REVIEW

Chemistry of pentafluorosulfanyl derivatives and related analogs: from synthesis to applications.

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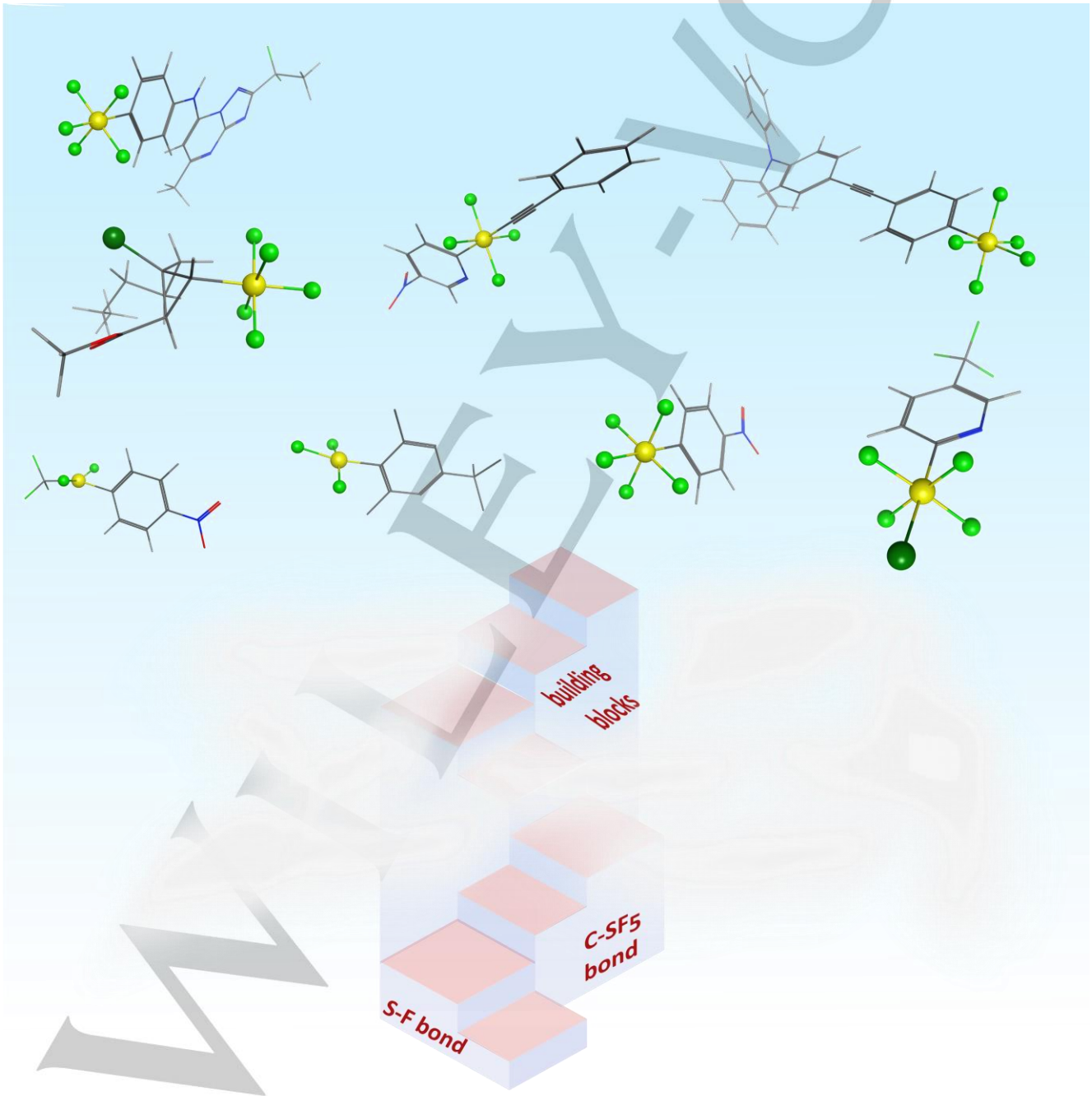

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Abstract: Pentafluorosulfanyl (SF_5)-containing compounds and corresponding analogs are a highly valuable class of fluorine-containing building blocks owing to their unique properties. The reason for that is the set of peculiar and tremendously beneficial characteristics they can impart on molecules once introduced onto them. Despite this, their application in distinct scientific fields remains modest, given the extremely harsh reaction conditions needed to access such compounds. The recent synthetic approaches via S–F, and C–SF_5 bond formation as well as the use of SF_5-containing building blocks embody a "stairway-to-heaven" loophole in the synthesis of otherwise-inaccessible chemical scaffolds only a few years ago. Herein, we report and evaluate the properties of the SF_5 group and analogs, by summarizing synthetic methodologies available to access them as well as following applications in material science and medicinal chemistry since 2015.

1. Introduction

The pentafluoro-λ^6-sulfanyl group is a remarkable functional group in organic chemistry. Aside from its carbon attachment point, the sulfur(VI) center is engulfed by fluorine atoms from its other five sides, which grant the moiety its unique properties. The sulfur center of the pentafluoro-λ^6-sulfanyl group adopts an octahedral structure, as predicted by the VSEPR model.[1] In ^{19}F NMR spectroscopy, the four 'equatorial' fluorine nuclei on the one hand, and the one 'axial' atom on the other, are nondegenerate and appear as a clear AB_4 spin system (Figure 1).[2]

With its six single bonds to neighbouring attachments, the sulfur atom has a formal valence electron count of greater than 8e$^-$ and is therefore hypervalent.[3] This deviation from the Lewis octet rule can be best understood in a framework of negative hyperconjugation.[4] A weighted average of several resonance forms describes the reality most accurately, with the highest contribution coming from the ionic 'no bond' form (Figure 1). Two of the equatorial fluorides can be understood as housing their electrons in the non-bonding orbitals via an n→σ* interaction (also known as a three-center four-electron 3c-4e bond).[4-5] Since the electrons in these nonbonding orbitals are almost exclusively localized on the fluoride atoms, the only electrons on the sulfur atom stem from the four lower-lying, bonding MOs, so that the octet rule remains valid. Derivatives of the type RSF_4X such as chlorotetrafluorosulfanyl species can exist in two forms, with the X group either axial (*trans*) or equatorial (*cis*).

The SF_5 group shows surprising levels of chemical and thermal stability, especially compared to other S^{VI}–F compounds like sulfonyl fluorides, which are typically considered electrophilic and easily substituted. Also, the metabolic stability of this perfluorinated chalcogen has been showcased on multiple occasions.[6] These features combine with two other characteristics that make the SF_5 group a very appealing substituent in drug discovery and materials development: high hydrophobicity and high electron-withdrawing character. The interest towards the SF_5 group arose in the context of bioisosteric replacements for trifluoromethyl, earning it the name of the "super-trifluoromethyl" group.[7]

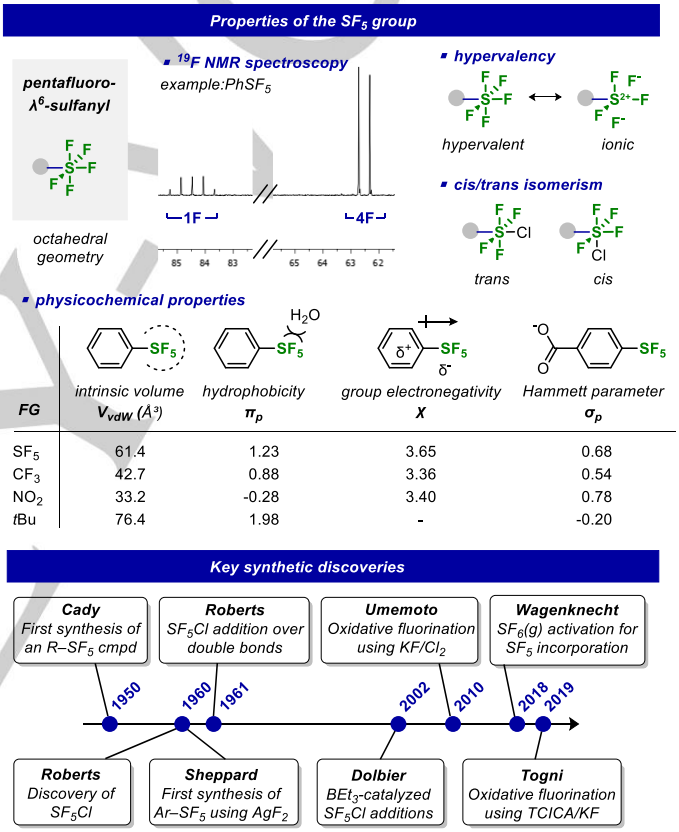


Figure 1 Properties of the SF_5 group and the major key discoveries reported in the field.

Indeed, of the various substituents it has been compared to, the trifluoromethyl group is the closest relative in terms of hydrophobicity and group electronegativity. Nevertheless, the SF_5 group is at the same time bulkier (as determined by the Van der Waals volume V_{vdW} estimated according to the method in ref[8]),[8] more lipophilic (considering the Hansch hydrophobicity parameter π_p),[9] and more electron-withdrawing (shown both in terms of electronegativity χ[10] and Hammett parameter σ_p).[11] Elsewhere, the SF_5 group has been compared as a bioisostere to a NO_2 substituent (similar electron-withdrawing character but opposite polarity) or to the *t*-Bu moiety (comparable lipophilicity and hindrance, but inverse electronic effects).[7, 12] An SF_5-containing structure was first reported by Silvey and Cady in 1950, making these organic pentafluorosulfanes among the youngest fluorine-

based functional groups.[13] A decade later, Roberts prepared gaseous SF_5Cl,[14] still the most widely used SF_5-containing reagent to date, and then in 1961 reported its thermally or photochemically induced addition over unsaturated bonds.[15] Sheppard meanwhile discovered that aromatic thiols could be transformed to $ArSF_5$ in low conversion using silver(II) fluoride as the fluorine source and oxidant.[16] While more variations of this method followed in the years thereafter, the next milestone in SF_5 introduction comprises Dolbier's Et_3B-catalyzed, radical chain-type chloropentafluorosulfanylation of double and triple bonds, still frequently used today.[17] The most effective oxidative fluorination was reported by Umemoto in 2010 using Cl_2 gas and dry KF,[18] and a gas-free alternative that relies on trichloroisocyanuric acid (TCICA) was proposed by Togni in 2019.[19] Recently, Wagenknecht was the first to realize the activation of SF_6 gas to incorporate pentafluorosulfanyl groups in specific substrates.[20]

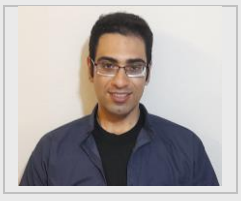
In 2015, Savoie and Welch published a key review on pentafluorosulfanyl-containing compounds.[21] Therein, an exhaustive survey is given of synthetic literature that either prepares SF_5-containing molecules, uses them as building blocks for other syntheses or shows their potential in more applied fields of chemistry.

The current work aims to provide an update to Welch's article. While we can thoroughly recommend other reviews that have appeared since that time,[22] the goal here is to provide an overview of chemical literature that has come out since 2015, wherein SF_5-containing structures play a dominant role. In the reviewing phase of this article, two more relevant review articles were published, the first by Cody-Pitts and co-workers, and the second by Sani and Zanda.[23]

The structure we adopt is the following: In Section 2, all synthetic approaches to SF_4X and SF_5 compounds by means of S–F bond formation are covered. Since these oxidative fluorination methods typically also allow access to lower-oxidation-state sulfur fluorides, we also cover SF_3-containing and SF_2-bridged products herein. In Section 3, we discuss C–S bond formations, i.e., those methods which install new pentafluorosulfanyl groups from SF_5X precursors. Next, Section 4 surveys preparations of complex organic molecules constructed with SF_5-containing building blocks. Ultimately, Section 5 discusses selected applications of the SF_5 functional group in material science and medicinal chemistry.

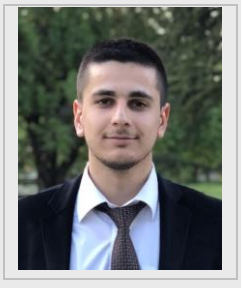
Ermal Ismalaj graduated in Pharmacy at the University of Siena. After a research experience at Green S.O.C. (University of Perugia), he joined the University of Lyon as a Marie Curie ESR (RADIOMI ITN), where he defended his PhD in fluorine chemistry. As a postdoc, Ermal joined KU Leuven, initially in the department of pharmaceutical sciences and later the department of chemistry, and did a postdoctoral stay at CIC-biomaGUNE (Spain). He is currently a Marie Curie-SoE-FWO fellow at KU Leuven and his scientific interests span fluorine chemistry, chemical biology, and imaging techniques.

Reza obtained his B.Sc. degree in Chemistry from Shiraz University in 2015. He then started his M.Sc. at the same university where he conducted green chemistry research under the supervision of Prof. Ali Khalafi-Nezhad. The main focuses of his Master's studies were the design of novel synthetic approaches (e.g. multicomponent reactions), and mesoporous and ionic liquid catalytic systems. Then, he joined the group of Prof. Wim De Borggraeve as a PhD researcher to explore the synthesis of fluorinated compounds.



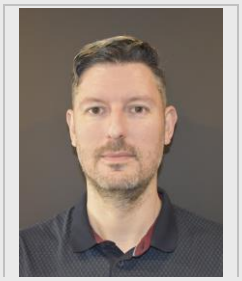
Bingyu Li obtained her bachelor's degree at the Beijing Institute of Technology (BIT, Beijing, China) in 2016 and her master's degree in BIT in 2019 focusing on organocatalyzed asymmetric organic synthesis in the lab of Prof. Da-Ming Du. In 2019, she began her doctoral study at KU Leuven (Leuven, Belgium) under the supervision of prof. Wim De Borggraeve. Her research interests include the ex situ generation of gaseous sulfur (VI) fluoride exchange (SuFEx) hubs in two-chamber reactors and further SuFEx reactions as well as the synthesis of sulfur(VI)–fluoride compounds.

Armir Zogu obtained his BSc degree at the University of Prishtina (Kosovo) in 2018. Being attracted more to organic chemistry, he decided to continue for his master's degree at the same institution, while also spending a 6 months research internship at the Karlsruhe Institute of Technology, where he worked on the synthesis of building blocks for materials science. Currently, he is a PhD student in the group of Professor Wim De Borggraeve. His research is oriented toward the SF_5 introduction in relevant bioactive scaffolds.



Joachim Demaerel obtained his MSc Chemistry degree at KU Leuven in 2014, after a research internship with Martin Klussmann (MPI Mülheim/Ruhr), and a MSc thesis with Wim De Borggraeve. He then continued in the same lab as a PhD student, working on radical and fluorine chemistry. After a research stay in the group of Rob Knowles (Princeton), he obtained the PhD degree in 2019. He then moved to RWTH Aachen as a postdoctoral researcher in the lab of Carsten Bolm, and is currently working on sulfur(VI)–fluoride chemistry under the advisorship of Wim De Borggraeve and Steven Verhelst.

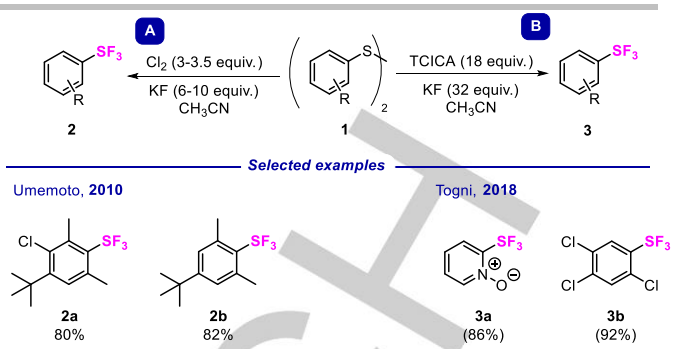
Wim De Borggraeve obtained his PhD in Chemistry at KU Leuven in 2002. After a postdoc with FWO Flanders and research stays in the groups of W.D. Lubell (Université de Montréal, Canada) and C. Toniolo (University of Padova, Italy), he was appointed at KU Leuven in 2009 where he currently holds a Professor position. His research interests are in organic synthesis methodology, heterocyclic and medicinal chemistry.



2. Synthesis of R–SF_5 compounds and analogs via S–F bond formation.

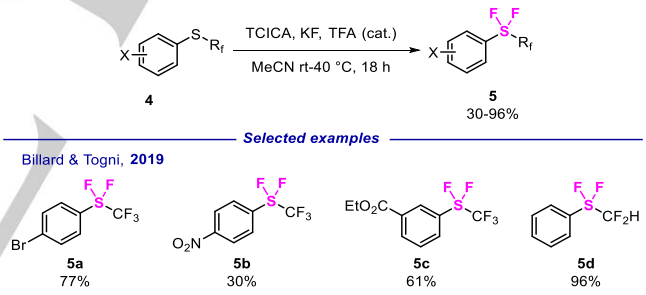
2.1. Synthesis of compounds having a sulfur(IV)–fluorine bond.

Sulfur trifluorides (–SF_3) are compounds having a hypervalent S(IV) atom attached to three fluorine atoms and a fourth atom being a carbon or a heteroatom such as nitrogen. Sulfur trifluorides are well-known for their application as potent deoxyfluorinating reagents. Alkylaminosulfur trifluorides were introduced as potential substitutes for gaseous SF_4 in the early '70s.[24] Nonetheless, inherent drawbacks related to the instability and related hazards of dialkylaminosulfur trifluorides, especially at higher temperatures, limit their use. To overcome such drawbacks, Umemoto et al. envisaged the design of an aromatic sulfur trifluoride. They accessed a whole library of aromatic sulfur trifluorides via oxidation of the corresponding disulfides with AgF_2 or Cl_2/KF method (Scheme 1, A). By employing different substituents on the phenyl ring, they tuned stability and reactivity,[25] dispatching FLUOLEAD™ (**2b**), a versatile fluorinating reagent with high thermal stability and unusual resistance to aqueous hydrolysis. More recently, Pitts, Santschi, Togni and co-workers, reported the synthesis of a few examples of (hetero)arylsulfur trifluorides **3a-b** by employing the TCICA/KF method. The *ortho*-substituted precursors having a substituent larger than a fluorine atom seem to yield Ar-SF_3 exclusively (Scheme 1, B).[19]



Scheme 1 Synthesis of $ArSF_3$ via oxidative fluorination by employing the Cl_2/KF or TCICA/KF method. Isolated yields are given and ^{19}F NMR yields are in parentheses.

In 2019, Billard, Togni and co-workers expanded the TCICA/KF methodology towards difluoro(aryl)(perfluoroalkyl)-λ⁴-sulfanes **5** (Scheme 2).[26] $ArSF_2R_f$ compounds (**5**) used to be merely accessible using notoriously hazardous reagents e.g. F_2 or XeF_2/HF. Moreover, this straightforward tactic renders a detailed characterization feasible in both solid (*via* SC-XRD) and solution (*via* ^{19}F and ^1H NMR) states over the crude material. Interestingly, it was also unveiled by the authors that **5a** has been used in the deoxyfluorination of alcohols. This provides evidence that the family of difluoro(aryl)(perfluoroalkyl)-λ⁴-sulfanes could potentially be applied as deoxyfluorinating agents.

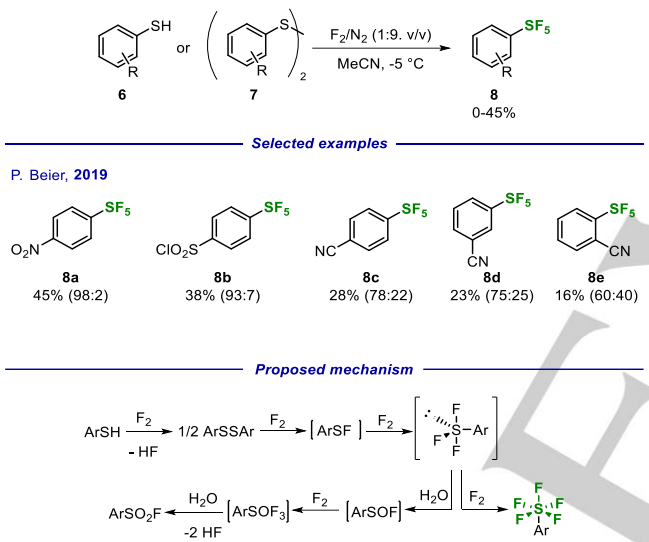


Scheme 2 Preparation of difluoro(aryl)(perfluoroalkyl)-λ⁴-sulfanes using the TCICA/KF system.

2.2. Synthesis of compounds having a sulfur(VI)–fluorine bond.

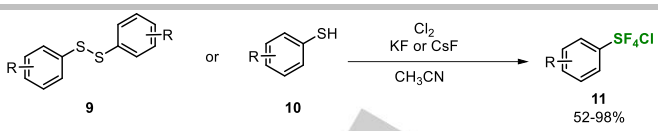
Recent synthetic pathways that lead to aromatic pentafluorosulfanyl-containing compounds include a) direct fluorination of aryl disulfides and b) chlorine-fluorine exchange of pre-synthesized chlorotetrafluorosulfanyl intermediates. The former is used in the industry on multikilogram scale, despite the known risks of elemental fluorine. The reason behind this preference is that this one-step approach provides access to key intermediates such as nitro(pentafluorosulfanyl)benzenes that could be derivatized into other SF_5-containing (hetero)aromatics.[27] It should also be taken into consideration that fluorine gas is inexpensive on larger scales. Despite providing a successful transformation, fluorine-mediated oxidation of sulfur-containing precursors had not been thoroughly investigated in terms of scope limitations until recently. Previous works

highlighted the need for strong electron-withdrawing substituents on the aromatic ring to avoid ring fluorination. Beier and co-workers provided a thorough study of the scope and limitation of this methodology and compared batch versus hybrid batch/flow transformations.[28] They could access *ortho*-, *meta*- and *para*-substituted pentafluorosulfanyl arenes, albeit the yield not exceeding 50% (Scheme 3). Nonetheless, given the nature of the transformation, such yields are expected. Another well-known issue in the fluorine-mediated oxidative fluorination of sulfur-containing arenes is the fluorination of the corresponding aromatic ring, which could be suppressed in the presence of a highly electron-withdrawing nitro group. The suggested mechanism includes stepwise oxidation of thiols into arylsulfur trifluorides, that undergo fluorination to yield arylsulfur pentafluorides or hydrolysis to yield other by-products (Scheme 3). Computational studies using distinct density functional and wave function methods exclude non-radical pathways, thus encouraging the authors to postulate a radical mechanism that starts with the homolytic cleavage of the F–F bond.



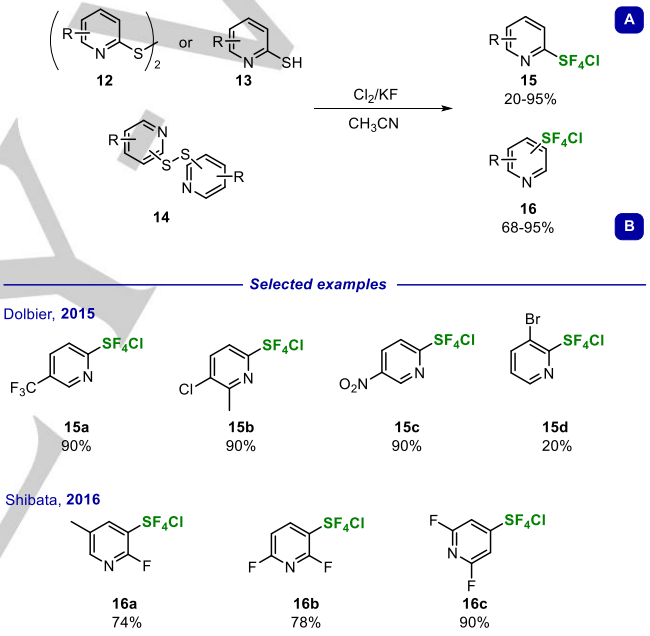
Scheme 3 Oxidative fluorination of aromatic sulfur-containing compounds. The reported yield is only for the aryl-SF_5. In parentheses the ratio of desired to Ar-SF_5 product **8** to Ar-SF_5 fluorinated products.

As mentioned before, F_2-mediated oxidative fluorination harbours inherent disadvantages ranging from the difficulty in handling fluorine gas to unwanted reactivity. For this, Umemoto et al. introduced a two-step approach to access Ar–SF5 compounds. In this case, the substitution of fluorine gas with the milder chlorine gas in the presence of fluoride salts such as KF or CsF could provide the Ar–SF_4Cl (**11**) via oxidative halogenation (Scheme 4).[18] Such intermediates proved highly useful as they could give rise to the Ar–SF_5 final products or participate as precursors in other transformations to yield R–SF_4–R bridged compounds.



Scheme 4 General scheme of the seminal work in oxidative halogenation reported by Umemoto et al.

A few years later, Kanishchev and Dolbier used the Cl_2/KF method to access 2-pyridylsulfur chlorotetrafluorides **15** (Scheme 5, A). They achieved excellent yields when 4-, 5- or 6-substituted mercaptopyridine precursors were employed. Nonetheless, oxidative halogenation of mercaptopyridines substituted in 3-position is heavily impacted by the steric effects of the substituent. Substituents with a larger steric scale than florine yield an increasing percentage of mercaptopyridyl trifluoride, in proportion to their size.[29]

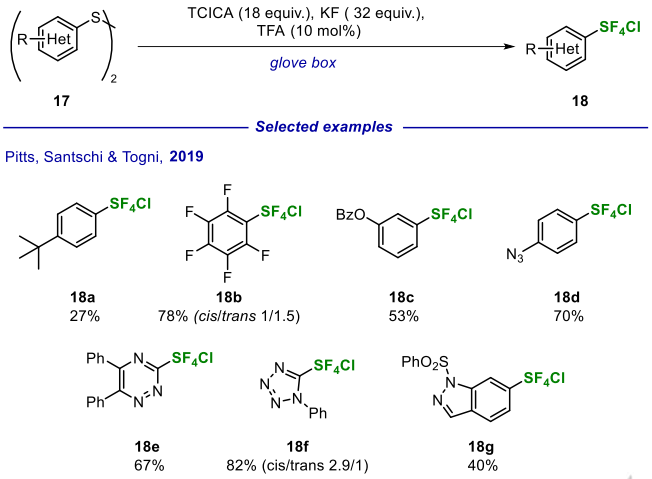


Scheme 5 Oxidative halogenation of *ortho*-, *meta*- and *para*-mercaptopyridines.

The group of Shibata reported the synthesis of *meta*- and *para*-pyridylsulfur chlorotetrafluorides **16** (Scheme 5, B), albeit the required presence of at least one fluorine atom attached to the aromatic ring of the pyridine. The role of the fluorine atom on the heteroaromatic ring seems two-fold. It decreases the basicity of the nitrogen atom, thus preventing unwanted reactivity, and stabilizes the three-center four-electron bond (3c-4e), thus increasing the stability of the product.[30]

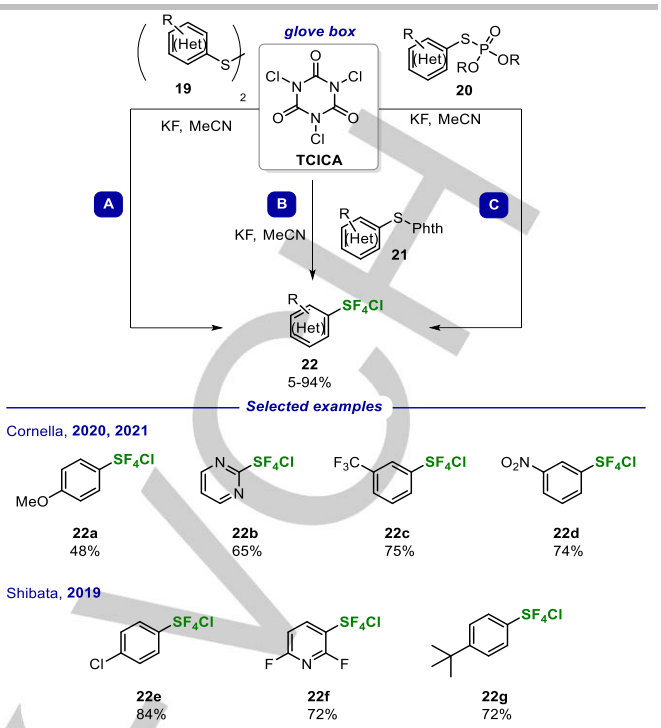
Despite the recognized importance of the Cl_2/KF method in dispatching many otherwise-inaccessible SF_4Cl-containing scaffolds, the use of the Cl_2 requires specialty installations. Pitts, Santschi, Togni and co-workers tackled such drawbacks with a very elegant approach. By employing trichloroisocyanuric acid as an in situ chlorine source, in presence of excess KF and a catalytic amount of trifluoroacetic acid (TFA) they were able to enrich the existing substrate scope with novel candidates (Scheme 6). The reaction conditions tolerate relatively sensitive

functional groups as in the case of compounds **18c** and **18d**. Interestingly, chlorotetrafluorination of disulfide precursors **17b** and **17f** yield a mixture of *cis-trans* isomers with a 2.9:1 and 1:1.5 ratio respectively. On the other hand, steric bulk in *ortho*-substituted disulfides with larger atoms than fluorine suppresses the formation of the chlorotetrafluorosulfanyl group, yielding the corresponding arylsulfur trifluoride. In addition, the authors highlighted by increasing TCICA/KF ratio or reaction temperatures (up to 40–50 °C) lead to increased ring chlorination.[19]



Scheme 6 Synthesis of chlorotetrafluorosulfanyl arenes using the TCICA/KF method.

Soon afterwards, the team of Shibata reported the same gas-free chlorotetrafluorination method in the absence of TFA (**22e–22g**, Scheme 7, A).[31] Two major advantages added by these conditions over the previous method are as follows; firstly, electron-donating groups at the *para* position afforded the desired product in high yields. Secondly, a considerably smaller amount of anhydrous KF is used, 20 equivalents compared to 32 equivalents. Furthermore, they screened a plethora of Cl-donating reagents and fluoride sources, confirming the importance of the TCICA/KF partnership for the reaction to proceed.

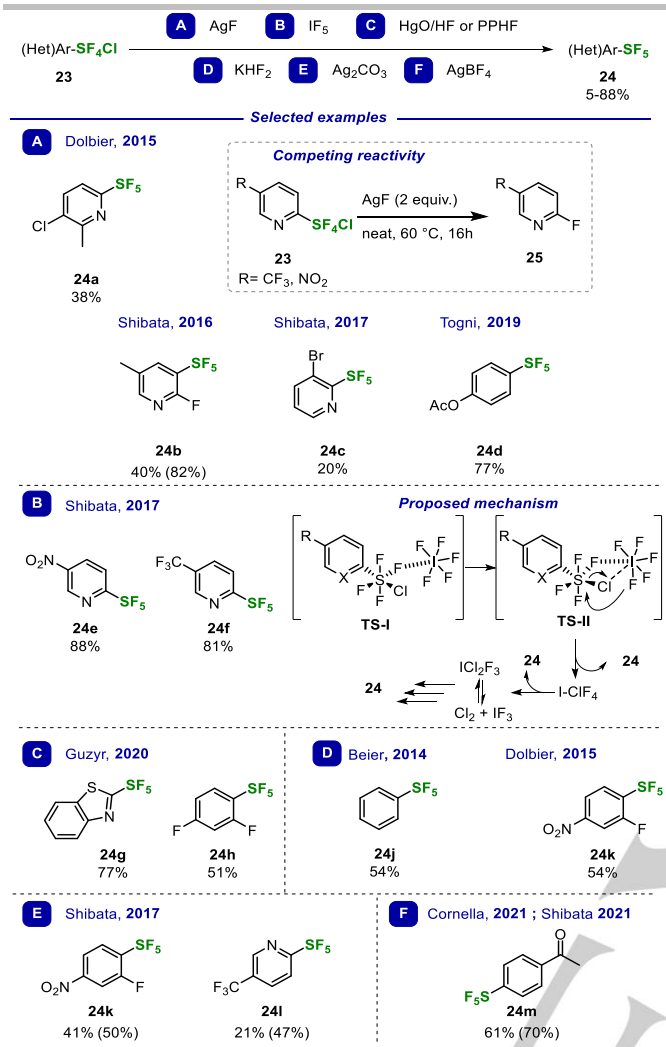


Scheme 7 Chlorotetrafluorination of sulfur-containing materials

Finally, the group of Cornella applied the Togni method to non-commercially available precursors including the (hetero)arylthiophtalimides and arylphosphorothiolates obtaining the desired SF_4Cl derivatives **22a–d** in good yields (Scheme 7, B and C). Among the reported derivatives, the electron-rich **22a** obtained from 4-mercaptoanisole deserves to be highlighted. Surprisingly, it seems that mercaptoanisole did not undergo ring chlorination under these reaction conditions.[32]

2.3. Cl-F exchange to access Ar–SF_5 compounds

Alongside the research carried out on the generation of Ar–SF_4Cl compounds, the notoriously challenging Cl-F exchange has also been investigated to a great extent. Herein, several fluorinating reagents have been introduced since 2015 (Scheme 8).



Scheme 8 Transformation of Ar-SF_4Cl to Ar-SF_5. Isolated yields are given and ^{19}F NMR yields are in parentheses.

AgF has been widely used and proved its efficiency as a reagent for the corresponding transformation (Scheme 1, A). Many research groups employed AgF as a fluorinating reagent to access aromatic and heteroaromatic pentafluorosulfanyl derivatives starting from the SF_4Cl precursors.[19, 29-30, 33] However, the group of Dolbier reported a competing reaction for 2-pyridylsulfur chlorotetrafluorides **23e–f** bearing strongly electron-withdrawing groups such as nitro or trifluoromethyl. Those precursors could undergo nucleophilic aromatic substitution at C-2 with the $–SF_4Cl$ acting as a good leaving group (Scheme 8, A) yielding the 2-fluoropyridines **25.**[29]

Shibata and co-workers tested a few fluorinating agents to suppress the abovementioned side reaction. They pinpointed IF_5 as a viable alternative to access 2-SF_5-pyridyl compounds bearing electron-withdrawing groups (Scheme 8, B). They proposed a mechanism that consists of a chlorine-fluorine exchange between IF_5 and the corresponding (Het)Ar–SF_4Cl via halogen bond intermediates TS-I and TS-II. DFT calculations confirm the prevention of the nucleophilic substitution in favour of the S_NI-like Halex reaction to deliver compounds **24e–f** (Scheme 8, B). Despite being effective for electron-withdrawing arenes, this method generates chlorine gas, which can lead to ring chlorination, especially for electron-rich substrates.[34]

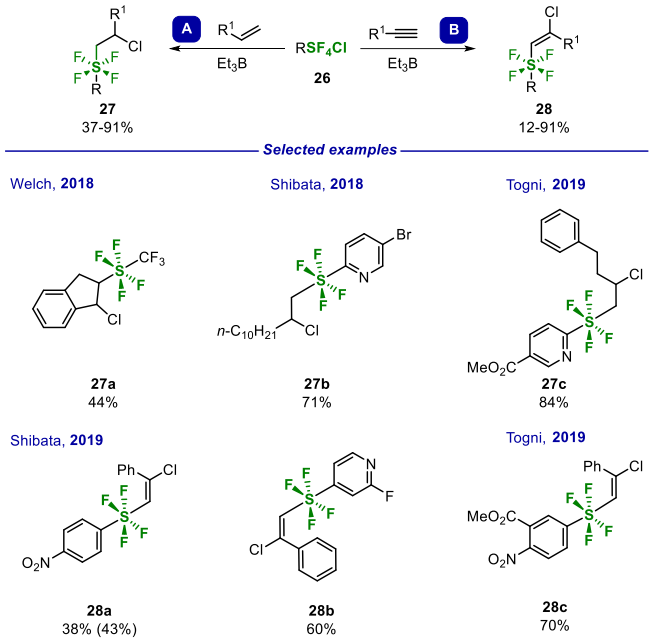
Guzyr and co-workers employed HgO and anhydrous HF or HF-pyridine as a fluoride source to convert heteroaryl-SF_4Cl into the corresponding SF_5-containing substrates **24g–h** (Scheme 8, C).[35]

Beier and co-workers developed a milder transformation by employing potassium hydrogen fluoride in trifluoroacetic acid to access aryl-SF_5 compounds, with **24j** reported as an example. The use of potassium bifluoride (KHF_2) in combination with anhydrous hydrogen fluoride as the fluorinating reagent has also been reported by Dolbier and co-workers (**24k** in Scheme 8, D).[36] Admittedly, the ever-increasing number of choices of unique fluorinating reagents for the Cl–F exchange renders the selection of the reagent highly substrate-dependent. In an attempt to side-step exogenous fluorides and to have a more general approach, Shibata and co-workers put forward a self-immolative process induced by silver (II) carbonate (**24k-l** in Scheme 8, E). Based on the mechanism proposed by the authors in which one SF_4Cl moiety can be used to fluorinate three other ones, the yield cannot exceed 75%. However, in some cases, higher yields were obtained, which is rationalized by a partial contribution from AgF generated throughout the process. The absence of S_NAr side products rules out the nucleophilic attack by naked fluoride ions. Another significant improvement made possible by this methodology is the use of ozone non-depleting Solkane® 365/227.[31, 37] Recently, Shibata and Cornella employed $AgBF_4$ as an easy-to-handle and stable source of fluorine for the chlorine-fluorine exchange reaction with good results (**24m** in Scheme 8, F).[32b, 38]

2.4. Chlorotetrafluorinated compounds as precursors to SF_4-bridged adducts.

SF_4-bridged compounds are gaining momentum in both material sciences and medicinal chemistry. The uniqueness of the SF_4 bridge comes from the fact that it can linearly connect two entirely independent scaffolds *via* the central hypervalent sulfur atom, and still keep some of the interesting features of the SF_5 moiety.[39] However, the synthetic routes leading up to these compounds have been very rarely explored—merely a handful of strategies available in the literature. For that reason, the applicability of these compounds heavily relies on the new synthetic methods. Up to date, the focus has been on the radical addition of R-SF_4Cl onto unsaturated organic structures, analogous to the procedures for the radical addition of SF_5Cl and SF_5Br. For instance, in 2018, Welch and colleagues reported an Et_3B-promoted addition of *trans*-CF_3SF_4Cl to alkenes to generate CF_3SF_4-containing adducts (**27a** in Scheme 9, A).[40]

The group of Shibata[41] followed by the group of Togni[19] reported the synthesis of pyridyl-SF_4-R structures **27b–c** and **28a–c** via the radical addition of 2-SF_4C-pyridyl precursors to alkenes and alkynes (Scheme 9, A and B) in the presence of Et_3B in CH_2Cl_2. X-ray structure elucidation disclosed an octahedral symmetrical *trans*-configuration of the SF_4 center. Furthermore, potential energy surfaces calculated by DFT demonstrated a high electron density in the $–SF_4–$ region comparable to the one of an alkyne, and an almost-linear structure of the corresponding linker. The linearity of the system was confirmed by X-ray analysis performed with one of the compounds.[41]



Scheme 9 Et_3B-promoted addition of RSF_4Cl to unsaturated organic compounds. Isolated yields are given and ^{19}F NMR yields are in parentheses.

The postulated reason for the *E*-isomer formation is the thermodynamic stability, which avoids the steric repulsions. DFT calculations confirm that hypervalent sulfur having a 3c-4e bond is more stabilized in pyridine-SF_4-Me and *p*-NO_2-Ph-SF_4Me, than Ph-SF_4-Me.[41]

Despite being reported as less stable compared to their heteroaryl counterparts, Ph–SF_4-bridged compounds **28a** and **28c** were independently isolated by the groups of Shibata and Togni.[19, 31]

3. Synthesis of SF_5-containing compounds and analogs via C-S bond formation.

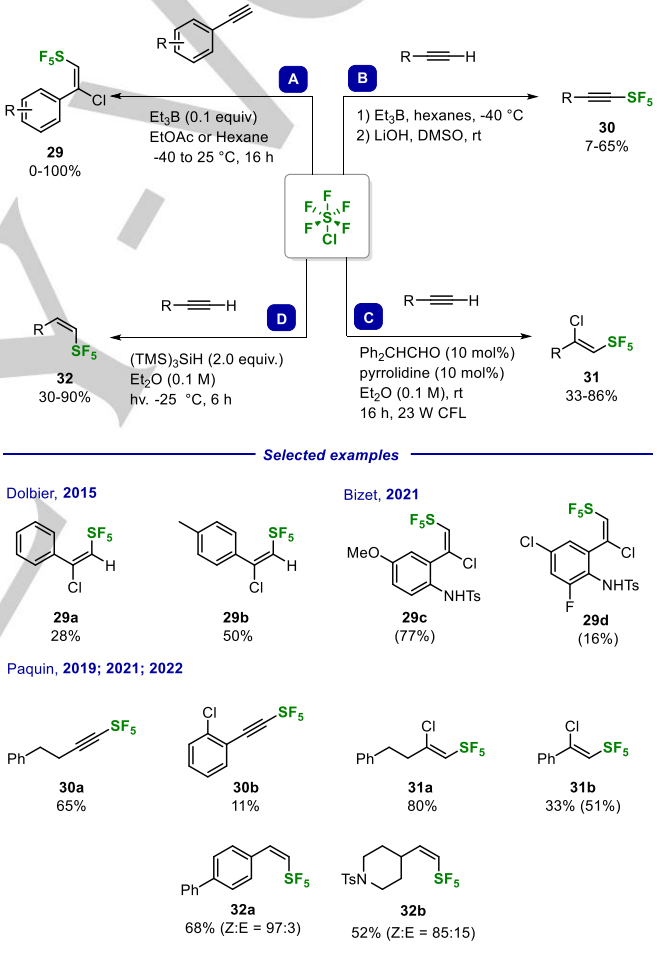
3.1. Use of SF_5Cl as a pentafluorosulfanyl donating reagent

Pentafluorosulfanyl chloride (SF_5Cl) is among the most employed SF_5 donors in organic synthesis and is being used mostly in radical addition reactions. This reactive species is gaseous at room temperature (b.p. -19 °C) and commercially available, yet often it is used as a concentrated solution in nonpolar solvents such as *n*-hexane and CH_2Cl_2. Early synthetic approaches to pentafluorosulfanyl chloride relied on the oxidation of sulfur-containing starting materials, including direct fluorination of SCl_2 or oxidative chlorination of S_2F_{10} by chlorine gas or BCl_3.[14, 42] Sulfur tetrafluoride (SF_4) also served as a precursor in the Cl_2-mediated preparation of SF_5Cl, either using CsF as the fluoride source[43] or later simply in the presence of KF.[44] Despite the high yields of some of the later examples, all the above-mentioned methodologies either require specialized autoclave setups, harsh reagents or difficult-to-obtain starting materials.

Various new applications of SF_5Cl reacting with unsaturated bonds have been reported since 2015. Dolbier and co-workers reacted arylacetylenes with SF_5Cl at -40 °C using Et_3B as a radical initiator to form SF_5-alkenes **29a-b** (Scheme 10, A).[45] The yields of the reaction were dependent upon the electronic character of the substituent with donating groups giving better yields. The authors then continued with these adducts in a few more synthetic steps to obtain pentafluorosulfanylated isoxazoles and isoxazolines (see Section 4.4).

Similarly, Bizet and co-workers studied arylacetylenes in the SF_5Cl addition reaction, albeit with an *N*-tosylamido group in *ortho* position (**29c–d**). By applying the above-mentioned reaction conditions, they added SF_5Cl to the triple bonds in a regio- and stereoselective fashion (Scheme 10, A).[46]

In 2019, Paquin and co-workers synthesized SF_5-alkynes **30a-b** in a one-pot fashion from the parent alkynes. Dolbier's Et_3B-initiated method was used,[17] followed by a base-promoted elimination of the chloropentafluorosulfanylated adducts using LiOH (Scheme 10, B).[47] The authors then used the obtained products **30** as precursors for α-SF_5 ketones (see Section 4.4).



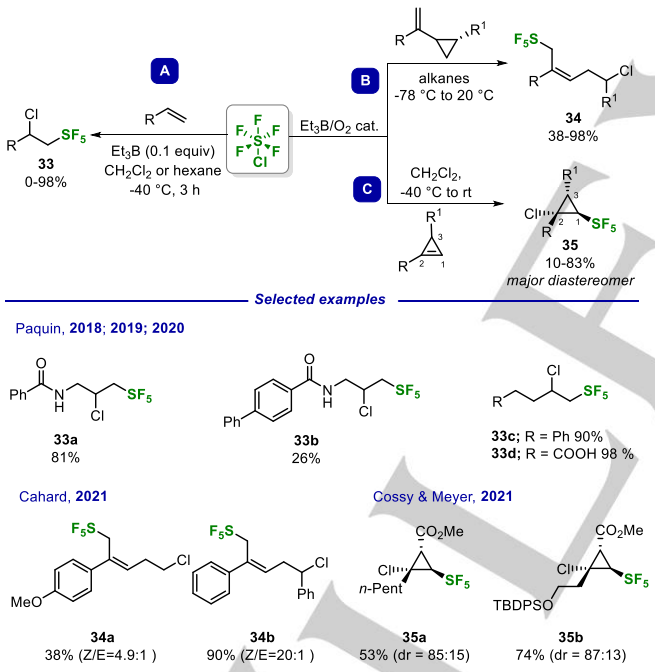
Scheme 10 Radical addition of SF_5Cl to alkynes. ^{19}F NMR yields are reported in parentheses.

Triethylborane is reported to be unstable and pyrophoric.[48] If Et_3B reacts slowly with the substrate, a large amount of oxygen is needed to initiate or maintain radical generation, and when it reacts fast a low concentration of the borane favors the reaction.[49] To circumvent such disadvantages, Paquin and co-workers used an air-stable amine-borane complex[50] (not shown) or electron donor-acceptor (EDA) complexes as photocatalysts[51] (Scheme 10, C) to promote SF_5Cl addition to alkynes. If the use

of amine-borane complexes as radical initiators yielded the expected *E*-isomer,[50] the EDA-photocatalyzed addition[51] surprisingly is reported to yield the unexpected *Z*-isomer (**31a–b**) as the major product. Furthermore, both synthetic strategies have been successfully applied to the SF_5Cl addition to alkenes.[51-52]

Very recently, Paquin and co-workers demonstrated the first example of a hydropentafluorosulfanylation of double bonds, i.e., with the incorporation of hydrogen rather than a chlorine atom, employing $(TMS)_3SiH$ as the H-atom donor. Thus, the selective formation of *Z*-(1-alken-1-yl)pentafluoro-λ^6-sulfanes **32a-b** was made possible using a photoinitiated reaction of a terminal alkyne with SF_5Cl and $(TMS)_3SiH$ (Scheme 10, D).[53]. A variety of substrates including esters, ketones, alcohols, protected amines, amides, imides, and carboxylic acids were synthesized. The hydropentafluorosulfanylated products showed excellent *Z*/*E* (95:5) diastereoselectivity and were isolated in decent to good yields (30–90%).

Paquin and co-workers disclosed more chloropentafluorosulfanylated products **33**, which were accessed in the usual Et_3B-initiated way from olefinic starting materials with varying yields from 26-100% (Scheme 11, A).[52, 54] They then used these compounds in cyclization chemistry to prepare libraries of SF_5-containing oxazolines[54a] and lactones (see Section 4.2,).[54b]

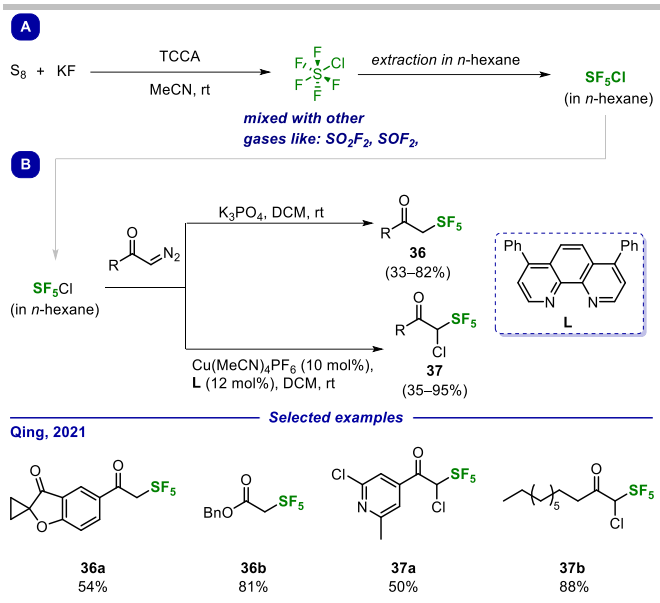


Scheme 11 Radical addition of SF_5Cl to alkenes.

Cahard and co-workers successfully added SF_5Cl to vinyl cyclopropanes, thus expanding the scope towards unexplored SF_5-containing aliphatic compounds **34** (Scheme 11, B). Interestingly, these olefins do not react in the typical 1,2 way but rather the resulting radical—after SF_5 addition to the terminal position—relays to the three-membered ring and opens it, creating a new unsaturated bond and a new radical in a formal 1,5 fashion. As a radical initiator, the Et_3B/O_2 system was used and single regioisomers were obtained depending on the nature of the substrate. In most of the substrates, the *Z*-stereoisomer was the major one with a varying yield of up to 90% (Scheme 11, B).[55]

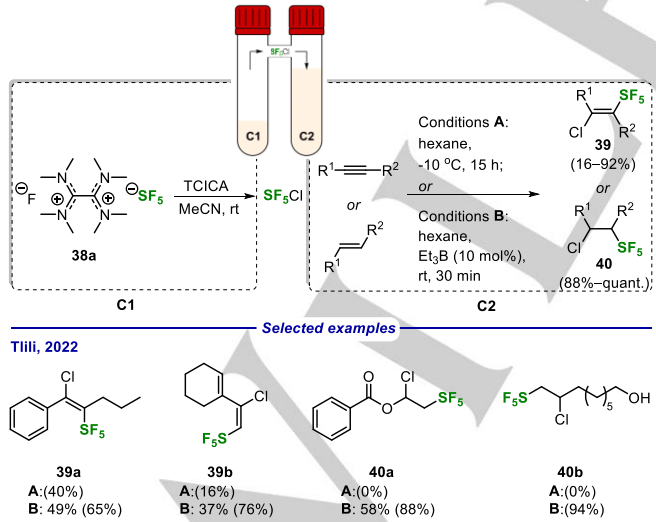
Meyer, Cossy and co-workers explored the reactivity of SF_5Cl with cyclopropenes and reported the synthesis of a novel class of substrates, pentafluorosulfanylcyclopropanes **35**. Interestingly, they found that the SF_5 addition was regioselective to the C1 carbon and fully diastereoselective to the R^1 substituent on the C3 position. Only the conformation of the Cl-attached C2-position gave rise to mixtures of diastereomers, which were confirmed via NOESY experiments. The C–Cl bond in these products is further prone to radical dechlorination or can be involved in radical cyclization processes (see Section 4.2, Scheme 37). The overall procedure gives rise to SF_5-cyclopropyl building blocks (Scheme 11, C).[56]

Recent advances in pentafluorosulfanylation chemistry allowed to overcome some of the drawbacks encountered with SF_5Cl synthesis and handling. Initially, Qing and co-workers reported a more accessible method for the synthesis of SF_5Cl, relying on elemental sulfur, trichloroisocyanuric acid (TCICA) as the oxidative chlorinating agent and KF as the fluoride source (Scheme 12, A).[57] While this produced a mixture of fluorinated S(IV) and S(VI) gases, an organic-organic extraction with *n*-hexane provided a relatively clean solution of SF_5Cl in hexane. Following the SF_5Cl production, the authors reacted to the mixture with α-diazo carbonyl starting materials (Scheme 12, B). They reported valuable α-SF_5-substituted carbonyl compounds, bearing an α-hydrogen or an α- chlorine. Indeed, chemoselectivity is achieved by either employing K_3PO_4 or a copper catalyst. Besides a rich substrate scope, the authors reported interesting mechanistic details. Control experiments suggested that the hydropentafluorosulfanylation reaction is initiated via the addition of an SF_5 radical to the diazo compound, yielding a highly electrophilic radical intermediate that favors hydrogen abstraction from the solvent rather than mismatched chlorine abstraction from SF_5Cl. Such reactivity could be overcome by employing a copper catalyst that enables chlorine umpolung and its subsequent transfer to the electrophilic radical intermediate previously formed.[57]



Scheme 12 Synthesis of SF_5Cl and subsequent use in pentafluorosulfanylations of α-diazo carbonyl compounds reported by Qing and co-workers.

Very recently, Tlili and co-workers further enriched this field of research by providing another alternative to SF_5Cl pressurized bottles. In a nutshell, they accessed a bench-stable ion pair salt **38a** (Scheme 14, D) via two-electron activation of SF_6 by TDAE (terakis(dimethylamino)ethylene). The complex was later used as an SF_5Cl source in a two-chamber reactor. The addition of TCICA to C1 (chamber 1) containing a solution of the ion pair in CH_3CN gave gaseous SF_5Cl, which reacted with triple and double bonds in C2 (chamber 2) under standard reaction conditions yielding classes of compounds **39** and **40** respectively.[58]



Scheme 13 SF_5Cl addition to double and triple bonds via the two-chamber reactor strategy.

3.2. Use of SF_6 as a pentafluorosulfanyl donating reagent

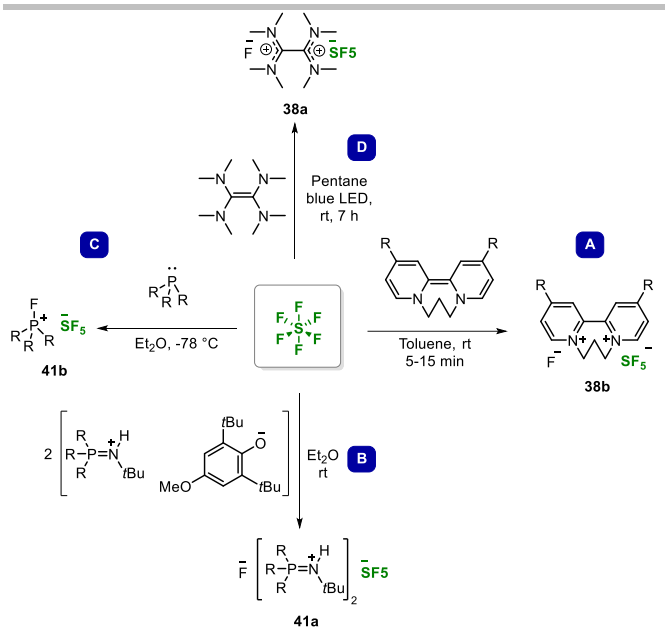
Despite the continuous use of SF_5Cl as a pentafluorosulfanyl group donor, its suspicious toxicity and high price (25 gr/900€) urge alternatives. Given such needs, sulfur hexafluoride (SF_6) has been proposed and to some extent employed as an SF_5 donor lately. However, SF_6 is extremely inert and has been recognized as the most potent greenhouse gas in the atmosphere.[59] In recent years we witnessed a few attempts to activate this species, either as a regulatory procedure to safely deplete the atmospheric accumulation of SF_6 or to render it a more reactive reagent. Herein, we highlight published works that led to isolable ion pairs having an SF_5 anion, or direct activation of SF_6 as a pentafluorosulfanylating reagent (Scheme 14, A–D).

Rueping et al. reported the initial use of electron donors as reducing agents to access bench-stable ionic complexes (Scheme 14, A). The structure of the dicationic-anionic complex **38b** (2,2′-bipyridyl[SF_5^-][F^-]) was confirmed via NMR and IR spectroscopy. Furthermore, they showcased potential applications of these isolated complexes as deoxyfluorinating reagents of benzylic alcohols, aldehydes and carboxylic acids.[60]

Other methods to activate the SF_6 gas include the use of phospazenium phenolates (Scheme 14, B) and superbasic phosphines (Scheme 14, C). The group of Hoge reported the two-electron and one–electron reduction of SF_6. In the first case, phosphazenium pentafluorosulfanide and fluoride salts (**41a**) were obtained (Scheme 14, B).[61] On the other hand, single–electron transfer (SET) reaction yields cationic-anionic pairs where the nature of the phenolate determines whether fluorine or pentafluorosulfanide salts are formed.[62]

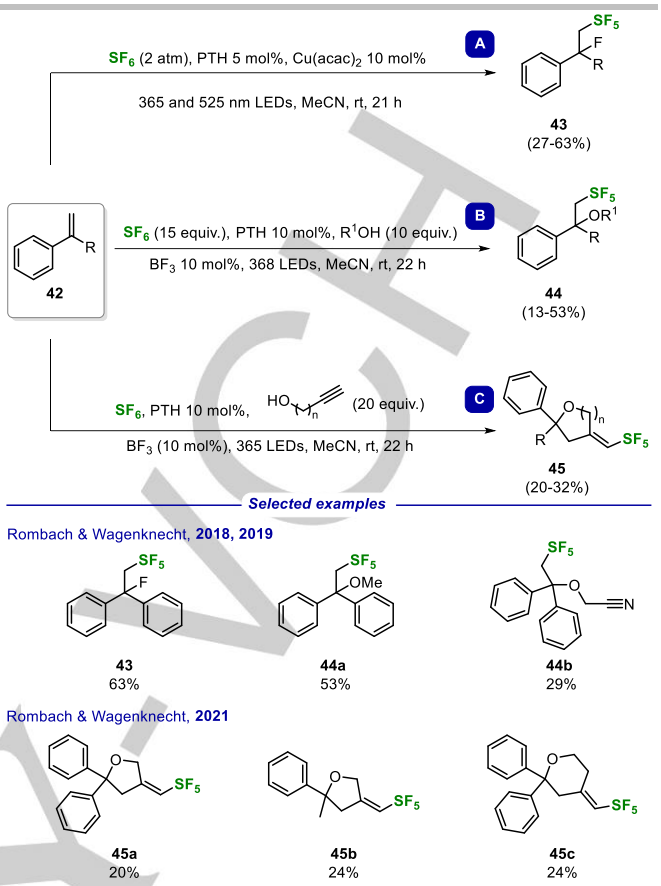
Dielmann and co-workers employed phosphines as Lewis bases to activate SF_6. In agreement with computational studies, activation seems to be achieved via an S_N2 mechanism that involves an initial fluorine transfer via nucleophilic attack of the phosphine. By tuning their basicity, the authors could selectively achieve complete degradation of the SF_6 or formation of salts **41b** having SF_5 as an anionic species.[63]

Tlili and co-workers employed commercially-available TDAE as a two–electron reducing agent to activate SF_6. Besides being used as a as a precursor for ex situ generation of Cl–SF_5 in presence of TCICA the the bench-stable salt **38a** was employed as deoxyfluorinating agent as well (Scheme 13).[58]



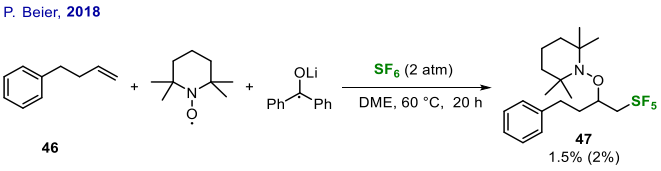
Scheme 14 Reduction of SF_6 using organic electron donors.

Important attempts to harness the potential of SF_6 as an SF_5 donor have been reported by the groups of Beier and Wagenknecht. Rombach and Wagenknecht reported the photoredox activation of SF_6 using catalytic amounts of *N*-phenylphenothiazine and copper salts as radical stabilizing agents. Through two consecutive photoredox catalytic cycles, they achieved compounds **43** via SF_5 radical formation and subsequent trapping by activated styrenes (Scheme 15, A). Furthermore, defluorination of **43** with boron trifluoride etherate yields the corresponding SF_5-substituted allylic compound.[20b] In the following work, the authors shifted towards the synthesis of ethers having a vicinal SF_5 group. The addition of the corresponding alcohols to the reaction mixture quenches the reactive intermediate yielding compounds **44** (Scheme 15, B). The obtained ethers could undergo post-transformations via ether elimination to yield vinylic or allylic SF_5-benzenes or transformation of the corresponding ether into an azide.[20a] Finally, the same group harnessed the potential of their method to access oxygen-containing pentafluorosulfanylated 5-, 6- and 7- membered heterocycles **45** via exo-dig-cyclization in agreement with Baldwin's rules (Scheme 15, C).[64] Albeit the moderate yields and these methods being limited to styrene precursors, the photoredox catalytic activation of SF_6 remains a pioneering approach for using this reagent as an SF_5 source.



Scheme 15 Photoredox catalytic activation to convert SF_6 into pentafluorosulfanylated organic compounds. PTH = *N*-phenylphenothiazine.

Beier and co-workers explored a novel mode of activation for SF_6 using lithium salts of stable radicals (TEMPO or TMINO). In presence of terminal alkenes, they were able to isolate **47**—albeit in a very low yield—deriving from the addition of SF_5 and TEMPO (Scheme 16).[65]



Scheme 16 Reductive activation of SF_6 with TEMPO-Li.

4. SF_5-building blocks and SF_4-bridged precursors in organic synthesis.

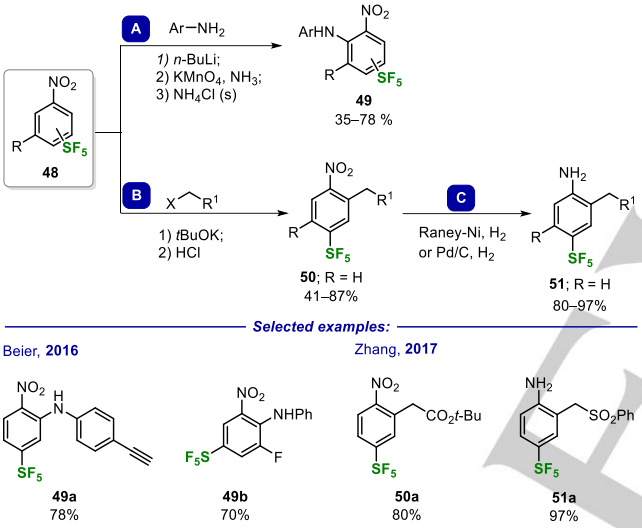
The synthesis of complex scaffolds that bear the SF_5 moiety is far from trivial, and currently cannot be addressed through the late-stage insertion of the SF_5 group. The often–harsh reaction conditions needed to install the SF_5 moiety, and the limited functional group tolerance obliged many research groups to use pre-functionalized building blocks. Below, we review major works that employed SF_5-containing building blocks, being aromatic or

aliphatic, to deliver otherwise-inaccessible SF_5-containing compounds.

4.1. Aryl-SF_5-containing as building blocks

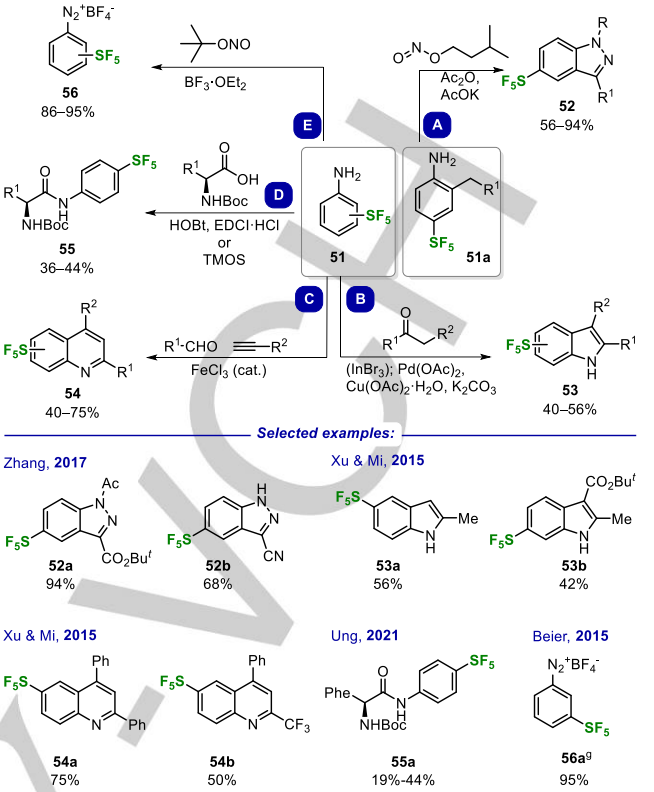
As valuable SF_5-containing building blocks, nitro(pentafluorosulfanyl)benzenes **48** were employed as primary industrial products generated by direct oxidative fluorination of nitrophenyl disulfides.[6] In 2016, Beier and co-workers reported the synthesis of substituted SF_5-containing *N*-aryl-2-nitroanilines **49** via oxidative nucleophilic aromatic amination of SF_5-substituted nitrobenzenes **48** with the lithium salts of anilines (Scheme 17, A).[66]

In 2017, the group of Zhang developed an efficient method to form SF_5-substituted anilines **51**, which could be readily prepared by reacting **48** with EWG-substituted chloromethane via vicarious nucleophilic substitution (VNS) reaction (Scheme 17, B). Subsequent reduction of the nitro group afforded SF_5-attached anilines **51** (Scheme 17, C).[67]



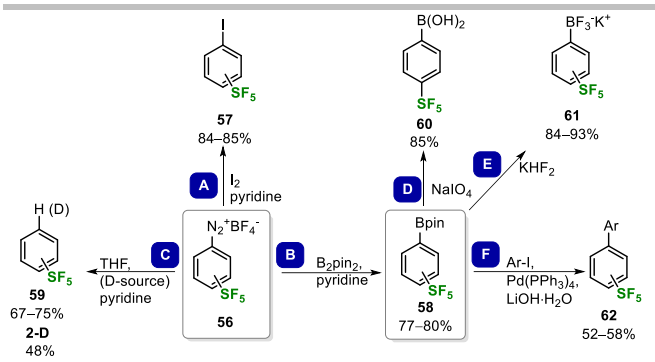
Scheme 17. SF_5-containing nitrobenzenes **48** as an SF_5-building block.

The same authors then used these *ortho*-substituted anilines **51** in a nitrosation/cyclization sequence to give a small library of SF_5-substituted indazoles **52** (Scheme 18, A).[67] Pentafluorosulfanyl anilines **51** have been involved in diverse reactions (Scheme 18). For instance, Mi and Xu developed a Pd-catalyzed direct oxidative cyclization reaction with SF_5-anilines **51** and ketones to give SF_5-substituted indoles **53** (Scheme 18, B).[68] Furthermore, they also synthesized the pentafluorosulfanyl quinolines **54** via a $FeCl_3$-catalyzed three-component tandem coupling/ hydroarylation/ dehydrogenation reaction (Scheme 18, C).[69] In addition, Ung and co-workers employed pentafluorosulfanyl anilines as coupling reagents in amide coupling reactions in the presence of *N*-Boc-protected amino acids (Scheme 18, D).[70] Both the groups of Beier[71] and Ung[70] reported the transformation of the SF_5-substituted anilines **51** into diazonium tetrafluoroborates **56** (Scheme 18, E), later used in downstream post-transformations.



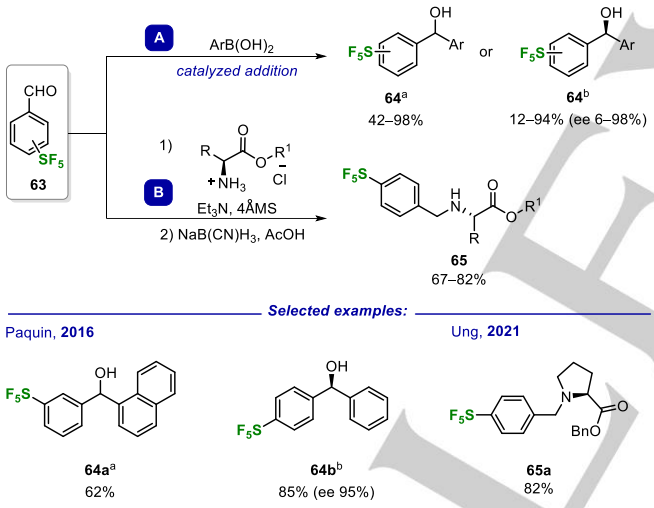
Scheme 18 SF_5-substituted anilines **51** as SF_5-building block. TMOS (tetramethylorthosilicate).

Aromatic diazonium compounds are useful intermediates in organic synthesis in general, and in this case, they represent versatile intermediates as SF_5-building blocks for further post-transformations (Scheme 19). The group of Beier reported a new strategy for efficient iodination (**57** in Scheme 19, A), borylation (**58** in Scheme 19, B) and hydrodediazoniation (59 in Scheme 19, C) of SF_5-phenyldiazonium tetrafluoroborates **56** with an excess of pyridine to induce decomposition of aryldiazonium salts.[71] Further post-transformations of pinacol boronic esters **58** include their oxidative hydrolysis into boronic acids **60** (Scheme 19, D), conversion into trifluoroborates **61** (Scheme 19, E), and coupling products **62** via Suzuki-Miyaura cross-coupling reaction(Scheme 19, F). Ung and co-workers investigated two more applications of the diazonium salt, namely the azo coupling with *N*-acyl protected tyrosine methyl ester, and reaction with $TMSN_3$ to form the corresponding azide product that underwent Cu(I)-catalyzed azide-alkyne cycloaddition (CuAAC).[70]



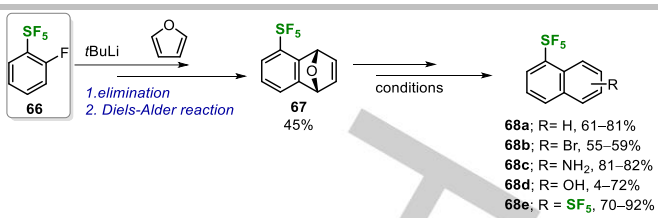
Scheme 19. Further transformations of aryldiazonium tetrafluoroborates and arylpinacolboronates.

Some recent advances in the chemistry of SF_5-benzaldehydes are summarized in Scheme 20. In 2016, Paquin and co-workers described the racemic and enantioselective metal-catalyzed addition of arylboronic acid to 4- and 3-(pentafluororosulfur)benzaldehydes **63,** for the production of SF_5-containing diarylmethanols **64** (Scheme 20, A).[72] In 2021, 4-(pentafluorosulfanyl)benzaldehyde and numerous C-protected amino acid esters gave compounds **65** via a reductive amination (Scheme 20, B).[70]



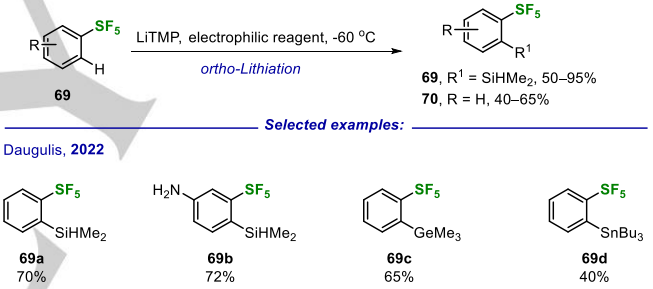
Scheme 20. SF_5-benzaldehydes **63** as the SF_5-building block. a) $PdCl_2$, P(1-Nap)$_3$, K_2CO_3; b) [Ru(p-cymene)Cl_2]$_2$, (R,R)-Me-BIPAM, K_2CO_3.

2-Fluoro-SF_5-benzene **66** also plays an important role in synthesizing the SF_5-containing compounds according to the research of Dolbier and his co-workers in 2016.[36] A lithiation/elimination strategy was used to produce the intermediate *ortho*-SF_5-benzyne, which was trapped in situ by furan to access the resulting stable Diels-Alder adducts **67**. Furthermore, a series of post-transformations of adduct **67** allowed them to obtain previously unknown 1-SF_5-naphthalene **68a** and its derivatives with bromo **68b**, amino **68c**, hydroxy **68d**, and bis-SF_5-substituted naphthalenes **68e** (Scheme 21).



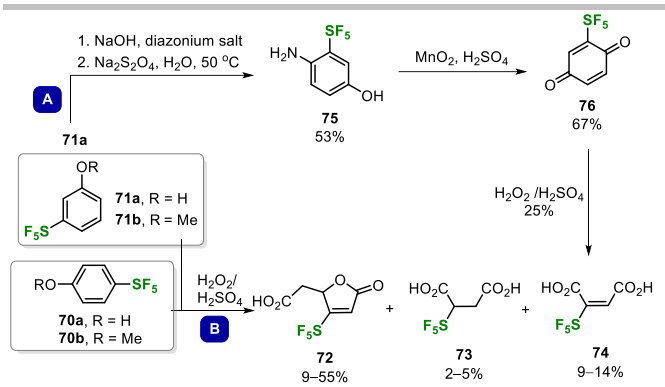
Scheme 21. Using 2-Fluoro-SF_5-benzene **66** as the SF5-building block.

Recently, the first universal approach for producing *ortho*-substituted pentafluorosulfanyl arenes has been established by Le and Daugulis.[73] In the presence of a silyl, germyl, or stannyl electrophile, *ortho*-lithiation by lithium tetramethylpiperidide (LiTMP) produced the substituted arylsulfur pentafluorides **69a–d** in moderate to high yields with outstanding regioselectivities at -60 °C. (Scheme 22). Since the pentafluorosulfanyl group could behave as a good leaving group at temperatures above -40 °C, a careful temperature regime is essential for successful reactions. It was also shown that 2-dimethylsilylpentafluorosulfanyl benzene **69a** could be converted to 2-halo-substituted derivatives, which can be used in cross-coupling reactions.



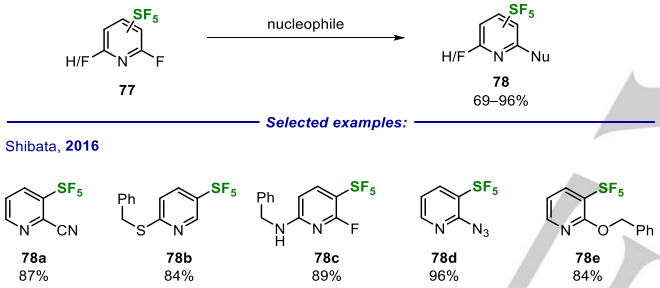
Scheme 22. In situ ortho-lithiation/functionalization of pentafluorosulfanyl arenes.

The group of Beier converted pentafluorosulfanyl benzenes **70** and **71** into SF_5-substituted aliphatic scaffolds (Scheme 23). Muconolactone **72**, succinic **73**, and maleic acids **74** were obtained as a mixture of products from the oxidation of the *para*-substituted adduct **70** with hydrogen peroxide and sulfuric acid (**Scheme 23**, B).[27] Another approach to selectively access SF_5-maleic acid includes the oxidation of the SF_5-substituted *para*-benzoquinone **76**—itself obtained via azo-coupling of **71** followed by reduction of the intermediate. The novel process led to an improved yield of 25% of compound **74** (Scheme 23, B). The SF_5-substituted *para*-benzoquinone **76** also could be catalytically hydrogenated to hydroquinone or be cyclized via Diels–Alder reaction. Through open-chain decarboxylation of SF_5-substituted muconolactone **72**, the SF_5-containing levulinic acid could be obtained and then transformed into the succinic acids **73.** In their work, the current limitation of synthesis of SF_5-containing aliphatics via costly and hazardous radical addition of SF_5Cl (Scheme 38) to unsaturated compounds was overcome.



Scheme 23. Synthesis of aliphatic sulfur pentafluorides from SF_5-anisole and phenol.

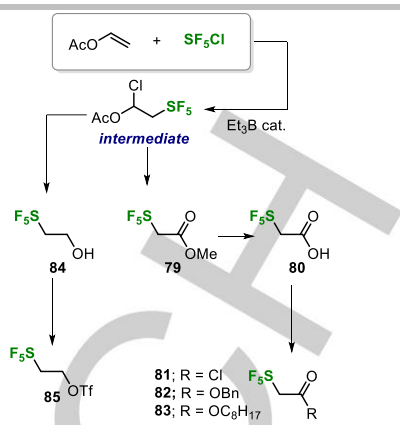
The group of Shibata reported nucleophilic substitution reactions with C-, S-, N-, and O-based nucleophiles carried out on SF_5-pyridines to give the SF_5-containing S_NAr substitution products **78** in good to excellent yields. The regioselectivity of 2,6-difluorinated SF_5-pyridine (for example **78c** in Scheme 24) can be explained by the SF_5 moiety's steric hindrance, which causes nucleophiles to react primarily at the *para* position.[30]



Scheme 24. S_NAr reactions of 2-fluorinated SF_5-pyridines with C-, S-, N-, and O-based nucleophiles.

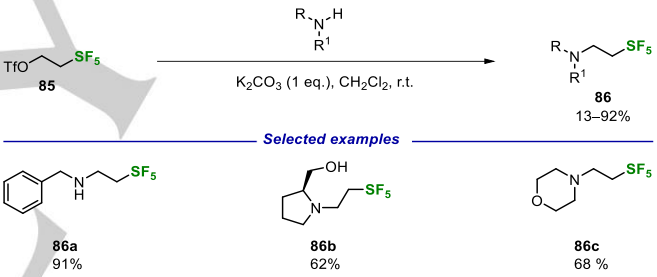
4.2. Aliphatic building blocks containing a C(sp^3)–SF_5-bond

The use of SF_5-containing aliphatic scaffolds in subsequent post-transformations enables the synthesis of chemical structures with increased complexity. Therefore, a consistent part of the research revolved around the preparation of such building blocks (Scheme 25) and their later use. In a nutshell, C(sp^3)-SF_5 building blocks are prepared via the borane-initiated radical addition of SF_5Cl to vinyl acetate following often multistep syntheses. The addition product undergoes oxidation using Caro's acid in MeOH to yield the corresponding ester **79**.[74] Simple base-mediated hydrolysis of **79** yields the corresponding carboxylic acid **80**,[74c, 75] which could be transformed into the acyl chloride **81** or esters **82**–**83**. Furthermore, reduction of the addition intermediate in presence of a hydride source yields the alcohol **84**.[74b, 76] Triflation of alcohol **84** yielded the corresponding triflate **85**.[76]



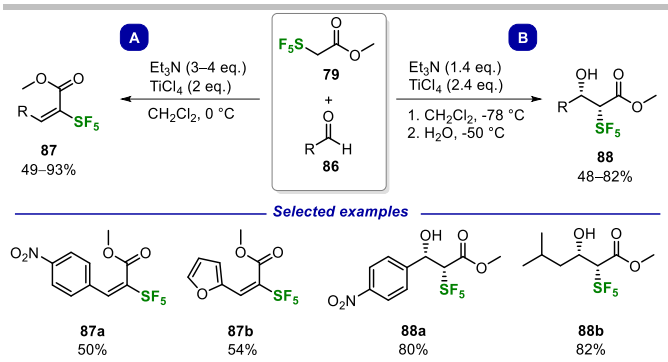
Scheme 25. Multistep synthesis of C(sp^3)-SF_5 building blocks.

The group of Paquin employed the triflate **85** as an electrophilic partner to access a range of *N*-(2-SF_5-ethyl)amines **86** via an S_N2 reaction (Scheme 26). Moreover, they evaluated the effect of the adjacent SF_5 group on the basicity and lipophilicity of the corresponding amines. The SF_5-substituted amines showed lower pK_{aH} and log D compared to the trifluoromethyl counterparts.[76]



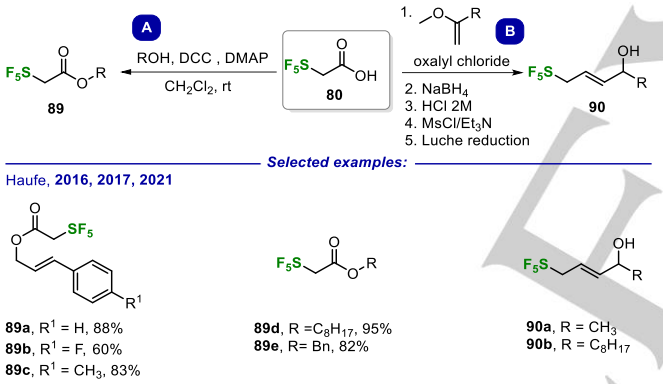
Scheme 26. Alkylation of aliphatic amines using the SF_5-containing electrophile.

The group of Fokin reacted the methyl SF_5-acetate **79** with aromatic aldehydes **86** in aldol reactions in presence of Ti(IV) (Scheme 27, A and B).[77] Both transformations are highly diastereoselective yielding mostly *trans* and *syn* products when the reaction is executed in non-nucleophilic solvents such as CH_2Cl_2 (Scheme 27, B). This has been rationalized by the fact that nucleophilic solvents would impede F···Ti interaction in transition state structures, thus favouring an increase of the *cis* adduct.



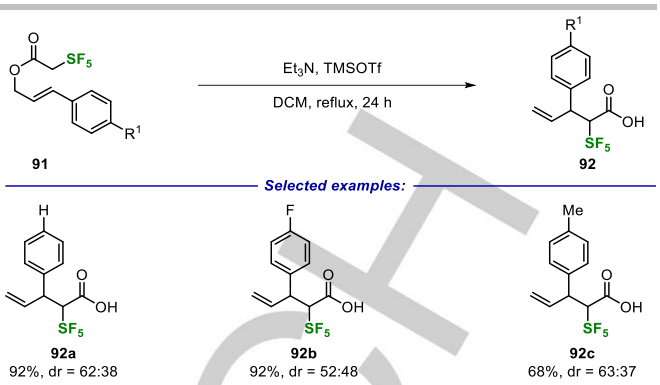
Scheme 27. 2-SF_5-acetate **79** as the SF_5-building block.

Since 2015, the pentafluorosulfanyl acetic acid has been employed as a building block mostly by the group of Haufe. In this regard, it has been used as a coupling partner in Steglich-type esterification reactions in presence of coupling agents and nucleophiles for the synthesis of **89** (Scheme 28, A).[75, 78] Furthermore, it was employed to access compounds **90a**–**b** in a multistep synthesis that includes the addition of the substituted vinyl ether, followed by reduction, hydrolysis, elimination and concludes with a Luche reduction of the corresponding vinyl ketone into the corresponding alcohol Scheme 28, B).[79]



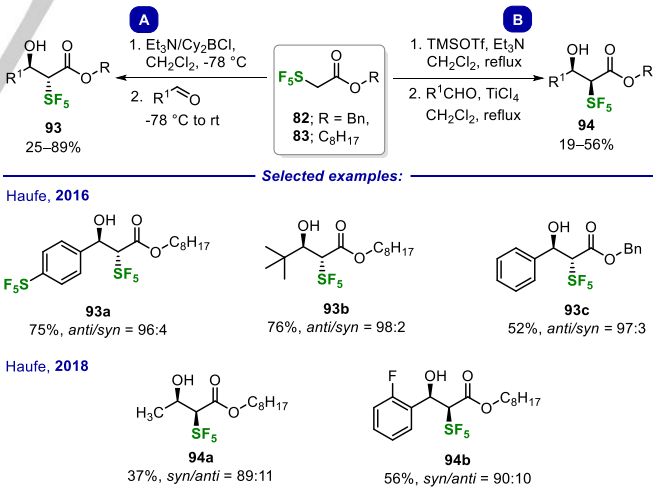
Scheme 28. 2-(pentafluorosulfanyl)acetic acid **80** as the SF_5-building block.

SF_5-cinnamyl esters **91** were used as starting materials in Ireland-Claisen [3,3]-sigmatropic rearrangements, yielding *syn*/*anti* diastereoisomeric mixtures of equal ratio (Scheme 29). The low diastereoselectivity arises from similar energies of *E* and *Z* reaction intermediates and the very small differences in energy barriers of the four different transition states, suggesting that the product could be formed via all the four transition states. Furthermore, compounds **92** were transformed into the corresponding methyl esters by applying Steglich esterification conditions.[78]



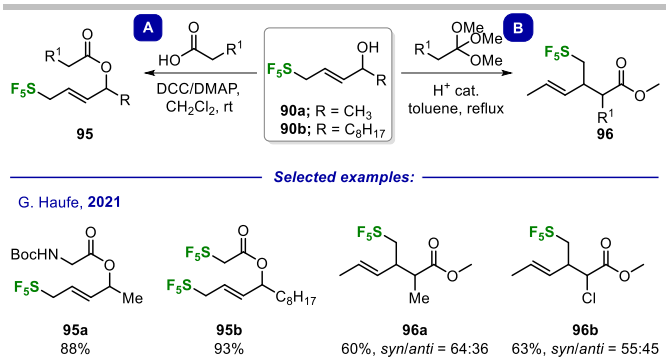
Scheme 29. Ireland-Claisen [3,3]-sigmatropic rearrangements of SF_5-cinnamyl esters.

SF_5-containing esters **82**–**83** were further employed in aldol reactions by the group of Haufe. Both octyl and benzyl SF_5-esters gave the desired addition products **93a**–**c** with excellent anti-diastereoselectivity (Scheme 30, A). The stereochemistry of the compounds was confirmed by NMR analysis and X-ray diffraction analysis. Hence, this work and the previous transformation from the group of Fokin could be considered complementary given that *syn* or *anti* esters could be obtained by varying the Lewis acid.[75a] The importance of the Lewis acid in determining the diastereoselectivity of the product was later confirmed by the group of Haufe. Indeed, they observed a shift in selectivity towards the *syn* conformation that led to compounds **94a**–**b** when $TiCl_4$ was employed as a Lewis acid (Scheme 30, B). However, in this case, the aldol addition is substrate-dependent and *p*-substituted benzaldehydes with EDG did not yield the desired product, probably due to the instability of intermediates.[80]



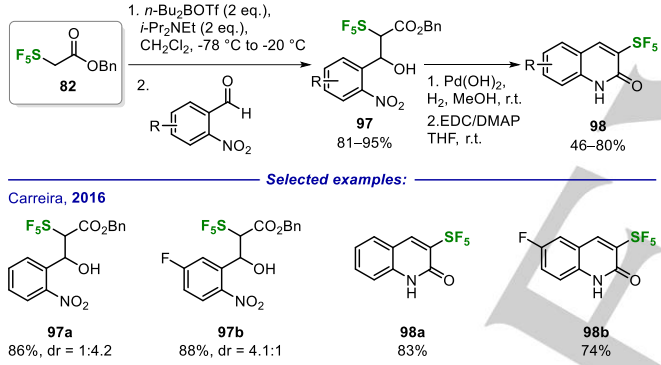
Scheme 30. Octyl and benzyl SF_5-acetates as the SF_5-building blocks.

Previously synthesized (Scheme 28) allylic alcohols **90a**–**b** were employed as coupling partners in the Steglich esterification reaction with carboxylic acids (Scheme 31, A). Furthermore, **90a** underwent Claisen rearrangement in presence of an ortho ester in acidic conditions, yielding *syn*/*anti* mixtures of diastereoisomers **96a**–**b** (Scheme 31, B).[79a]



Scheme 31. Allylic SF_5-alcohols as the SF_5-building blocks.

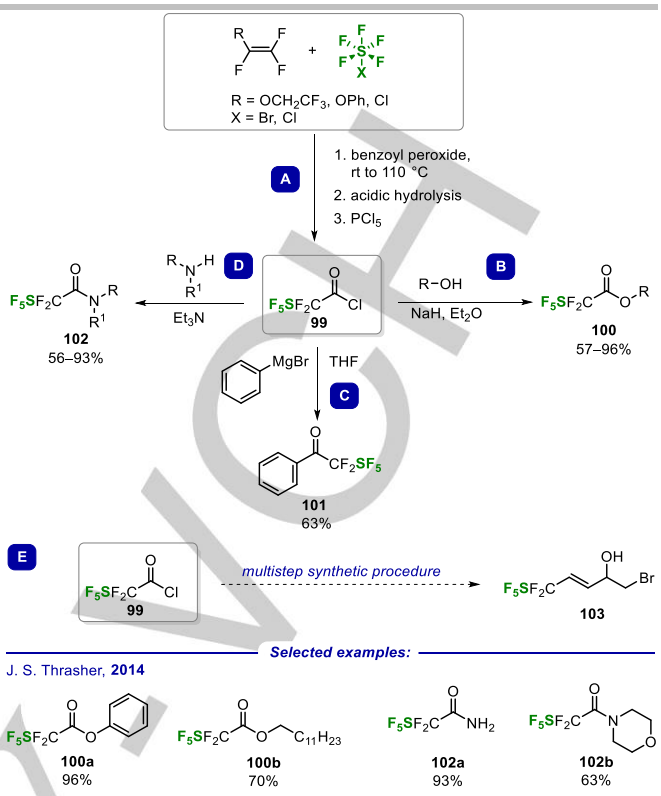
The group of Carreira activated the benzyl SF_5-acetate **82** via a boron-mediated enolate to access a small library of aldol addition products, predominantly having an *anti* configuration.[75b] The derived products **97** were transformed into SF_5-quinolinones **98** in a two-step synthesis, being reduction and intramolecular amide coupling (Scheme 32). Furthermore, SF_5-quinolinones were converted into halogenated quinolines, which underwent further post-transformations.



Scheme 32. Synthesis of 3-SF_5-quinolin-2-ones from α-SF_5-enol via aldol adducts.

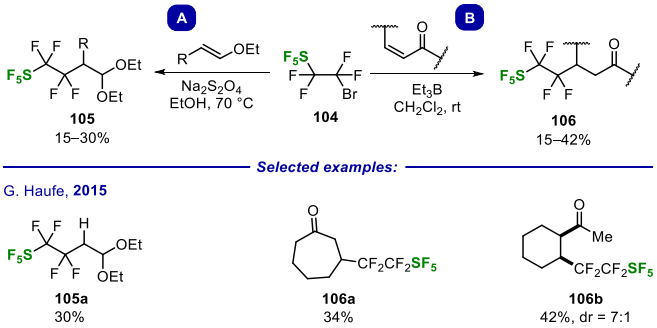
Other building blocks that found recent use are the difluoromethyl SF_5-acetic acid and derivatives. Haufe and co-workers reported the synthesis of pentafluosulfanyldifluoroacetic acid from three distinct starting materials (Scheme 33, A). Radical addition of SF_5Cl to trifluorovinyl ethers or of SF_5Br to chlorotrifluoroethylene followed by hydrolysis of the isolated intermediate yielded the corresponding acid. The acid was converted to its acyl chloride and reacted with alcohols (Scheme 33, B), Grignard reagents (Scheme 33, C) and amines (Scheme 33, D) to yield compounds **100**–**102**.[81]

Furthermore, the same group reported the synthesis of the allylic alcohol **103** (Scheme 33, E) following a similar multistep procedure as reported in Scheme 28, A.[79b] The adduct **103** was tested in a Claisen rearrangement reaction under the same conditions reported in Scheme 31 B but undergoes loss of the SF_5 group.[79a]



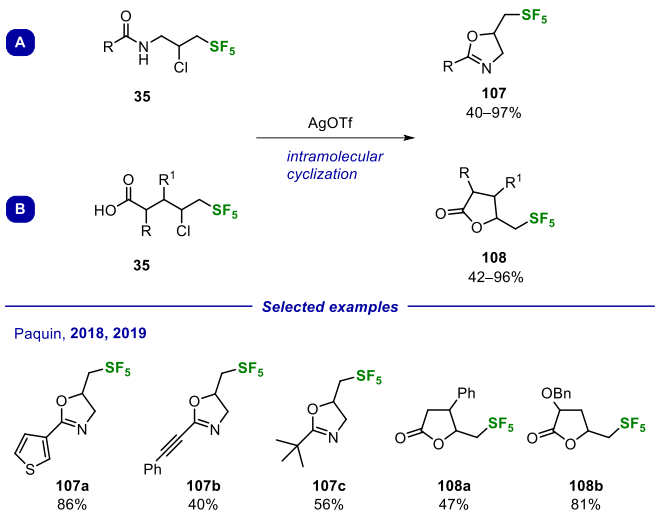
Scheme 33. Pentafluorosulfanyldifluoroacetyl chloride as the SF_5-building block.

Longer perfluoroalkyl chains bearing SF_5 have been employed as building blocks as well. Haufe and co-workers reported the radical addition of SF_5-perfluoroalkyl bromide to ethyl vinyl ethers (Scheme 34, A) and *α,β*-unsaturated ketones (Scheme 34, B) by employing sodium dithionite or triethyl borane as radical initiators, respectively. Despite the interesting results and the successful activation of **104**, the reaction suffers from low yields and limited substrate scope. Nonetheless, the ambiphilic character of the formed radical renders **104** a decent reaction partner for both electron-rich and electron-deficient alkenes.[82] More recently, Thrasher and co-workers transformed three SF_5-perfluoroalkyl halides into their corresponding hydrofluorocarbons SF_5CF_2H and $SF_5CF_2CF_2H$ in presence of triethylborane or tributyltin hydride.[83] Besides, SF_5-iododifluoromethane and SF_5-iodotetrafluoroethane have been employed as radical donors in presence of metallic copper for decorating fullerenes with SF_5-perfluoroalkyl groups.[84]



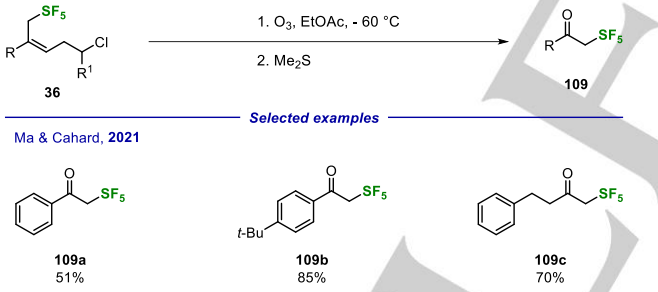
Scheme 34. Halogenated perfluoroalkyl chains bearing SF_5 as SF_5-building blocks.

More recently, Paquin and co-workers reported a silver-mediated intramolecular cyclization of substituted amides and carboxylic acids **35**. The chlorine in β-position to the SF_5 group undergoes substitution instead of elimination, yielding the corresponding oxazolines **107** and lactones **108** (Scheme 35, A and B).[54]



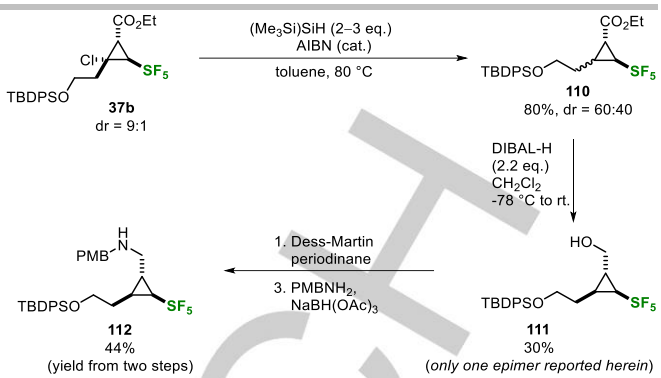
Scheme 35. Intramolecular cyclization reactions that lead to the formation of oxazolines (A) and γ-butyrolactones (B).

Feng, Ma, and Cahard transformed the previously synthesized *α*-SF_5-alkenes **36** (Scheme 11) to *α*-SF_5 ketones via ozonolysis. In addition, the reaction applies to the formation of both aromatic and aliphatic ketones (**109a**–**c** as examples in Scheme 36).[55]



Scheme 36. Synthesis of α-SF_5 ketones.

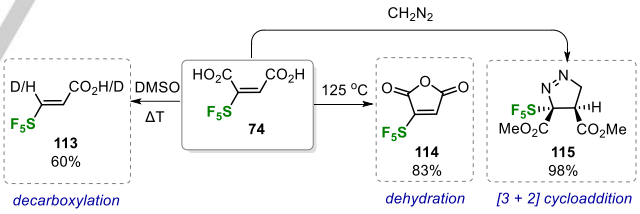
Cossy, Meier and co-workers reported many post-transformation reactions of the scope deriving from the radical addition of SF_5Cl to cyclopropenes (Scheme 11, C). A diastereoisomeric mixture (d.r = 9:1) of **37b** (Scheme 11) underwent hydrodechlorination in presence of tris(trimethylsilyl)silane as a hydrogen donor and AIBN as a radical initiator yielding an epimeric mixture of final products **110**. The same mixture **110** was reduced to the corresponding alcohol **111** in excess of DIBAL-H, yielding equimolar amounts of both diastereoisomers (only diastereoisomer having *S*-configuration at C-2 is shown). Then, compound **111** was transformed into compound **112** in two steps including oxidation with DMP followed by reductive amination of the aldehyde (Scheme 37). These transformations showcase once more the stability of the SF_5 group towards the abovementioned reaction conditions.[56]



Scheme 37. Transformations of cyclopropanes bearing an SF_5 group.

4.3. Aliphatic building blocks containing a C(sp^2)–SF_5 bond

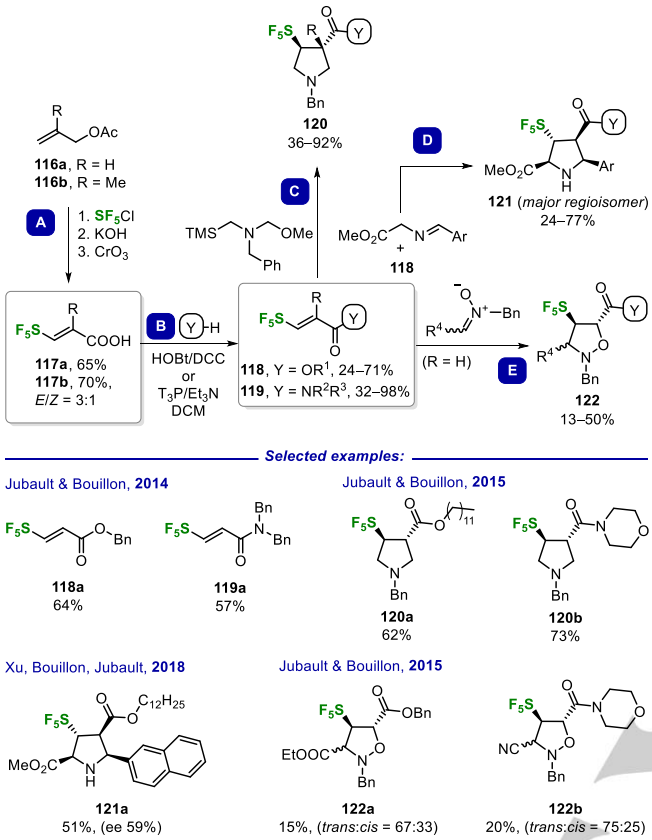
Aside from the C(sp^3)–SF_5-containing aliphatic building blocks we summarized above in section 4.2, the C(sp^2)–SF_5 attached counterparts also play a crucial role in building SF_5-substituted compounds. As already mentioned in Scheme 23, the group of Beier obtained SF_5-substituted maleic acid **74** from SF_5-substituted phenols. They also reported further post-transformations of **74** to prepare a variety of aliphatic SF_5-containing compounds (Scheme 38).[27] For example, with an excess of diazomethane, the transformation of SF_5-substituted maleic acid **74** to the (3+2) cycloaddition product **115** was successful in 98% yield. The SF_5-substituted maleic acid **74** could also give way to anhydride **114** in a good yield (83%), which could be used in subsequent Diels-Alder reactions with cyclopentadiene. Importantly, via decarboxylation, maleic acid **74** afforded a handy SF_5-building block, acrylic acid **113** as well as its deuterated counterpart.



Scheme 38 Further transformations of SF_5-substituted maleic acid **74**.

As Jubault and Bouillon reported in 2014, SF_5-acrylic acids could also be prepared via the radical addition of SF_5Cl to allyl acetate **116** (Scheme 39, A).[85] After esterification and amidation of SF_5-acrylic acid **117**, the corresponding acrylate esters **118** and acrylamides **119** were obtained smoothly (Scheme 39, B). This provided a platform for various, more complex, SF_5-containing structures. For example, they reported the first effective synthesis of SF_5-pyrrolidines **120** by means of a 1,3-dipolar cycloaddition with azomethine ylides (Scheme 39, C).[86] Similarly, doing the cycloaddition with glycine Schiff bases in the presence of a chiral ligand permitted them the production of enantioenriched SF_5-pyrrolidines **121** bearing four contiguous carbon stereocenters (Scheme 39, D).[87] In addition, SF_5-substituted isoxazolidines

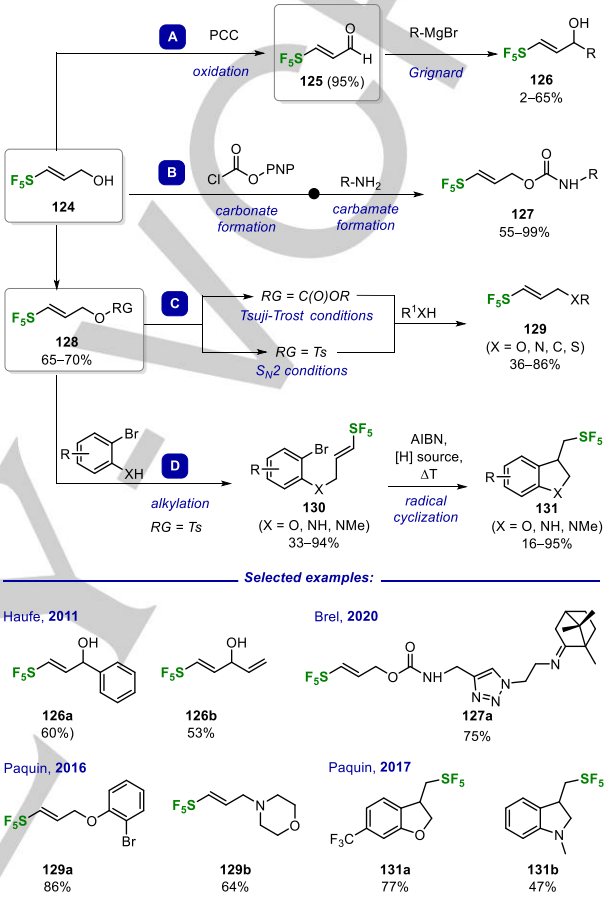
122a–**b** were obtained from 1,3-dipolar cycloadditions of nitrones in reasonable yields (Scheme 39, E).[88]



Scheme 39. Preparation and transformations of SF_5-acrylic esters **118** and SF_5-acrylic amides **119**.

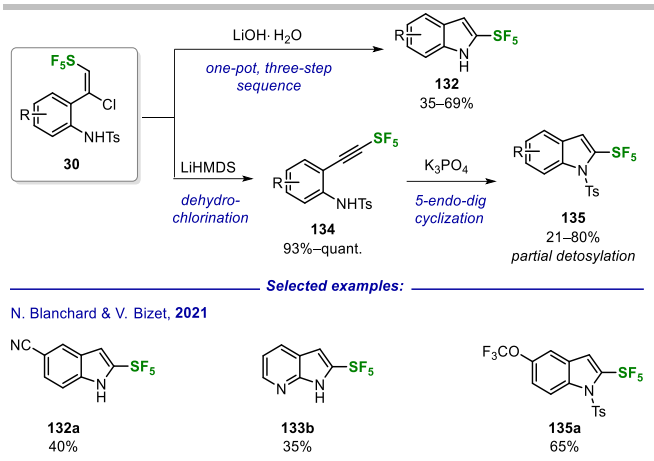
SF_5-allylic alcohol **124** is another core structure that serves as a useful predecessor to other pentafluorosulfanylated motifs. It can be prepared from SF_5Cl addition onto allyl acetate **116**[85] or allyl alcohol,[89] although it is currently also sold by some providers. In 2011, Haufe and co-workers showed how alcohol **116** could be turned into 3-SF_5-acrolein **125** by Cr(VI)-mediated oxidation. These in turn could undergo Grignard additions to prepare various *γ*-SF_5-substituted allyl alcohols **126** (Scheme 40, A).[90] In a follow-up work, they studied several carboxylate esters of the abovementioned allyl alcohols but found that the resulting products were very reluctant to undergo [3,3]-sigmatropic Claisen rearrangements, in sharp contrast to CF_3-substituted allyl species.[79a] In 2020, Brel and co-workers built the SF_5-allyl alcohol into an activated carbonate, which could be easily substituted by various primary amines to form carbamates **127**. In the case of propargylamine, a subsequent click step was applied to attach a pentafluorosulfanylvinyl moiety to bioactive substrates like camphecene as in compound **127a** (Scheme 40, B).[91]

In 2016, the group of Paquin investigated two strategies using SF_5-allylic alcohol **126a** as starting building block to attach the *E*-3-(pentafluorosulfanyl)allyl chain onto various nucleophiles.[92] One strategy was using the palladium-catalyzed Tsuji–Trost coupling between allyl carbonate **128** and the desired nucleophiles, which was especially effective for phenols and carbon acids. On the other hand, the nucleophilic substitution reactions on the corresponding tosylate also afforded the same range of products **129**, which proved more fruitful for secondary amines and thiols (Scheme 40, C). The year thereafter, the group used similar methods to access acyclic structures **130**, as starting materials for the radical, intramolecular hydroarylation of the double bond to give SF_5-decorated dihydrobenzofuran and indoline derivatives **131** (Scheme 40, D).[93]



Scheme 40 Using SF_5-allylic alcohol **124** as SF_5-building block. RG = reactive group, PNP = *p*-nitrophenyl.

Another class of interesting C(sp^2)–SF_5-containing aliphatic building blocks, chloro pentafluorosulfanylated olefin **30**, was developed from 2-ethynylaniline derivatives **29** by Blanchard and Bizet in 2021 (Scheme 11). This styrene derivative could produce the hitherto unknown 2-SF_5 indoles **132** via a one-pot three-step sequence consisting of dehydrochlorination, 5-*endo-dig* cyclization, and deprotection. By tuning the choice of base, this process could be split up to first deliver SF_5-alkynes **134** and subsequently *N*-protected 2-SF_5 indoles **135**. Various post-transformations of 1- and 3-positions were demonstrated as well (Scheme 41).[46]

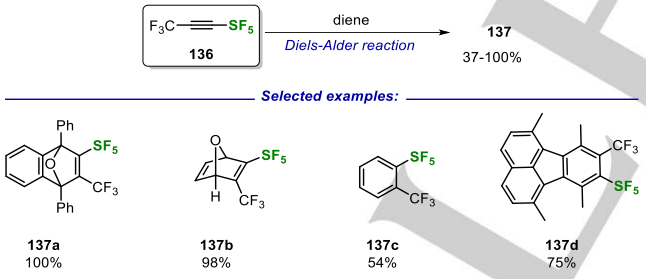


Scheme 41 The use of chloropentafluorosulfanylated olefin **30** and SF_5-alkynes **134**.

4.4. Aliphatic building blocks containing a C(sp)–SF_5-bond

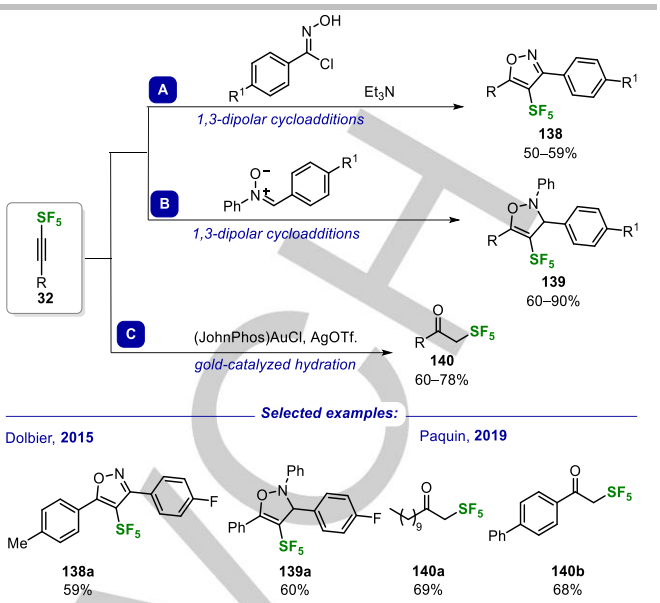
Apart from the SF_5-alkyne substituted arylamines generated as intermediates in the synthesis of the azaheterocycles reported in Scheme 41,[46] other C(sp)–SF_5-containing aliphatic compounds were prepared and used as building blocks in synthetic transformations.

In 2015, Duda and Lentz reported the synthesis of F_5S–C≡C–CF_3 (**136**) in two steps from 3,3,3-trifluoropropyne and used it in Diels-Alder reactions with various dienes such as diphenylbenzoisofuran, furan, cyclohepta-1,3,5-triene, 2*H*-pyran-2-one, and a cyclopentadienone derivative to name a few. The respective addition products **137a-d** were obtained in fair to excellent yields (Scheme 42).[94]



Scheme 42. F_5S–C≡C–CF_3 **136** as a dienophile in Diels-Alder reactions.

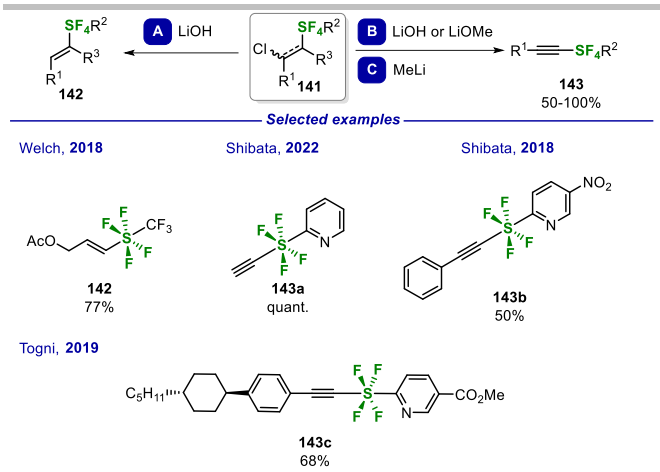
Moreover, the transformations of other SF_5-alkynes **32** were explored by the groups of Dolbier in 2015 and Paquin in 2019 (Scheme 10).[45, 47] First, using SF_5-substituted aryl acetylenes as dipolarophiles with in situ produced nitrile oxides and nitrones as 1,3-dipoles, 4-SF_5-isoxazoles **138** (Scheme 43, A) and 4-SF_5-isoxazolines **139** (Scheme 43, B) were respectively generated in good to excellent yields.[45] Additionally, the regioselective hydration of SF_5-alkynes catalyzed by gold(I) complexes was investigated. Herein, the corresponding SF_5-substituted ketones **140** were obtained as single regioisomers in good yield when SF_5-alkynes substituted both with aliphatic and aromatic substituents were used (Scheme 43, C).[47]



Scheme 43. SF_5-alkynes with aliphatic or aromatic substituents as SF_5-building blocks in dipolar cycloaddition and hydration reactions.

4.5. Post-transformations of SF_4-bridged compounds

As briefly mentioned in section 2.4, research around the SF_4-bridged compounds is being developed only recently. Adducts obtained from the addition of R–SF_4Cl intermediates to unsaturated organic compounds can serve as steppingstones to various SF_4-bridged molecules. This also depicts the stability of the SF_4 linking group towards many typical organic synthesis reagents as well as higher temperatures.[40] Base-catalyzed dehydrochlorination of *β*-chlorinated SF_4-bridged compounds has surfaced in the literature multiple times. In 2018, Welch and colleagues reported an allyl acetate **142** with an -SF_4CF_3 group connected to a double bond via dehydrochlorination in presence of LiOH (Scheme 44, A).[40] In addition, SF_4-bridged alkynes **143** can be afforded via a dehydrochlorination reaction starting from R–SF_4-alkene species (Scheme 44, B and C). Treatment of the corresponding alkenes with methyl lithium,[95] LiOH[39a] or LiOMe[19] yields the substituted alkynes **143a–c**. Shibata and co-workers transformed a high number of *ortho*-, *meta*- and *para*-SF_4-pyridine alkenes into their corresponding alkynes that underwent consecutive post-transformations (Scheme 45, E).[39a] On the other hand, the use of a stronger base such as methyl lithium on the tri-substituted alkene **141** yields the terminal pyridine-SF_4-alkyne **143a** that has been later used as a precursor for downstream transformations (Scheme 44, B).[39a, 95]

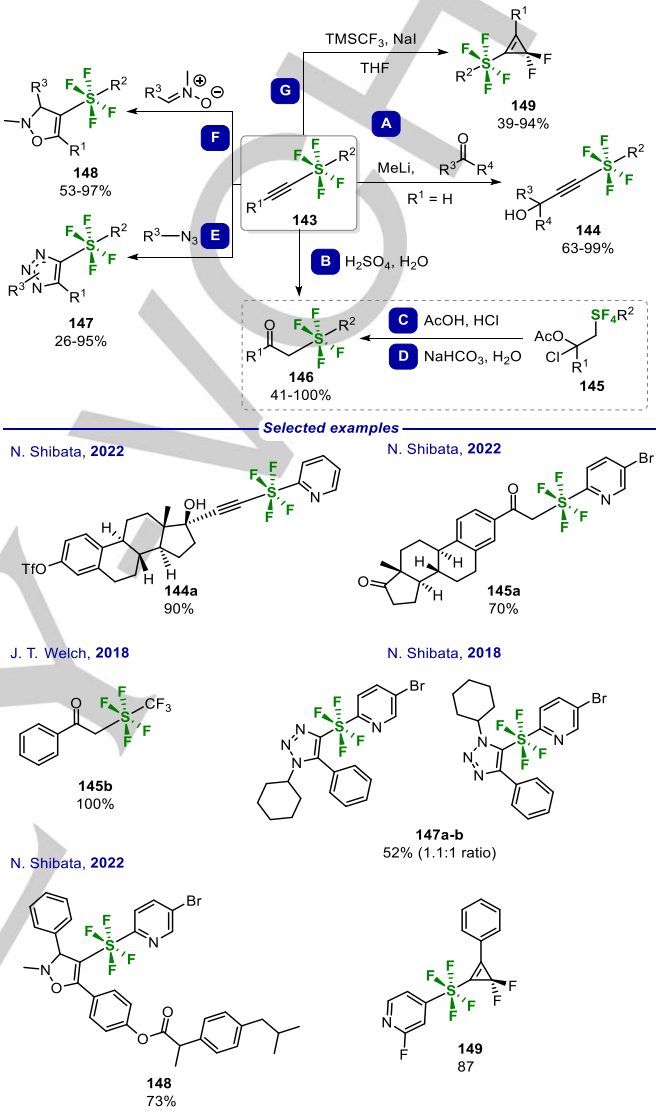


Scheme 44 Dehydrochlorination of β-chlorinated SF_4-bridged compounds

It is also worth mentioning that structures with an SF_4 linker attached to a C≡C bond are becoming increasingly attractive starting materials in synthesis due to the rich chemistry of C≡C bonds in constructing more complex moieties. Taking that into account, research groups have reported interesting syntheses involving R-SF_4-alkynes as starting materials. For example. Shibata and colleagues synthesized a wide variety of pyridine-SF_4-ethynyls **144** through alkynylation of different carbonyl compounds in good to excellent yields (Scheme 45, A).[95]

Furthermore, metal-free regioselective hydration of the C≡C bond to give previously inaccessible *α*-pyridine-SF_4-methyl ketones **146** was reported by the group of Shibata (Scheme 45, B).[96] However, this has not been the only strategy to acquire R-SF_4-methyl ketones. The team of Welch prepared the targeted structures **146** under either acidic or basic conditions, starting from chloroacetates (Scheme 45, C and D).[97]

Rod-like molecules with two independent (hetero)aromatic rings are gaining attention in medicinal chemistry.[39] In recent years, successful attempts to synthesize SF_4-bridged bis-heteroaryl compounds having a *trans* configuration from R–SF_4-alkynes have been reported.[39] A short while ago, instances of heterocycles linearly bonded via the SF_4 moiety were, for the first time, introduced by the team of Shibata. Therein, a thermal Huisgen 1,3-dipolar cycloaddition reaction between pyridine-SF_4-alkynes and organoazides provides unique linearly linked pyridine-triazole structures **147** in high yields (Scheme 45, E). Using the same protocol, aryl-SF_4-triazoles were prepared as well. A vast range of starting materials incorporating highly complex moieties was applied in this reaction providing easy access to drug-like compounds. Nevertheless, it is unfortunate that in virtually all cases, this methodology does not provide satisfying regioselectivity as to which regioisomer is the main product.[39a] To further expand the library, another type of these compounds was lately presented by the same research group. From a 1,3-dipolar cycloaddition of pyridine-SF_4-alkynes and nitrones, they regioselectively achieved rod-like pyridine-SF_4-isoxazolines **148** (Scheme 45, F). It appears that the functional groups on either side of the SF_4 bridge do not affect the regioselectivity of the [3+2] cycloaddition.[39b] Very recently, the group of Shibata reported a [2+1] cycloaddition of electron-deficient pyridine-SF_4-alkynes with the Ruppert-Prakash reagent $TMSCF_3$ as an electrophilic difluorocarbene source to access pyridine-SF_4-*gem*-difluorocyclopropenes **149** (Scheme 45, G).[98] It is worth mentioning that the methodology is not only limited to pyridine-SF_4-alkynes but extendable to benzene analogs as well.



Scheme 45 Synthetic applications of R-SF_4-alkynes

5. Applications of SF_5-containing compounds and analogs.

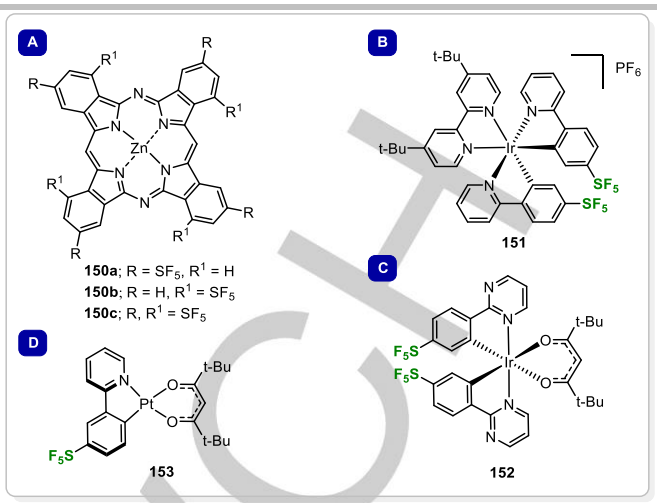
Insertion of fluorine atoms or fluorinated groups in organic structures modulates reactivity, lipophilicity, stability, conformational properties, as well as the acidity of adjacent functional groups.[99] Simultaneously, they infer minimal steric hindrance compared to their non-fluorinated counterparts. As such, fluorinated building blocks find widespread applications in many fields spanning medicinal and materials chemistry, agrochemicals, and organic chemistry.[100] In this context, the SF_5 moiety remains one of the least exploited polyfluorinated groups when it comes to applications. Synthetic bottlenecks— which have only been addressed recently —may have restrained its

subsequent applications compared to the CF_3 counterpart. Nonetheless, there are many examples applied to materials and biosciences highlighting the superiority of SF_5-containing molecules compared to mainly CF_3-bearing analogues. Herein, we will discuss the most recent applications.

5.1. Pentafluorosulfanyl group in materials sciences

In the last two decades, the SF_5 group and closely related analogs, have been employed in materials science. Its incorporation in distinct building blocks offers the opportunity to fine-tune the optoelectronic properties of many functional materials.[101] Early applications include the design of novel polymers and liquid crystals. Gard and co-workers reported a series of distinct classes of polymers featuring SF_5-containing aliphatic sidechains.[102] X-ray photoelectron spectroscopy (XPS) showed non-stoichiometric surface enrichment in the SF_5 functionality, even in presence of large excess of the non-fluorinated monomer. Kirsch and co-workers designed many liquid crystals bearing the "polar hydrophobic" SF_5 as a terminal group.[103] They achieved strong dielectric anisotropy values (up to 22.3) and reasonably high extrapolated clearing points.

Since 2015, the use of SF_5-enriched scaffolds expanded towards the design of luminescent functional materials including metallocycles, transition metal complexes, and organic fluorophores. Along this line of research, the group of Shibata reported a series of directly and indirectly SF_5-decorated phthalocyanines and subphthalocyanines **150a–c**.[104] In agreement with computational calculations, the presence of the SF_5 group in the β-position of the phthalocyanines shifts the Q-band (S0→S1 transition) to a longer wavelength. Furthermore, it confers an exceptionally high quantum yield (Φ) compared to the α-substituted and α,β-disubstituted phthalocyanines (Scheme 46, A).[104b] Simultaneously, Wiehe and co-workers accessed a series of SF_5 substituted macrocycles including corroles, porphyrins, BODIPYs as well as their corresponding dipyrrane precursors (not shown).[105] Luminescent transition metal complexes bearing SF_5 include iridium- and platinum-based complexes. Samuel, Zysman-Colman and co-workers reported a series of green- to yellow-green-emitting phosphorescent SF_5-functionalized Ir(III) complexes **151** (Scheme 46, B). The presence of a strong electron-withdrawing SF_5 group induces a hypsochromic shift and increases redox gaps and oxidation potentials compared to fluorine or trifluoromethyl-substituted complexes. The irreversible reduction of SF_5 in cyclic voltammetry might pose a problem in employing these complexes in organic electronics. Despite this, they exhibit electroluminescence when incorporated into doped multilayer organic light-emitting diodes (OLEDs).[106] Pope, Brown, and co-workers adopted a machine-assisted approach to deliver a series of Ir(III)-based complexes. All complexes are blue-green-yellow emitters with low quantum yields (Φ = 0.1–0.19).[107]

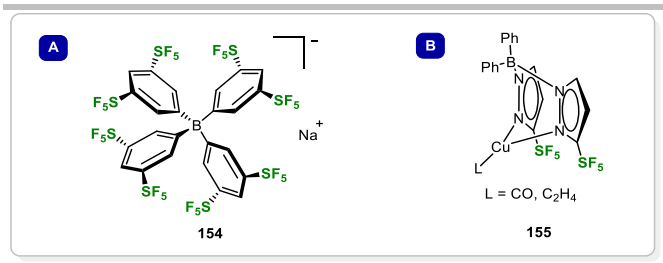


Scheme 46 Structure of SF_5 substituted phthalocyanines reported by Shibata [104b] (A), Zysman-Colman [106, 108] (B and D) and Zuo [109] (C).

Zuo, Zheng and co-workers used distinct combinations of ancillary and cyclometalated ligands to design neutral Ir(III) complexes with good to excellent quantum yields (0.49–0.95).[109] When SF_5-phenyl bearing isoquinolines were used as cyclometalated ligands, phosphorescent emissions shifted towards red (up to 607 nm). Furthermore, complex **152** (Scheme 46, C) harbours potential as a colorimetric probe for detecting Hg^{2+} ions.

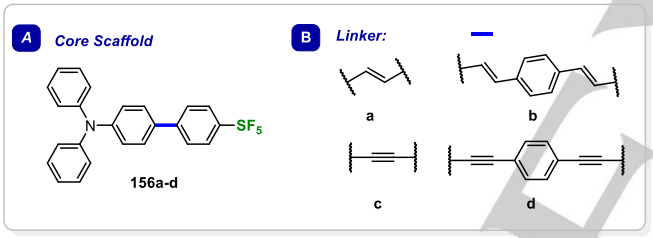
Besides Ir(III) complexes, two isomeric Pt(II)-based phosphorescent complexes were reported by the group of Zysman-Colman (Scheme 46, D). The presence of SF_5 exhibited a marked effect on the properties of the complexes.[108] For instance, *meta*-substituted complexes undergo a bathochromic effect compared to non-substituted ones, owing to the stabilizing effect of the lowest triplet excited state. On the contrary, *para*-substitution stabilizes the metal-based orbitals rather than affecting the triplet state, thus leading to a hypsochromic effect (Scheme 46, D only *para*-substituted complex **153** shown).

The pentafluorosulfanyl group has recently been employed in catalyst design as well. SF_5-decorated ligands that are used as catalyst support seem to meet many of the required criteria. For instance, the SF_5 group is stable and inert, highly electron-withdrawing and imparts the expected hindrance to the ligands. Furthermore, its higher lipophilicity increases catalyst solubility in organic solvents. Mecking and co-workers employed aryl-SF_5 scaffolds in designing weakly coordinating boron anions in nickel catalysis. The catalyst showed a two-fold increase in polymerization activity compared to the trifluoromethyl counterpart (Scheme 47, A).[110] Mykhailiuk, Dias and co-workers designed SF_5-bearing poly(pyrazolyl)borates **155** as supporting ligands for copper catalysts.[111] Compared to the trifluoromethylated analog, the SF_5-tagged catalyst provided higher yields in cyclopropanation reactions (Scheme 47, B). The SF_5 moiety was incorporated as well in phosphine-based ligands by Braun and co-workers. Their X-ray data showed that SF_5-triphenylphosphines have a larger Tolman cone angle compared to *para*-substituted phosphine ligands bearing $N(CH_3)_2$, CH_3, OCH_3, F, and CF_3 substituents.[112]



Scheme 47 Structure of (A) SF_5-containing weakly coordinating borate anions for Ni-catalysed polymerizations reported by Mecking;[110] (B) SF_5-containing poly(pyrazolyl)borate ligands for Cu catalysts reported by Mykhailiuk and Dias.[111]

Finally, the SF_5 group has been used as an electron acceptor in organic fluorophores. The group of Chan reported a series of push-pull dyes **156a**–**d** featuring an amine donor and SF_5 acceptor group. Such systems exhibit a very large Stokes shift (117–150 nm) and decent quantum yields (Φ = 0.24–0.49).[113] In addition, some of the candidates have relatively large two-photon absorption cross sections, a hint to potential use in two-photon excitation microscopy.[114] Other attempts to discover useful dyes applicable to bioimaging include the synthesis of azulene dyes bearing phenyl-SF_5. These isomers share similar absorption spectra, but upon protonation, the spectroscopic response varies between isomers.[115]



Scheme 48 Selected examples of push-pull dyes developed by the group of Chan.[114]

Overall, the use of the SF_5 group in distinct fields of materials science is steadily increasing. The recent applications of the SF_5 group in the design of luminescent materials and supports for transition metal catalysts denotes its versatility. In perspective, we expect to witness increased applicability of SF_5-containing candidates in catalysis and bioimaging.

5.2. Pentafluorosulfanyl group in medicinal chemistry

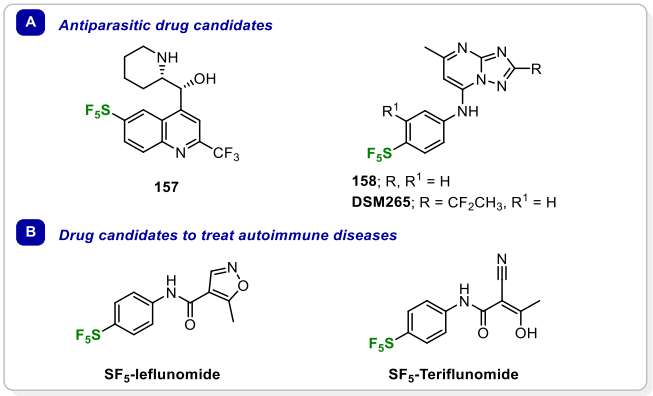
Commercial pharmaceuticals having at least one fluorine atom account for approximately 20 % of the market. Such numbers are particularly high given that only a handful of organofluorine compounds—and most of them highly toxic—have been discovered in nature. According to a recent analysis carried out by Inoue and Shibata, monofluorinated and trifluoromethylated moieties comprise 86 % of the fluoropharmaceuticals.[116] However, the synthetic accessibility towards these moieties is exceedingly high compared to many other fluorinated emerging moieties. In the last two decades, synergistic efforts of distinct research teams de-risked the synthesis of many other "exotic" fluorinated groups including -OCF_2R, -SCF_2R and -$SeCF_2R$ to mention a few.[117] This preceded the blooming of these fluorinated motifs in drug discovery, with many candidates reaching the market or entering clinical trials. Among these, it is worth highlighting: *i*) riluzole, one of the few available treatments used in amyotrophic lateral sclerosis; *ii*) the recently FDA-approved antituberculosis pretomanid; and *iii*) flomofex, an investigational candidate to treat urinary tract infections.[118] The pentafluorosulfanyl group and related analogs can be considered underutilized moieties in this setting, most likely owing to synthetic bottlenecks. Nonetheless, the SF_5 group is considered a prominent bioisostere of many functional groups including trifluoromethyl, *t*-butyl, NO_2, and halogens. For instance, bioisosteric replacement of NO_2 with an SF_5 group increases electronegativity and reverts lipophilicity, thus potentially modulating absorption, distribution, and membrane permeation of drug candidates to reach the active site. On the other hand, the SF_5 hindrance ensures a tailor-made replacement for bulkier groups such as *t*-butyl. Given that apolar substituents such as the *t*-butyl group often suffer metabolic instability, optimal bioisosteres that conserve overall lipophilicity and simultaneously consolidate drug stability are of utmost importance.[119] Besides complying with both requisites, the "polar hydrophobic" nature of the SF_5 increases the drug solubility, when used as *t*-butyl bioisostere.[120]

Colby and co-workers reviewed research works reported before 2017, by comparing the SF_5 bioisosteres to their analogs.[7] In this section, we will focus mostly on the literature reported after 2017 following a target-based classification.

Wipf et al. proposed the mefloquine analogs as the first SF_5-containing drug candidate to treat malaria.[121] The analog **157** bearing the SF_5 in 6-position showed higher activity towards four different drug-resistant strains of *Plasmodium falciparum* and greater selectivity compared to mefloquine (Scheme 49, A). The most promising SF_5-containing antimalarial candidates target the dihydroorotate dehydrogenase (DHODH) enzyme. DHODH plays a crucial role in *de novo* pyrimidine biosynthesis, an important source of energy for the malaria parasite.[122] Triazolopyrimidines are reported as highly active scaffolds towards *Pf*DHODH. Among these, compound **158** showed nanomolar IC_{50}, and higher activity compared to the CF_3 and H analogs (Scheme 49, A).[123] Further optimization of these scaffolds through substitutions on the 2-position of the triazolopyrimidine ring led to the highly potent **DSM265** having an IC_{50} of 33 nM (Scheme 49, A).[124] **DSM265** showed activity towards drug-resistant strains including *P. falciparum* in vivo in a murine model and *Pv*DHODH (from *P. vivax*). Furthermore, its excellent in vivo pharmacokinetic profile achieved with QD (*quaque die*; daily) dosing, rendered **DSM265** a potential candidate for clinical trials. Further preclinical characterization including efficacy, interspecies pharmacokinetic properties and toxicity studies supported the advancement of **DSM265** to phase 1 clinical trials.[125] Phase 1 clinical trials concluded that the drug has causal prophylactic activity when administered one day before controlled human malaria infection.[126] In phase 2a studies, **DSM265** showed effective clearance of *P. falciparum* but the clearance of *P. vivex* was less effective and slower.[127] Furthermore, the study reported evidence of resistance-associated mutations in genes encoding for DHODH in *P. falciparum* parasites within the context of single-dose regimens as well. However, despite some initially promising results, at the time of writing this review, we could not

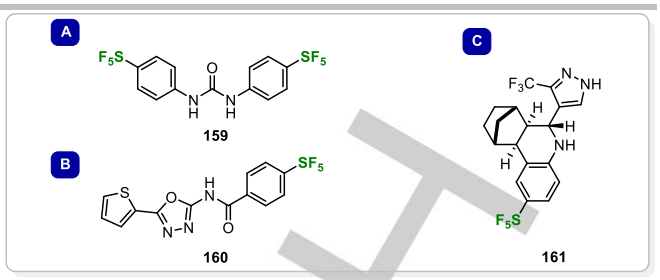
find details regarding whether **DSM265** advanced to phase 3 clinical trials.

The DHODH enzyme is found in humans as well, and *h*DHODH inhibitors such as **leflunomide** and **teriflunomide** are used to treat autoimmune diseases (Scheme 49, B). Very recently, Spencer and co-workers accessed the SF_5 analogs of these two drug candidates, achieving more potent analogs with a two-fold decrease in IC_{50}.[128] According to docking studies, such an increase in potency could be rationalized owing to the larger portion of the SF_5 substituent fitting better into the binding pocket compared to the CF_3 moiety.



Scheme 49 DHODH inhibitors for the treatment of parasitic diseases (A) and autoimmune diseases (B).

Pentafluorosulfanyl-containing *N,N'*-diarylureas have been reported by Vasquez, Torrents, and co-workers, as viable alternatives to the recently banned antibacterial triclocarban (TCC).[129] The novel diarylurea **159** (Scheme 50, A) showed higher potency and a broader spectrum of activity towards Gram-positive bacteria compared to TCC. The same class of compounds has been recently repurposed as antischistosomal agents.[130] Despite the promising in vitro activity towards worms and high selectivity index, they lack anti-worm activity and harbour potential toxicity in vivo. Other SF_5-containing scaffolds with antimicrobial activity have been reported by the group of Sintim. These include the oxadiazol SF_5-benzamide **160** and the SF_5-substituted tetrahydroquinoline **161 (**Scheme 50, B and C).[131] Compared to the other reported analogs, **160** and **161** seem among the most active candidates together with the SCF_3 derivatives. Both **160** and **161** were able to exert their bactericidal activity toward a wide spectrum of Gram-positive bacterial strains. In addition, haemolysis tests carried out on mammalian red blood cells showed good tolerability of these antibiotics even at relatively high doses. Compound **160** showed a synergistic effect when used in combination with methicillin. On the other hand, **161** showed bactericidal activity of two resistant strains and no potential for triggering antibiotic resistance development after repeated exposures. Membrane permeabilization assays showed that compound **161** permeabilized bacterial membranes even at relatively low concentrations.



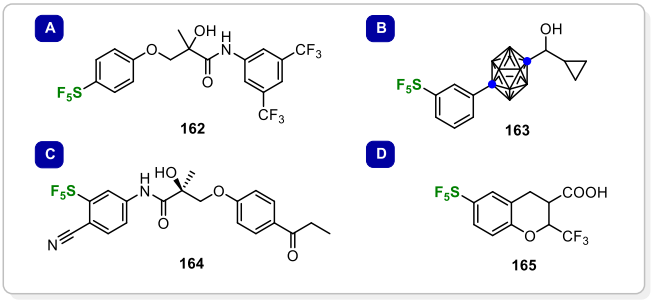
Scheme 50 SF_5-containing biologically active compounds that showed antimicrobial activity in vitro.

SF_5-decorated hormone receptor modulators have been reported recently as well. Pertusati and colleagues developed an extensive library of polyfluorinated derivatives of bicalutamide and enobosarm as potential anticancer agents. The SF_5 analogs showed the highest in vitro potencies and full androgen receptor (AR) antagonism. Compound **162** (Scheme 51, A) stands out for its in vivo activity in a mouse model xenograft, albeit lower than standard first-line chemotherapy docetaxel.[132]

Another example is the SF_5-tagging of a carborane scaffold to deliver the antagonist of the progesterone receptor (PR) **163**. PR ligands require a hydrophobic backbone and a polar functional group. By harnessing the hydrophobicity of the carborane scaffold and the polarity of the phenyl-SF_5 heads the authors obtained a dozen of non-steroidal PR antagonists with micromolar to sub-micromolar IC_{50} (Scheme 51, B). Nonetheless, despite the low IC_{50} value, substituents having π electrons such as nitrophenyl and cyanophenyl groups resulted in a ten-fold increase in potency compared to the analogs bearing a phenyl-SF_5.[133]

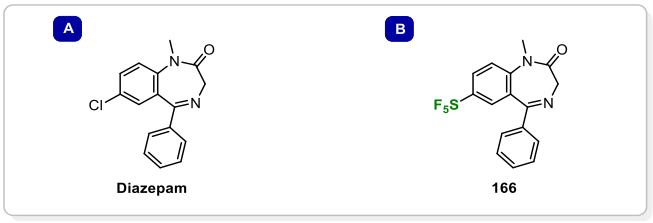
Jin and co-workers reported a small library of SF_5-bearing analogs of ostarine as AR agonists, with **164** (Scheme 51, C) showing the highest agonist activity. However, compounds bearing only SF_5 as substituents on the aromatic ring showed no activity towards AR. The authors conclude that the nitrile present on the aromatic ring is crucial for conserving AR-agonism.[134]

Other uses of the SF_5 group have been applied in the design of non-steroidal anti-inflammatory drugs. Talley and co-workers disclosed a small library of cyclooxygenase-2 (COX-2) blockers having an SF_5-tagged benzopyran scaffold. The racemic SF_5-benzopyran **165** (Scheme 51, D) showed a high potency and selectivity towards COX-2. In addition, in vivo pharmacokinetic profiling of **165** exhibits high bioavailability, a long half-life, and in vivo efficacy in rodent models of inflammation and pain.[135]



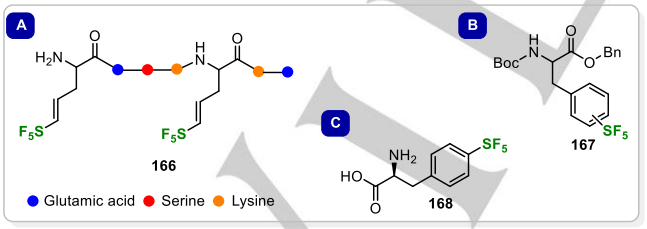
Scheme 51 Biologically active SF_5-containing derivatives that have been tested as hormone receptor modulators.

Very recently, Spencer and Bagley substituted the chlorine present on the aromatic core of diazepam with SF_5 and obtained compound **166** to disclose a more potent derivative (Scheme 52). However, such modification induced a loss of potency and $GABA_A$ selectivity compared to diazepam.[136]



Scheme 52 Diazepam (A) and its SF_5-containing analogue (B).

Besides the abovementioned applications in medicinal chemistry, the SF_5 group has been recently deployed to protein design, through the incorporation of unnatural SF_5-containing amino acids. The first reported amino acid sequence bearing an SF_5 has been reported by the group of Welch.[137] Initially, they prepared SF_5-norvaline (SF_5Nva) via radical addition of SF_5Br to a protected allyl glycine derivative. This was followed by dehydrobromination and saponification to yield the SF_5Nva amino acid **166**. By alternating peptide coupling and protection-deprotection steps, they synthesized the heptapeptide reported in Scheme 53 bearing SF_5Nva in 1-position and 5-position. Three-dimensional conformational analysis via NMR spectroscopy disclosed an almost ideal α-helix conformation of the heptapeptide. More recently, Cobb and co-workers extended SF_5-tagging of amino acids to aromatic scaffolds **167** that were obtained via Negishi cross-coupling reaction.[138] Furthermore, they showed that the amino acid having the *R*-configuration could undergo peptide coupling to yield a dipeptide. Other work focusing on SF_5-tagged amino acid synthesis has been carried out by Mazuela, Johansson and co-workers. They accessed unnatural *N*-alkylated phenylalanine analogues via asymmetric hydrogenation of *N*-alkyl imine precursors in presence of an iridium catalyst.[139]



Scheme 53 A) The heptapeptide containing the SF_5 unnatural amino acid reported by Welch. Unnatural amino acids synthesized

A recent breakthrough in SF_5-tagging of proteins has been reported by Huber and co-workers. They disclosed the genetic encoding of SF_5-phenylalanine **168** via newly developed aminoacyl-tRNA synthetases that allow site-specific incorporation into protein chains with high yields. They probed the ^{19}F-^{19}F nuclear overhauser effect in a genetically encoded *E. Coli* isomerase containing two SF_5Phe motifs. In addition, they observed an increase in affinity of the clamp binding motif towards the sliding clamp of the *E. Coli* DNA polymerase, when the terminal phenylalanine was substituted by SF_5-phenylalanine. Finally, they reported a higher affinity of β-cyclodextrins towards the SF_5Phe-containing ubiquitin compared to the CF_3Phe-containing one, probably owing to the larger volume of the SF_5 that better fills the β-CD cavity and its increased hydrophobicity favouring such interaction.[140]

Very recently, the first evidence describing the use of the SF_5 group as a probe in medical imaging has been reported as well. Waiczies and co-workers synthesized polyfluorinated derivatives of teriflunomide, including the *para*-substituted pentafluorosulfanylphenyl analog (Scheme 49, B), and tested them as theranostic markers. The **SF_5-teriflunomide** showed the best ^{19}F MR signal-to-noise ratio and efficiency in combination with an ultra-short echo time (UTE) MRI method. In addition, it inhibits the proliferation of T cells more efficiently than the teriflunomide analog.[141]

Overall, in this section, we showcase the utility, and to some extent, the superiority of the pentafluorosulfanyl group compared to other bioisosteres. Nonetheless, despite the enthusiastic claims regarding the SF_5 superiority in medicinal chemistry, there is only one candidate that reached phase 2A clinical trials up to date, and no drug candidate in clinics yet. This of course could reflect the existing synthetic bottlenecks in the state of art to access these compounds.

6. Conclusions and future outlook

A brief glance at the recent outstanding advancements in SF_5 synthetic and applied chemistry demonstrates its growing significance. On the synthetic front, new remarkable approaches have appeared such as gas-free and catalyst-free methods and convergent substrates for Ar-SF_4Cl synthesis. It is also noteworthy to highlight the synthesis of aliphatic SF_5 compounds can rely on novel synthetic approaches such as the ex situ generation of SF_5Cl, and the use of a stable solution of SF_5Cl in hexane and photoredox catalysis by employing SF_6 as an SF_5 source. Improvement in the synthesis of aromatic-SF_5 adducts includes gas-free procedures that foresee the use of TCICA as a chlorine source in presence of an excess amount of KF to yield valuable Ar-SF_4Cl intermediates, that are subsequently transformed into Ar-SF_5 via chlorine-fluorine exchange methods. However, multiple limitations, such as multistep syntheses, the requirement of specialized and costly apparatuses and the use of excess reagents, deserve to be addressed shortly.

Important steps forward were also taken in the development of many SF_5- and SF_4-containing building blocks to unlock unprecedented reactivities and increase structure diversification.

Unambiguously, we witness an increase in applications of SF_5-bearing compounds and analogs both in material science as well as in medicinal chemistry. Applications in material science extended towards the design of SF_5-bearing luminescent functional materials being transition-metal complexes, metallacycles or organic fluorophores. On the other hand, applications for biological purposes include the use of these adducts in drug design as novel bioisosteres and more recently expanded towards the use in the design of proteins bearing

unnatural SF_5-tagged aminoacids as well as first applications as probes in medical imaging.

From a future perspective, the major challenge to be surmounted, as overly ambitious as it may sound, would be providing a safe, facile, inexpensive and straightforward late-stage introduction of the SF_5 onto aliphatic or aromatic organic structures. Such an approach, in analogy to what is available for other fluorinated groups, has the potential to expand structure diversification and boost its applicability in distinct fields.

Author Contribution

EI proposed the topic and coordinated the work. All authors performed literature research. RK drafted sections 2, 3.2, and 4.5. B-YL drafted sections 4.1-4.4. AZ drafted section 3.1. JD drafted section 1. EI drafted section 5. WMDB, JD and EI revised the manuscript. WMDB, EI and JD secured funding. All authors proof-read the manuscript and agreed with the content.

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Keywords: fluorine • pentafluorosulfanyl group • sulfur hexafluoride • chlorotetrafluorosulfanyl • organic synthesis •

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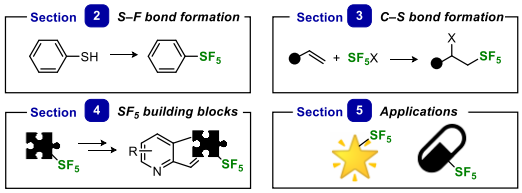
Entry for the Table of Contents



This review article mainly summarizes the recent synthetic methodology dedicated to pentafluorosulfanyl derivatives and their related analogs. Besides, the properties and up-to-date applications in materials sciences and medicinal chemistry of SF_5-containing compounds are also discussed here.

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