedral geometry of the ligands. The pentafluorosulphanyl 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

* Corresponding author at: Kosterlitz Centre for Therapeutics, Institute of Medical Sciences, and John Mallard Scottish PET Centre, University of Aberdeen, Foresterhill, Aberdeen AB25 2ZD, Scotland, UK.
E-mail addresses: m.zanda@abdn.ac.uk, matteo.zanda@polimi.it (M. Zanda).

0022-1139/$ – see front matter © 2012 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.jfluchem.2012.06.030

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.

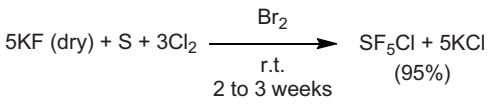
2. Synthesis of SF_5-compounds (primary reactivity)

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) pentafluorosulphanylating agents or (2) fluorination of suitable precursors. Sulphur 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 pentafluorosulphanylating 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 disulphide function.

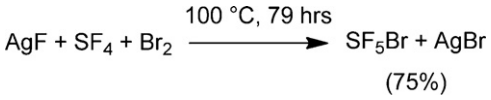
2.1. Pentafluorosulphanylating agents

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 F_5S–SF_5 has been also occasionally reported as a pentafluorosulphanylating 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.

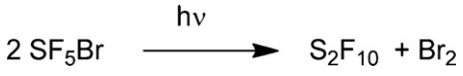
One of the most recent improvements of the preparation of SF_5Br was developed by Gard et al. who reported that a slow reaction (6–11 days at r.t.) between molecular bromine and BrF_3 in the presence of caesium fluoride, followed by an even slower reaction of the resulting BrF with SF_4 (36 days at r.t. or 20 days with moderate heating) afforded high yields (99.6% and 88.2%, respectively) of SF_5Br [16]. Replacement of CsF with dry and carefully powdered KF was reported to be a key factor in the improvement of the preparation of SF_5Cl, using the reaction between SF_4 and Cl_2 [17]. However, recently a more convenient synthetic method for the preparation of both SF_5Cl and SF_5Br was



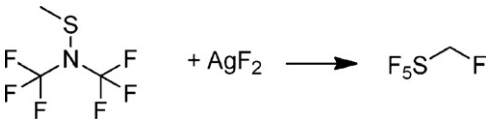
Scheme 1.



Scheme 2.



Scheme 3.



Scheme 4.

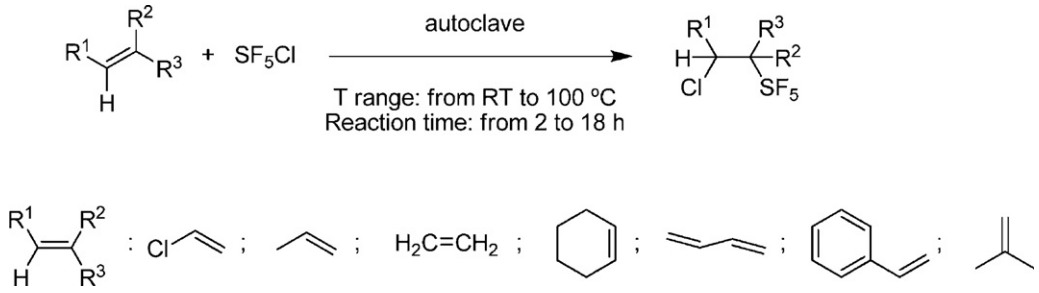
reported in the patent literature [18]. According to this protocol, dry KF, sulphur powder and Cl_2 were mixed in a reactor in the presence of Br_2 which apparently acted as a catalyst (no reaction took place in the absence of Br_2), affording excellent yields of SF_5Cl after two to three weeks at r.t. The reaction was found to take place through the formation of SF_4 as an intermediate (Scheme 1). Analogously, SF_5Br was prepared in good yields by reaction of AgF, SF_4 and Br_2, but the latter in this case was a true reagent and was consumed in the process (Scheme 2).

The dimer $(SF_5)_2$ can be efficiently prepared (99% yield) by photochemical decomposition of SF_5Br in a quartz vessel (Scheme 3) [19].

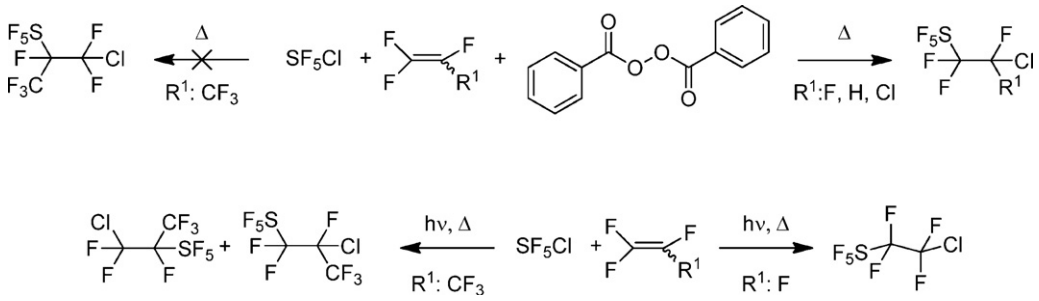
The chemistry of SF_5–X compounds above is dominated by the proclivity to form the $SF_5^{\bullet}$ radical. In particular, thepentafluorosulphanyl radical can be generated from $(SF_5)_2$ under thermal conditions (heating to 125–140 °C), from SF_5Cl using photo-irradiation or heating in the presence of a peroxide catalyst, and from the more reactive SF_5Br 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 SF_6 [10].

2.2. Synthesis of alkyl and fluoroalkyl SF_5-compounds

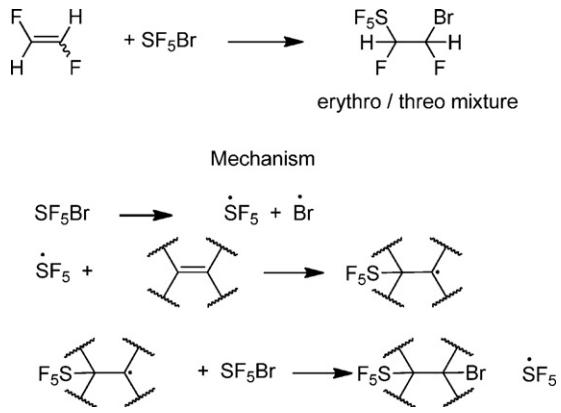
This chapter reviews the preparation of compounds having an SF_5–C(sp^3) bond. The first efforts directed at the synthesis of simple fluoroalkyl-SF_5 compounds dates back to the 1950s when CF_3SF_5 was obtained from both CH_3SH and CS_2 by reaction with CoF_3 in yields up to 40% [20]. In the following years, several



Scheme 5.



Scheme 6.



Scheme 7.

electrochemical fluorination versions of the same process were also published [21–23].

The fluoromethyl analogue was prepared in very good yields (86%) by AgF_2 promoted fluorination of a *N*,*N*-bistrifluoromethyl sulphenamide (Scheme 4) [24].

In a seminal contribution to the chemistry of SF_5-compounds, Case et al. reported that SF_5Cl is able to add thermally to a wide range of olefins, affording the corresponding SF_5-alkanes incorporating a β-chlorine atom (Scheme 5) [25].Although SF_5Cl 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-pentafluorosulphanylation reaction, the reactants were submitted to photochemical irradiation (Scheme 6) [26] (for related chemistry see [27]).

Table 1

Entry	R^1	Reaction time (h)	% Yield of $SF_5(CF_2)_2C_6H_4$-R^1
1	*m*-Br	18	53
2	*p*-Br	25	53
3	*p*-Cl	20	52
4	*p*-CH_3	48	41
5	*p*-CF_3	20	22[a]
6	*p*-NO_2	51	80
7	*o*-F	17	82
8	*o*-CF_3	18	74
9	*o*-$CH(CH_3)_2$	18	67

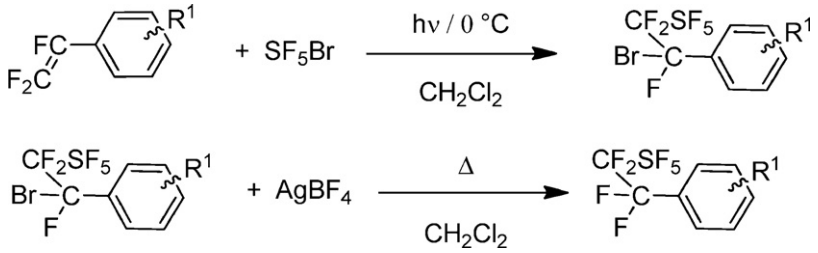
[a] Low yield due to volatility of product.

Addition of SF_5Br to tetrafluoroethylene and other fluoroethylenes was also reported to take place [28] and later on was used to prepare SF_5-fluoropolymers [29].SF_5Br was found to react with 1,2-difluoroethylene through a radical non-stereospecific addition, resulting from a homolytic cleavage of the F_5S–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].

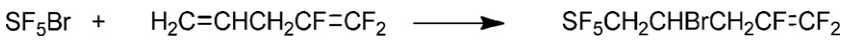
Other fluoroolefins, such as 3,3,3-trifluoropropene and chlorofluoroethylenes, were also shown to react with SF_5Br leading to the corresponding addition products [31]. Bromo- and bromofluoroethylenes were also found to undergo addition of SF_5Br [32].

SF_5–CF_2CF_2–Ph was synthesised by means of SF_5Br addition to CF_2=CF–Ph followed $AgBF_4$ promoted displacement of the secondary bromine atom by fluoride [33].

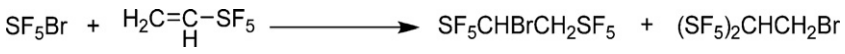
The scope of the methodology was subsequently expanded to a series of *ortho*-, *meta*- and *para*-(SF_5-perfluoroethyl)benzene derivatives. In fact, regioselective photochemical addition of SF_5Br



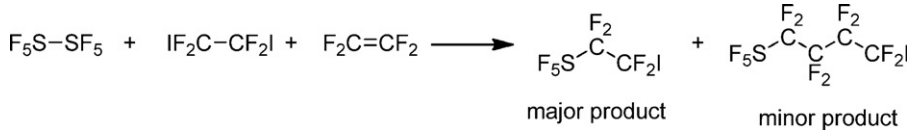
Scheme 8.



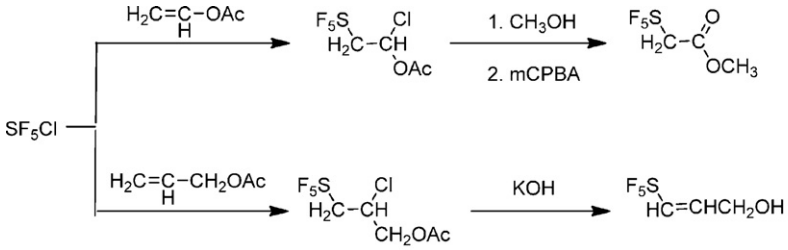
Scheme 9.

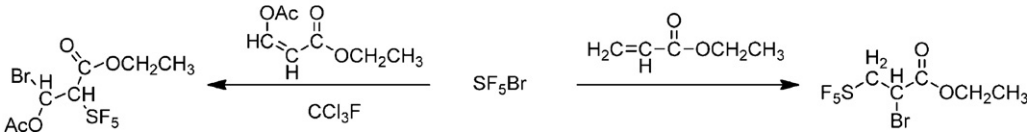


Scheme 10.

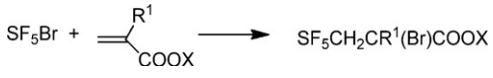


Scheme 11.





Scheme 12.



Scheme 13.

to the corresponding CF_2=CF-aryl substrates, followed by $AgBF_4$ treatment afforded the target compounds in moderate to good yields (Scheme 8 and Table 1) [34].

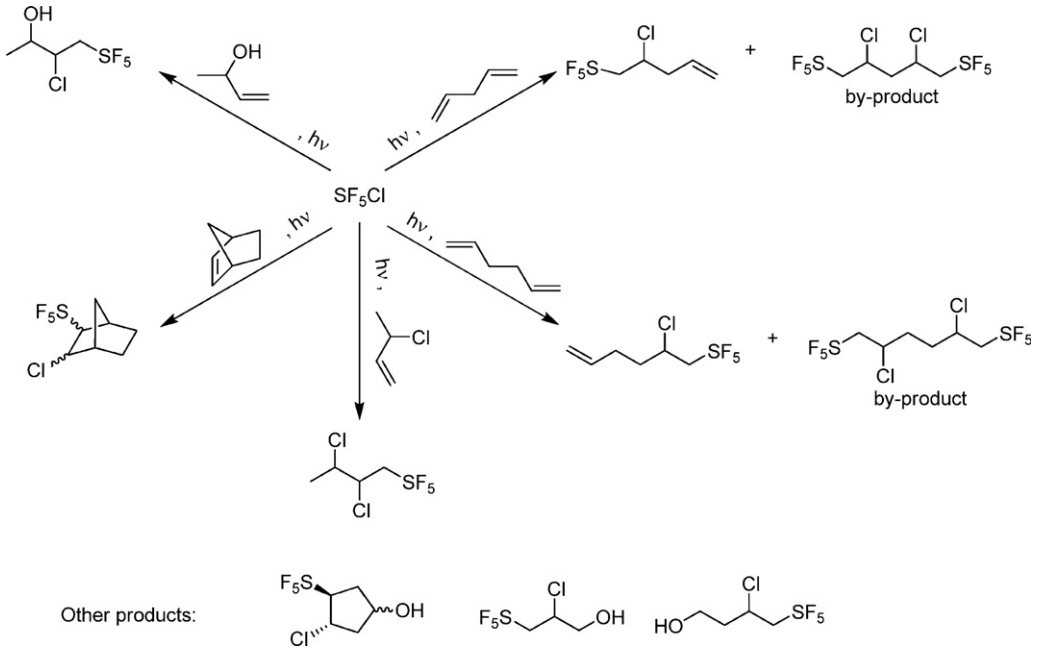
In the presence of two different terminal C=C bonds, one hydrogenated and one perfluorinated, SF_5Br added to the former through a thermally induced radical process (Scheme 9) [35].

Bis-SF_5-ethenes were obtained by SF_5Br addition to the mono-SF_5 precursor upon heating to 70 °C. No reaction was observed with fluorinated analogues like SF_5–CF=CF_2 (Scheme 10) [36].

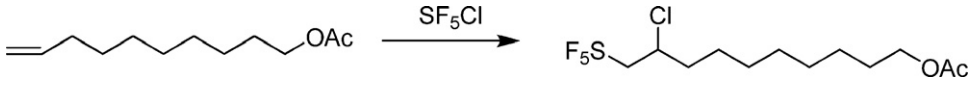
Table 2

Entry	R^1	X
1	H	*t*-Bu
2	CH_3	CH_3
3	CH_2Cl	C_2H_5
4	*n*-C_7H_{15}	C_2H_5

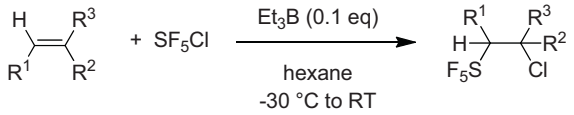
Since SF_5–I was unknown, SF_5-iodoperfluoroalkanes were obtained by reaction of $(SF_5)_2$ (1.1 equiv.) with $(ICF_2)_2$ (1.1 equiv.) and tetrafluoroethylene (1 equiv.) in a stainless steel vessel at 155 °C. The reaction occurred through a radical process and produced minor amounts of 4-iodo-perfluorobutyl-SF_5 as a



Scheme 14.



Scheme 15.



Scheme 16.

Table 3

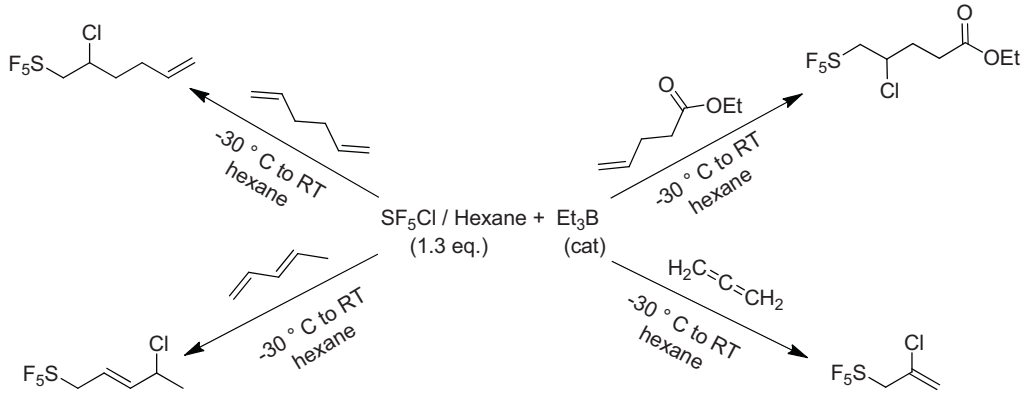
R^1	R^2	R^3	Yield (%)
H	n-C_6H_{13}	H	95
H	n-C_4H_9	H	98
H	t-C_4H_9	H	96
H	C_2H_5	C_2H_5	89
n-C_3H_7	H	n-C_3H_7	95[b]
$(CH_2)_4$	$(CH_2)_4$	H	98[b]
H	p-tolyl	H	79
H	OAc	H	98

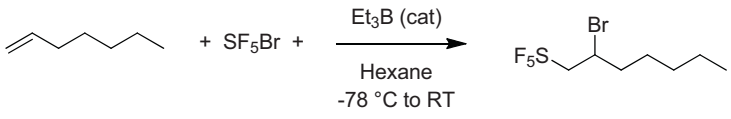
[b] One major diastereomer (>90% by NMR).

co-product (Scheme 11) [15]. A related process was previously used for the preparation of SF_5-telomers [14].

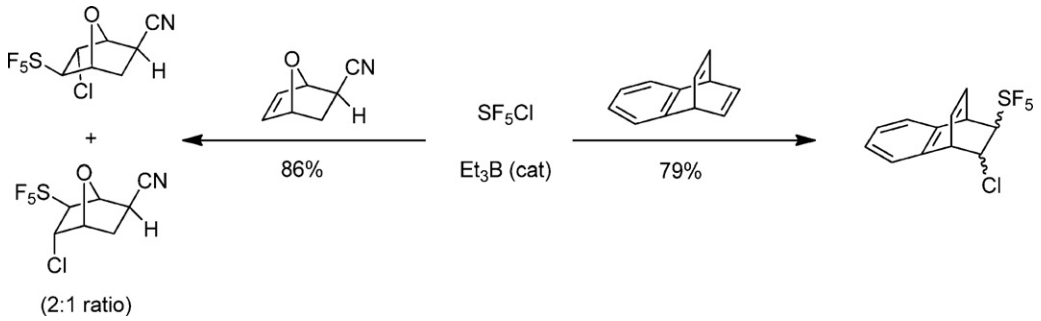
SF_5Cl was found to add to electron-rich and very reactive vinyl acetate and also with allyl acetate affording good yields of the corresponding primary SF_5-adducts, which were then subjected either to oxidation to yield SF_5-acetate or to elimination of hydrochloric acid to give γ-SF_5-allyl alcohol (no epoxide formation was observed). More reactive SF_5–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 CCl_3F as solvent. Rewardingly, SF_5–Br was found to add to less reactive acrylate affording β-SF_5-α-Br-acrylate (Scheme 12) [37].

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-chloromalonate, SF_4 and fluoroethylene instead (Scheme 13 and Table 2) [38].

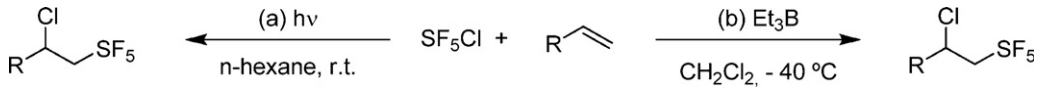




Scheme 17.

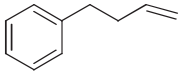
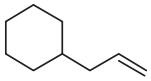
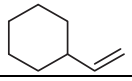


Scheme 18.



Scheme 19.

Table 4

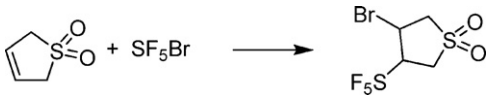
Entry	R	Method	Reaction time (h)[a]	Yield (%)
1		a	8	25
		b	6	48
2[b]		a		
		b	4	92
3		a	8	56
		b	4	91
4		a	6	84
		b	2	95

[a] In hour.
[b] The volatility of olefin 2 meant that only method (b) was used.

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].

A long chain aliphatic system bearing an ω-SF_5 group was obtained by SF_5Cl addition to the corresponding ω-unsaturated acetate (Scheme 15) [44].

A wide range of β-chloro SF_5-alkyl compounds were obtained by Et_3B-catalysed regioselective and highly diastereoselective radical addition of SF_5Cl 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 SF_5Cl addition (partly due to cross-reactivity of Et_3B with the ester moiety), whereas alkynes like phenylacetylene afforded lower yields (49%) of the corresponding SF_5-β-chloroalkene and partial dimerisation (Scheme 16 and Table 3) [45].



Scheme 21.

Later on, the methodology was expanded to include the regioselective synthesis of functionalised SF_5-β-chloro alkyl derivatives, incorporating C=C bonds and ester moieties (Scheme 17). Allene successfully underwent the reaction producing the 2-chloroallyl-SF_5 product. The same strategy worked also when SF_5Cl was replaced by SF_5Br, and β-Br SF_5-alkanes could be obtained by this route. The use of SF_5Br seemed to be more appropriate for the reaction with electron deficient alkenes [46].

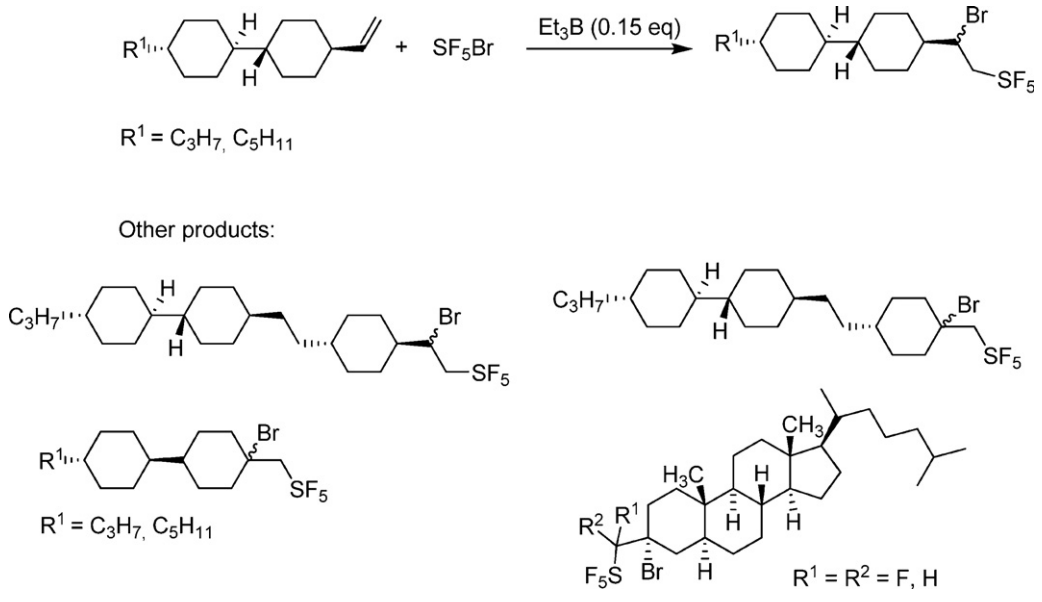
Another synthetic application of this methodology eventually resulted in an efficient entry to 2-SF_5-naphthalene. One of the key steps was the Et_3B-promoted addition of SF_5Cl to benzobarralene [47]. Another substrate which underwent addition of SF_5Cl under the same conditions is a furan-acrylonitrile exo-adduct which afforded the corresponding SF_5Cl-addition product in very good yields and 2:1 diastereomeric ratio (Scheme 18) [48].

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].

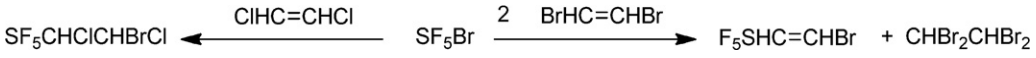
The methodology was also used for the addition of SF_5Br to different alkenes which afforded a series of compounds that showed interesting properties as liquid crystals (Scheme 20) [51].

3-SF_5-4-bromo sulpholane was obtained by addition of SF_5Br to sulphol-3-ene (Scheme 21) [52]. This molecule was then used as an efficient precursor of 2-SF_5-butadiene (see Section 3.2, Scheme 75).

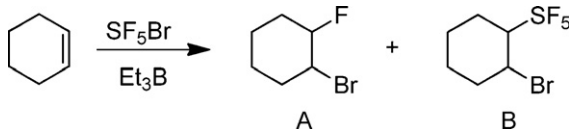
Dihaloethylenes were found to react with SF_5Br through a radical mechanism, producing different reaction outcomes depending on the nature of the halogen. Indeed, ClCH=CHCl afforded the expected standard 1:1 adduct, whereas BrCH=CHBr reacted in a more complex way affording two different products,



Scheme 20.



Scheme 22.



Scheme 23.

Table 5

Entry	Conditions[a]	Solvent	A[b]	B
1	KF	CH_2Cl_2	9	1
2	–	CH_2Cl_2	9	1
3	SF_5Br (sol in CH_2Cl_2) and KF	CH_2Cl_2	9	1
4	SF_5Br (sol in CH_2Cl_2)	CH_2Cl_2	9	1
5	KF	Pentane	7	3
6	–	CCl_3F	4	6

[a] All reactions, 0.1 equiv. Et_3B, 1.2 equiv. SF_5Br, temp: −78 °C to RT.
[b] Product ratio determined by ^{19}F NMR.

one saturated and one unsaturated, the latter incorporating the SF_5 group. Interestingly the reaction producing SF_5–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 SF_5-alkyl compounds was recently achieved by Welch et al. who reported that the use of CCl_3F as a solvent can strongly improve the Et_3B-catalysed addition of SF_5Br 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].

The use of CCl_3F as a solvent was then successfully extended to the Et_3B-catalysed addition of SF_5Br to various unsaturated esters, which produced the corresponding bromo-pentafluorosulphanylated esters in excellent yields (Scheme 24 and Table 6). The use of SF_5Cl afforded lower yields, and addition of DBU resulted in efficient dehydrobromination of the products [54]. Addition of SF_5Cl to allyl acetate was subsequently described to occur efficiently [55].

Dimethyl itaconate was also successfully reacted with SF_5Br affording the expected addition product in good yields (Scheme 25) [56].

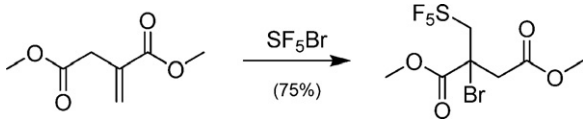
An interesting addition reaction of SF_5Cl to a diene, occurring with concomitant transannular cyclisation was recently reported by Röschenthaler et al. Without any radical initiation, the process affords low yields of the target SF_5-substituted adamantane-type cyclised product, with the formation of significant amounts of dichloro and chlorofluoro-substituted by-products, which may arise from the dissociation of SF_5Cl into FCl and SF_4. However, upon UV irradiation the process delivered high yields of target SF_5-compound. Under UV-irradiation also norbornadiene reacted with SF_5Cl affording two diastereoisomers of the corresponding transannulated SF_5-product, in ca. 3:1 ratio. Finally, cycloocta-1,5-diene failed to produce transannulation, affording the product arising from simple addition of SF_5Cl to one of the C=C bonds, in rather modest yields (Scheme 26) [57].

The addition of SF_5Cl and SF_5Br to vinyl silanes was reported to occur efficiently and under mild conditions. The authors were

Table 6

Entry	R^1	Reaction time (h)[a]	Yield (%)[a]
1	C(O)O*t*-Bu	20	94
2	$CH_2C(O)OMe$	10	85
3	$CH_2CH_2C(O)OEt$	20	93
4	$CH_2CH(CH_3)C(O)OEt$	10	92
5	$CH_2OC(O)CH_3$	10	99

[a] Isolated, purified yield.



Scheme 25.

unable to assign unambiguously the regioisomery of the products on the basis of spectroscopic and analytical data (Scheme 27) [58].

Ketene was also found to be reactive towards SF_5–Cl, affording SF_5-acetyl chloride [59]. This intermediate was then used as a starting material for the preparation of SF_5-ketene through hydrolysis followed by dehydration (Scheme 28) [60].

2.3. Synthesis of aryl SF_5-compounds

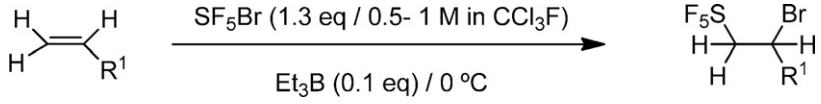
This chapter reviews the preparation of compounds having an SF_5-group attached to an aromatic residue. Following unsuccessful efforts to prepare aromatic SF_5-compounds by Emeleus et al. [61], the first aryl-pentafluoride C_6H_5–SF_5 was successfully obtained by Sheppard by action of AgF_2 on $(C_6H_5S)_2$ in Freon which produced the intermediate trifluoride, then converted into the target phenyl-SF_5 upon heating to 130 °C (yields 5–14%) (Scheme 29) [62].

The same transformation was achieved 40 years later by using XeF_2 as fluorinating agent (up to 25% yield) [63].

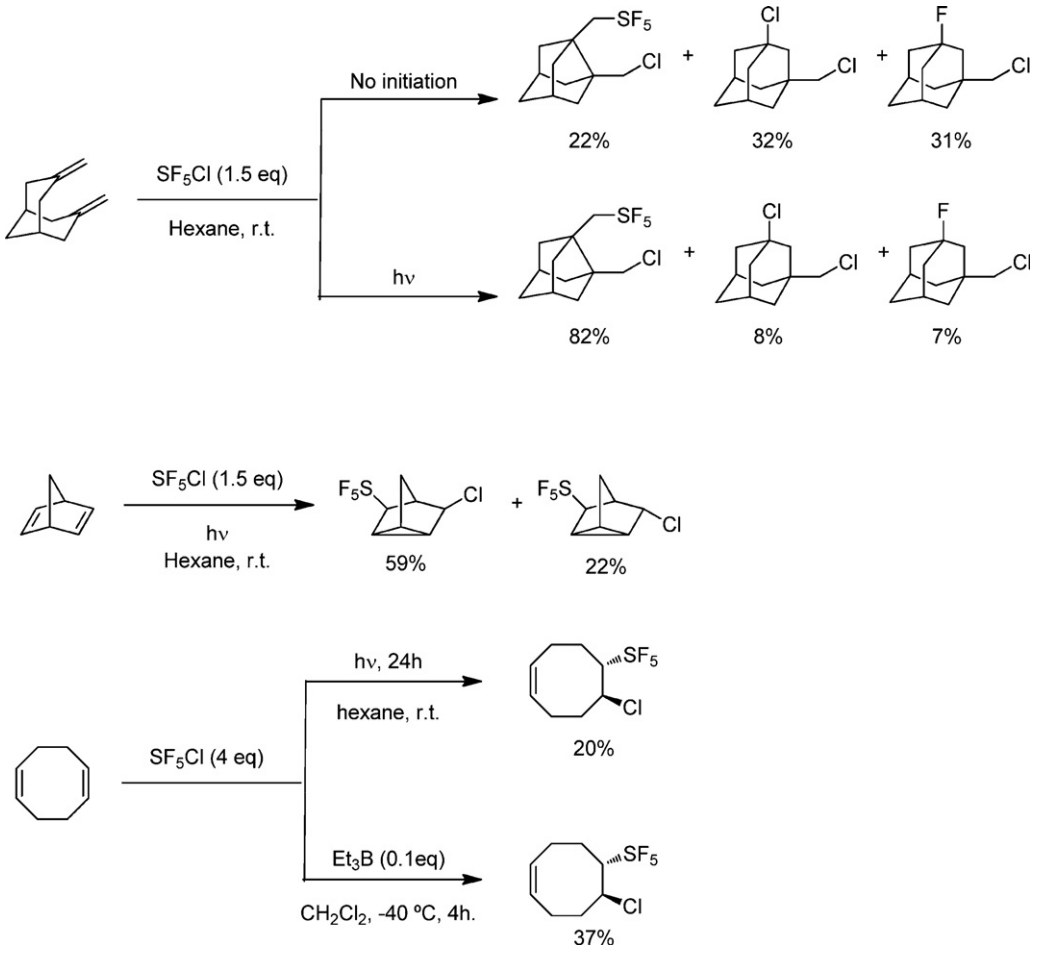
The scope of the reaction was subsequently extended to *meta*- and *para*-nitrophenyl-SF_5 compounds by using a Teflon reactor (5–14% yields), whereas the use of a copper reactor increased the yields to 15–30%. Interestingly, bis-3,5-SF_5 nitrobenzene could be obtained, albeit in low yields, starting from the corresponding bis-sulphonyl chloride (Scheme 30) [64].

A related methodology was used later on for the synthesis of two other nitro-substituted SF_5-benzenes (yields 29–43%) (Scheme 31) [65].

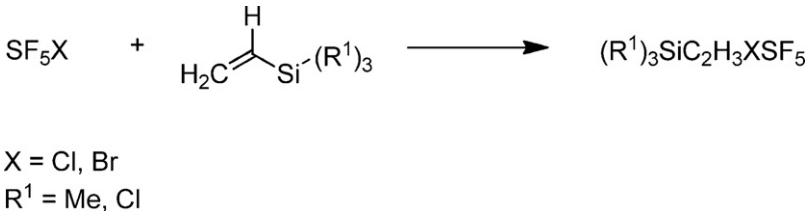
Elemental fluorine (10% F_2 in N_2), that was used to convert at room temperature aromatic nitrothiols and nitro-methylsulphides into the corresponding SF_5 compounds in moderate yields (Scheme 32) [66]. Remarkable results were achieved by employing micro-reactors for fluorinations that were used to convert bis(*m*-NO_2-phenyl)-disulphide and *p*-NO_2-phenyl-SF_3 into the corresponding SF_5 compounds at room temperature [67].The first *ortho*-substituted SF_5-benzene was synthesised by AgF_2-promoted fluorination of the corresponding disulphide (Scheme 33), although the scope of the reaction seems to be limited because other structurally



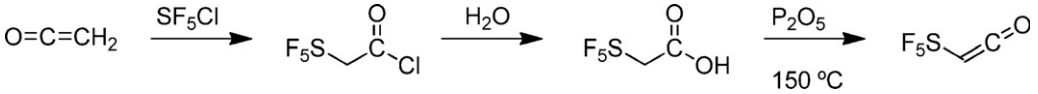
Scheme 24.



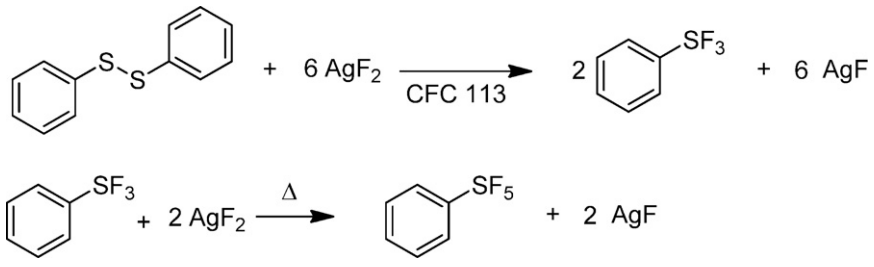
Scheme 26.



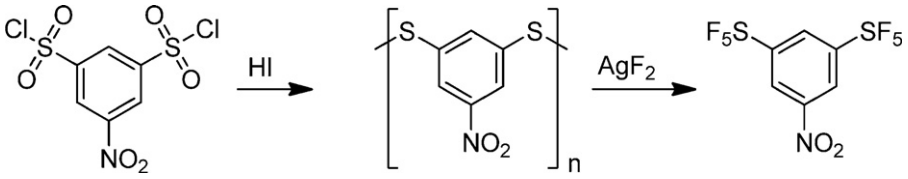
Scheme 27.



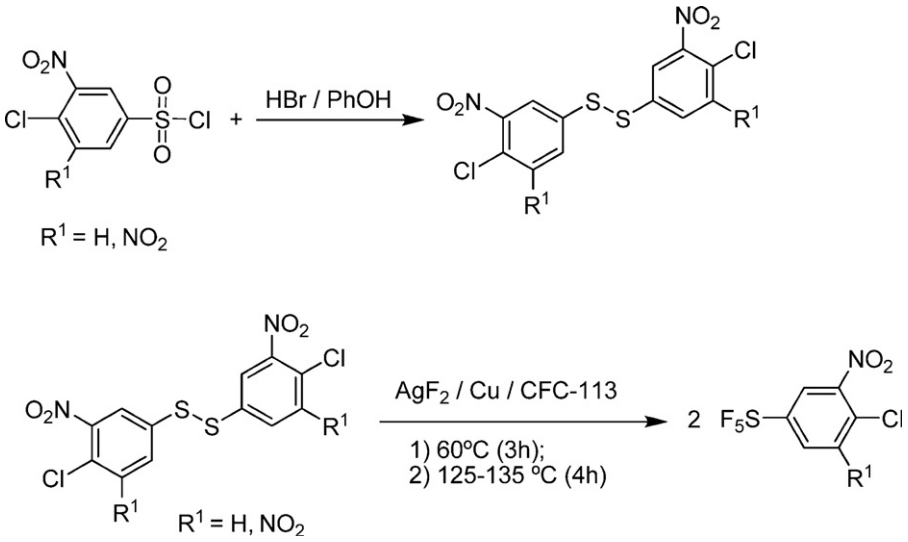
Scheme 28.



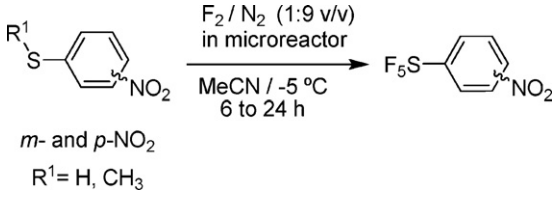
Scheme 29.



Scheme 30.



Scheme 31.



Scheme 32.

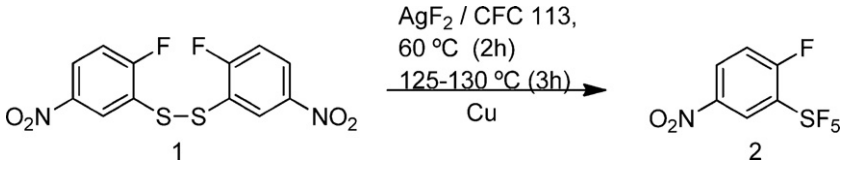
related substrates did not afford the desired SF_5-compounds [68]. A few years later, more *ortho*-fluorinated SF_5-aryl compounds were obtained in low yields (<10%) by treatment of a disulphide precursor with F_2/N_2 [69].

A remarkably more efficient synthesis of SF_5-benzene was achieved by chlorination of cyclohexa-1,4-diene with SO_2Cl_2 followed by treatment of the resulting dichloro-intermediate with SF_5Cl and then easy aromatisation resulting from elimination of three molecules of HCl (Scheme 34) [70].

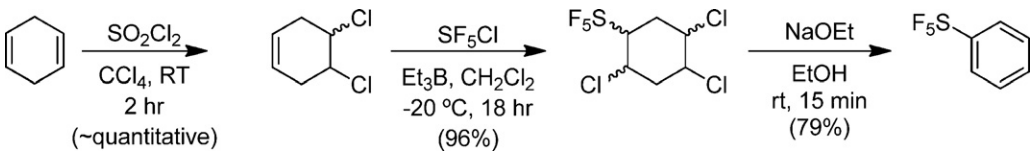
A conceptually related entry to SF_5-benzene was developed starting from 3,6-diacetoxy-cyclohex-1-ene, which upon treatment with SF_5Br followed by aromatisation resulting from elimination of HBr and 2 molecules of acetic acid or water afforded the target SF_5-benzene (Scheme 35) [71].

The method worked also when less reactive SF_5Cl was used instead of SF_5Br; in that case, cyclohexene was used as starting material followed by NBS-promoted dibromination of the intermediate 1-SF_5-cyclohexene (Scheme 36) [71].

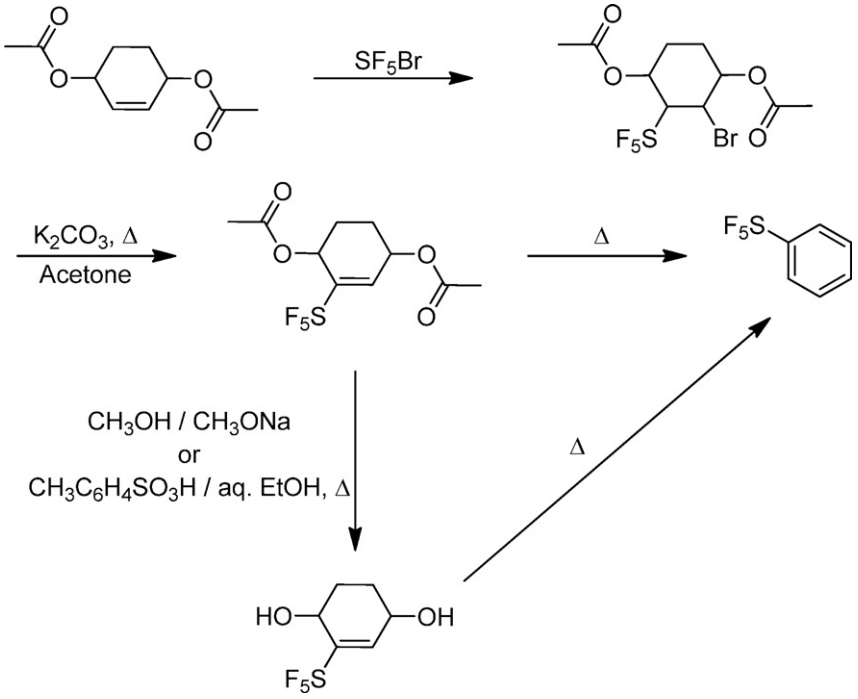
Very recently Umemoto et al. published a novel two-steps synthesis of SF_5-aromatics, which appears to be a significant improvement over previous methods. The synthesis is based on the conversion of aryl-disulphides or thiols into the corresponding SF_4Cl derivatives by action chlorine and potassium or caesium fluoride (Scheme 37). Subsequent treatment with a fluoride source such as ZnF_2 or Sb(III/V) fluorides effectively produced a displacement of the chlorine atom by fluoride affording the target SF_5-aryl compounds. Bis-SF_5-aromatics could be also prepared from the corresponding thiols [72].



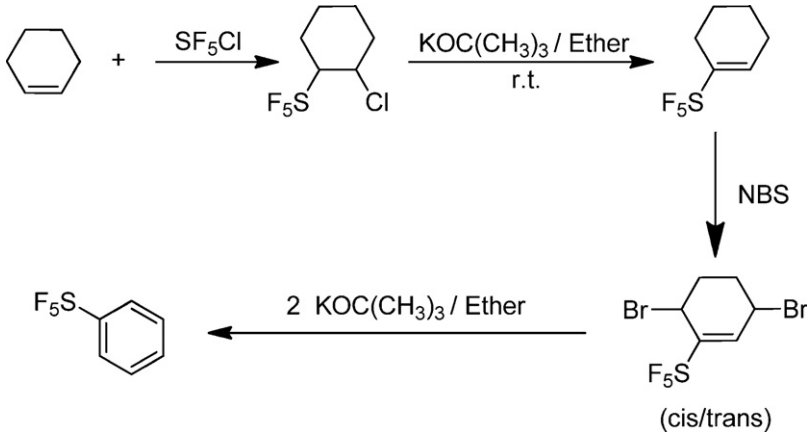
Scheme 33.



Scheme 34.



Scheme 35.



Scheme 36.

2.4. Synthesis of alkenyl, alkynyl and acyl SF_5-compounds

This section reviews the preparation of compounds having an SF_5–C(sp^2) or SF_5–C(sp) bond. The first example of addition of SF_5Cl to an alkyne dates back to 1964 when Hoover and Coffman reported the formation of 1-SF_5-2-Cl-ethylene from acetylene under thermal conditions (Scheme 38) [73]. The corresponding reaction with SF_5Br was described 20 years later to afford 80% yield of $F_5SCH{=}CHBr$ [74].

Propyne and trifluoropropyne efficiently reacted with SF_5Br affording the corresponding SF_5-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].

The addition of SF_5Br to alkynes was also exploited as a means to prepare SF_5-alkynes, which were obtained by treating the intermediate 1-SF_5-2-Br-alkenes with KOH that resulted in an elimination reaction (Scheme 40) [76].

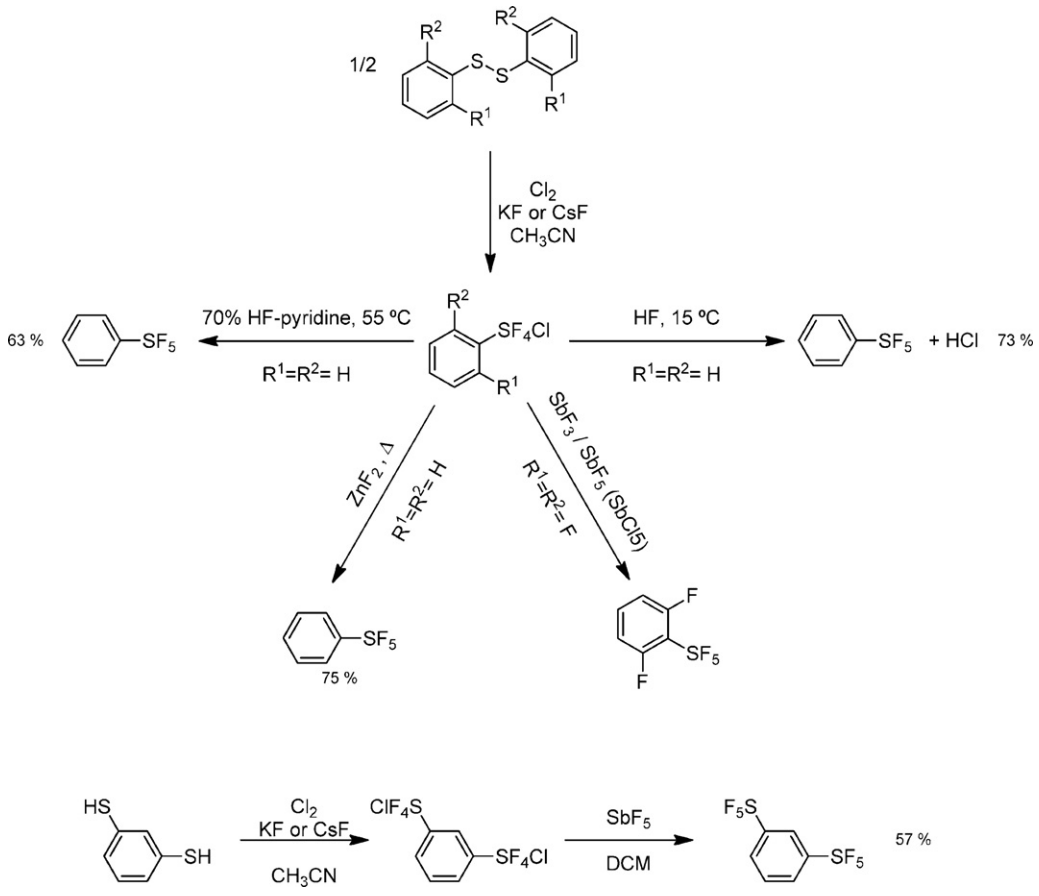
Further SF_5-acetylene derivatives were prepared by means of a conceptually related synthetic protocol based on Et_3B-catalysed addition of SF_5Cl to terminal alkynes, followed LiOH-promoted elimination (Scheme 41) [77].

The same methodology was recently used to prepare SF_5-substituted acetylenes having liquid crystal properties (Scheme 42). The SF_5-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 SF_5-alkenes in 65–72% yields [78].

β-SF_5-acrylate monomers were obtained by reaction of SF_5Br with ethyl propiolate (Scheme 43) [79].

A conceptually different approach to an SF_5-alkene was reported by Winter and Gard who described the silicic acid promoted isomerisation 3-SF_5-4-sulpholene to the corresponding 3-sulpholene (Scheme 44) [52].

One of the few acyl-SF_5 compounds described so far was obtained by radical addition of $(SF_5)_2$ to oxalyl fluoride (Scheme 45). The resulting product was then used as an intermediate in the preparation $SF_5OC(O)F$ and $SF_5O_2C(O)F$ [80].



Scheme 37.

Table 7

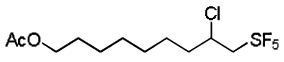
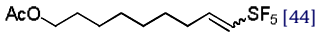
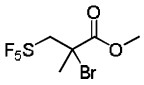
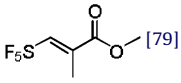
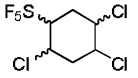
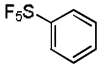
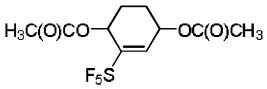
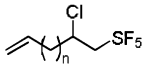
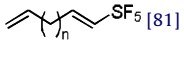
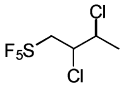
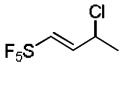
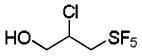
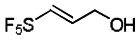
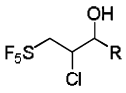
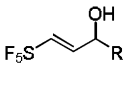
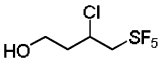
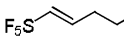
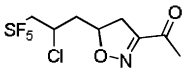
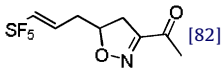
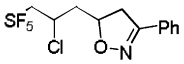
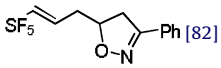
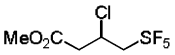
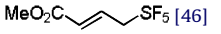
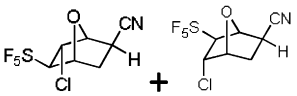
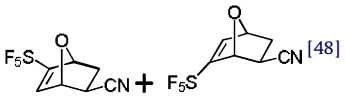
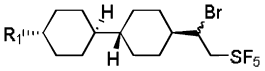
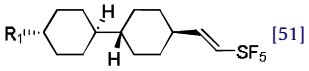
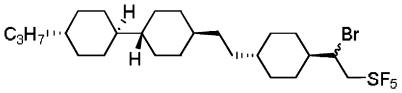
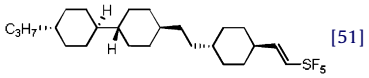
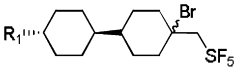
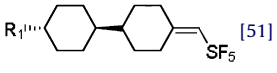
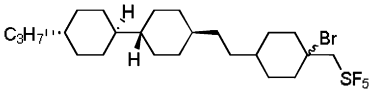
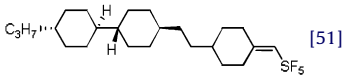
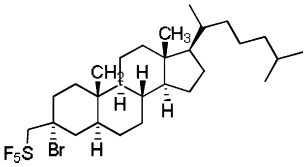
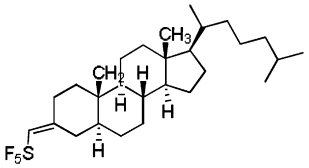
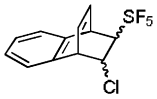
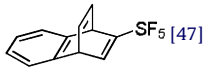
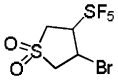
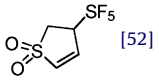
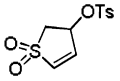
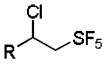
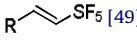
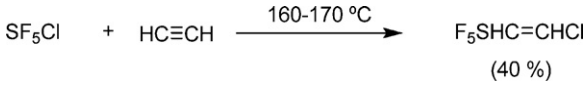
Entry	Starting material	Product [Ref]	Base/Temp	Yield[a] (%)	Comments
1		 [44]	NaOMe/r.t.	91	
2		 [79]	$NaOCH_3$/0 °C	71	Two isomers in ratio 3:97
3		 [70]	NaOEt/r.t.	79	
4		 [71]	K_2CO_3/56 °C	98, 70[b]	Heating to 265 °C 
5		 [71]	$KOC(CH_3)_3$/r.t.	71	
6		 [81]	K_2CO_3/60 °C	*n* = 1, 79 *n* = 2, 86	
7		 [81]	K_2CO_3/55 °C	50	Heating to 75–80 °C 
8		 [40]	KOH/30 °C	67	
9		 [41]	KOH/30 °C		R = H, CH_3

Table 7 (*Continued*)

Entry	Starting material	Product [Ref]	Base/Temp	Yield[a] (%)	Comments
10		 [41]	KOH/30 °C		
11		 [82]	K_2CO_3/60 °C	87	
12		 [82]	K_2CO_3/60 °C	90	
13		 [46]	NaOMe/r.t.	76	
14		 [48]	LiOH * H_2O/r.t.	96	
15		 [51]	KOH/35 °C	R = C_3H_7 74 R = C_5H_{11}, 84	
16		 [51]	KOH/35 °C	97	
17		 [51]	KOH/65 °C	R = C_3H_7 87 R = C_5H_{11}, 89	
18		 [51]	KOH/65 °C	96	
19		 [51]	KOH/65 °C	81	
20		 [47]	NaOMe/50 °C	95	
21		 [52]	AgOTs/82 °C	52	By-product 
22		 [49]	K_2CO_3/50 °C	R = Cy, 91 R = *i*-Pr, 88 R = $(CH_2)_2Ph$ 87 R = CH_2Cy, 78	

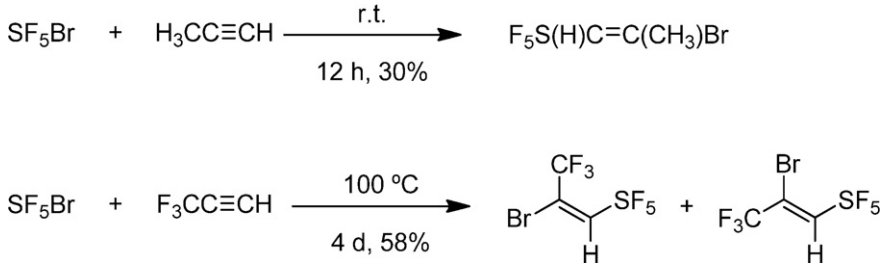
[a] Total yield.
[b] Starting from the *trans* isomer, 98% of *trans* product has been obtained. Starting from the *cis*, 70% of *cis* product has been obtained.



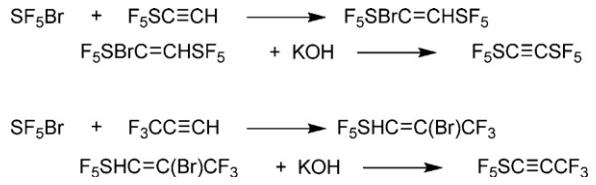
Scheme 38.

3. Chemistry of SF_5-compounds (secondary reactivity)

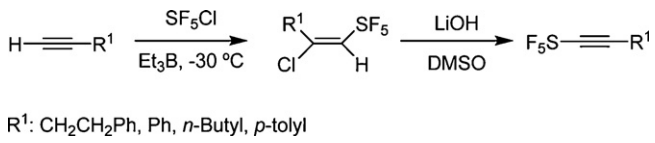
This section will review the reactivity of "primary" SF_5-building blocks, obtained as described in Section 2, for producing more complex SF_5-derivatives (secondary reactivity).



Scheme 39.



Scheme 40.



Scheme 41.

3.1. Reactions of SF_5-alkanes

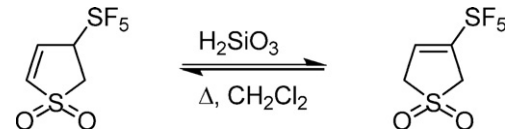
The reactivity of SF_5-alkanes, i.e. derivatives having a pentafluorosulphanyl group bound to an sp^3-carbon which are generally obtained by addition of SF_5X to the parent alkenes (see Section 2.2), is dominated by the β-elimination of HX to afford the corresponding SF_5-alkenes. De Marco and Fox described the KOH-promoted elimination of HCl from α-chlorodifluoromethyl-SF_5-compounds (Scheme 46) [27].

This reactivity has been extensively exploited from 2000 to date for preparing a number of structurally diverse SF_5-alkenes, using a wide range of different bases and conditions, as summarised in Table 7.

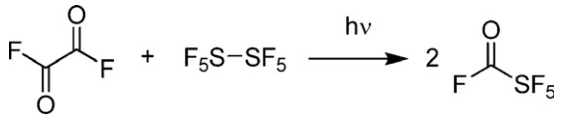
SF_5-cylopentadiene was obtained as a mixture of two tautomeric forms from two different starting materials. In both cases elimination of HCl was the key step, followed by either a retro-Diels–Alder reaction or a P_2O_5-promoted dehydration (Scheme 47) [39].

1,3,4-Oxadiazoles incorporating SF_5-perfluoroalkyl/alkyl substituents were synthesised starting from the corresponding SF_5-containing carboxylic acids through the corresponding hydrazides which were coupled to a second carboxylic acid, and then submitted to intramolecular condensation (Scheme 48) [83].

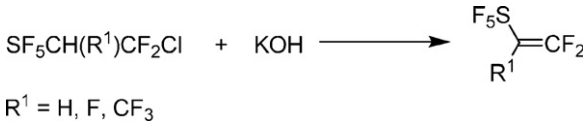
Aliphatic SF_5-substituted C-3 building blocks such as 3-Br-pentafluorosulphanyl-propane and 3-SF_5-propionic acid were prepared by radical reduction of the parent 2-Br-propionates



Scheme 44.



Scheme 45.



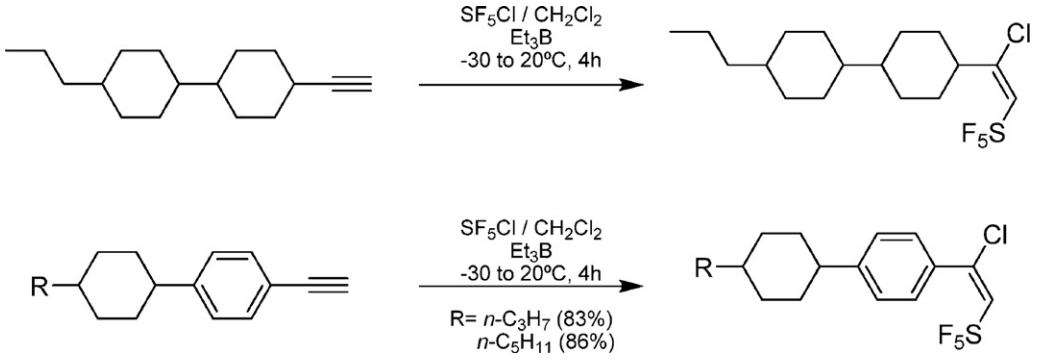
Scheme 46.

followed by manipulation of the carboxy function (Scheme 49) [38]. A related halide displacement was reported to occur when $SF_5CF_2CFBrPh$ was treated with $AgBF_4$ affording $SF_5CF_2CF_2Ph$ together with AgBr and BF_3 [33]. The scope of the method was subsequently extended to the synthesis of an array of $SF_5CF_2CF_2Ar$ compounds (Ar = substituted aryl groups) [34].

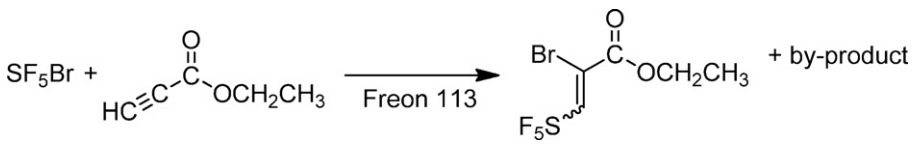
An SF_5-perfluoroalkyl thiol was obtained by S_N2-reaction of thiolacetic acid with an ω-iodo precursor followed by $LiAlH_4$ reduction (Scheme 50) [44].

Similarly, a series of quaternary trifluoromethanesulphonimide 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 SF_5-alkyl residues, heterocyclic rings and perchlorate, nitrate, and related counterions [85].

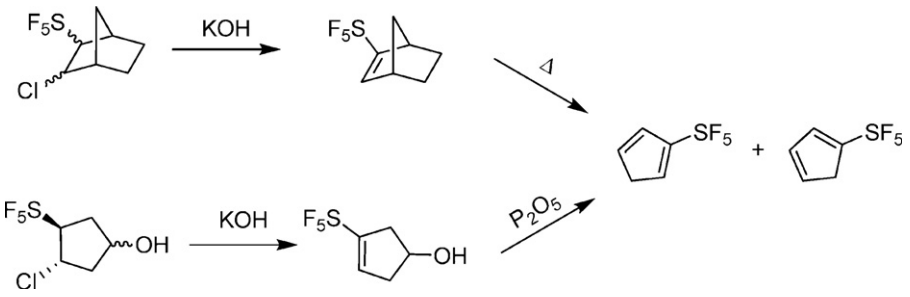
A broad range of ω-SF_5-alkyl building blocks were prepared by halogen displacement with *o*-nucleophiles by treatment with the corresponding silver and alkali metal salts. Interestingly, treatment of 1-SF_5-2-bromoethyl derivatives with AgOAc and acetic



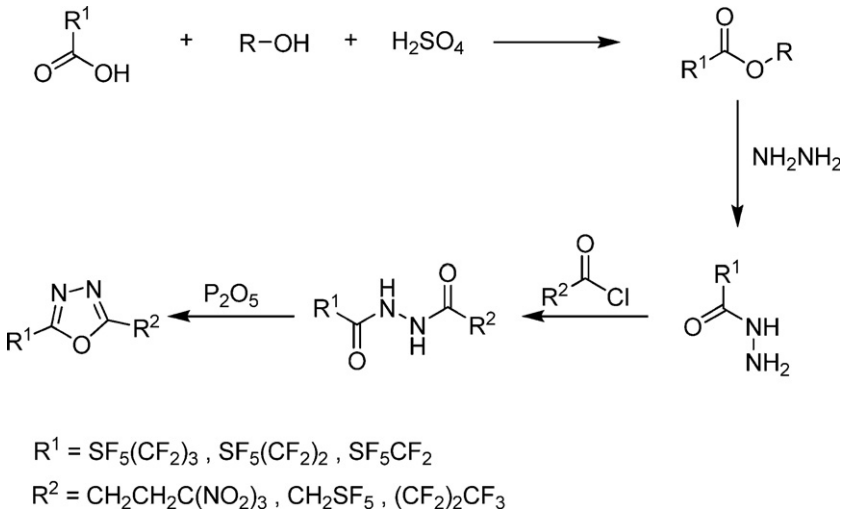
Scheme 42.



Scheme 43.



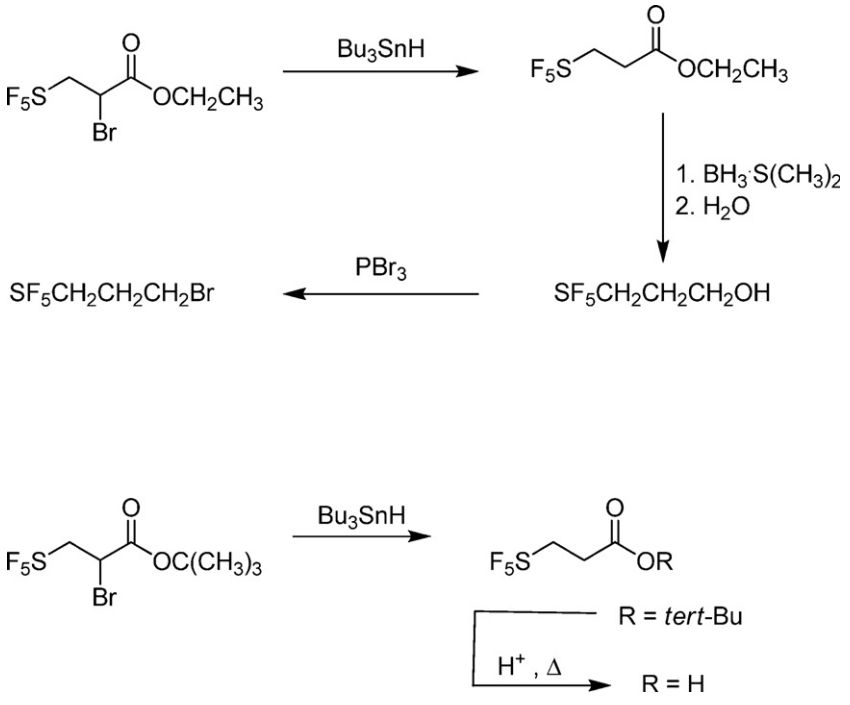
Scheme 47.



$R^1 = SF_5(CF_2)_3$, $SF_5(CF_2)_2$, SF_5CF_2

$R^2 = CH_2CH_2C(NO_2)_3$, CH_2SF_5 , $(CF_2)_2CF_3$

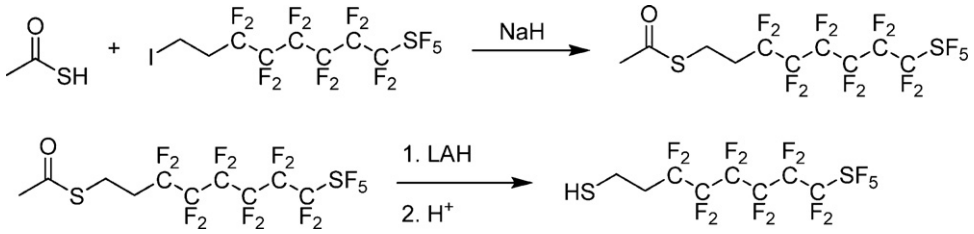
Scheme 48.



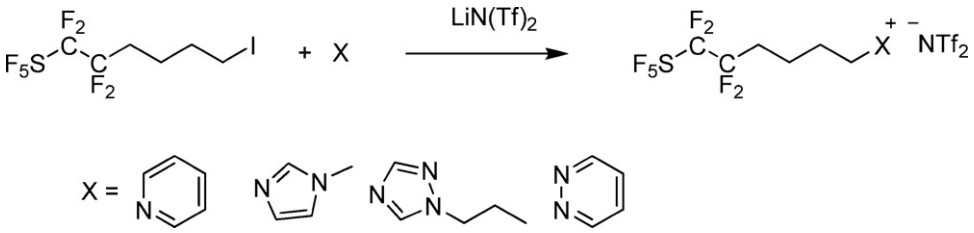
Scheme 49.

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 SF_5. (3-SF_5-propyl)malonate was then prepared from the corresponding bromide and decarboxylated to give ω-SF_5-pentanoic acid (Scheme 52) [56].

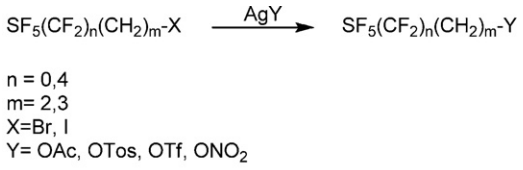
An extremely interesting development related to the preparation of SF_5-substituted azides for click-chemistry was recently reported (Scheme 53) [86]. SF_5-Ethyl and propyl azides were synthesised by nucleophilic substitution of the parent tosylates with 1.2 equiv. of sodium azide at 60 °C, whereas an attempt to

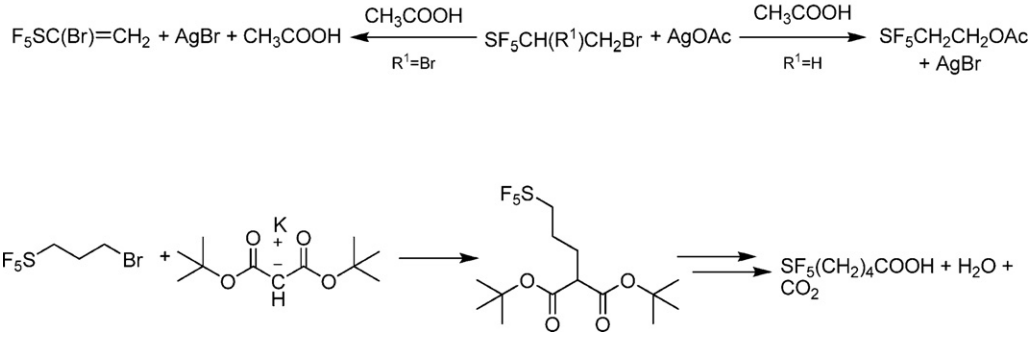


Scheme 50.

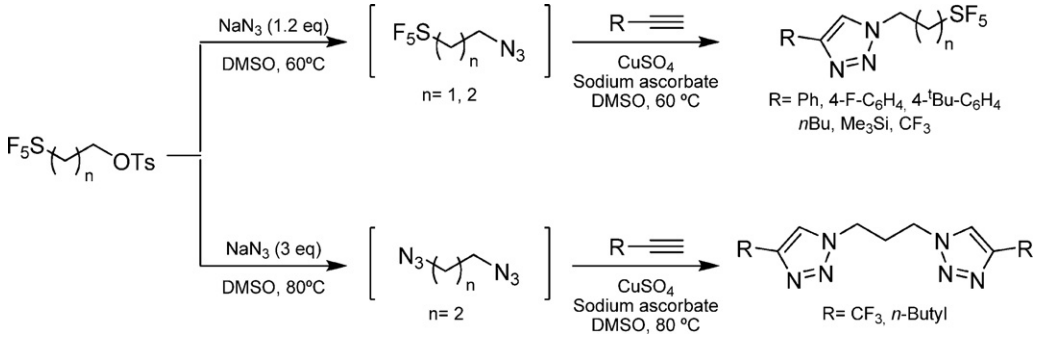


Scheme 51.





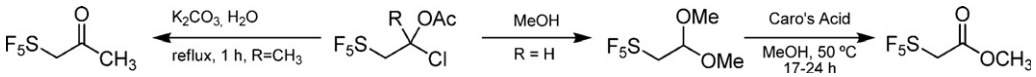
Scheme 52.



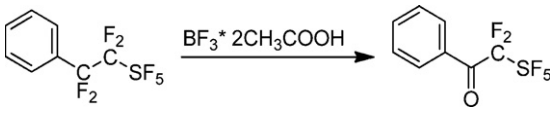
Scheme 53.

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.

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



Scheme 54.



Scheme 55.

Table 8

Entry	R	Yield[a] (%) method A	Yield[b] (%) method B
1	C_5H_{11}	65	38
2	$C_{14}H_{29}$	62	26
3	Ph	60	30
4	C_6H_{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.

Table 9

Entry	R	Method[a]	Product Isomers formed	Ratio[b]	Yield[c] (%)
1	H	C	(2Z,4E);(2E,4E)	16:84	72
2		D	(2Z,4E);(2E,4E)	2:98	46
3	C_6H_{11}	C	(2Z,4E);(2E,4E)	14:86	60
4		D	(2Z,4E);(2E,4E)	0:100	46
5	$C_{14}H_{29}$	C	(2Z,4E);(2E,4E)	43:57	57
6		D	(2Z,4E);(2E,4E)	39:61	74
7	Ph	C	(2E,4E);(2Z,4E)	–	0
8		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 ^{19}F NMR.
[c] Combined yields.

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 SF_5 group rather than to its steric bulk (Scheme 54) [46]. SF_5-acetate was recently utilised by Dolbier et al. in the synthesis of energetic materials [87]. SF_5-acetyl chloride was also used as a starting material for the synthesis of high-energy SF_5-nitro compounds [59].

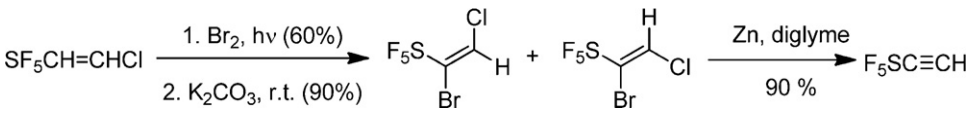
Another example of SF_5-substituted ketone was obtained by hydrolysis of SF_5-tetrafluoroethyl-benzene (Scheme 55) [88].

3.2. Reactions of SF_5-alkenes: addition, addition-elimination, elimination and cycloaddition

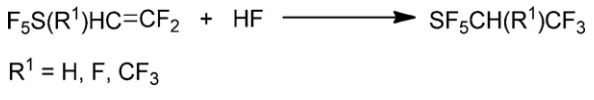
One of the first reactions involving SF_5-alkenes, specifically SF_5–CH=CHCl, was described in 1964. Photochemical addition of bromine followed by basic elimination produced a regioisomeric mixture of SF_5–CBr=CHCl that was eventually reduced by zinc to SF_5-acetylene in high yields (Scheme 56) [73].

Later on, the addition of HF, indirectly generated from KF + formamide, to SF_5-difluoroethylenes was reported to produce a small array of α-CF_3-pentafluorosulphanyl compounds (Scheme 57) [27].

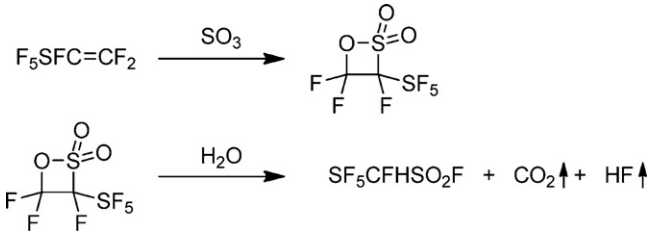
Perfluorinated β-sultone was obtained by addition of SO_3 to SF_5-trifluoroethylene, and then hydrolysed with water at 45–60 °C producing the corresponding sulphonyl fluoride and CO_2 + HF as co-products (Scheme 58) [89]. This finding built on extensive previous work dedicated to the preparation of SF_5-substituted β-sultones and their conversion into fluorosulphonyl derivatives [90] (for a review see [91]).



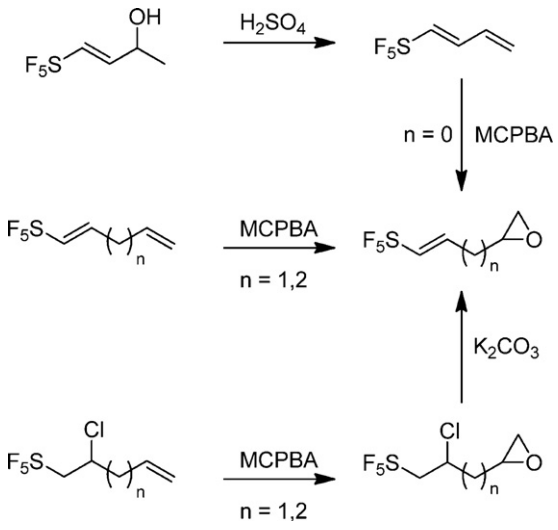
Scheme 56.



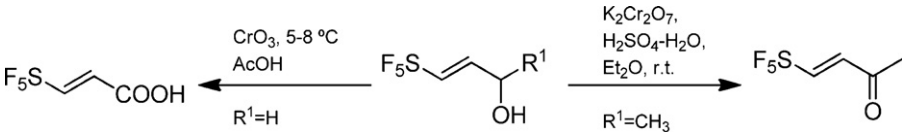
Scheme 57.



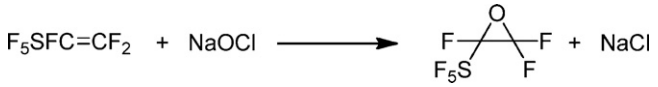
Scheme 58.



Scheme 59.



Scheme 60.



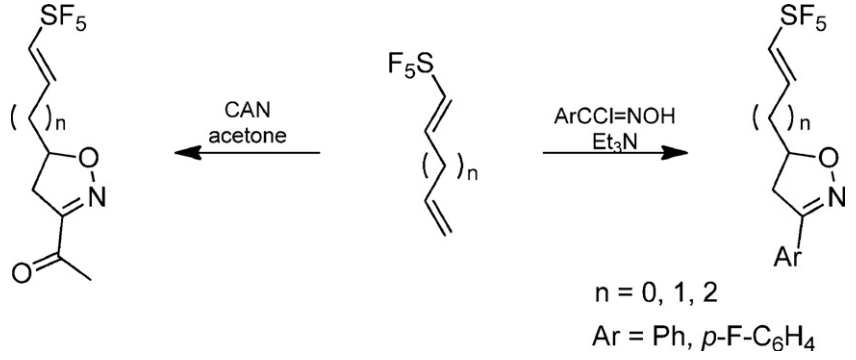
Scheme 61.

An interesting example of the peculiar reactivity of SF_5-dienes was described by Brel, who demonstrated that the SF_5-substituted C=C bond is unreactive in the presence of an oxidant like MCPBA whereas another double bond in the same molecule, including a conjugated one, is epoxidised (Scheme 59) [81].

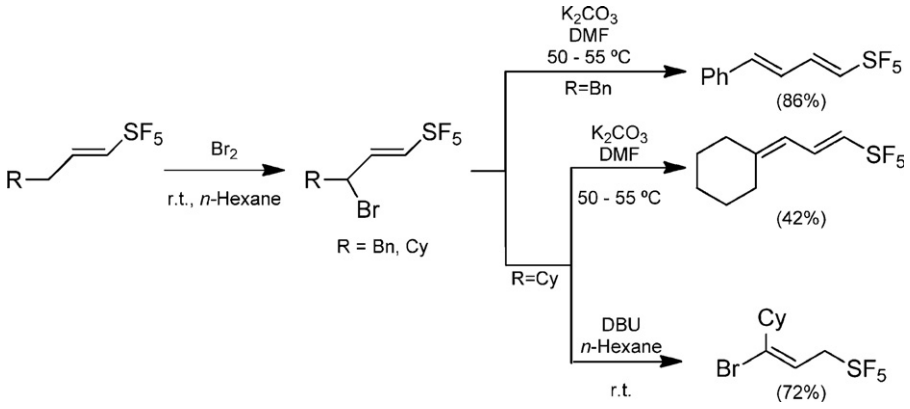
A similar protective behaviour of the SF_5 group towards C=C bond oxidation was observed for the treatment of SF_5-allylic alcohols with Cr(VI) oxidants which resulted exclusively in the oxidation of the carbinol function (Scheme 60) [41].

However, hypochlorite oxidation of SF_5-trifluoroethylene successfully produced the corresponding epoxide. As the reaction involves the formation of an anionic intermediate, the SF_5 group was found to facilitate the reaction and was more effective than a CF_3 group in terms of negative charge stabilisation (Scheme 61) [92].

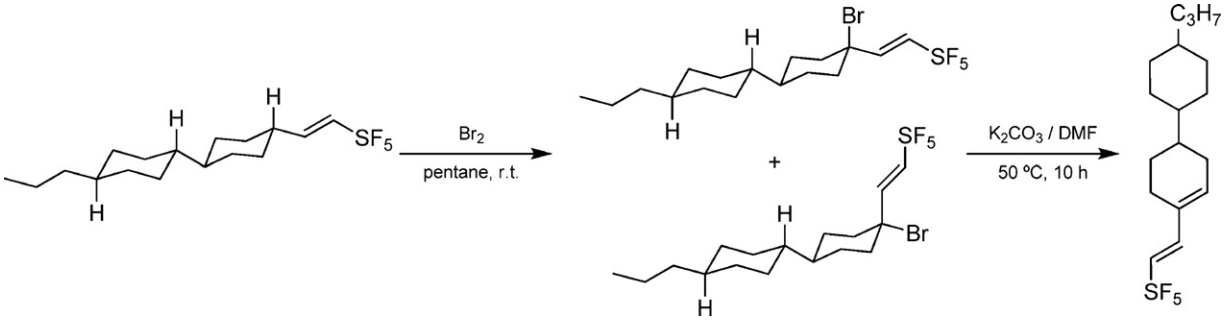
Similarly, SF_5-dienes showed chemoselective reactivity towards cycloaddition reactions, affording under different conditions the corresponding 4,5-dihydroisoxazoles originated by exclusive reaction of the non-SF_5-substituted C=C bond (Scheme 62) [41].



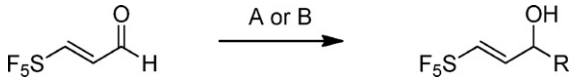
Scheme 62.



Scheme 63.



Scheme 64.



Scheme 65.

Treatment of SF_5-alkenes with bromine did not result in addition across the C=C bond but rather in allylic bromination, confirming the lack of reactivity of SF_5-substituted C=C bonds. The allylic bromides were submitted to base-elimination affording a set of terminally SF_5-substituted buta-1,3-dienes (Scheme 63) [49,50].

The same kind of reactivity towards bromination was very recently observed in SF_5-alkene systems deemed to be used for novel liquid crystals (Scheme 64) [78].

SF_5-1,3-dienes were prepared exploiting a key Wittig or Horner–Wadswarth–Emmons (HWE) reaction. The starting allylic alcohols were prepared by Grignard-reagent 1,2-addition to β-SF_5-acrolein, which occurred in low to moderate yields (Scheme 65 and Table 8).

Oxidation of the SF_5-allylic alcohols to β-SF_5-oxo-compounds was achieved via PCC-oxidation in the presence of silica gel (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).

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 dehydroxybromination with CBr_4/triphenylphosphine (Scheme 68) [55].

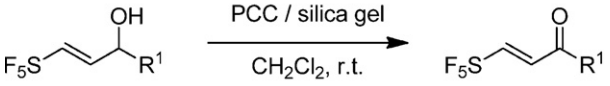
A series of useful SF_5-alkene compounds were prepared from SF_5-allyl alcohol, which was selectively oxidised to SF_5-acrolein by action of CAN and then converted into a regioisomeric mixture of oximes, which were dehydrated to SF_5-acrylonitrile (Scheme 69).

These compounds, as well as SF_5-acrylates, were then employed as dienophiles in Diels–Alder reactions (Scheme 70) [42] (see also [43]).

3-Chloro-1-SF_5-propene demonstrated a peculiar reactivity. In fact, following its preparation from the corresponding SF_5-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].

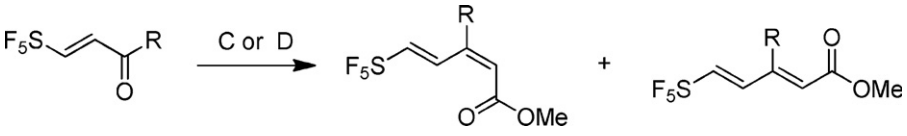
SF_5-susbtituted C=C bonds proved to be reactive under Diels–Alder reaction conditions, and the corresponding cyclohexenes were obtained by reaction with 2,3-dimethyl-butadiene upon heating for 8–10 hr at 100–110 °C (Scheme 72) [41].

A retro-Diels–Alder reaction was used to prepare 3-SF_5-furane in good yields, with the concomitant formation of acrylonitrile as a

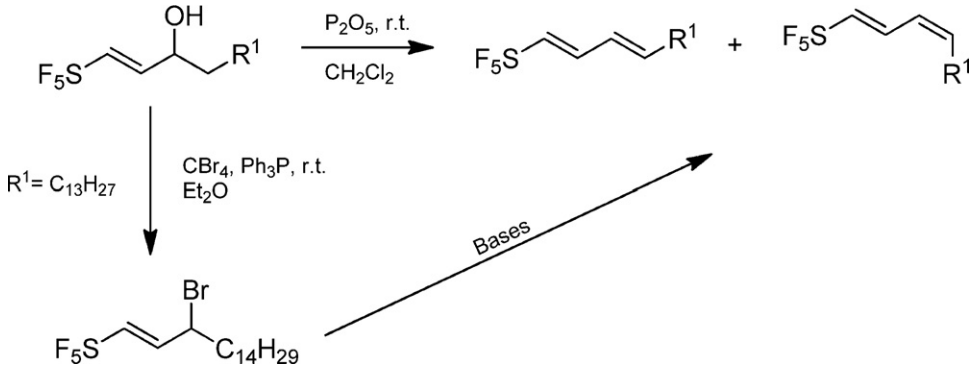


R^1	Yield (%)
H	95
C_5H_{11}	17
$C_{14}H_{29}$	91
Ph	98
C_6H_{11}	41

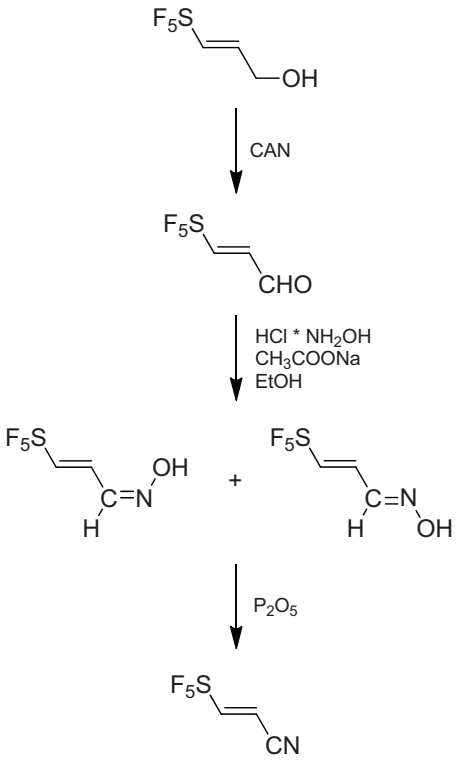
Scheme 66.



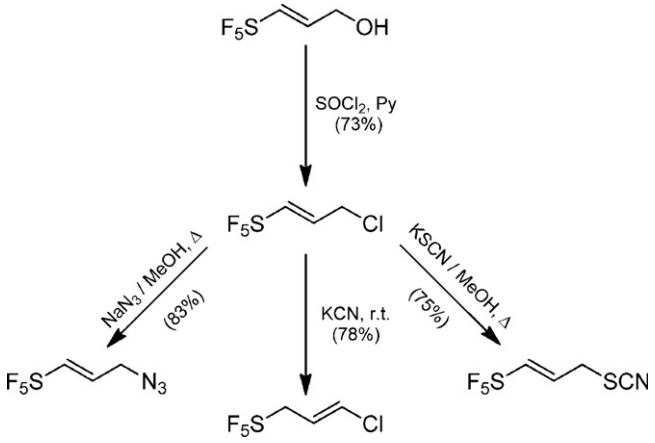
Scheme 67.



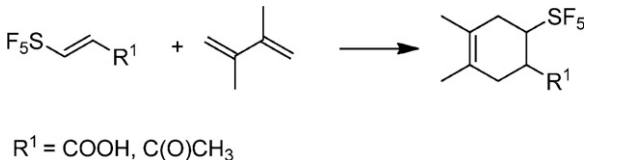
Scheme 68.



Scheme 69.



Scheme 71.



Scheme 72.

co-product. 2-Methyl-3-SF_5-furane was prepared following the same protocol (Scheme 73) [48].

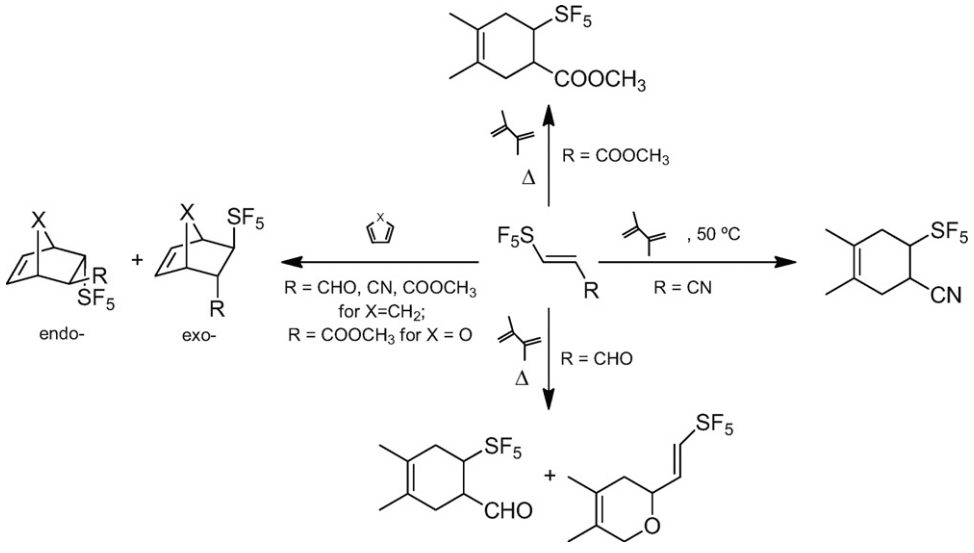
In contrast, 2-SF_5-benzobarralene did not undergo the expected thermal retro-Diels–Alder reaction to 2-SF_5-naphthalene, therefore an indirect approach to the target compound was sorted out. A bis-pyridyl tetrazine was submitted to Diels–Alder reaction with 2-SF_5-benzobarralene affording the corresponding adduct, which underwent first a loss of N_2 and then a retro-Diels–Alder affording the target compound, which proved to be thermally stable up to 250 °C (Scheme 74) [47].

3-SF_5-sulpholane was found to be a synthetic precursor of 2-SF_5-butadiene and successfully used as a substrate in Diels–Alder reactions leading to an array of SF_5-substituted cyclic compounds (Scheme 75) [52].

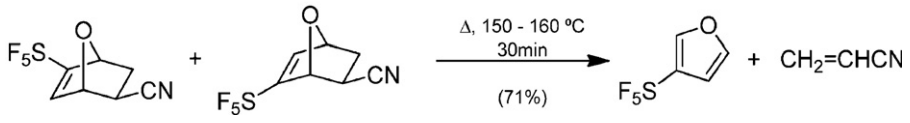
3.3. Reactivity of SF_5-alkynes

A limited number of SF_5-substituted heterocycles have been reported and many of them were obtained via dipolar cycloadditions involving SF_5-alkynes. 1-SF_5-Hex-1-yn underwent a tandem Diels–Alder/retro-Diels–Alder reaction with 4-phenyl-oxazole that afforded 3-SF_5-4-butyl-furane with the formation of cyanobenzene as a co-product (Scheme 76) [48].

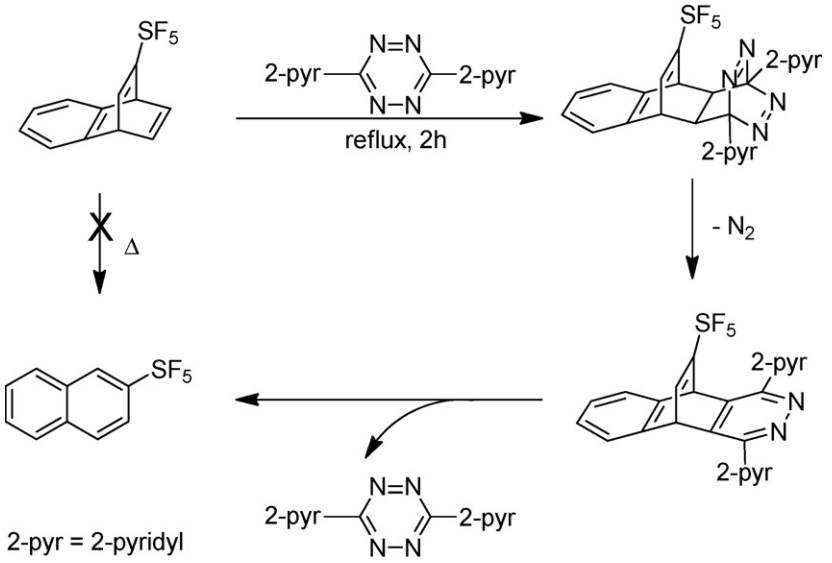
SF_5-azoles, including pyrazoles and 1,2,3-triazoles, were synthesised by 1,3-dipolar cycloaddition reaction of diazomethane or azides, respectively, with different SF_5-alkynes. The resulting compounds demonstrated interesting properties as energetic materials, with detonation properties similar to those of TNT. The SF_5-group was shown to play an important role by increasing the density of these molecules and therefore their detonation performance (Scheme 77) [93].



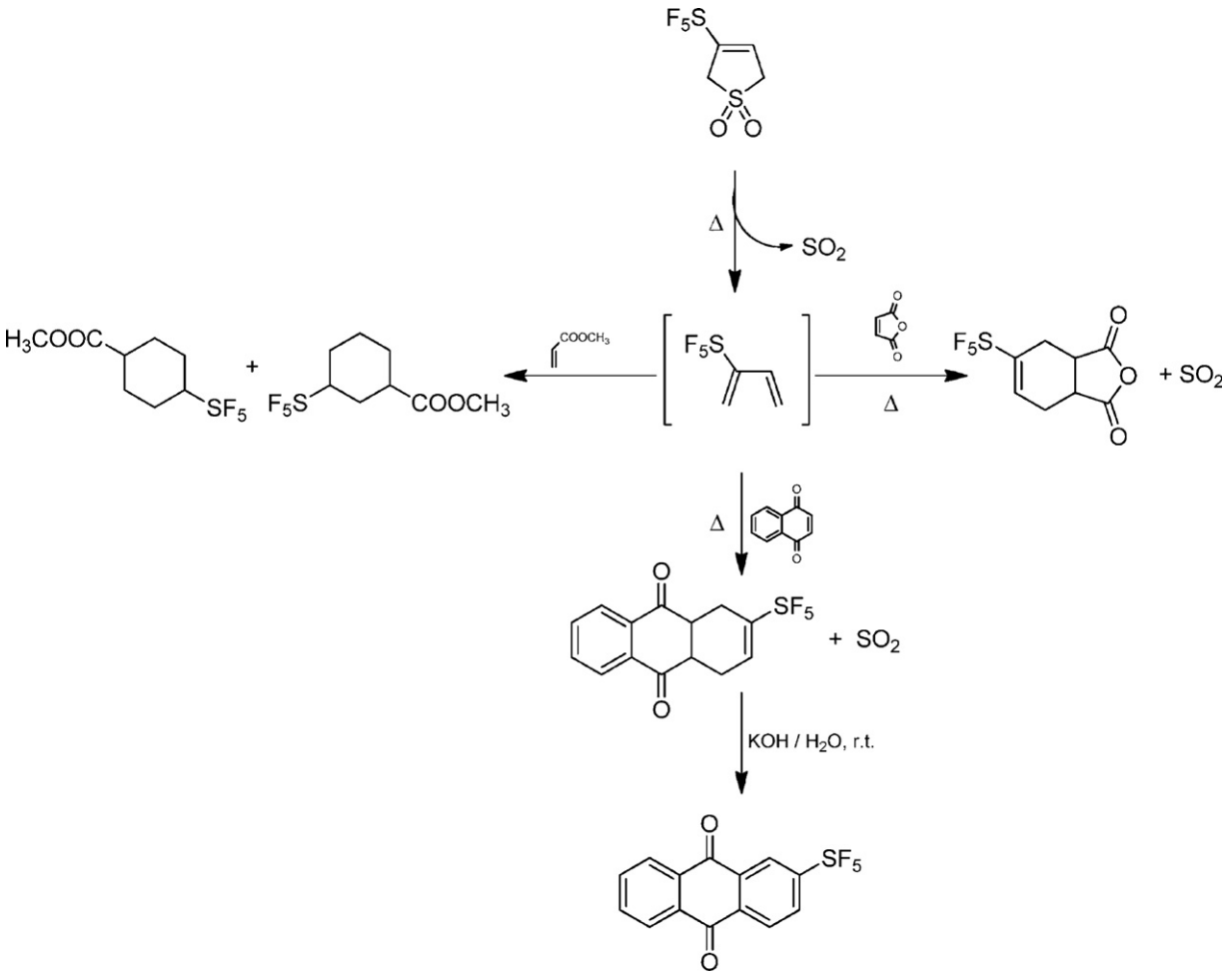
Scheme 70.



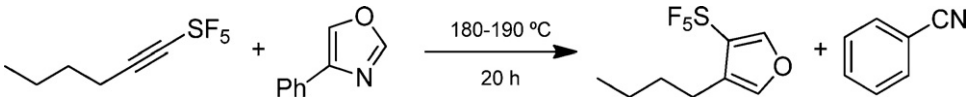
Scheme 73.



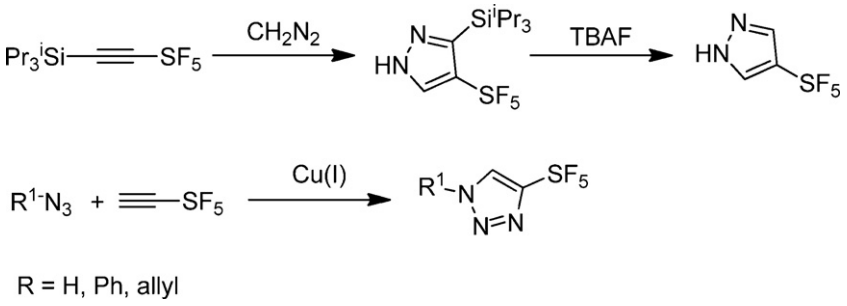
Scheme 74.



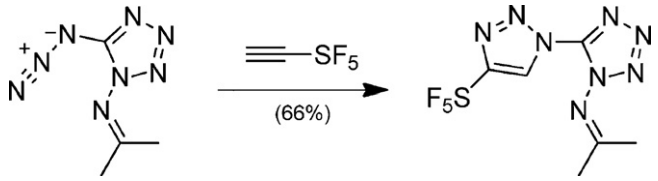
Scheme 75.



Scheme 76.



Scheme 77.



Scheme 78.

An SF_5-triazole bearing a tetrazolyl substituent was analogously synthesised by cycloaddition reaction of a tetrazolyl-azide with SF_5-acetylene (Scheme 78) [94].

A broad range of dense stable energetic materials incorporating multiple 1,2,3-triazine units was prepared by addition of azides and polyazides with SF_5-acetylene in generally good yields. The trifluoromethyl-analogues were also prepared and compared to the SF_5-counterparts, which invariably showed more negative enthalpies of formation and higher densities (Scheme 79) [95].

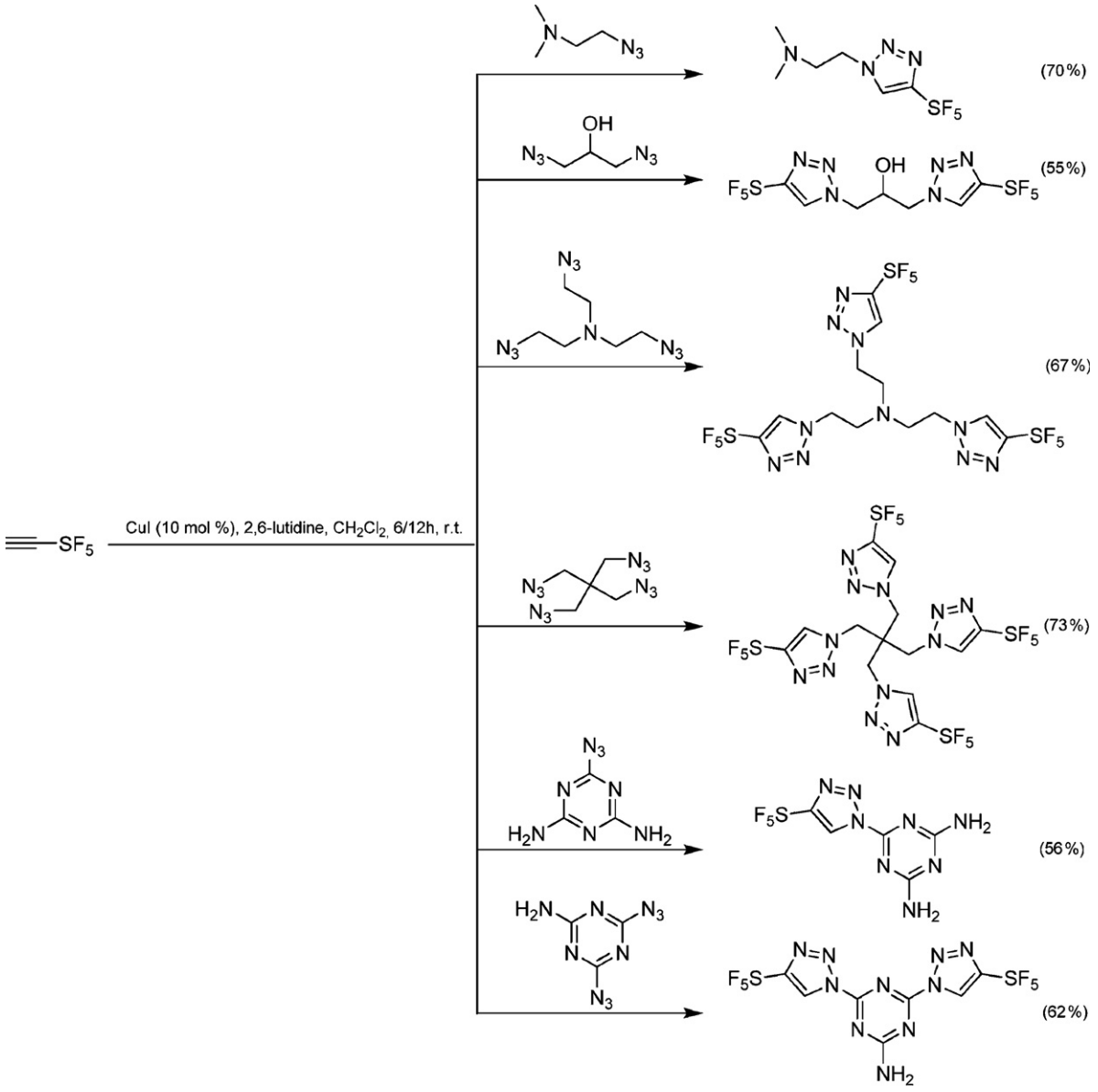
A series of SF_5-alkynes, generated by base-elimination from the corresponding β-chloro-alkenes (for another example see [46]), were reacted with an azomethine ylide thermally obtained from *N-tert*-butyl-carbomethoxy aziridine affording the corresponding dihydropyrroles which were then oxidised by DDQ 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].

SF_5-pyrroles were synthesised through a reaction sequence involving 1,3-dipolar cycloaddition of SF_5-alkynes with azomethine ylides, followed by DDQ-oxidation of the resulting pyrrolines. SF_5-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 SO_2Cl_2 (Scheme 81) [96].

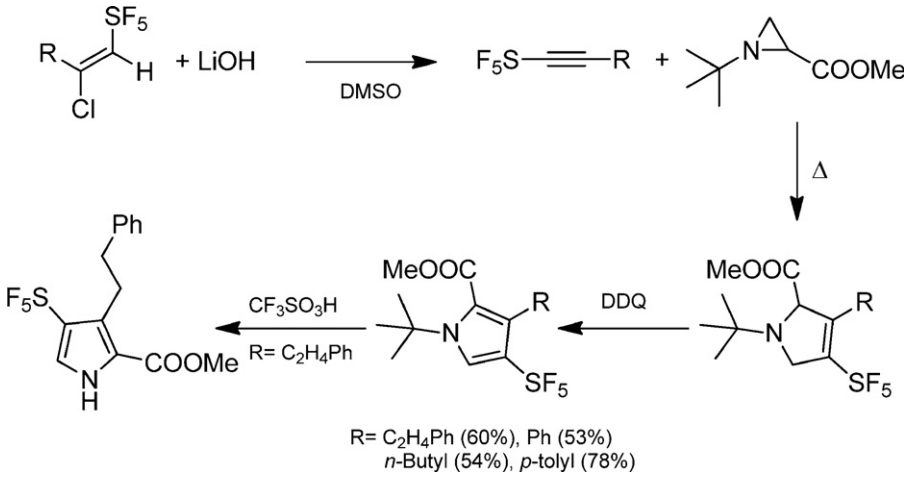
Table 10

Entry		X^1	R^1	R^2	R^3	X^2	Yield[a] (%)	*o*-CH(R^1)R^2/*p*-CH(R^1)R^2 ratio (relative to NO_2)
1	*p*-SF_5	Cl	H	$PhSO_2$			84	
2	*p*-SF_5	Cl	H	CO_2Et			76	
3	*p*-SF_5	Cl	H	CO_2Bu-*t*			91	
4	*p*-SF_5	Cl	Cl	CO_2Me			83	
5	*p*-SF_5	Cl	Me	CO_2Me			9	
6	*p*-SF_5	Cl	H	$P(O)(OEt)_2$			84	
7	*p*-SF_5	PhO	H	CN			74	
8	*p*-SF_5	Cl	Cl	Cl			74	
9	*p*-SF_5	Br	Br	Br			74	
10	*p*-SF_5	Cl	H	CO_2Et	$PhCH_2$	Br	59	
11	*p*-SF_5	PhO	H	CN	CH_3	I	57	
12	*m*-SF_5	Cl	H	$PhSO_2$			94 [c]	96:4
13	*m*-SF_5	Cl	H	CO_2Bu-*t*			94 [c]	94:6
14	*m*-SF_5	Cl	Cl	CO_2Me			79 [d]	98:2
15	*m*-SF_5	Cl	H	$P(O)(OEt)_2$			73 [c]	95:5
16	*m*-SF_5	PhO	H	CN			73[c]	85:15
17[b]	*m*-SF_5	Cl	Cl	Cl			91 [d]	96:4
18[b]	*m*-SF_5	Br	Br	Br			84 [d]	98:2
19	*m*-SF_5	Cl	H	$PhSO_2$	CH_2=$CHCH_2$	Br	84	
20	*m*-SF_5	Cl	Cl	CO_2Me	*n*-Bu	I	0	

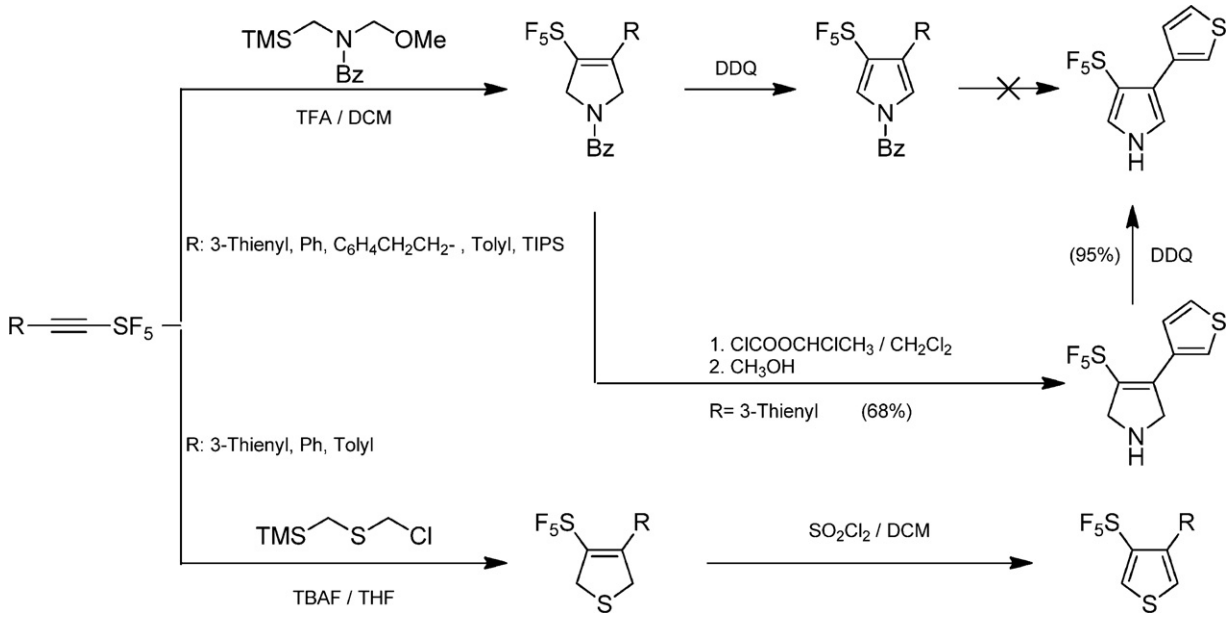
[a] Isolated yields.
[b] Determined by ^{19}F NMR of the crude product mixture.
[c] Relative to the sum of *o*-CH(R^1)R^2 and *p*-CH(R^1)R^2 products.
[d] Relative just to the *o*-CH(R^1)R^2 product.



Scheme 79.



Scheme 80.



Scheme 81.

Table 11

Entry		RM	Time (h)	Yield[a] (%)
1	*p*-SF_5	MeONa	1	83
2	*m*-SF_5		5	52
3	*p*-SF_5	*n*-PrONa	0.5	71
4	*m*-SF_5		1	41
5	*p*-SF_5	$PhCH_2OK$	1	96
6	*m*-SF_5		2.5	42
7	*p*-SF_5	PhOK	17	59
8	*m*-SF_5		16	Traces[b]
9	*p*-SF_5	MeSNa	16	64
10	*m*-SF_5		21	Traces[b]

[a] Isolated yields.
[b] Detected by GCMS analysis in trace amounts.

3.4. Reactivity of SF_5-aromatic compounds

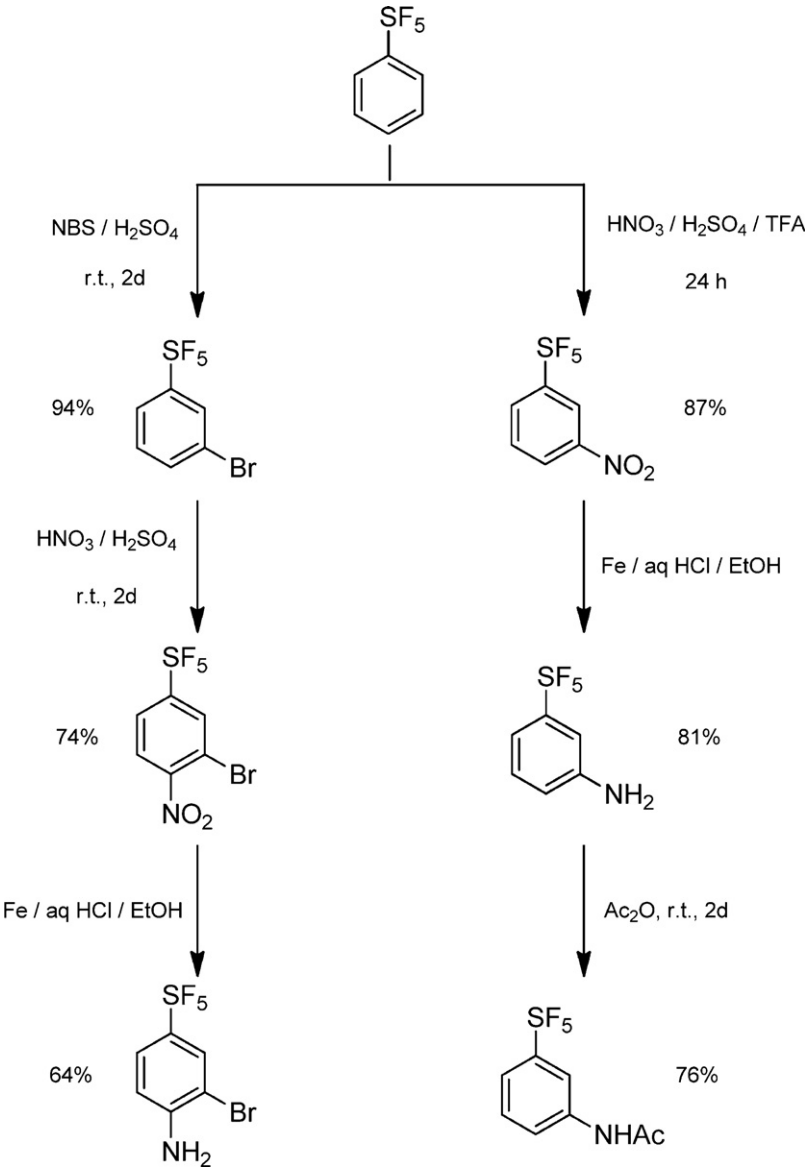
The reactivity of SF_5-substituted aromatic compounds is dominated by (1) the *meta*-directing, deactivating inductive effect that the electron-withdrawing SF_5 group displays in electrophilic substitution reactions, (2) the activating *ortho*- and *para*-effect displayed in nucleophilic substitution reactions. SF_5-nitrobenzene is a key building block for the synthesis of aromatic pentafluorosulphanyl compounds. The original synthesis from aromatic nitrothiols and disulphides (see Section 2.3) was recently improved by Dolbier et al. who successfully achieved the nitration of SF_5-benzene in high yields and *meta*-regiocontrol (Scheme 82) [70]. *Meta*-SF_5-nitrobenzene was then reduced with Fe/HCl to the aniline, which was *N*-acetylated too. *Meta*-bromination of SF_5-benzene was also performed in high yield and the resulting *m*-SF_5-bromobenzene was *para*-nitrated in good yields. Eventually, the aniline derivative was synthesised using the same NO_2-reduction conditions.Recently, a synthesis of 3,5-dinitro-SF_5-benzene was reported in the patent literature [97]. The method relies on the dinitration of *para*-SF_5-toluene, followed by oxidation of the methyl group to carboxylic function and finally thermal decarboxylation (Scheme 83).

A number of aromatic SF_5-compounds were synthesised starting from the *meta*- and *para*-nitro SF_5-precursors, which were initially reduced to the corresponding anilines, and then submitted to a range of different reactions including Sandmayer iodination followed by Sonogashira alkynylation, Suzuki arylation and Heck olefination (Scheme 84) [66]. Interestingly, the authors demonstrated that 4-SF_5-aniline and 4-CF_3-aniline show similar stability towards acid hydrolysis, namely treatment with concentrated sulphuric acid at 160 °C leads to hydrolysis of both CF_3 and SF_5 groups. However under basic conditions (2 N NaOH) the CF_3 group was readily hydrolysed to CO_2H whereas the SF_5 group was perfectly stable. The authors rationalised this behaviour on the basis of electronic stabilisation of the planar difluoromethylene

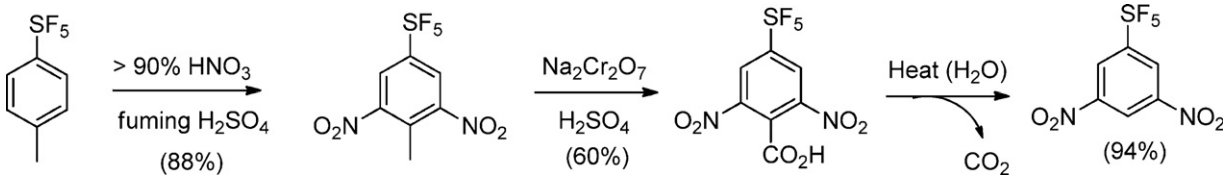
Table 12

	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]	[107]
Volume	49.2 cm^3/mol (calculated in liquids)	20.49 cm^3/mol (van der Waals volume)	[83] (SF_5); [111] (CF_3) and references therein

[a] Referred to the *m*-position of the substituent.
[b] Referred to the *p*-position of the substituent.
[c] Determination of acidity constant of Anilinium ions from optical density measurement.



Scheme 82.



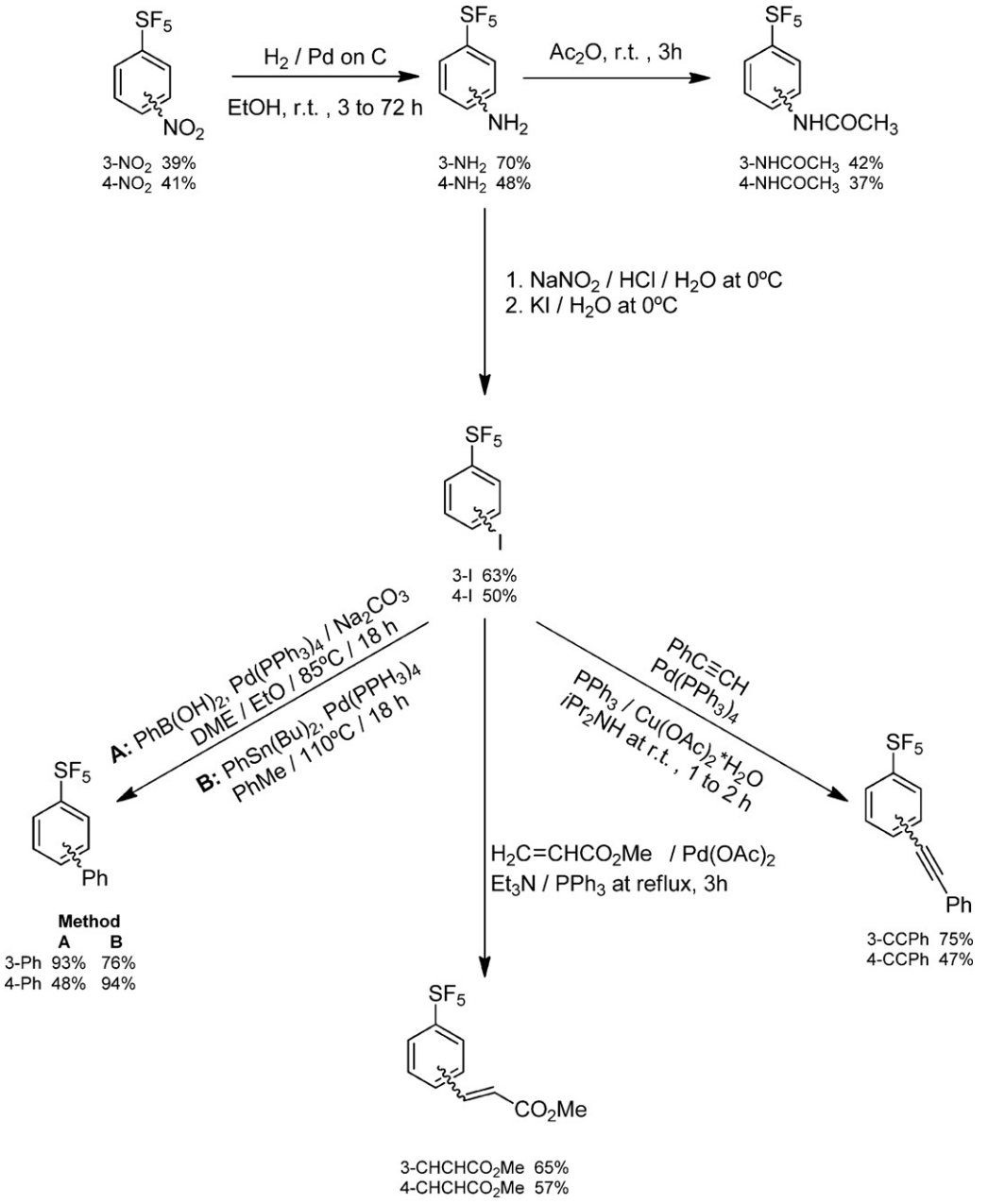
Scheme 83.

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 SF_5 group, because the sulphur atom has an octahedral geometry whereas the carbon atom in the $-CF_3$ is tetrahedral.

A small library of *ortho*-substituted SF_5-compounds was obtained starting from 2-fluoro-5-nitro-SF_5-benzene which is highly activated towards nucleophilic aromatic substitution and was therefore submitted to a range of reactions with different nitrogen-, oxygen- and sulphur-centred nucleophiles such as piperidine, potassium ethylate, ammonia, sodium thiolate affording the corresponding fluoride-substitution products (Scheme 85) [68].

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-pentafluorosulphanyl 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].

4-Chloro-3,5-dinitro SF_5-benzene was submitted as well to nucleophilic substitution reaction with secondary amines affording good yields of the resulting tertiary amines (Scheme 87) [65].



Scheme 84.

An interesting observation on the reactivity difference between CF_3 and SF_5-compounds came from the reaction of the two 4-chloro-3,5-dinitrobenzene derivatives with potassium ethyl xanthate. In the CF_3-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 SF_5-compound underwent only loss of COS affording the monomeric ethylthio derivative (Scheme 88) [65].

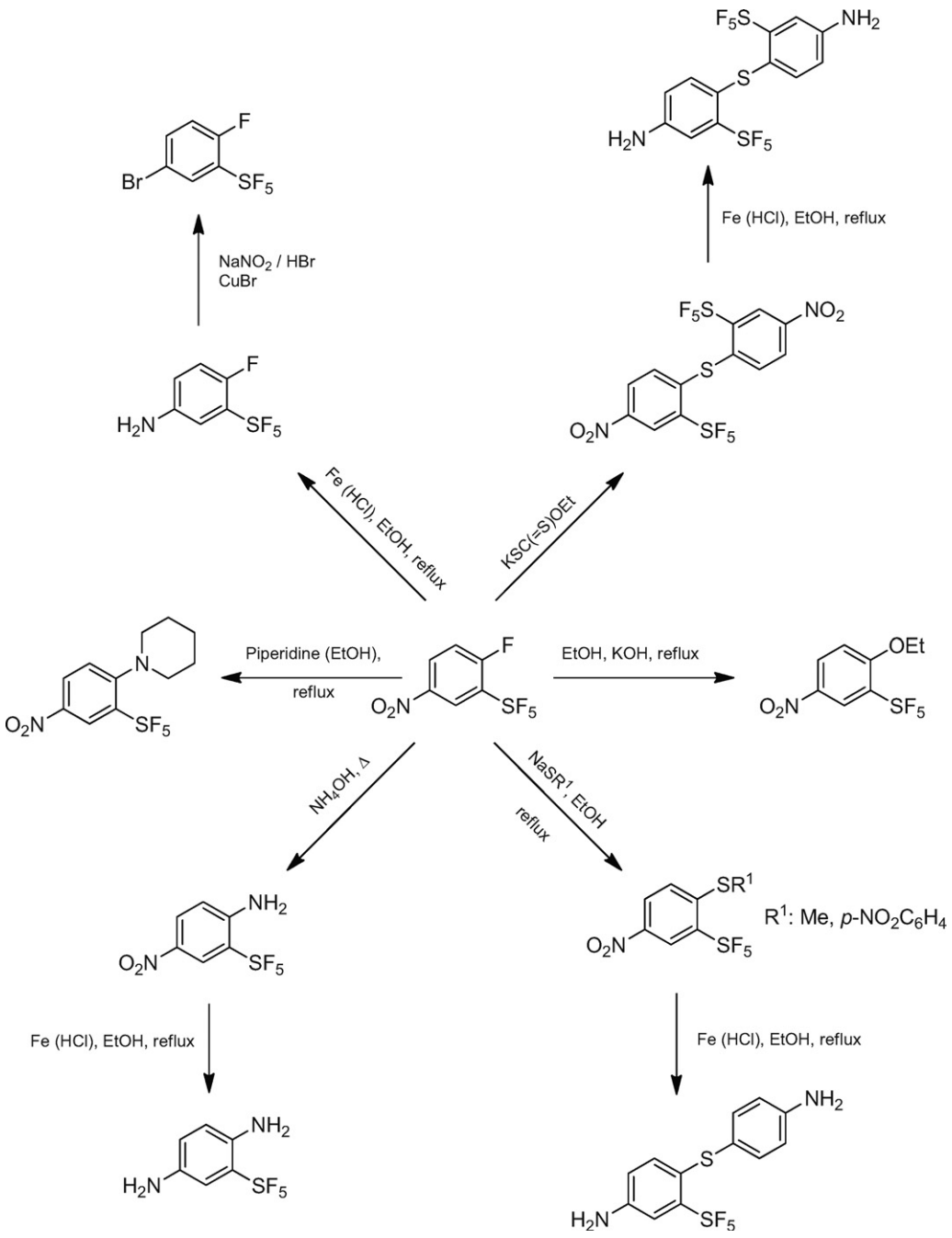
Reaction of the same 4-chloro-3,5-dinitro-SF_5-benzene with another S-centred nucleophile, i.e. ethyl thiolacetate, provided the expected nucleophilic substitution product which was subjected to intramolecular condensation affording a benzothiazole *N*-oxide (Scheme 89) [65].

A wide range of SF_5-perfluoroethyl-benzene derivatives were synthesised starting from SF_5-perfluoroethyl-benzene which was *meta*-nitrated, reduced to the corresponding aniline, and transformed into the key diazonium salt intermediate. Sandmayer-type chemistry was then used to functionalise the scaffold with a number of different functionalities including halogens, hydroxyl and acyloxy functions, SO_2Cl, vinyl and azide groups (Scheme 90) [98,99]. The corresponding sulphonic acids were also obtained by treatment of the same substrate with chlorosulphonic acid [100].

SF_5-aryl compounds for liquid crystals applications were synthesised by Suzuki cross-coupling with a *para*-bromo-SF_5-benzene derivative prepared from the parent aniline via Sandmayer bromination. An ether derivative was obtained by aromatic nucleophilic substitution, activated by the SF_5-group, with an alkoxide (Scheme 91) [69].

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

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].



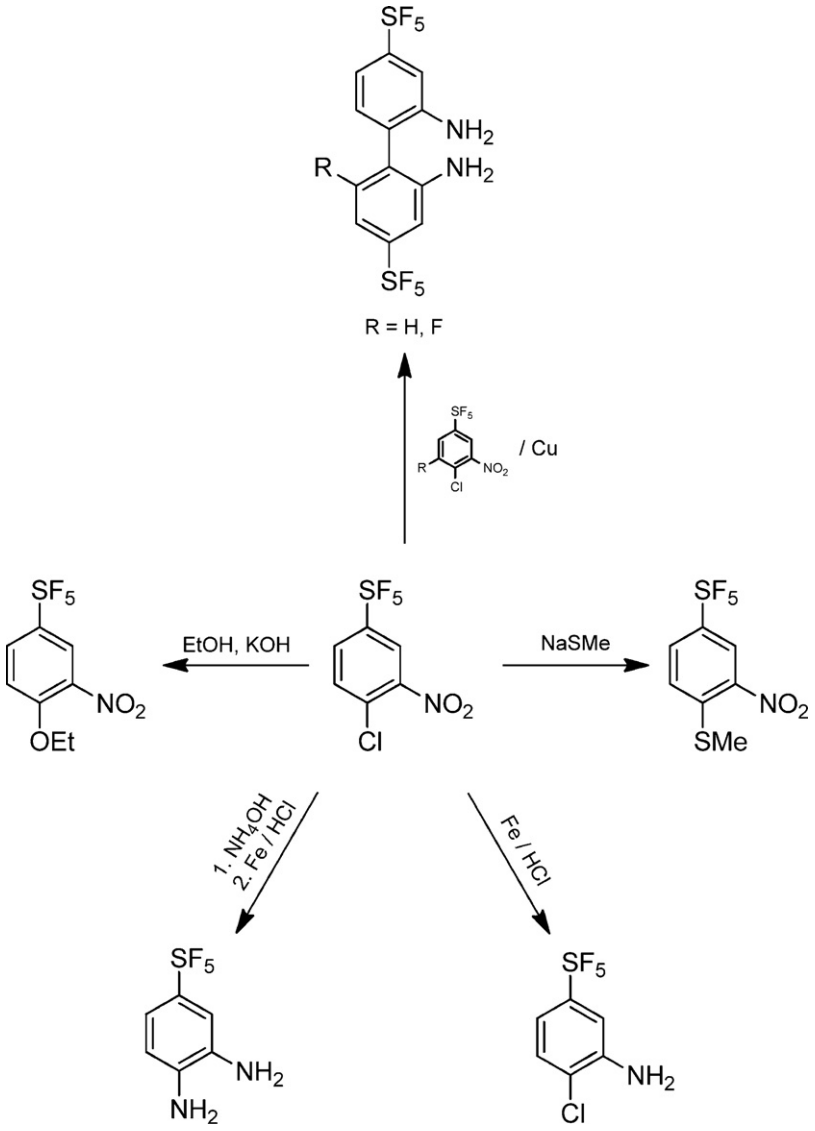
Scheme 85.

An interesting example of vicarious nucleophilic substitution reaction involving SF_5-nitrobenzenes and activated halides was exploited to synthesise a library of functionalised SF_5-nitroaromatic derivatives. Treatment of α-chloro or -bromo acetates, sulphones, 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*-SF_5-nitrobenzene was regioselective producing exclusive *meta*-SF_5 reaction, whereas the *meta*-regioisomer produced a mixture of two regioisomers with large predominance of the *para*-SF_5 products (Scheme 94 and Table 10) [103].

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, stabilised by delocalisation 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 SF_5-group determines the regioselectivity of the process.

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].

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 86.

In another example, SF_5-nitrobenzenes were used as building blocks taking advantage of the good leaving-group nature of the nitro group activated by the pentafluorosulphanyl moiety. As expected, treatment of the more activated *para*-SF_5-nitrobenzene with a wide range of nucleophiles occurred under milder conditions and afforded higher yields of the corresponding substitution products than the *meta*-SF_5-isomers (Scheme 98 and Table 11) [106].

4. Biological activity of SF_5-substituted compounds

The SF_5 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 SF_5-group slightly prevailing over the CF_3 in all of these aspects. Some quantitative parameters for the two groups are summarised in Table 12.

Importantly, both the SF_5 and CF_3 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 CF_3-group is a bioisosteric equivalent of an ethyl group [112], the corresponding features for the SF_5-group have not been investigated in detail yet. However, it is apparent that the volume of the SF_5 group is slightly less than that of a *tert*-butyl group, but remarkably larger than the CF_3 volume (see also Table 12) [110]. In spite of these considerations, the SF_5 group has been shown to behave often like a CF_3 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 SF_5 group will present a pyramidal electron density, whereas the CF_3 will display an inverted cone of density [113]. For all of the reasons above it is reasonable to predict that future research will show that, besides some similarities, the SF_5 and the CF_3 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 $-CF_3$- and $-SF_5$-aniline-containing pyrazoles the SF_5 compounds consistently had lower K_i for the CB_1 receptor than the CF_3-counterparts in in vitro assays (Fig. 1). This could be very roughly explained with a "better fit" of the SF_5 group into the corresponding pocket of the CB_1 receptor relative to the CF_3 group, which confirms that the two groups are not "biologically" equivalent. The most potent compounds in the series displayed

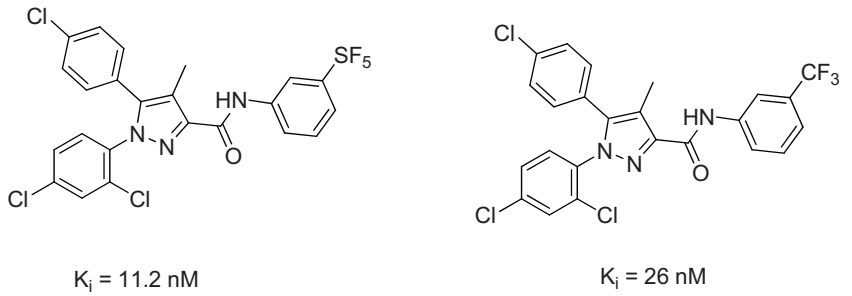
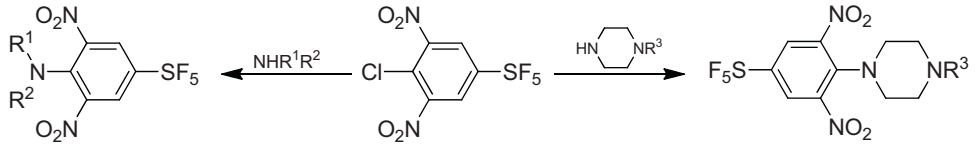
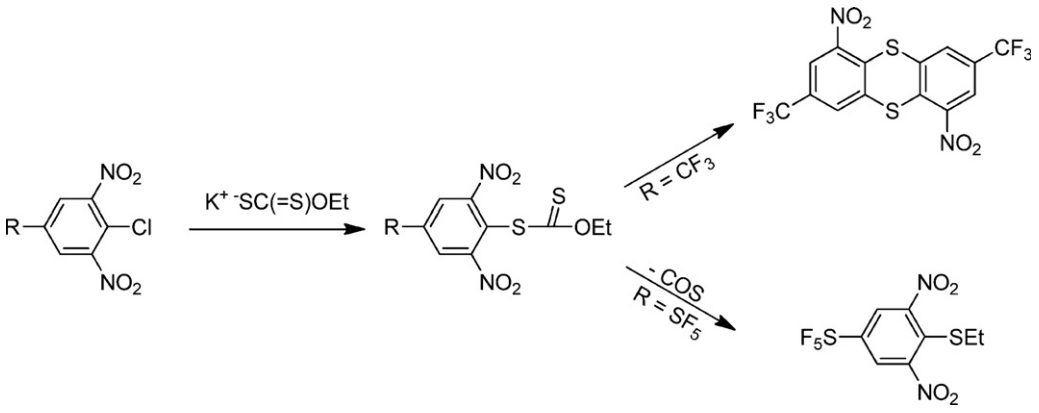


Fig. 1.

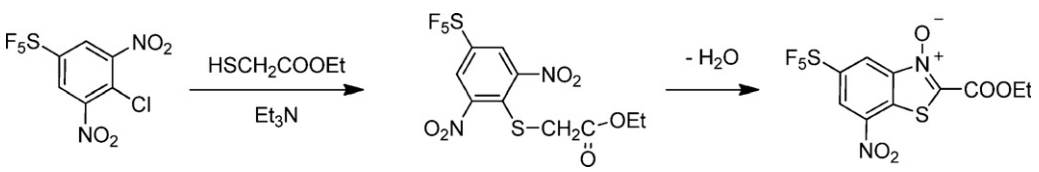


R^1	R^2	R^3
C_3H_7	C_3H_7	
C_3H_7	$CH_2C_3H_5$	
C_2H_5	*n*-C_4H_9	
C_2H_5	$CH_2C(CH_3)=CH_2$	
C_3H_7	C_4H_7O	
		H
		CH_3

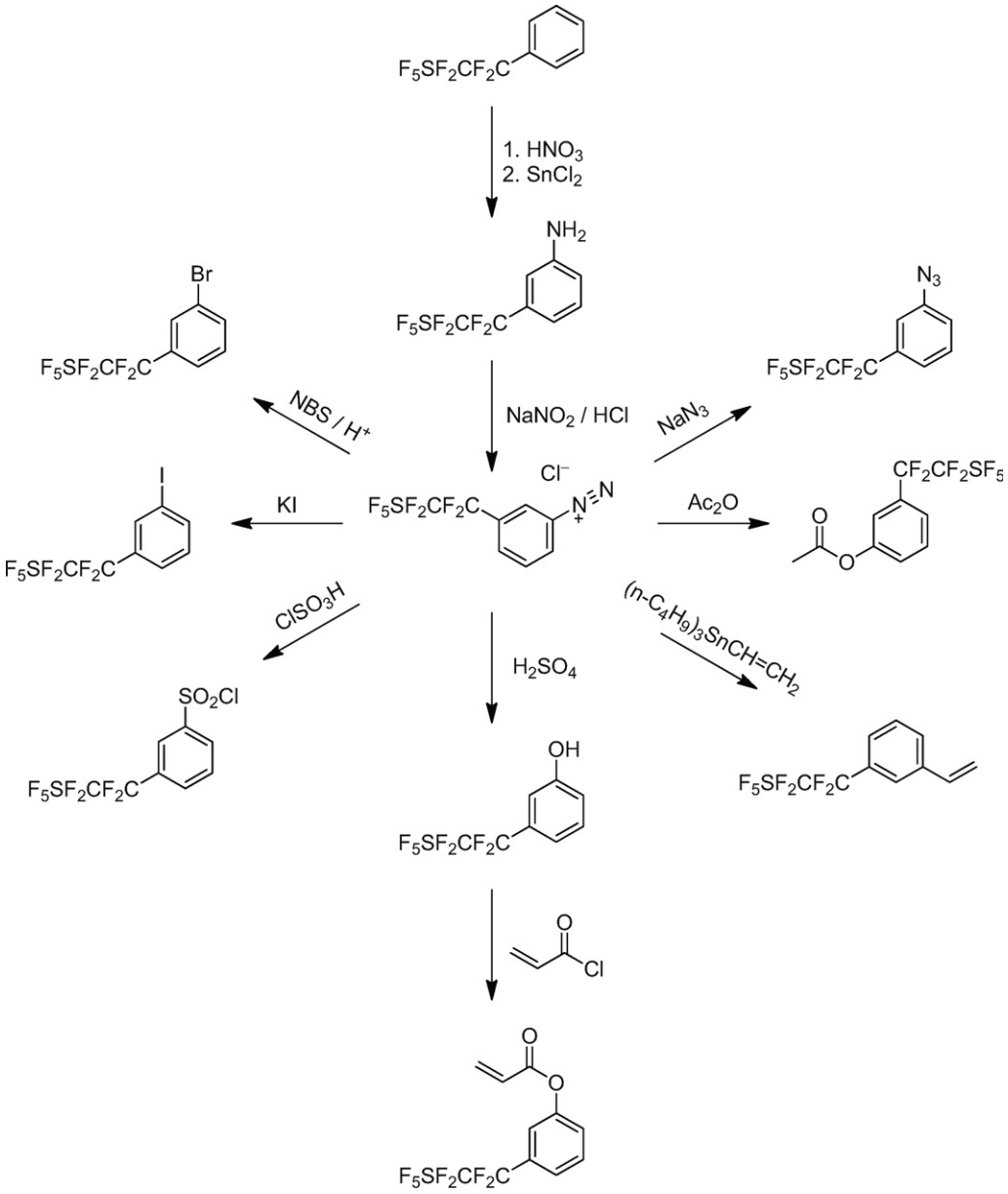
Scheme 87.



Scheme 88.



Scheme 89.



Scheme 90.

nanomolar K_i values for CB_1, and are currently tested for their pharmacological properties [114].

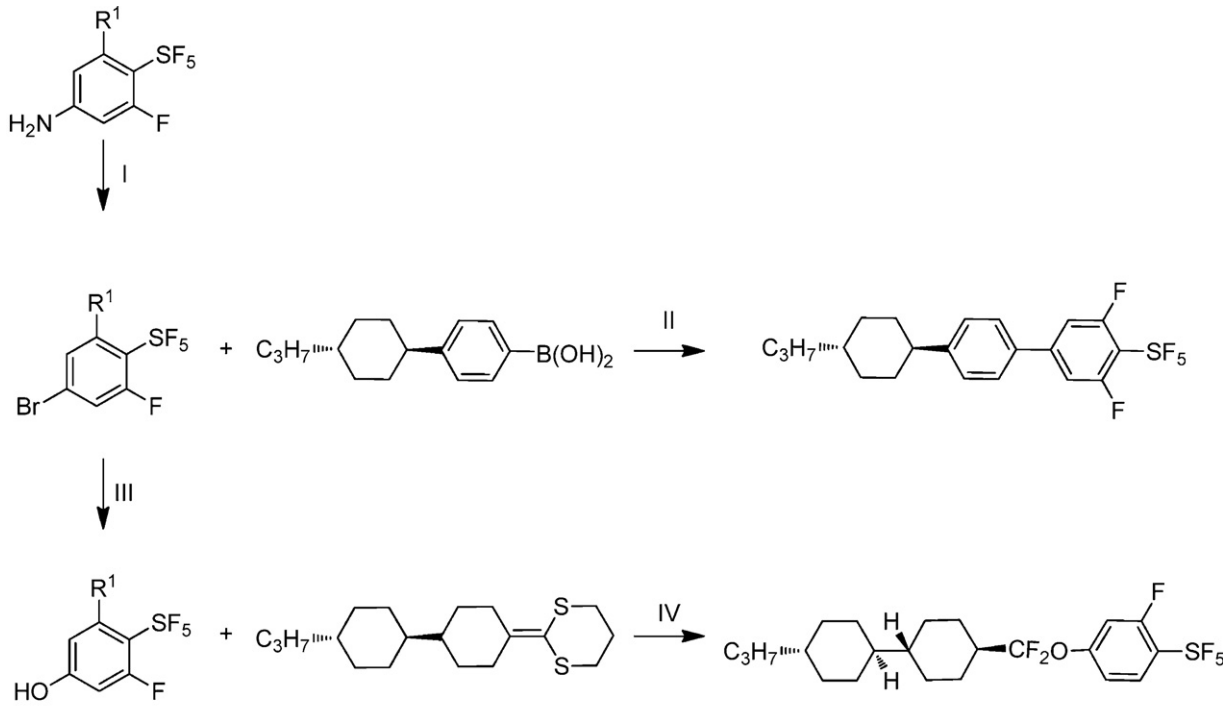
These findings are in line with previous work that showed that SF_5-analogues of the popular serotonin uptake inhibitors fluoxetine (Prozac), fenfluramine and norfenfluramine, which incorporate a CF_3-group, could lead to enhanced selectivity and, in the case of fluoxetine, SF_5-substitution enhanced potency vs. some of the 5-HT receptors. The synthesis of SF_5-fluoxetine started from 4-SF_5-nitrobenzene, which was submitted to the usual conversion of the NO_2 group into Br via reduction to NH_2. Nitration occurred in *meta* to the SF_5 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) [113].

The SF_5-fenfluramine and norfenfluramine were prepared by *meta*-bromination of pentafluorosulphanyl-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).

A key intermediate in the synthesis of SF_5-fluoxetine was also used for the preparation of an SF_5-analogue of the herbicide trifluralin (Scheme 101). Remarkably, the SF_5-trifluralin demonstrated 5-fold greater herbicidal potency relative to the parent CF_3-compound. This was rationalised according to a favourable interaction of the SF_5 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 CF_3 [108].

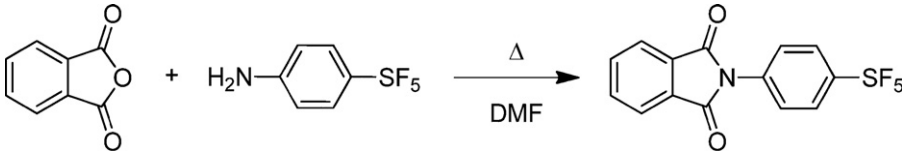
Among the first reports of biological activity of SF_5-compounds one should also mention the use of SF_5–CF=CF_2 and SF_5–CFI–CF_3 as effective fumigants, and the insecticidal properties of the non-fluorinated versions of these compounds [10].

Wipf et al. reported the synthesis of 6- and 7-SF_5 analogues of Mefloquine, which is an antimalarial drug used against chloroquine-resistant *Plasmodium falciparum* strains. Mefloquine incorporates two CF_3 groups, one of them in position 8 of the quinoline heterocycle. However the authors initially could not access to the exact 8-SF_5 mefloquine analogue because the necessary starting material, *ortho*-SF_5-nitrobenzene, was not

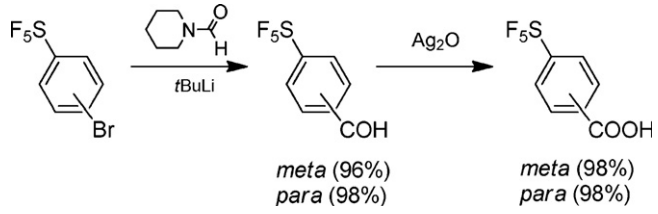


Key: Synthesis of the liquid crystals; reagents and conditions: I) 1. $NaNO_2$,HBr, 0-5 °C; 2. CuBr, 85 °C; II) $NaBO_2 \cdot 8H_2O$, H_2O, THF, cat. $Pd(PPh_3)_4$, reflux, 18 h (16 %); III) 1. *t*-BuLi, Et_2O, -70 °C; 2 . $B(OMe)_3$; 3. HOAc, H_2SO_4, 30% H_2O_2, -20 to 35 °C (crude product used for next step); IV) 1. CF_3SO_3H, CH_2Cl_2, 0 °C (5 min) to r.t. (30 min) to -70 °C; 2 . NEt_3, CH_2Cl_2, -70 °C; 3. $NEt_3 \cdot 3HF$,-70 °C; 4. Br_2, CH_2Cl_2, -70 to -10 °C (7 %)

Scheme 91.



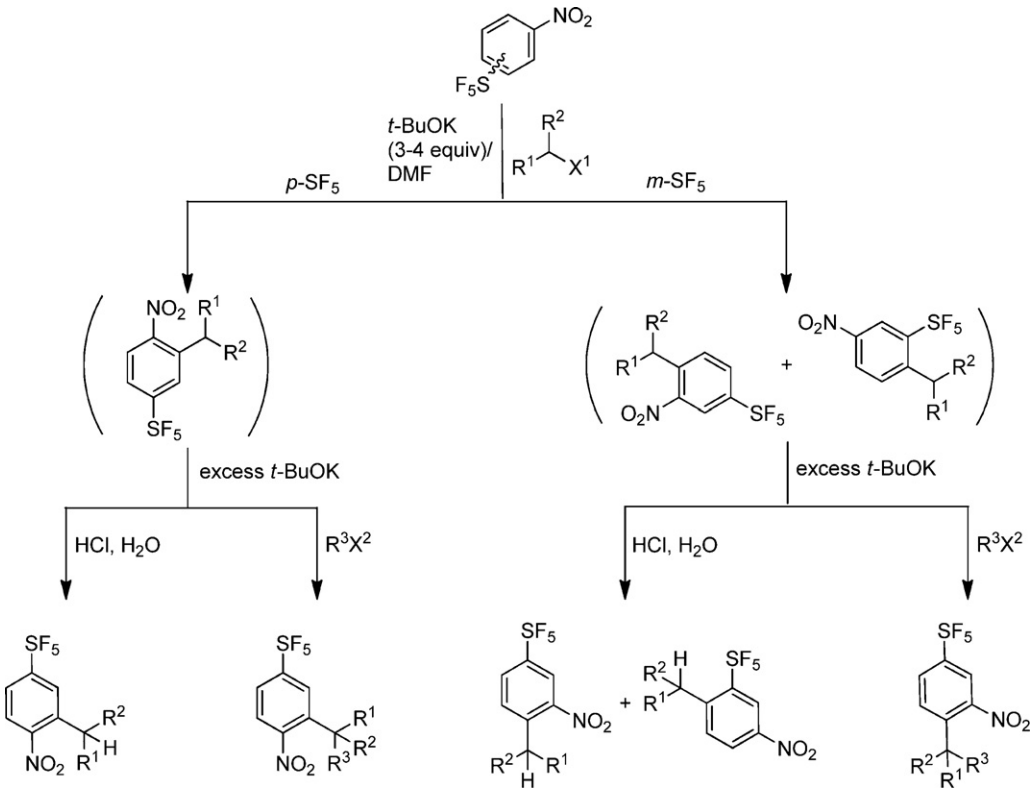
Scheme 92.



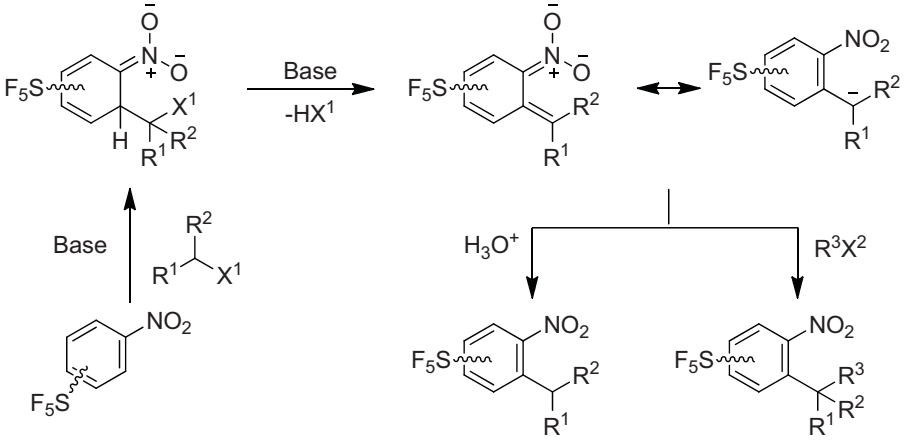
Scheme 93.

available (Scheme 102). Therefore, *meta*- and *para*-SF_5-anilines were condensed with trifluoroacetoacetate and the resulting 4-hydroxy quinoline was dehydroxychlorinated. 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 PtO_2-catalysed hydrogenation to the target SF_5-mefloquine analogues. The two molecules were tested on different strains of the malaria parasite showing improved activity (IC_{50}s were as low as 3.3 ng/mL for both isomers) and selectivity towards a mammalian cell line relative to the parent CF_3-substituted mefloquine [110].

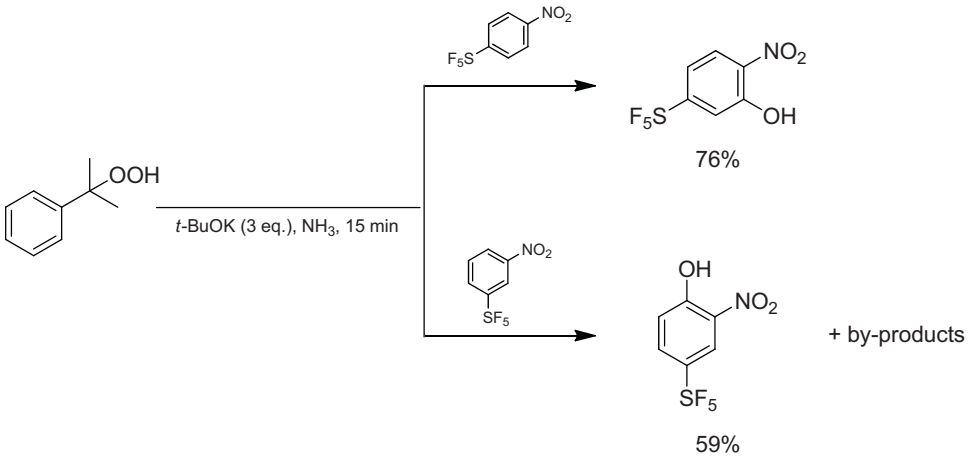
The exact 8-SF_5-mefloquine analogue was published by the same group one year later, when *ortho*-SF_5-aniline became available. Commercially available 3-SF_5-phenol was submitted to nitration but unfortunately the strong *ortho*-directing effect exerted by the hydroxyl group afforded poor *para*-regioselectivity (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



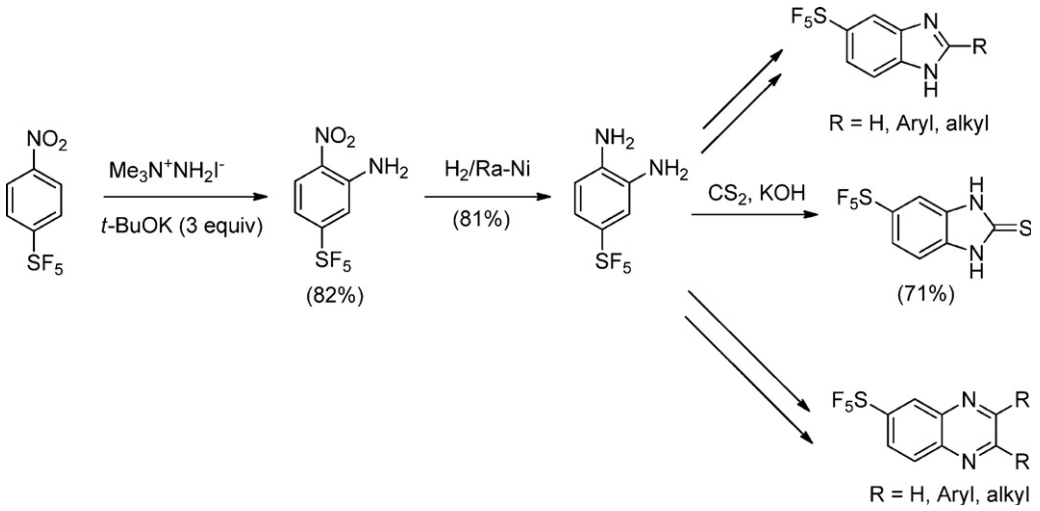
Scheme 94.



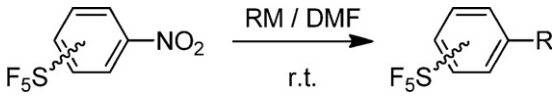
Scheme 95.



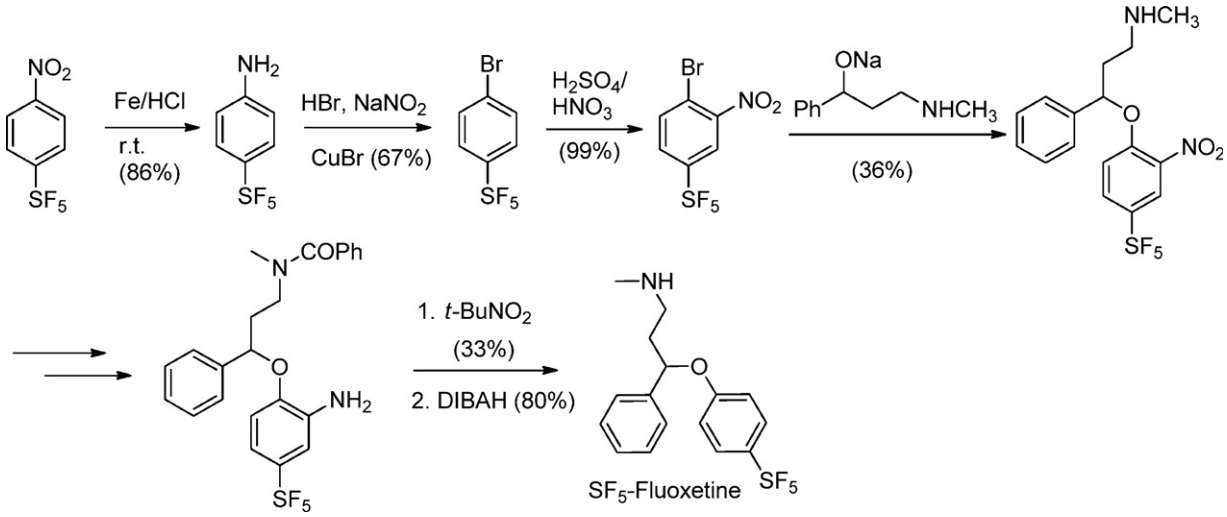
Scheme 96.



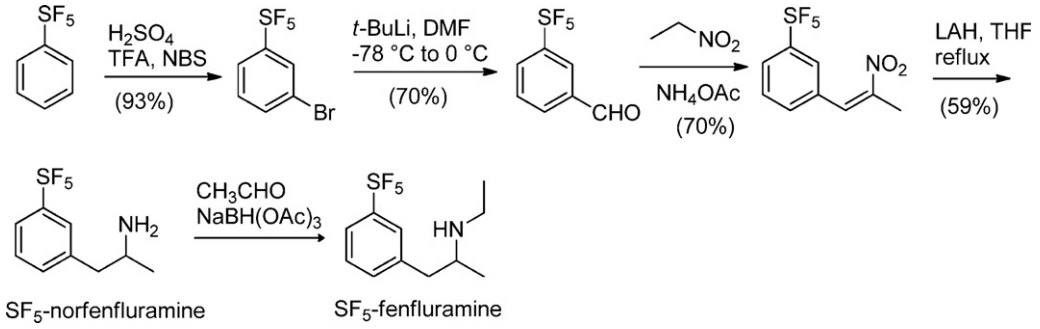
Scheme 97.



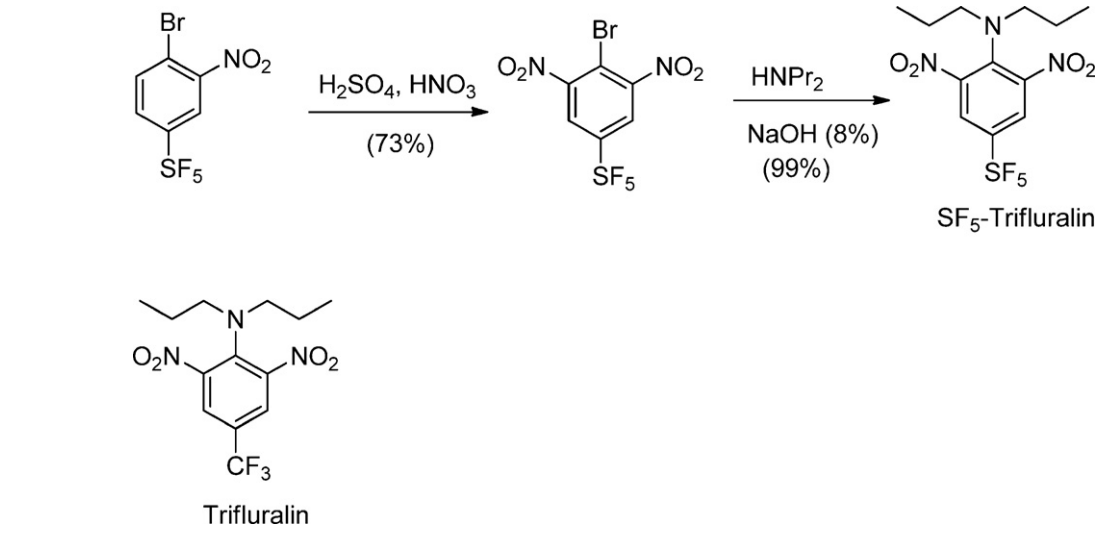
Scheme 98.



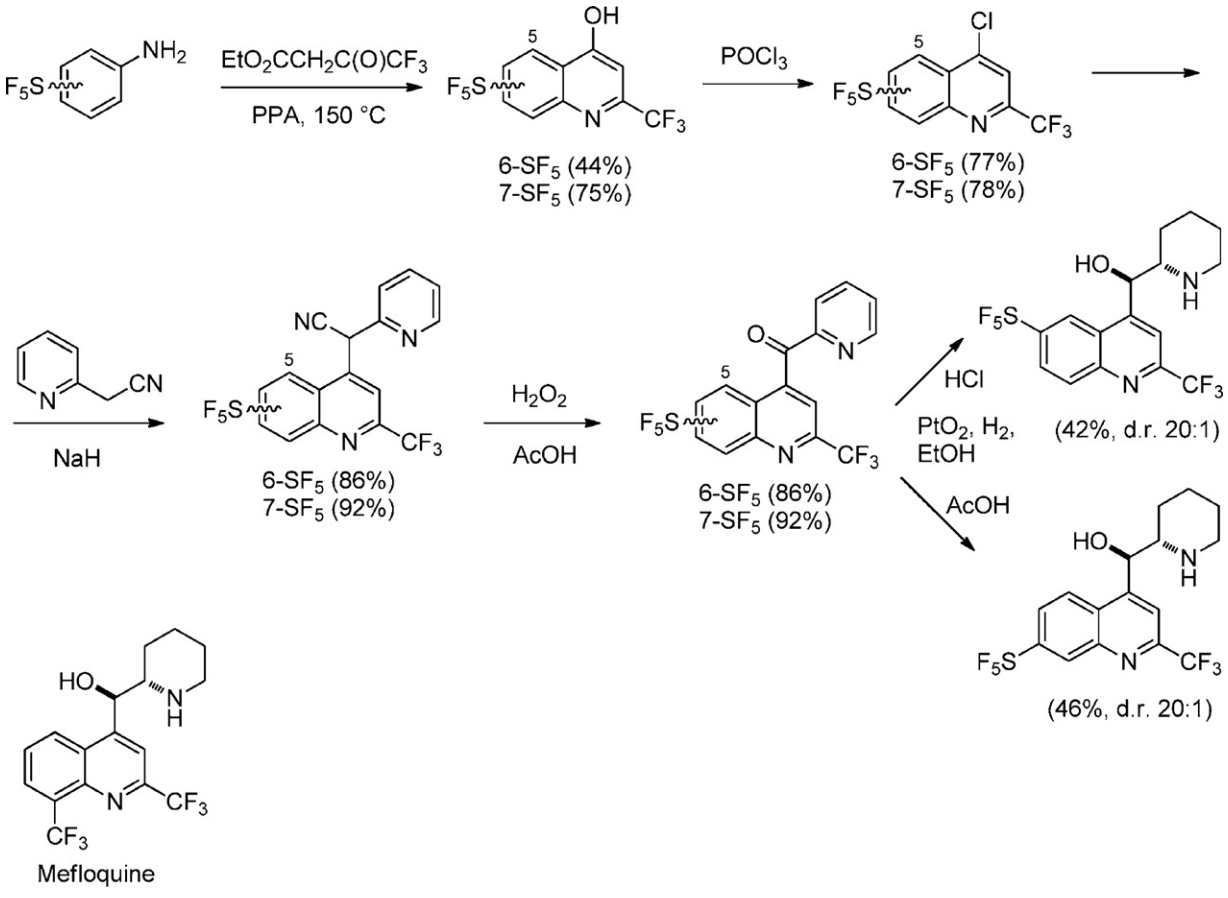
Scheme 99.



Scheme 100.



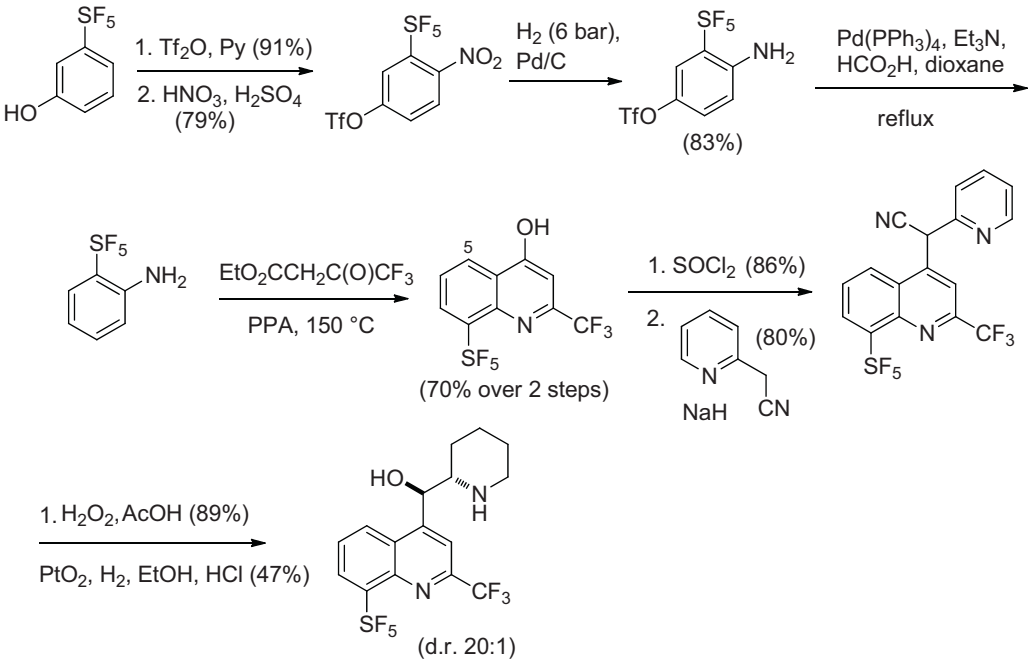
Scheme 101.



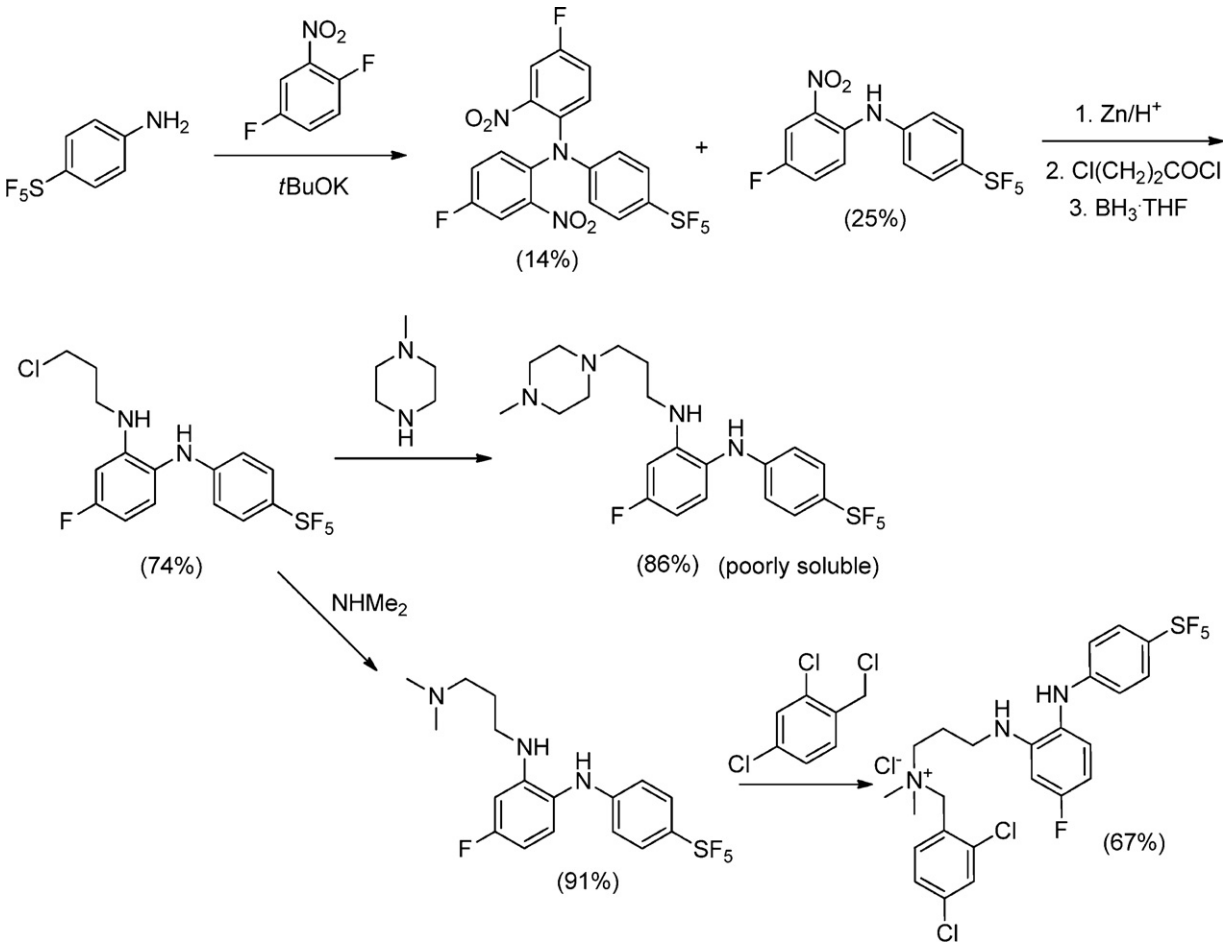
Scheme 102.

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*-SF_5-aniline in hand the synthesis of 8-SF_5-mefloquine was performed along the lines previously followed for the 6- and 7-SF_5 analogues [115]. This compound showed the best balance activity/permeability through blood-brain barrier among the different SF_5-mefloquines. Furthermore, administrated in mice, 8-SF_5-mefloquine showed a higher activity than mefloquine itself, with a longer half-life (68 h vs. 23 h) [116].

Diederich et al. recently described a rationally-designed SF_5-substituted diarylamine as a potential antiprotozoal compound. The molecule was obtained from *para*-SF_5-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



Scheme 103.



Scheme 104.

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

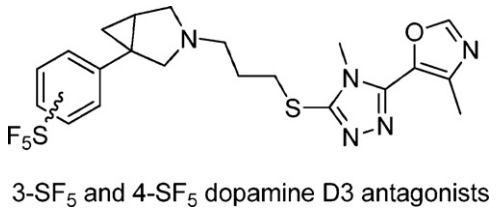


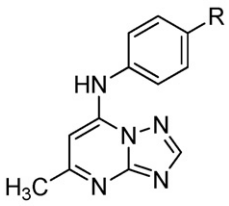
Fig. 2.

amine was reacted further with 2,4-dichlorobenzyl chloride affording a quaternary ammonium salt. This compound showed interesting inhibitory properties with an IC_{50} = 1.5 μM, similar to that displayed by the exact analogues having CF_3- and *tert*-butyl groups replacing the SF_5. Furthermore, the SF_5-derivative showed the lowest cytotoxicity among all the compounds tested, showing also good membrane permeability. Interestingly, switching from CF_3 to SF_5 the mode of inhibition changed from purely competitive to competitive-uncompetitive, respectively. Molecular modelling simulations indicated that the SF_5-group can effectively occupy the hydrophobic "mepacrine binding site" of the receptor [117].

A series of SF_5- and CF_3-substituted selective dopamine D_3 antagonists were recently compared both in terms of in vitro and in vivo properties (Fig. 2). No specific information on the synthesis of these SF_5-compounds was provided (the CF_3-analogues were synthesised in [118]). In general, the two series of compounds showed rather similar biological properties in vitro, as well as in vivo [119].

Recently, aryl amine-based triazolopyrimidine derivatives incorporating both a CF_3 and an SF_5 group were reported as *P. falciparum* dihydroorotate dehydrogenase (*Pf*DHODH) inhibitors, showing antimalarial activity in mice [120]. The substitution of the 4-CF_3 group with a 4-SF_5 resulted in a compound with 2–3-fold better activity against *Pf*DHODH, possibly due to the increase in hydrophobicity with SF_5 relative to CF_3.The SF_5-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 ED_{50} of 17 mg/kg and better efficacy than the CF_3-compound (Fig. 3).

The compounds above were subsequently optimised and a number of novel derivatives having the structure below where synthesised and tested for their ability to inhibit *P. falciparum* and *P. berghei* DHODH [121]. The compounds having R = CF_2CH_3 were found to display the highest inhibitory potency and the DHODH/CF_3-triazolopyrimidine complex was successfully crystallised confirming that the CF_3 group (and therefore the SF_5 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 SF_5-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 SF_5-triazolopyrimidine appears to be a very promising antimalarial drug candidate (Fig. 4).



DHODH = dihydroorotate dehydrogenase

Pf = P. falciparum
Pb = P. berghei
h = Human

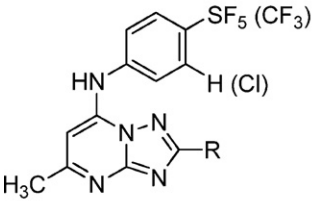
R = CF_3

IC_{50}(μM)			EC_{50} (μM)
*Pf*DHODH	*Pb*DHODH	*h*DHODH	*Pf* 3D7 cells
0.28	0.38	>100	0.34

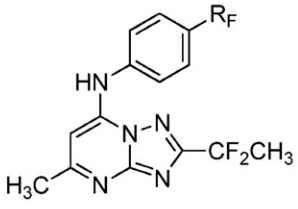
R = SF_5

IC_{50}(μM)			EC_{50} (μM)
*Pf*DHODH	*Pb*DHODH	*h*DHODH	*Pf* 3D7 cells
0.13	0.28	>100	1.3,

Fig. 3.



R = H, Et, *i*-Pr, *i*-Bu, *s*-Bu, *t*-Bu, *cyclo*-Pr, CH_2-*cyclo*-Pr, CF_2CH_3, $CF_2CH_2CH_3$, CF_3, MOM, $(CH_2)_2OCH_3$



DHODH = dihydroorotate dehydrogenase

Pf = P. falciparum
Pb = P. berghei
h = Human

R_F = CF_3

IC_{50}(μM)			EC_{50} (μM)
*Pf*DHODH	*Pb*DHODH	*h*DHODH	*Pf* 3D7 cells
0.038	2.4	>100	0.0062

R_F = SF_5

IC_{50}(μM)			EC_{50} (μM)
*Pf*DHODH	*Pb*DHODH	*h*DHODH	*Pf* 3D7 cells
0.033	2.5	>100	0.0078

Fig. 4.

5. Conclusions

As demonstrated by the body of work reviewed in this article, pentafluorosulphanyl 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 SF_5-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.

Note-added-in-proof

A review on the applications of SF5-compounds in life science research was published after acceptance of this manuscript [122].

Acknowledgements

We thank the European Commission for financial support (Industry Academia Partnerships and Pathways project "PET BRAIN", Contract No 251482). S.A. thanks the Northern Research Partnership (www.northscotland-research.ac.uk/) and Pharmaness (www.pharmaness.it) for co-funding a PhD studentship.

References

[1] R. Verma, R. Kirchmeier, J. Shreeve, Advances in Inorganic Chemistry, Elsevier, 1994, pp. 125–169.
[2] D. Lentz, K. Seppelt, in: K.-Y. Akiba (Ed.), Chemistry of Hypervalent Compounds, Wiley-VCH, New York, 1999, p. 295.
[3] P. Kirsch, Modern Fluoroorganic Chemistry Synthesis, Reactivity, Applications, Wiley-VCH, Weinheim, 2004.
[4] H.L. Roberts, Quarterly Reviews of the Chemical Society 15 (1961) 40–47.
[5] J. Mohtasham, R.J. Terjeson, G.L. Gard, R.A. Scott, K.V. Madappat, J.S. Thrasher, J. Mohtasham, R.J. Terjeson, G.L. Gard, R.A. Scott, K.V. Madappat, J.S. Thrasher, Inorganic Syntheses, John Wiley & Sons, Inc., New York, 1992, pp. 33–38.
[6] R. Winter, G.L. Gard, in: J.S. Thrasher, S.H. Strauss (Eds.), Inorganic Fluorine Chemistry, American Chemical Society, Washington, DC, 1994, pp. 128–147.
[7] P. Kirsch, M. Bremer, Angewandte Chemie International Edition in English 39 (2000) 4216–4235.
[8] W.R. Dolbier, Chimica oggi – Chemistry Today 21 (2003) 66–69.
[9] D.A. Jackson, "Breaking Down the Substituent of the Future": Environmental Properties of Pentafluorosulfanyl Compounds, University of Toronto, 2008.
[10] R.W. Winter, R.A. Dodean, G.L. Gard, in: V.A. Soloshonok (Ed.), Fluorine-Containing Synthons, American Chemical Society, Washington, DC, 2005, pp. 87–118.
[11] J.W. George, F.A. Cotton, Proceedings of the Chemical Society (1959) 317–318.
[12] B. Cohen, A.G. MacDiarmid, Inorganic Chemistry 4 (1965) 1782–1785.
[13] H.L. Roberts, Journal of the Chemical Society (1962) 3183–3185.
[14] J. Hutchinson, Journal of Fluorine Chemistry 3 (1974) 429–432.
[15] R.J. Terjeson, J. Renn, R. Winter, G.L. Gard, Journal of Fluorine Chemistry 82 (1997) 73–78.
[16] R. Winter, R.J. Terjeson, G.L. Gard, Journal of Fluorine Chemistry 89 (1998) 105–106.
[17] U. Jonethal, R. Kuschel, K. Seppelt, Journal of Fluorine Chemistry 88 (1998) 3–4.
[18] R. Winter, Patent WO/2009/152385, 2009, December 17.
[19] R. Winter, P.G. Nixon, G.L. Gard, Journal of Fluorine Chemistry 87 (1998) 85–86.
[20] G.A. Silvey, G.H. Cady, Journal of the American Chemical Society 72 (1950) 3624–3626.
[21] A.F. Clifford, H.K. El-Shamy, H.J. Emeléus, R.N. Haszeldine, Journal of the Chemical Society (1953) 2372–2375.
[22] R.N. Haszeldine, F. Nyman, Journal of the Chemical Society (1956) 2684–2689.
[23] R.D. Dresdner, J.A. Young, Journal of the American Chemical Society 81 (1959) 574–577.
[24] H.J. Emeléus, B.W. Tattershall, Journal of Inorganic and Nuclear Chemistry 28 (1966) 1823–1827.
[25] J.R. Case, N.H. Ray, H.L. Roberts, Journal of the Chemical Society (1961) 2066–2070.
[26] J.R. Case, N.H. Ray, H.L. Roberts, Journal of the Chemical Society (1961) 2070–2075.
[27] R.A. De Marco, W.B. Fox, Journal of Fluorine Chemistry 12 (1978) 137–151.
[28] J. Steward, L. Kegley, H.F. White, G.L. Gard, Journal of Organic Chemistry 34 (1969) 760–762.
[29] R.J. Terjeson, G.L. Gard, Journal of Fluorine Chemistry 35 (1987) 653–662.
[30] A.D. Berry, W.B. Fox, Journal of Organic Chemistry 43 (1978) 365–367.
[31] Q.C. Mir, R. Debuhr, C. Haug, H.F. White, G.L. Gard, Journal of Fluorine Chemistry 16 (1980) 373–383.
[32] R.J. Terjeson, R. Willenbring, G.L. Gard, Journal of Fluorine Chemistry 76 (1996) 63–65.
[33] R.W. Winter, G.L. Gard, Journal of Fluorine Chemistry 118 (2002) 157–159.
[34] R.W. Winter, R. Dodean, J.A. Smith, R. Anilkumar, D.J. Burton, G.L. Gard, Journal of Fluorine Chemistry 122 (2003) 251–253.
[35] P.G. Nixon, J. Renn, R.J. Terjeson, Y.S. Choi, R. Winter, G.L. Gard, Journal of Fluorine Chemistry 91 (1998) 13–18.
[36] A.D. Berry, W.B. Fox, Journal of Fluorine Chemistry 7 (1976) 449–452.
[37] R. Winter, G.L. Gard, Journal of Fluorine Chemistry 66 (1994) 109–116.
[38] R. Winter, G.L. Gard, Journal of Fluorine Chemistry 102 (2000) 79–87.
[39] A. Klauck, K. Seppelt, Angewandte Chemie International Edition in English 33 (1994) 93–95.
[40] I.V. Trushkov, V.K. Brel, Tetrahedron Letters 46 (2005) 4777–4779.
[41] V.K. Brel, Synthesis (2006) 339–343.
[42] V.K. Brel, Journal of Fluorine Chemistry 128 (2007) 862–867.
[43] V.K. Brel, Phosphorus Sulfur Silicon and the Related Elements 186 (2011) 1284–1287.
[44] R. Winter, P.G. Nixon, G.L. Gard, D.H. Radford, N.R. Holcomb, D.W. Grainger, Journal of Fluorine Chemistry 107 (2001) 23–30.
[45] S. Ait-Mohand, W.R. Dolbier, Organic Letters 4 (2002) 3013–3015.
[46] W.R. Dolbier Jr., S. Aït-Mohand, T.D. Schertz, T.A. Sergeeva, J.A. Cradlebaugh, A. Mitani, G.L. Gard, R.W. Winter, J.S. Thrasher, Journal of Fluorine Chemistry 127 (2006) 1302–1310.
[47] W.R. Dolbier Jr., A. Mitani, R.D. Warren, Tetrahedron Letters 48 (2007) 1325–1326.
[48] W.R. Dolbier Jr., A. Mitani, W. Xu, I. Ghiviriga, Organic Letters 8 (2006) 5573–5575.
[49] M. Ponomarenko, Y. Serguchev, G.-V. Röschenthaler, Synthesis (2010) 3906–3912.
[50] Corrigendum: Synthesis (2011) 827–828.
[51] P. Kirsch, J.T. Binder, E. Lork, G.-V. Röschenthaler, Journal of Fluorine Chemistry 127 (2006) 610–619.
[52] R.W. Winter, G.L. Gard, Journal of Fluorine Chemistry 128 (2007) 896–901.
[53] R.W. Winter, G.L. Gard, Journal of Fluorine Chemistry 129 (2008) 1041–1043.
[54] D.S. Lim, S.C. Ngo, S.G. Lal, K.E. Minnich, J.T. Welch, Tetrahedron Letters 49 (2008) 5662–5663.
[55] W.S. Husstedt, J.S. Thrasher, G. Haufe, Synlett (2011) 1683–1686.
[56] R.W. Winter, G.L. Gard, Journal of Fluorine Chemistry 127 (2006) 1188–1194.
[57] M.V. Ponomarenko, Y.A. Serguchev, G.-V. Röschenthaler, Journal of Fluorine Chemistry 131 (2010) 270–273.
[58] A.D. Berry, W.B. Fox, Journal of Fluorine Chemistry 6 (1975) 175–180.
[59] E.F. Witucki, M.B. Frankel, Journal of Chemical and Engineering Data 24 (1979) 382–383.
[60] G. Kleemann, T. Krügerke, K. Seppelt, Journal of Fluorine Chemistry 35 (1987) 135.
[61] H.J. Emeléus, H.G. Heal, Journal of the Chemical Society 1946 (1946) 1126–1131.
[62] W.A. Sheppard, Journal of the American Chemical Society 82 (1960) 4751–4752.
[63] X. Ou, A.F. Janzen, Journal of Fluorine Chemistry 101 (2000) 279–283.
[64] W.A. Sheppard, Journal of the American Chemical Society 84 (1962) 3064–3072.
[65] A.M. Sipyagin, V.S. Enshov, S.A. Kashtanov, C.P. Bateman, B.D. Mullen, Y.-T. Tan, J.S. Thrasher, Journal of Fluorine Chemistry 125 (2004) 1305–1316.
[66] R.D. Bowden, P.J. Comina, M.P. Greenhall, B.M. Kariuki, A. Loveday, D. Philp, Tetrahedron 56 (2000) 3399–3408.
[67] R.D. Chambers, R.C.H. Spink, Chemical Communications (1999) 883–884.
[68] A.M. Sipyagin, C.P. Bateman, Y.-T. Tan, J.S. Thrasher, Journal of Fluorine Chemistry 112 (2001) 287–295.
[69] P. Kirsch, A. Hahn, European Journal of Organic Chemistry 2005 (2005) 3095–3100.
[70] T.A. Sergeeva, W.R. Dolbier, Organic Letters 6 (2004) 2417–2419.
[71] R.W. Winter, G.L. Gard, Journal of Fluorine Chemistry 125 (2004) 549–552.
[72] T. Umemoto, L.M. Garrick, N. Saito, Beilstein Journal of Organic Chemistry 8 (2012) 461–471.
[73] F.W. Hoover, D.D. Coffman, Journal of Organic Chemistry 29 (1964) 3567–3570.
[74] J.M. Canich, M.M. Ludvig, G.L. Gard, J.M. Shreeve, Inorganic Chemistry 24 (1985) 3668–3670.
[75] Q.C. Wang, H.F. White, G.L. Gard, Journal of Fluorine Chemistry 13 (1979) 455–461.
[76] A.D. Berry, R.A. De Marco, W.B. Fox, Journal of the American Chemical Society 101 (1979) 737–738.
[77] W.R. Dolbier, Z. Zheng, Journal of Organic Chemistry 74 (2009) 5626–5628.
[78] M.V. Ponomarenko, N. Kalinovich, Y.A. Serguchev, M. Bremer, G.-V. Röschenthaler, Journal of Fluorine Chemistry 135 (2012) 68–74.
[79] R.W. Winter, R. Dodean, L. Holmes, G.L. Gard, Journal of Fluorine Chemistry 125 (2004) 37–41.
[80] R. Czerepinski, G.H. Cady, Journal of the American Chemical Society 90 (1968) 3954–3959.
[81] V.K. Brel, Synthesis (2005) 1245–1250.
[82] V.K. Brel, Synthesis (2006) 2665–2670.
[83] M.E. Sitzmann, Journal of Fluorine Chemistry 70 (1995) 31–38.
[84] R.P. Singh, R.W. Winter, G.L. Gard, Y. Gao, J.M. Shreeve, Inorganic Chemistry 42 (2003) 6142–6146.
[85] H. Gao, C. Ye, R.W. Winter, G.L. Gard, M.E. Sitzmann, J.M. Shreeve, European Journal of Inorganic Chemistry (2006) 3221–3226.
[86] Y. Huang, G.L. Gard, J.M. Shreeve, Tetrahedron Letters 51 (2010) 6951–6954.

[87] H. Martinez, Z. Zheng, W.R. Dolbier Jr., J. Fluorine Chem (2012), http://dx.doi.org/10.1016/j.jfluchem.2012.03.010.
[88] R.W. Winter, R. Dodean, J.A. Smith, R. Anilkumar, D.J. Burton, G.L. Gard, Journal of Fluorine Chemistry 126 (2005) 1202–1214.
[89] N.N. Hamel, P.G. Nixon, G.L. Gard, R.L. Nafshun, M.M. Lerner, Journal of Fluorine Chemistry 79 (1996) 81–86.
[90] R. Winter, G.L. Gard, R. Mews, M. Noltemeyer, Journal of Fluorine Chemistry 60 (1993) 109–123.
[91] J. Mohtasham, G.L. Gard, Coordination Chemistry Reviews 112 (1992) 47–79.
[92] R. Winter, G.L. Gard, Journal of Fluorine Chemistry 50 (1990) 141–149.
[93] C. Ye, G.L. Gard, R.W. Winter, R.G. Syvret, B. Twamley, J.M. Shreeve, Organic Letters 9 (2007) 3841–3844.
[94] T. Abe, G.-H. Tao, Y.-H. Joo, R.W. Winter, G.L. Gard, J.M. Shreeve, Chemistry: A European Journal 15 (2009) 9897–9904.
[95] S. Garg, J.M. Shreeve, Journal of Materials Chemistry 21 (2011) 4787–4795.
[96] W.R. Dolbier Jr., Z. Zheng, Journal of Fluorine Chemistry 132 (2011) 389–393.
[97] T. Umemoto, J. Chika, Patent US 2011/0301382 A1, 2010, December 7.
[98] A.M. Hodges, R.W. Winter, S.W. Winner, D.A. Preston, G.L. Gard, Journal of Fluorine Chemistry 114 (2002) 3–8.
[99] R.W. Winter, S.W. Winner, D.A. Preston, J. Mohtasham, J.A. Smith, G.L. Gard, Journal of Fluorine Chemistry 115 (2002) 101–105.
[100] S.W. Winner, R.W. Winter, J.A. Smith, G.L. Gard, N.A. Hannah, S.B. Rananavare, B. Piknova, S.B. Hall, Mendeleev Communications 16 (2006) 182–184.
[101] H. Nakayama, J. Nishida, N. Takada, H. Sato, Y. Yamashita, Chemistry of Materials 24 (2012) 671–676.
[102] C. Zarantonello, A. Guerrato, E. Ugel, R. Bertani, F. Benetollo, R. Milani, A. Venzo, A. Zaggia, Journal of Fluorine Chemistry 128 (2007) 1449–1453.
[103] P. Beier, T. Pastýříková, G. Iakobson, Journal of Organic Chemistry 76 (2011) 4781–4786.
[104] P. Beier, T. Pastýříková, Tetrahedron Letters 52 (2011) 4392–4394.
[105] T. Pastýříková, G. Iakobson, N. Vida, R. Pohl, P. Beier, European Journal of Organic Chemistry (2012) 2123–2126.
[106] P. Beier, T. Pastýříková, N. Vida, G. Iakobson, Organic Letters 13 (2011) 1466–1469.
[107] W.A. Sheppard, Journal of the American Chemical Society 84 (1962) 3072–3076.
[108] D.S. Lim, J.S. Choi, C.S. Pak, J.T. Welch, Journal of Pesticide Science 32 (2007) 255–259.
[109] C. Hansch, R.M. Muir, T. Fujita, P.P. Maloney, F. Geiger, M. Streich, Journal of the American Chemical Society 85 (1963) 2817–2824.
[110] P. Wipf, T. Mo, S.J. Geib, D. Caridha, G.S. Dow, L. Gerena, N. Roncal, E.E. Milner, Organic & Biomolecular Chemistry 7 (2009) 4163–4165.
[111] M. Jagodzinska, F. Huguenot, G. Candiani, M. Zanda, ChemMedChem 4 (2009) 49–51.
[112] K. Muller, C. Faeh, F. Diederich, Science 317 (2007) 1881–1886.
[113] J.T. Welch, D.S. Lim, Bioorganic and Medicinal Chemistry 15 (2007) 6659–6666.
[114] S. Altomonte, M. Zanda, et al, in preparation.
[115] T. Mo, X. Mi, E.E. Milner, G.S. Dow, P. Wipf, Tetrahedron Letters 51 (2010) 5137–5140.
[116] G. Dow, E. Milner, P. Wipf, T. Mo, Patent WO/2010/144434 A1, 2010, December 16.
[117] B. Stump, C. Eberle, W.B. Schweizer, M. Kaiser, R. Brun, R.L. Krauth-Siegel, D. Lentz, F. Diederich, ChemBioChem 10 (2009) 79–83.
[118] F. Micheli, L. Arista, G. Bonanomi, F.E. Blaney, S. Braggio, A.M. Capelli, A. Checchia, F. Damiani, R. Di-Fabio, S. Fontana, G. Gentile, C. Griffante, D. Hamprecht, C. Marchioro, M. Mugnaini, J. Piner, E. Ratti, G. Tedesco, L. Tarsi, S. Terreni, A. Worby, C.R. Ashby, C. Heidbreder, Journal of Medicinal Chemistry 53 (2010) 374–391.
[119] F. Micheli, D. Andreotti, S. Braggio, A. Checchia, Bioorganic and Medicinal Chemistry Letters 20 (2010) 4566–4568.
[120] R. Gujjar, F. El Mazouni, K.L. White, J. White, S. Creason, D.M. Shackleford, X. Deng, W.N. Charman, I. Bathurst, J. Burrows, D.M. Floyd, D. Matthews, F.S. Buckner, S.A. Charman, M.A. Phillips, P.K. Rathod, Journal of Medicinal Chemistry 54 (2011) 3935–3949.
[121] J.M. Coteron, M. Marco, J. Esquivias, X. Deng, K.L. White, J. White, M. Koltun, F. El Mazouni, S. Kokkonda, K. Katneni, R. Bhamidipati, D.M. Shackleford, I. Angulo-Barturen, S.B. Ferrer, M.B. Jiménez-Díaz, F.-J. Gamo, E.J. Goldsmith, W.N. Charman, I. Bathurst, D. Floyd, D. Matthews, J.N. Burrows, P.K. Rathod, S.A. Charman, M.A. Phillips, Journal of Medicinal Chemistry 54 (2011) 5540–5561.
[122] J.T. Welch (Ed.), Fluorine in Pharmaceutical and Medicinal Chemistry, Imperial College Press, 2012, pp. 175–207.