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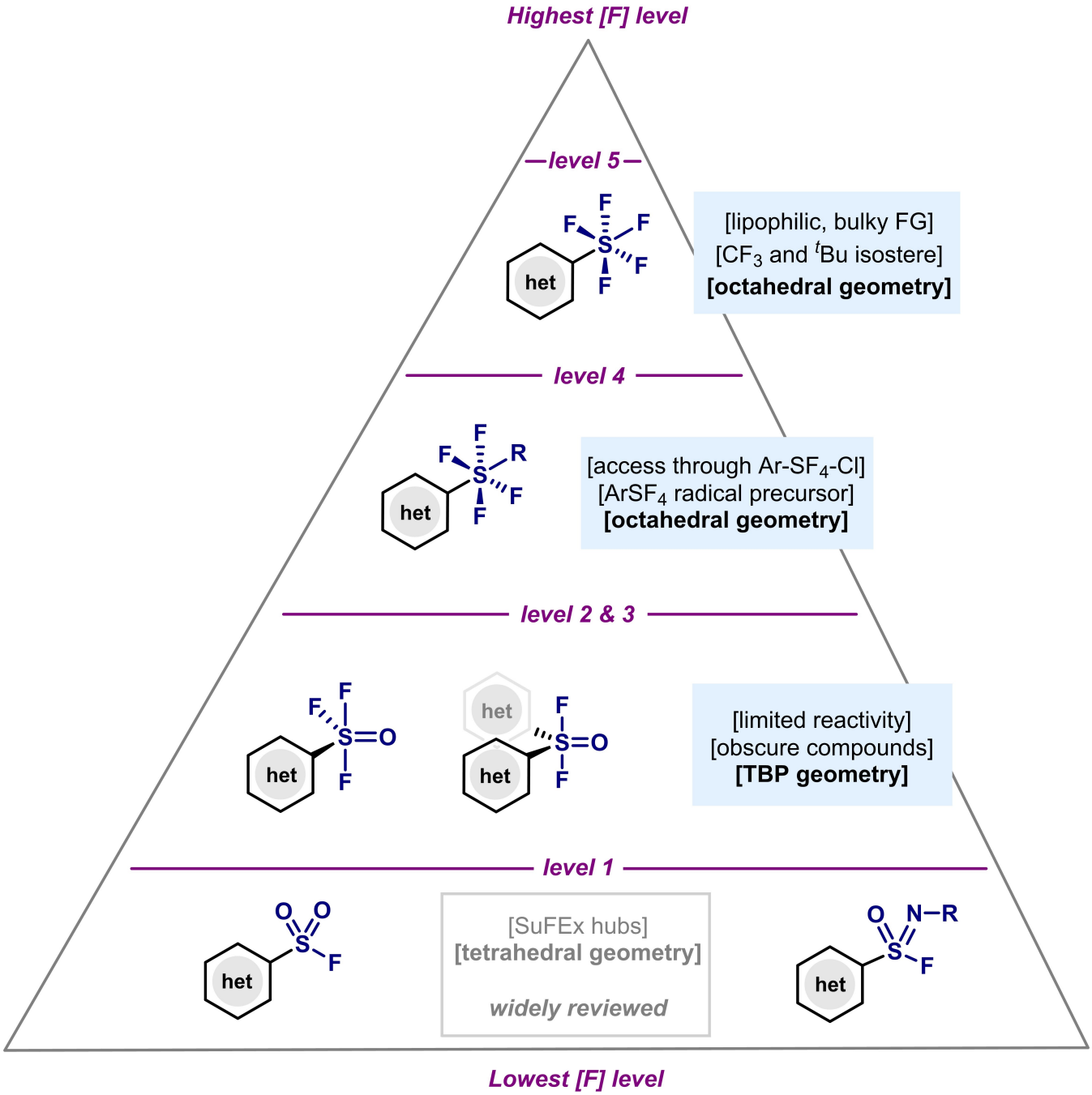
Fluorine Chemistry

(Hetero)aryl-S^{VI} Fluorides: Synthetic Development and Opportunities

*Marc Magre, Shengyang Ni, and Josep Cornella**



Abstract: (Hetero)arylsulfur compounds where the S atom is in the oxidation state VI represent a large percentage of the molecular functionalities present in organic chemistry. More specifically, (hetero)aryl-S^{VI} fluorides have recently received enormous attention because of their potential as chemical biology probes, as a result of their reactivity in a simple, modular, and efficient manner. Whereas the synthesis and application of the level 1 fluorination at S^{VI} atoms (sulfonyl and sulfonimidoyl fluorides) have been widely studied and reviewed, the synthetic strategies towards higher levels of fluorination (levels 2 to 5) are somewhat more limited. This Minireview evaluates and summarizes the progress in the synthesis of highly fluorinated aryl-S^{VI} compounds at all levels, discussing synthetic strategies, reactivity, the advantages and disadvantages of the synthetic procedures, the proposed mechanisms, and the potential upcoming opportunities.

1. Introduction

Aryl-S^{VI} compounds (including also heteroaryl ones) are ever-present functionalities in organic synthesis, spanning from the well-known arylsulfonyl chloride electrophiles[1] to the aryl sulfonamides that are widely present in many pharmaceuticals and agrochemicals.[2] Indeed, the synthesis and applications of these compounds has been widely reviewed and their synthesis is common textbook knowledge.[3] Within the group of aryl-S^{VI} compounds, however, there is a class of compounds that has received comparatively less attention: these are aryl-S^{VI} fluorides, where the S^{VI} center is directly attached to F atoms. Indeed, compounds of this class have recently been re-evaluated, as they have shown interesting properties and applications in various fields of expertise.[4] For example, arylsulfonyl fluorides[5] and arylsulfonimidoyl fluorides[6] have been studied in sulfur–fluoride exchange reactions (SuFEx), and their use as chemical probes for chemical biology has proved highly valuable.[7] However, from a structural and molecular point of view, arylsulfonyl and arylsulfonimidoyl fluorides both represent the lowest level of fluorination at the S atom, with only one fluorine atom attached to the tetrahedral S atom (level 1, Figure 1). Despite the success of level 1,[8] compounds with a S atom at higher levels of fluorination are less well known, but still accessible. For example, diarylsulfur oxide difluorides (level 2) and arylsulfinyl trifluorides (level 3), which present a sulfur atom with a trigonal bypyramidal (TBP) geometry, have been the least studied of the fluorinated aryl-S^{VI} compounds, with untapped reactivity and applications. Moving up the pyramid, one can find aryltetrafluoro-λ^6-sulfanyl chlorides and aryltetrafluoro-λ^6-sulfanes, with various synthetic procedures reported in the literature for their preparation. In particular, aryltetrafluoro-λ^6-sulfanyl chlorides have been widely studied and applied as precursors for pentafluoro(aryl)-λ^6-sulfane (Ar–SF_5) and deoxyfluorinating agents.[9] In contrast to the lower levels of fluorination, the S atom at level 4 presents an octahedral geometry, which leads to potential structural isomerism. Finally, the highest level (level 5) is occupied by pentafluoro(aryl)-λ^6-sulfanylarenes (Ar–SF_5), which recently gained the attention of the chemistry community because of the unique properties of the SF_5 group in material science and medicinal chemistry fields.[10] With an octahedral geometry around the S center and a square-pyramidal array of fluorine atoms, the symmetrical SF_5 group is sterically highly demanding, thus it can be considered as an isostere of the *tert*-butyl (^{t}Bu) and the trifluoromethyl (CF_3) groups.[11,12]

In this Minireview, the synthetic methods, substrate scope, mechanism, and applications of levels 2 to 5 will be evaluated and summarized. Compounds belonging to level 1 (Figure 1) have already been extensively reviewed and will not be included.[8] The organization of this Minireview will follow an increase in the fluorination level, and the different synthetic procedures will be presented and discussed chronologically.

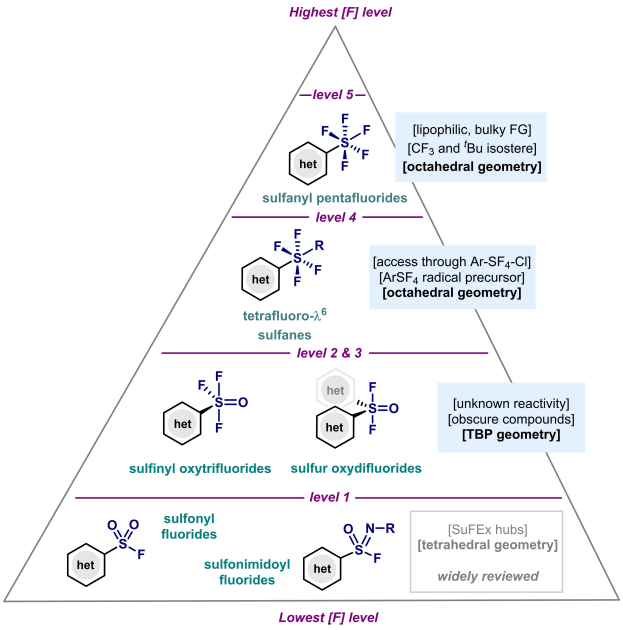


Figure 1. Fluorinated arylsulfur(VI) compounds.

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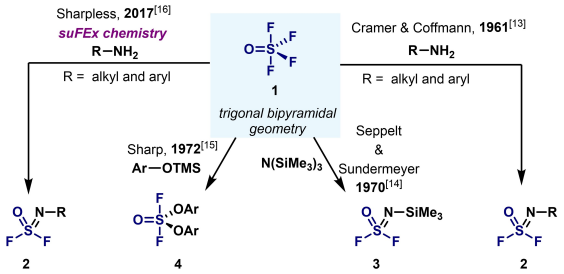
2. Fluorination Level 2

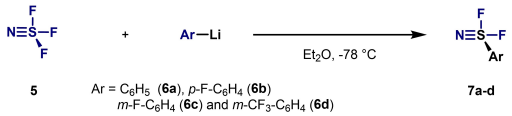
In 1961, Cramer and Coffman reported the reaction of gaseous thionyl tetrafluoride (**1**, SOF_4) with primary amines leading to iminosulfur oxydifluorides **2** in good yields (Scheme 1).[13] This seminal example set a foundation stone for further applications, such as those of Seppelt and Sundermeyer as well as Sharp and co-workers,[14,15] who capitalized on the strong Si–F bond to react silylated nucleophiles with SOF_4. This field, however, remained dormant until Sharpless and co-workers realized the balanced reactivity and stability of iminosulfur oxydifluorides **2**, and their value in organic synthesis and chemical biology (Scheme 1).[16]

In 1978, Clifford et al. reported the synthesis of aryl-S^{VI} difluorides **7** by reacting thiazyl trifluoride (SNF_3; **5**) with various aryllithium compounds **6** at −78 °C (Scheme 2).[17] NMR spectroscopy studies revealed that the -SNF_2 group is more strongly electron-withdrawing than the -NO_2 and -SF_5 groups.

A year later, Ruppert reported the first examples of diarylsulfur(VI) oxide difluorides.[18] Diaryl sulfoxides **8** could be fluorinated directly by liquid-phase fluorination using fluorine (F_2) at low temperatures (Scheme 3). This synthetic procedure allowed, for the first time, access to diarylsulfur(VI) oxide difluorides **9**, which cannot be obtained by the direct arylation of SOF_4 (**1**). The use of other strong fluorinating agents, such as XeF_2, failed as alternatives for direct difluorination. The reactivity of the newly synthesized diaryl-S^{VI} difluorides **9** was also evaluated: they are highly sensitive to moisture and can only be handled under dried protective gas. During these reactivity studies it was found that the $Ar_2S(O)F_2$ compounds display high activity as fluorinating agents. Interestingly, in the presence of BF_3, oxo-cationic species **11** were obtained.

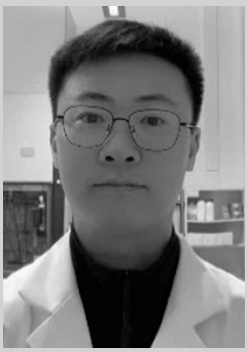


Scheme 1. Use of sulfur(VI) fluoride (SOF_4) gas as a SuFEx reagent.



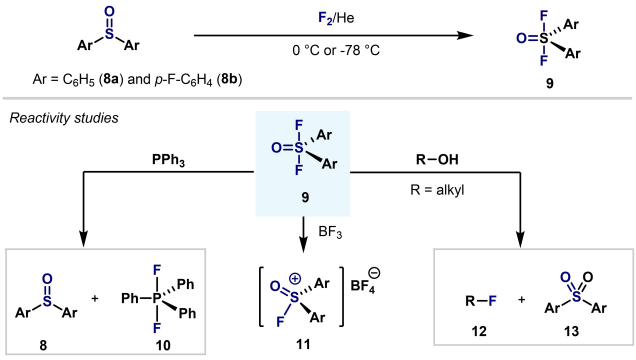
Scheme 2. Synthesis of $ArSNF_2$ by Clifford et al.[17]

Marc Magre earned his PhD under the supervision of Prof. Montserrat Diéguez and Prof. Oscar Pàmies at Universitat Rovira i Virgili (Spain) in 2016, working on tailor-made chiral Pd- and Ir-based catalysts for enantioselective transformations. In 2017, he joined the group of Prof. Magnus Rueping (RWTH Aachen; Germany) as a postdoctoral researcher, where he developed novel magnesium-catalyzed hydrofunctionalizations of unsaturated systems. In 2020, he joined the Max Planck Institut für Kohlenforschung (Mülheim an der Ruhr, Germany) as a postdoctoral researcher in the group of Dr. Josep Cornella, where he focuses on bismuth catalysis.



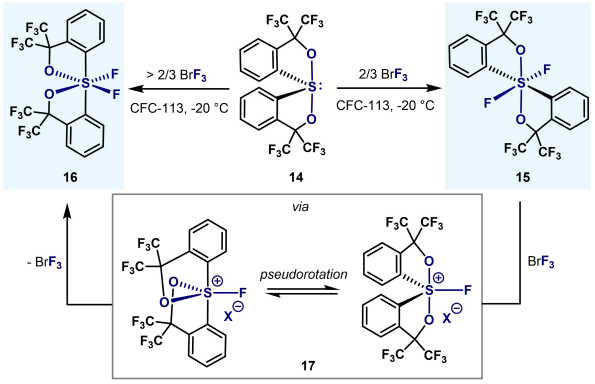
Shengyang Ni was born in Yancheng (China), in 1992. He earned his PhD under the supervision of Prof. Yi Pan at Nanjing University (China) in 2019, working on Ni-catalyzed reductive cross-coupling reactions. During this time, he was a visiting PhD student (2017–2019) in the group of Prof. Phil Baran at Scripps Research Institute (US). After his PhD, he stayed in the same group to continue his postdoctoral research. In 2021, he joined the Max Planck Institut für Kohlenforschung (Mülheim an der Ruhr, Germany) as a postdoctoral researcher in the group of Dr. Josep Cornella, where he focuses on Ni-catalyzed N_2O activation.

Josep Cornella (Pep) studied chemistry at the University of Barcelona (2008) and completed his PhD in 2012 at Queen Mary University (UK) under the supervision of Prof. Igor Larrosa. He then pursued postdoctoral studies in the groups of Prof. Ruben Martin (ICIQ, Spain) as a Marie Curie Postdoctoral Fellow and Prof. Phil S. Baran (The Scripps Research Institute, California, USA) as a Beatriu de Pinos Fellow. In 2017, he was appointed as a Max Planck Research Group Leader in the Department of Organometallic Chemistry at the Max-Planck-Institut für Kohlenforschung in Mülheim an der Ruhr, Germany, where he leads the Sustainable Catalysis Laboratory.

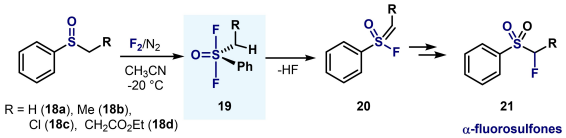


Scheme 3. Synthesis and reactivity studies of Ar_2SOF_2 by Ruppert.[18]

Michalak and Martin reported that sulfurane **14** can be oxidatively fluorinated using an equimolar amount of BrF_3 as the difluorinating agent, thereby obtaining *all-trans* difluoride **15** (Scheme 4).[19] Surprisingly, when the same difluorination was studied using an excess of BrF_3, the *cis*-isomer **16** was obtained. Both isomers exhibited the same reactivity towards hydrolysis (highly reactive). Structures **15** and **16** were confirmed by means of NMR spectroscopy and single-crystal XRD.[20] Whereas heating a solution of **15** did not show isomerization to **16**, the presence of catalytic amounts of the Lewis acid SbF_5 afforded *cis*-isomer **16** quantitatively, presumably via a persulfonium salt intermediate **17**. Thus, it was hypothesized that the formation of **16**, rather than **15**, in the oxidation of the sulfurane **14** with excess of BrF_3 arises from the Lewis acidity of BrF_3 present in solution leading to the formation of the persulfonium



Scheme 4. Synthesis of *cis*- and *trans*-difluoropersulfuranes by Michalak and Martin.[19,20]



Scheme 5. Synthesis of α-fluorosulfones via aryl-alkyl-sulfur(VI) difluoride.[21]

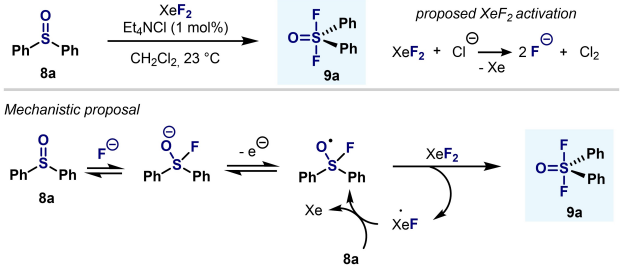
intermediate **17**, which leads to isomer **16** after pseudorotation and fluoride capture.

In 1995, Kaneko and co-workers capitalized on Ruppert's methodology for the synthesis of α-fluorosulfones (Scheme 5). Interestingly, when aryl-alkyl sulfoxides **18** were treated with F_2/N_2, S^{VI} difluoride species **19** were observed by ^{19}F NMR spectroscopy, and these species readily evolved into the dehydrofluorinated products **20**, by virtue of the loss of HF.[21]

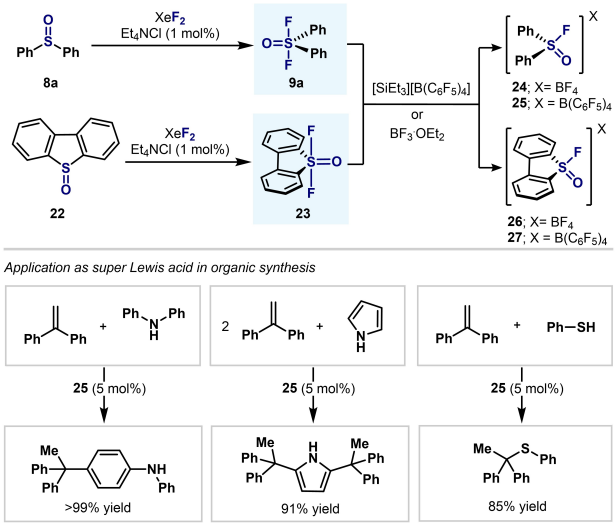
A breakthrough in the synthesis of aryl-S^{VI} difluorides was made in the same year by Janzen and Ou (Scheme 6). Oxidative fluorination of aryl-S(IV) compounds such as diphenyl sulfoxide or diphenylsulfur difluoride occurs under mild conditions in the presence of XeF_2 and catalytic amounts of chloride anions.[22] In this manner, diarylsulfur-(VI) difluorides were obtained in quantitative yields and in short reaction times. Mechanistically, it was postulated that a Cl-mediated activation of XeF_2 for the oxidative fluorination of diarylsulfoxides would initiate the reaction, which would be followed by a radical chain reaction propagated by $Ph_2S(O^{\bullet})F$ species.[23]

In 2016, Stephan and co-workers developed a variety of diaryl fluorosulfoxonium cations (**24**–**27**) and applied them to several Lewis acid catalyzed reactions (Scheme 7).[24] Synthetically inspired by the procedure developed by Janzen and Ou, Stephan and co-workers were able to oxidize diaryl sulfoxides **8a** and **22** to their corresponding diarylsulfur(VI) difluorides in excellent yields and, after fluoride abstraction with either BF_3 or $[SiEt_3][B(C_6F_5)_4]$, fluorosulfoxonium cations **24**–**27** could be isolated and characterized by NMR spectroscopy and single-crystal XRD. Experimental analysis (Gutmann–Beckett method) and theoretical calculations (DFT) confirmed the high Lewis acidity of fluorosulfoxonium cations **24**–**27**. Finally, compound **25** was demonstrated to be highly active in Friedel–Crafts-type reactions with 1,1-diphenylethene (Scheme 7, bottom).

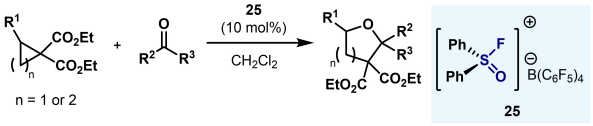
Similarly, in 2021 Panossian and co-workers applied Lewis acidic sulfoxonium cation **25** in ring-opening [3+2] and [4+2] annulations (Scheme 8). Excellent yields for a wide substrate scope were obtained, thus validating the excellent Lewis acid character of sulfoxonium cation **25**.[25]



Scheme 6. XeF_2/Cl^- system: synthesis of Ar_2SOF_2 reported by Janzen and Ou.[22,23]



Scheme 7. Synthesis and application of diarylfluorosulfoxonium cations by Stephan and co-workers.[24]



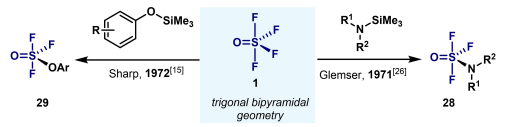
Scheme 8. Application of diarylfluorosulfoxonium cation **25** in annulation reactions by Panossian and co-workers.[25]

3. Fluorination Level 3

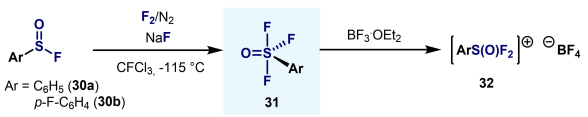
Aryl-S^{VI} trifluorides are the least studied of the fluorination levels known, with few examples described in the literature. To place their development into context, it is important to mention the seminal studies by the groups of Glemser and Sharp in 1971 and 1972: SOF_4 (**1**) can react with trimethylsilylamines[26] and trimethylsilyl aryl ethers[15] to afford the corresponding monosubstituted sulfur(VI) trifluorides **28** and **29** (Scheme 9).

Similar to aryl-S^{VI} difluorides, the direct monoarylation of SOF_4 (**1**) is not synthetically viable and, therefore, alternative synthetic routes were required. In 1980, Ruppert showed that aryl-S^{VI} oxytrifluorides **31** could be obtained by direct fluorine addition to sulfinic fluorides **30** using F_2 at very low reaction temperatures.[27] ^{19}F NMR spectroscopy confirmed the finding through the presence of an AX_2 pattern, which is in agreement with a trigonal bipyramidal geometry of an S atom with two fluorine atoms occupying the axial positions (Scheme 10). When subjecting the aryl-S^{VI} oxytrifluoride **31** to BF_3, oxocationic species **32** could be obtained, similar to the difluoride analogues (Scheme 3).[18] However, structural evidence was not provided.

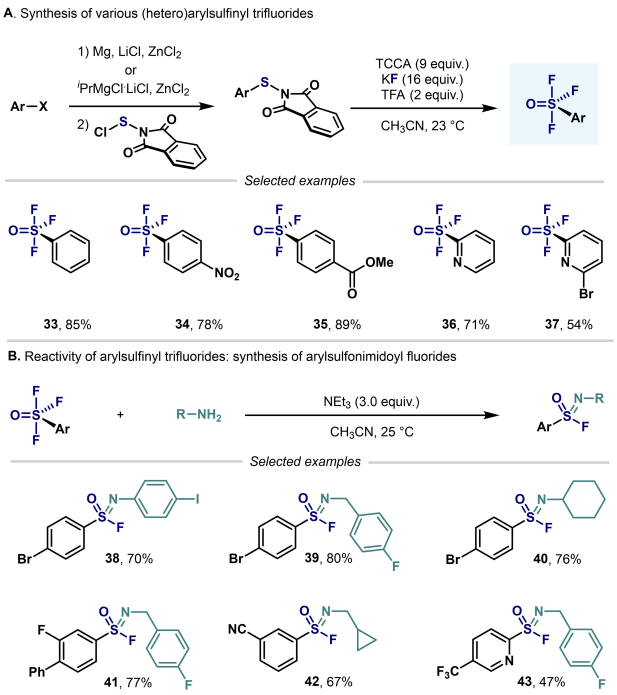
An advance in the area arrived in 2020, when Wang and Cornella developed a new method for the synthesis of $ArSOF_3$ compounds (Scheme 11).[28] This method provided a safer and more general platform to access $ArSOF_3$, with excellent yields obtained for a wide range of compounds. This method capitalizes on the oxidative fluorination of Ar-S(Phth) (generated in situ from aryl halides) to the corresponding $ArSOF_3$ using easy-to-handle reagents and mild reaction conditions. Such compounds exhibit extremely high reactivity and rapidly evolve into their corresponding arylsulfonyl fluoride analogues ($ArSO_2F$) upon exposure to trace amounts of H_2O. The high sensitivity of the compounds made all efforts to isolate them unsuccessful. However, the high electrophilicity of $ArSOF_3$ was turned into an advantage, and a wide range of primary aryl- and alkylamines were engaged in good yields, thus delivering highly coveted arylsulfonimidoyl fluorides.



Scheme 9. Pioneering syntheses of sulfur(VI) trifluorides.



Scheme 10. Synthesis of aryl-S^{VI} oxytrifluorides by Ruppert.[27]



Scheme 11. Synthetic procedure for $ArSOF_3$ developed by Wang and Cornella.[28]

4. Fluorination Level 4

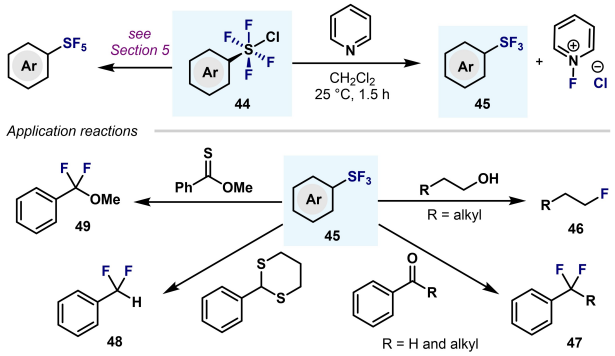
The synthesis of aryl-S^{VI} chlorotetrafluorides (Ar–SF_4Cl) has been widely studied due to their potential subsequent applications. Ar–SF_4Cl compounds are not only the most commonly utilized precursors to access level 5 (see Section 5), but also widely applied as deoxy- and desulfafluorinating agents (Scheme 12).[29] Their high reactivity towards deoxyfluorination makes these reagents a good alternative to deoxyfluorinating agents such as SF_4,[30] DAST (diethylaminosulfur trifluoride),[31] PhenoFluor [1,3-bis(2,6-diisopropylphenyl)2,2-difluoro-2,3-dihydro-1*H*-imidazole],[32] CpFluor (3,3-difluoro-1,2-diarylcyclopropene),[33] Fluolead (4-*tert*-butyl-2,6-dimethylphenylsulfur trifluoride),[34] and PyFluor (2-pyridinesulfonylfluoride),[35] among others. Tetrafluoro-λ^6-sulfanyl chlorides **44** do not react with C–O and C–S bonds; however, upon activation with a reductant such as pyridine, $ArSF_3$ **45** is generated in situ and acts as a highly effective reagent for the deoxyfluorination of alcohols, aldehydes, ketones, carboxylic acids, and sulfur compounds (Scheme 12).

Early in the 1950s, aryl-S^{VI} tetrafluorides were observed in crude mixtures from reactions between organosulfur(II) compounds and anhydrous hydrogen fluoride under electrolytic conditions.[36] The harsh conditions resulted in low-yielding mixtures of perfluorinated species (Scheme 13A). Years later, the groups of Sharp[37] and Shreeve[38] independently developed strategies to afford perfluoroaryl-SF_4Cl compounds, by using Cl_2 or ClF as oxidants (Scheme 13B).

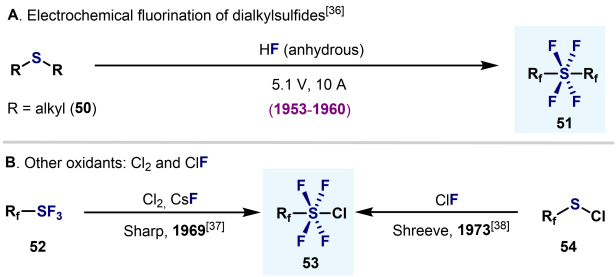
It was in 1973 when Denney et al. developed a method for the synthesis of diaryl-S^{VI} tetrafluorides using CF_3OF as the oxidant (Scheme 14).[39] Whereas dialkyl sulfides **50** reacted quickly at low temperatures, diphenylsulfide (**55**) required the presence of a large excess of CF_3OF. Based on ^{19}F NMR spectroscopy results, it was proposed that after an initial oxidation to the corresponding diaryl-S(IV) difluoride **57**, cationic intermediate **58** forms, which eventually leads to **56** upon warming.

A breakthrough in the synthesis of Ar–SF_4Cl arrived in 1997 when Janzen and co-workers reported the oxidation of aryldisulfides with XeF_2 in the presence of $[Et_4N][Cl]$ (Scheme 15).[40] A large excess of XeF_2 favored the formation of the *trans* isomer (method A), whereas lower amounts of oxidant favored the *cis* isomer (method B). Regardless of the method employed, analytically pure stereoisomers could not be obtained.

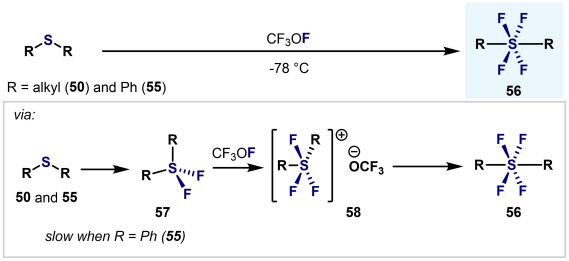
It was proposed that after oxidation of the disulfide, Ar–SF_3 species are formed. At this point, two pathways can be envisaged. As already reported by Janzen and Ou,[22,23] chlorine radicals (or Cl_2) and fluoride anions are formed when XeF_2 is mixed with chloride anions. Therefore, in path a (Scheme 15), fluoride anions react with Lewis acidic Ar–SF_3, and after oxidation and radical coupling with a



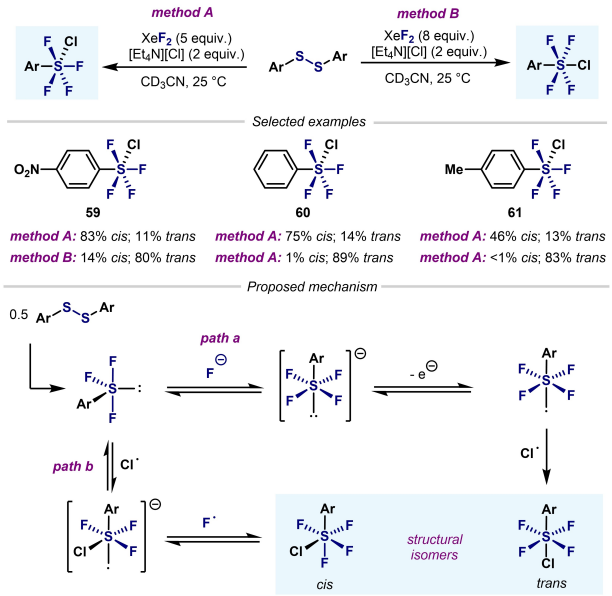
Scheme 12. Applications of Ar–SF_4Cl in organic synthesis.



Scheme 13. Early examples of perfluoroalkyltetrafluorosulfanes.



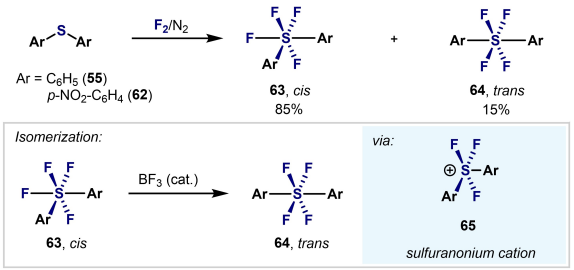
Scheme 14. Early examples of alkyl- and aryltetrafluorosulfanes by Denney et al.[39]



Scheme 15. Synthesis of Ar–SF_4Cl by Janzen and co-workers.[40]

chlorine radical, the *trans* isomer is formed. On the other hand, Ar–SF_3 can initially react with a chlorine radical (Scheme 15, path b) followed by radical coupling with a fluorine radical, thereby leading to the *cis* isomer. It was observed that over time, the *trans* isomer isomerizes to the *cis* isomer under the reaction conditions. Unfortunately, the authors did not provide an explanation for the effect of the Cl anions and excess XeF_2 in the slow *trans*-to-*cis* isomerization.

Kirsch et al. reported the direct fluorination of diarylsulfides using F_2/N_2, which produced a mixture of *cis* and *trans* Ar_2SF_4 isomers (Scheme 16).[41] Importantly, single-crystal XRD structures were obtained for both isomers. Ab initio and DFT calculations suggested that a *cis*-to-*trans* isomerization can occur from a BF_3-based catalytic process via a sulfuranonium cation intermediate **65**, thus precluding thermal isomerization.



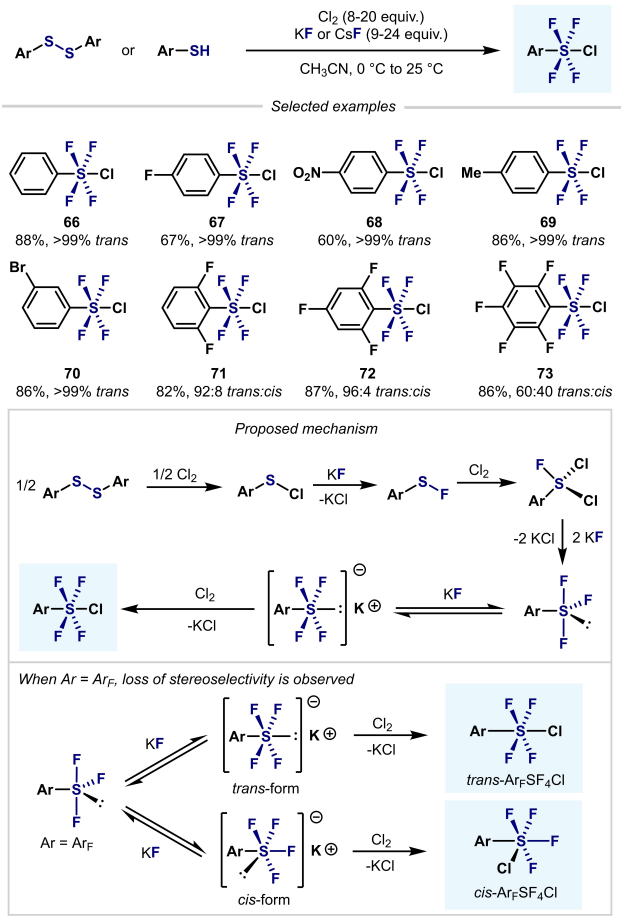
Scheme 16. Synthesis of *cis*- and *trans*-diaryltetrafluorosulfane mixture reported by Kirsch et al.[41]

An advance in this area was reported in 2012 by Umemoto et al. (Scheme 17),[42] who used mild reaction conditions and a Cl_2/KF system to convert a wide range of aryldisulfides or arylthiols into the corresponding aryltetrafluoro-λ^6-sulfanyl chlorides in excellent yields and *trans* selectivity. Interestingly, when polyfluoroaryl-SF_4Cl was synthesized, mixtures of *trans* and *cis* isomers were obtained. Since thermal isomerization did not occur over time, the authors concluded that each isomer was formed through each isomeric salt (*trans* and *cis* form).

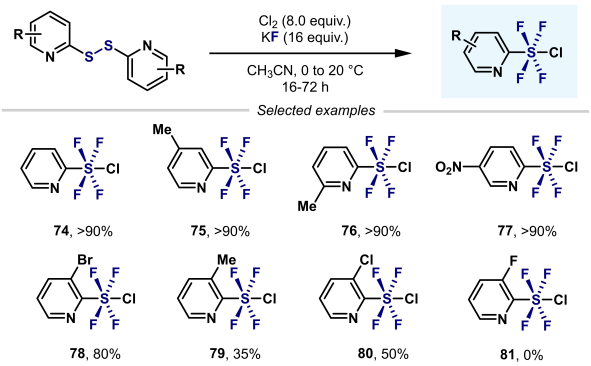
Inspired by the procedure developed by Umemoto et al., Kanishchev and Dolbier and co-workers synthesized a wide range of 2-pyridyl-S^{VI} chlorotetrafluorides with excellent *trans* stereoselectivity (Scheme 18).[43] However, the presence of *ortho* substituents (F, Me, and Cl) to the S atom decreased the yield considerably (**79**–**81**), with the corresponding heteroaryl-SF_3 compounds afforded as side products in almost all cases.

Shibata and co-workers expanded this reactivity to 3- and 4-pyridyl-SF_4Cl (Scheme 19).[44] The presence of fluorine atoms on the pyridine ring is essential for the successful conversion of pyridyldisulfides into the corresponding *meta*- and *para*-aryl-SF_4Cl compounds. The presence of another substituent (H, Me, or Cl) on the pyridine moiety (**87**–**89**) led to the undesired heteroaryl-SF_3 being obtained. The authors hypothesized that the presence of an electron-withdrawing group (EWG) such as fluorine would decrease the nucleophilicity of the N atom in the pyridine ring and, hence, stabilize the SF_4Cl group.

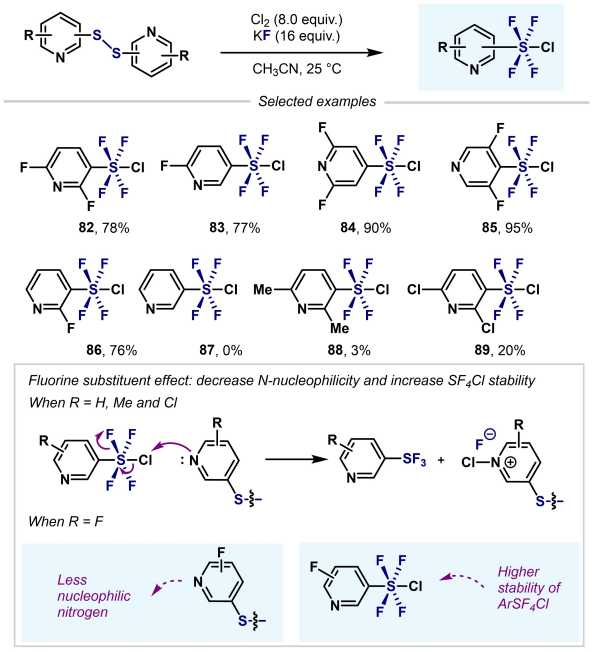
A remarkable breakthrough in this topic came in 2019 when Togni, Santschi, Pitts, and co-workers presented the first approach to aryl-SF_4Cl that avoided the use of hazardous, gaseous oxidizing agents (e.g. F_2 and Cl_2). The method featured the easy-to-handle solid trichloroisocyanuric acid (TCCA), potassium fluoride (KF), and catalytic amounts of trifluoroacetic acid (TFA). This simple synthetic method permitted the synthesis of a wide range of aryl- and heteroaryl-SF_4Cl compounds in good yields (Scheme 20).[45]



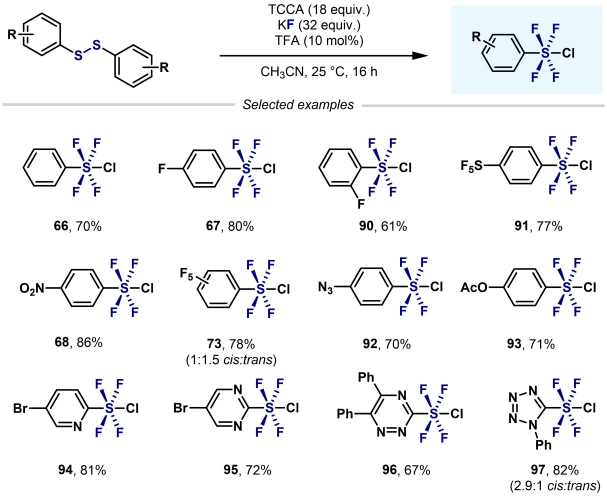
Scheme 17. Synthesis of *trans*-Ar–SF_4Cl by Umemoto et al.[42]



Scheme 18. Synthesis of 2-pyridyl-SF_4Cl by Kanishchev and Dolbier.[43]



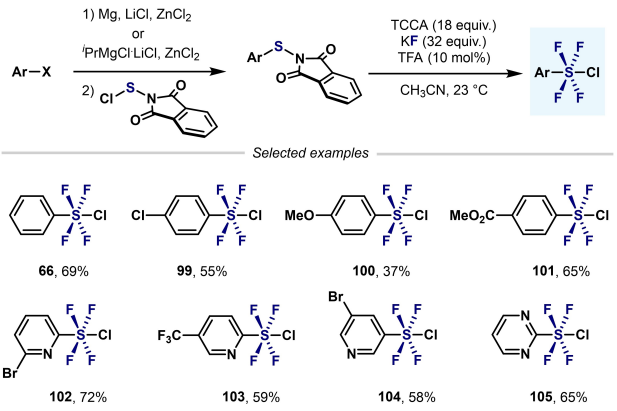
Scheme 19. Effect of a fluorine substituent on the synthesis of pyridyl-SF_4Cl.[44]



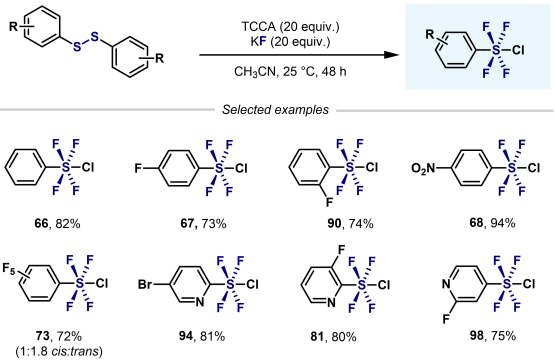
Scheme 20. Synthesis of aryl- and heteroaryl-SF_4Cl developed by Pitts, Togni, Santschi et al..[45]

Shibata and co-workers used the method developed by Togni and co-workers—without TFA—to obtain various (hetero)aryl-SF_4Cl (Scheme 21).[46] However, longer reactions times were required.

Another improvement in the synthesis or aryl- and heteroaryl-SF_4Cl has recently been reported by Wang and Cornella (Scheme 22).[28] Inspired by the synthetic method developed by Togni, Santschi, Pitts, and co-workers, the authors were able to convert (hetero)aryl halides into the corresponding tetrafluoro-λ^6-sulfanyl chlorides in excellent yields. It is important to highlight that, by slightly modifying the oxidation step, both level 3 (Scheme 11) and level 4 aryl-



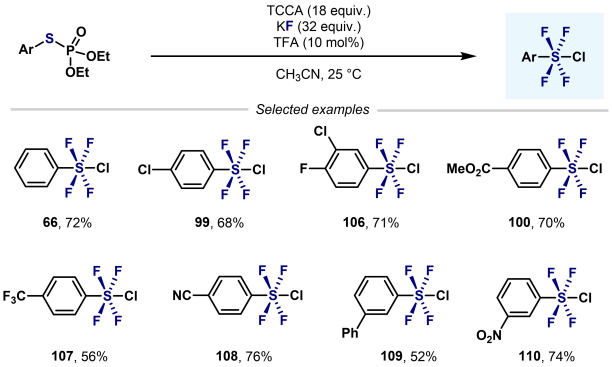
Scheme 21. Synthesis of aryl- and heteroaryl-SF_4Cl from aryl halides developed by Wang and Cornella.[28]



Scheme 22. Synthesis of aryl- and (hetero)aryl-SF_4Cl developed by Shibata and co-workers.[46]

S^{VI} fluorides could be obtained in excellent yields from the same Ar-S(Phth) starting materials.

The same group, also reported the use of arylphosphorothiolates as convergent substrates for the synthesis of Ar–SF_4Cl (Scheme 23).[47] In this regard, similar yields were obtained as with the previous procedure using Ar-S(Phth) (Scheme 22) as starting materials.[28]



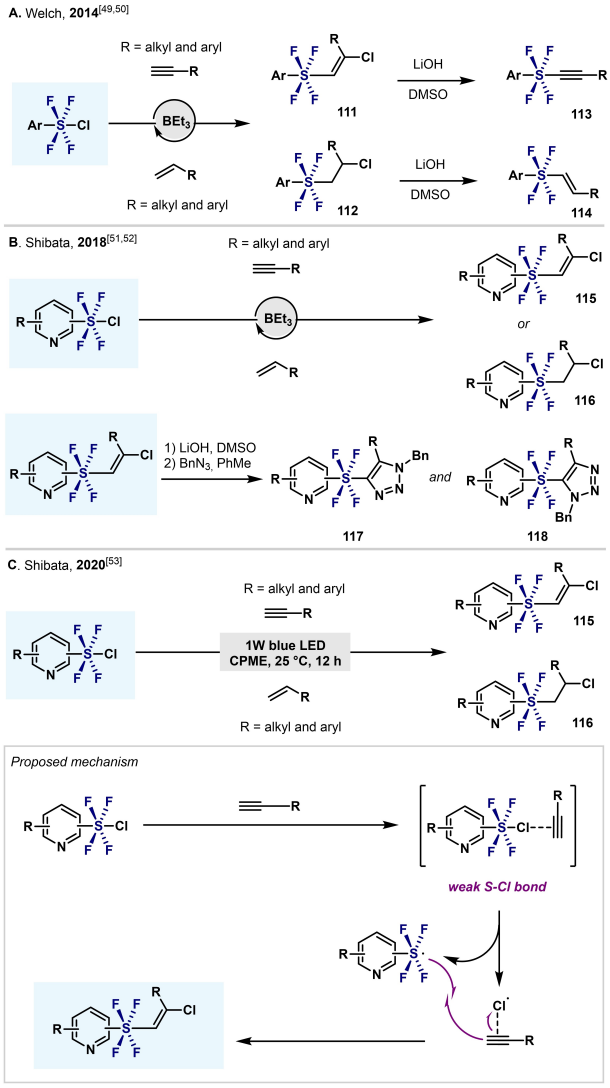
Scheme 23. Synthesis of aryl-SF_4Cl from arylphosphorothiolates developed by Wang and Cornella.[47]

Recently, Pascali and co-workers reported a strategy to obtain aryltetrafluoro-λ⁶-sulfanyl chlorides by flow microfluidic technology.[48] Unfortunately, this preliminary study only provided the Ar–SF_4Cl compounds in low yields (5–10 %) together with undesired compounds such as $ArSO_2F$ and ArSOF.

As mentioned before (Scheme 12), (hetero)-aryltetrafluoro-λ⁶-sulfanyl chlorides have attracted great attention as precursors of (hetero)aryl-SF_5 and as deoxyfluorinating agents.[29] However, Ar–SF_4Cl compounds have also been utilized in the synthesis of alkynyl- and alkenyl-aryltetrafluoro-λ⁶-sulfanes, by capitalizing on the labile S–Cl bond (Scheme 24).

In 2014, Welch and co-workers developed a BEt_3-catalyzed direct addition of Ar–SF_4Cl to primary alkynes and alkenes through a S–Cl homolytic cleavage (Scheme 24A).[49,50] Single-crystal XRD revealed an octahedral geometry at the S atom, with all the fluorine atoms in the axial positions.[49] Moreover, dehydrochlorination of the addition products (**111**, **112**) with lithium hydroxide formed the alkynyl **113** and (*E*)-alkenyl-aryltetrafluoro-λ⁶-sulfanes **114** in excellent yields, with no decomposition of the SF_4 group. In 2018, Shibata and co-workers synthesized pyridyl-tetrafluoro-λ⁶-sulfanes with alkenyl **115** or alkyl **116** substituents through a radical addition of pyridine-SF_4Cl to terminal alkynes and alkenes (Scheme 24B).[51] By means of single-crystal XRD and DFT calculations, the authors disclosed an octahedral geometry with a *trans* configuration of the hypervalent S^{VI} center. Furthermore, the *trans*-tetrafluoro-λ⁶-sulfanes bearing an alkenyl group **115** were further derivatized through a thermal Huisgen 1,3-dipolar cycloaddition to provide a wide range of three-dimensional building blocks with two independent N-heterocycles (**117**, **118**).[52]

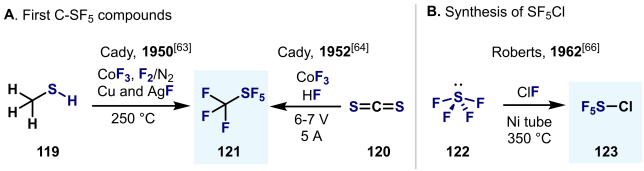
In 2020 Shibata and co-workers also reported the addition of Py-SF_4Cl to terminal alkynes and alkenes under irradiation with light (1 W blue LED; Scheme 24C). This procedure is an excellent alternative to BEt_3-catalyzed processes, as the borane is often the source of undesired side reactivity or substrate decomposition. In agreement with previous reports, the authors proposed a radical process to explain the reactivity observed.[53]



Scheme 24. Application of Ar–SF_4Cl in the synthesis of alkyl- and alkenyltetrafluoro-λ⁶-sulfanes and their derivatization.

5. Fluorination Level 5

In this level, only one type of compound reigns sovereign: namely, Ar–SF_5. Although known for many years, it was only recently that the pentafluorosulfanyl group (SF_5) became an interesting fluorine-containing building block because of its thermal and chemical stability[54] as well as inertness under physiological conditions.[55] The electrostatic surface presented by the SF_5 moiety is comparable to that of CF_3 and its electron-withdrawing effect suggests that the effects of SF_5 and CF_3 groups are similar in magnitude.[56] The electronegativity of the SF_5 group has been measured to be as high as 3.65, compared to a value of 3.36 for the CF_3 group.[57] The SF_5 group is the newest member of a short list of functional groups that possess both high electronegativity and high lipophilicity, two properties that are generally juxtaposed. As a result of such unique properties, aryl-SF_5 compounds have attracted attention, and synthetic efforts towards their preparation have been the focus of intensive research.[11] Investigations on Ar–SF_5 span from applications as ^{t}Bu and CF_3 isosteres in medicinal chemistry,[10,58] optoelectronic materials,[59] or agrochemicals,[60] to their ability to function as push-pull fluoro-[61] and choromophores.[62] Before discussing Ar–SF_5 compounds, it is important to mention that the first syntheses of C–SF_5 compounds were reported in the 1950s by Cady and co-workers (Scheme 25).[63,64] The authors reported the conversion of either methylmercaptan (**119**) or carbon disulfide (**120**) into CF_3-SF_5 (**121**) using CoF_3 and F_2[63] or HF in an electrochemical setup.[64] Although the yields and purity of the mixtures were low, these synthetic procedures truly opened the door to a new era of S^{VI} pentafluoride chemistry.[65] Equally important is the synthesis of SF_5Cl (**123**) reported by Nyman and Roberts by the direct



Scheme 25. Pioneering syntheses of C–SF_5 and SF_5Cl.

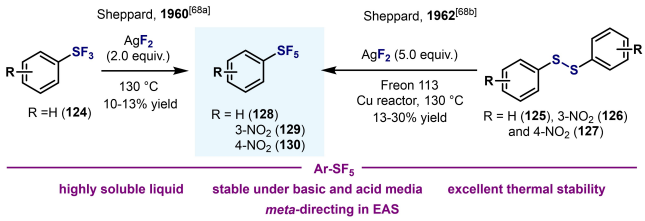
oxidation of SF_4 (**122**) with ClF.[66] Nowadays, SF_5Cl (**123**) gas has become a benchmark reagent for the synthesis of SF_5 compounds, and efforts toward its practical usage are of great interest.[67]

The synthesis of arylsulfanyl pentafluorides (Ar–SF_5) can be classified on the basis of the synthetic approach. Therefore, we have organized this section in three subsections.

5.1. Direct Oxidation of Diaryldisulfides or Arylthiols

The direct oxidation of diaryl disulfides or aryl thiols with strong fluorinating agents was the first approach toward the synthesis of arylsulfanyl pentafluorides (Ar–SF_5).[68] In all cases, low yields and narrow substrate scope were common features of those pioneering methods (Scheme 26). The first synthetic procedure for aryl-SF_5 compounds was reported by Sheppard et al. in 1960.[68a] When phenylsulfur trifluoride (**124**, $PhSF_3$) is heated gradually to 130 °C with AgF_2 in a reactor made of copper or Teflon, phenylsulfur pentafluoride (**128**, Ph-SF_5) is obtained, albeit in low yields (10–13 %, Scheme 26).

Two years later, the same author slightly modified the previous procedure by adding aryl disulfides **125**–**127** to five molar equivalents of AgF_2 suspended in 1,1,2-trichloro-1,2,2-trifluoroethane ("Freon" 113) in a copper reactor.[68b] This modified procedure was found to be particularly effective when NO_2-substituted Ar–SF_5 **126** and **127** were utilized (Scheme 26). Several important conclusions arose from this work: 1) Ph-SF_5 is a colorless liquid that is soluble in common organic solvents, even hydrocarbons; 2) Ph-SF_5 shows excellent stability under basic conditions (NaOH) and acidic conditions (H_2SO_4), being hydrolyzed under the latter conditions only above 100 °C; 3) Ph-SF_5 also shows excellent thermal stability, even at 400 °C; 4) Ph-SF_5 directs nitration at the *meta*-position; 5) the SF_5 group is stable under



Scheme 26. Early syntheses of Ar–SF_5: synthesis and study of the physical and chemical properties by Sheppard.[68, 69]

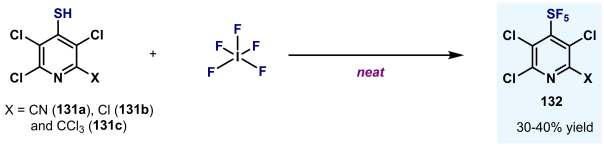
catalytic hydrogenation conditions. Although low yields were obtained in all cases, this pioneering study from Sheppard et al. opened a new pathway in the synthesis or arylsulfur(VI) fluorides[69] and the further application to several fields such as biology and medicinal chemistry.[11]

Another direct oxidation procedure was developed by Karstev and co-workers (Scheme 27),[70] who synthesized polychloropyridine-SF_5 **132** by the direct oxidation of the corresponding thiols **131** with IF_5. However, this procedure also suffered from low yields and narrow scope.

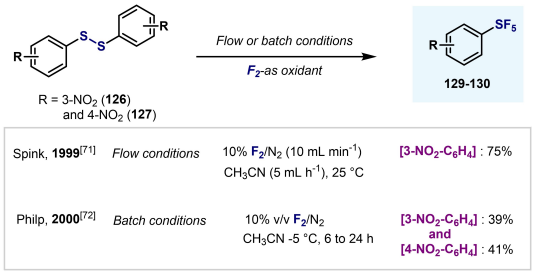
A few years later, the groups of Spink and Philp independently reported the use of F_2 for the conversion of diaryldisulfides **126** and **127** into the corresponding Ar–SF_5 compounds **129** and **130** (Scheme 28). Whereas Chambers and Spink developed the oxidation in flow conditions,[71] Philp and co-workers performed the oxidation in batch.[72] Both methods led to improved yields and milder reaction conditions compared to Sheppard's AgF_2-based procedure.[68]

In 2000, Ou and Janzen applied the XeF_2-Et_4NCl system to the conversion of a limited number of diaryldisulfides (**125** and **133**) into Ar–SF_5 compounds (Scheme 29). In this case, low-to-moderate yields were obtained along with *trans*-Ar–SF_4Cl as the main by-product.[23b]

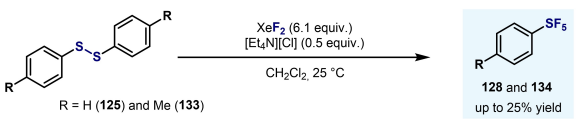
In 2016 and 2019, Beier and co-workers reported the direct fluorination of *ortho*-, *meta*-, and *para*-substituted aromatic thiols and disulfides using F_2 (Scheme 30).[73] By



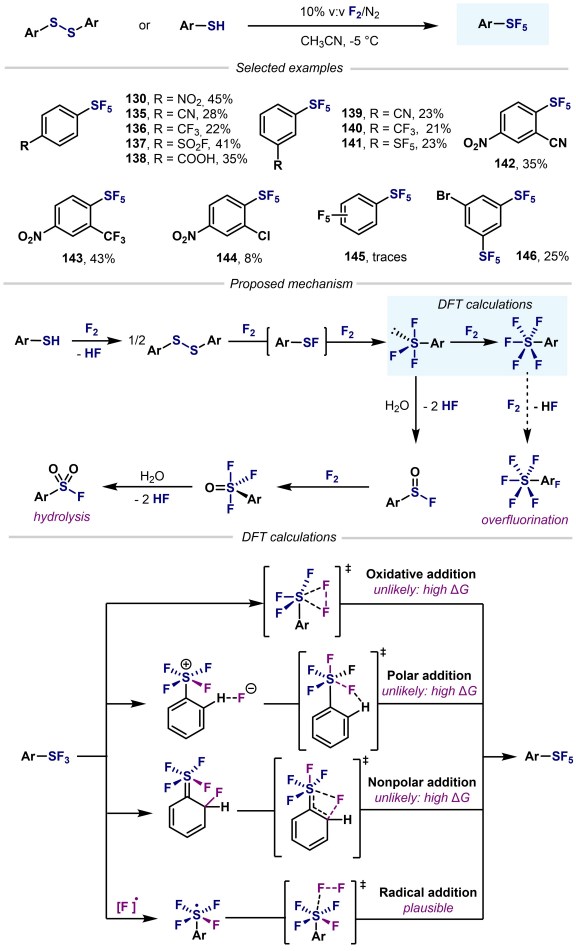
Scheme 27. Other preliminary synthetic methods for the synthesis of Ar–SF_5.[70]



Scheme 28. First examples of the synthesis of Ar–SF_5 by direct oxidation using F_2.



Scheme 29. Synthesis of Ar–SF_5 by direct oxidation using XeF_2-Et_4NCl.[23b]



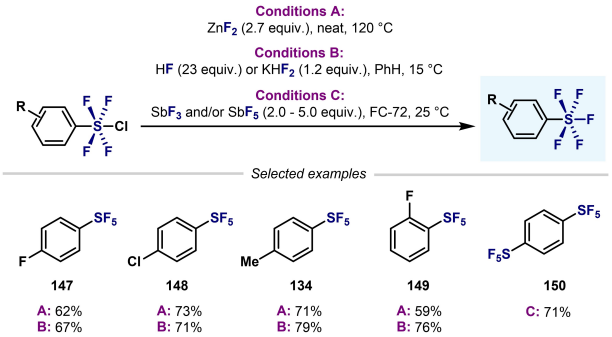
Scheme 30. Synthesis of Ar–SF_5 by direct oxidation using F_2, as developed by Beier and co-workers.[73]

comparing the synthetic performance under batch and flow conditions, it was found that a hybrid batch-flow process (synthesis of Ar–SF_3 in batch, then Ar–SF_5 in flow) provided good yields.[73b] By benchmarking experimental data with DFT calculations, the authors ruled out three nonradical pathways for the conversion of Ar–SF_3 into Ar–SF_5. It was finally proposed that the reaction proceeds through a radical mechanism after homolytic cleavage of the F–F bond. Propagation and termination steps are almost barrierless and the reaction depends on the stability of the Ar–SF_4 radical species. However, further mechanistic insights are required to elucidate the mechanism for the direct fluorination of diaryldisulfides using F_2.

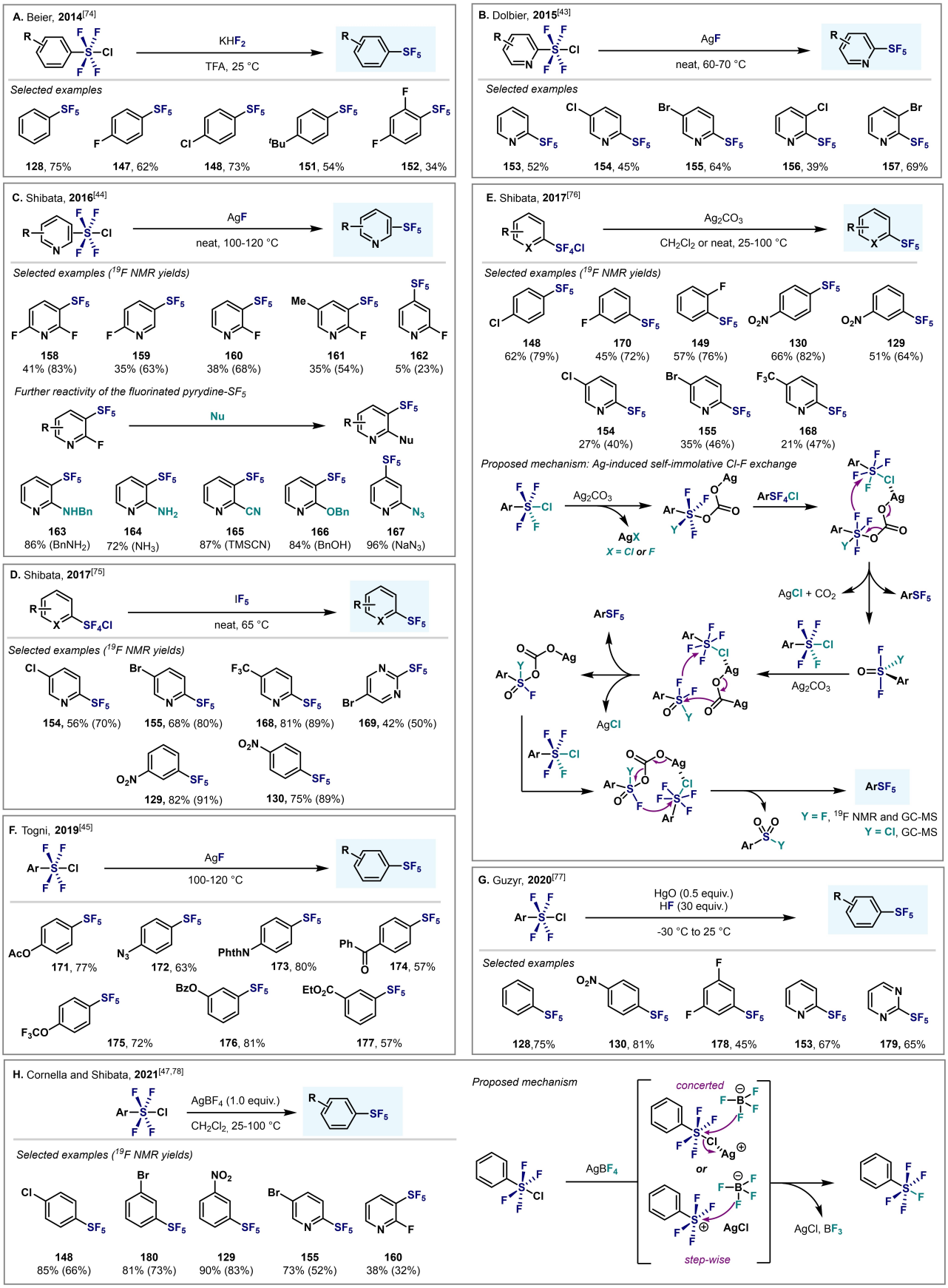
5.2. Synthesis of Ar–SF_5 from Ar–SF_4Cl

As mentioned in Section 4, Ar–SF_4Cl species have been used as synthetic precursors of Ar–SF_5 through Cl–F exchange. Compared to the direct fluorination of thiols or diaryldisulfides, the use of Ar–SF_4Cl as precursors leads to higher yields of the desired Ar–SF_5 under milder and safer conditions. In 2012, Umemoto et al. converted a wide range of Ar–SF_4Cl into their corresponding Ar–SF_5 compounds in good to excellent yields under mild reaction conditions, through a Cl–F exchange using either ZnF_2-HF (KHF_2) or $Sb^{III/V}$ fluorides (Scheme 31).[42] Since then, several Cl–F exchange methods have been reported to expand the scope of possibilities to access Ar–SF_5, and accommodate more functional groups (Scheme 32).

Beier and co-workers reported that a combination of KHF_2 and TFA at room temperature was optimal to convert various Ar–SF_4Cl into their corresponding Ar–SF_5 products (Scheme 32A).[74] In this regard, comparable yields were obtained in almost all cases to those obtained with Umemoto's methodology. Kanishchev and Dolbier reported the conversion of 2-pyridyl-SF_4Cl into the corresponding 2-pyridyl–SF_5 by using AgF as the fluoride source (Scheme 32B). These were pioneering examples of the efficient synthesis of highly sought after N-heterocyclic–SF_5 compounds.[43] In 2016, Shibata and co-workers reported a similar method for the conversion of a wide range of fluoro-containing 3- and 4-pyridyl–SF_4Cl compounds, with moderate to good yields obtained (Scheme 32C).[44] When treating 2-fluoropyrdine-SF_5 compounds with different N- and O-nucleophiles, nucleophilic aromatic substitution occurred, thus illustrating the great EWG ability of SF_5. IF_5 was also demonstrated to be a good fluoride source for the same purpose (Scheme 32D).[75] Several years later, the same group reported a novel strategy for the synthesis of aryl- and heteroaryl-S^{VI} pentafluorides by a Ag_2CO_3-induced Cl–F exchange (Scheme 32E).[76] Remarkably, this fluorination does not require any external fluoride sources; rather, the reaction proceeds through a self-immolative mechanism of Ar–SF_4Cl. In 2019, Togni and co-workers also converted a wide variety of Ar–SF_4Cl compounds into the corresponding Ar–SF_5 derivatives by using AgF as the classic external fluoride source (Scheme 32F).[45] Recently, Guzyr et al. reported the synthesis of aryl- and heteroaryl-S^{VI} pentafluorides using HgO and HF (Scheme 32G).[77] Very recently, the Cornella and Shibata groups independently showed that $AgBF_4$ is also a valid source of F for the synthesis or Ar–SF_5 compounds (Scheme 32H).[47,78] The authors proposed activation of the Cl atom of (hetero)aryl-SF_4Cl by Ag^+, and subsequent attack of the fluoride atom of



Scheme 31. First synthesis of Ar–SF_5 from Ar–SF_4Cl by Umemoto et al.[42]



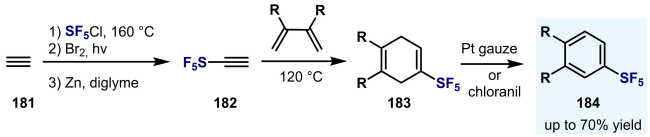
Scheme 32. Conversion of Ar–SF_4Cl into Ar–SF_5: state-of-the-art.

the BF_4 anion to the S center by either a concerted or stepwise mechanism.

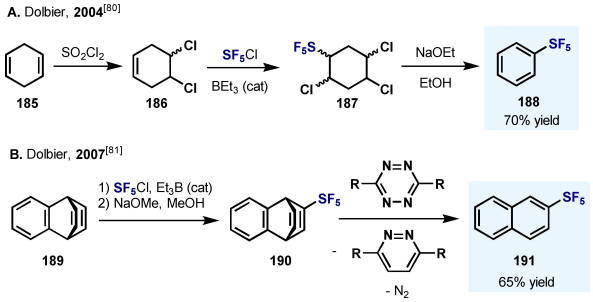
5.3. Alternative Syntheses Using SF_5Cl

In Sections 5.1 and 5.2 it was shown that direct oxidative fluorination and F–Cl exchange from Ar–SF_4Cl represents the standard approach for the synthesis of Ar–SF_5 compounds. Nevertheless, other alternative synthetic procedures involving the de novo synthesis of the aromatic ring have appeared in the literature. For example, Ar–SF_5 can be assembled through a Diels–Alder reaction of ethynylsulfur pentafluoride (**182**) with different dienes, as demonstrated by Hoover and Coffmann (Scheme 33).[79]

Sergeeva and Dolbier developed a convenient three-step synthesis of Ph-SF_5 from 1,4-cyclohexadiene (**165**) with an overall yield of 70 %. The key step in this synthesis is the radical addition of SF_5Cl to an alkene, thereby forging a C–SF_5 bond in almost quantitative yield (Scheme 34A).[80]



Scheme 33. Synthesis of Ar–SF_5 developed by Hoover and Coffmann.[79]



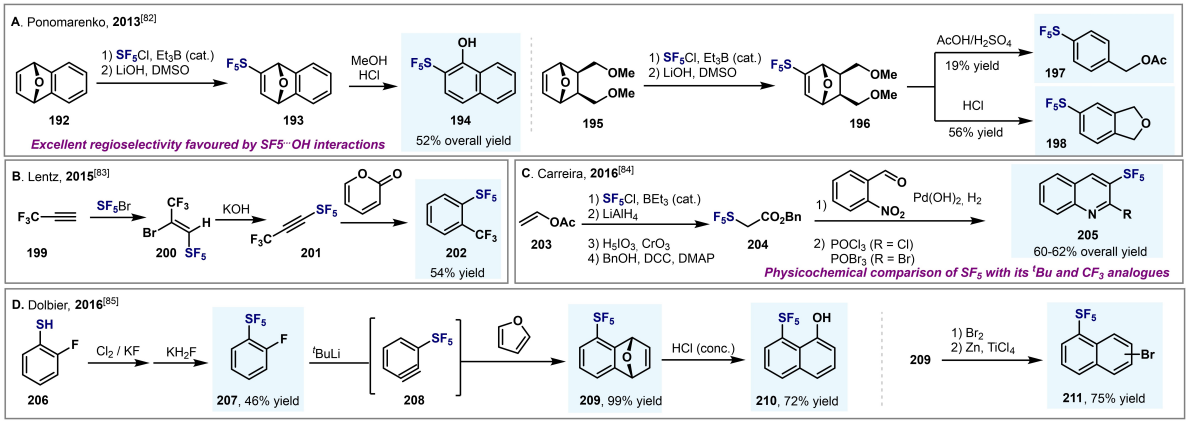
Scheme 34. Synthesis of Ar–SF_5 developed by Sergeeva and Dolbier.[80]

The same group also developed a three-step synthesis of 2-pentafluorosulfanylnaphthalene (**191**) by the initial addition of SF_5Cl to benzobarralene **189**. Elimination of the ethylene bridge by a cycloaddition/retro-cycloaddition sequence with 3,6-bis-(2-pyridyl)-1,2,4,5-tetrazine afforded the Ar–SF_5 **191** in good yield (Scheme 34B).[81]

Ponomarenko et al. reported the Et_3B-catalyzed SF_5Cl radical addition reactions of substituted aryl- and naphthyl-SF_5 from 7-oxanorbornene derivatives **192** and **195** (Scheme 35A).[82] The high regioselectivity observed for the formation of 2-SF_5-1-naphthol (**194**) is consistent with ab initio computational studies, which revealed a SF_5···HO hydrogen bond that renders additional stabilization to the product. Duda and Lentz prepared pentafluoro(3,3,3-trifluoroprop-1-yn-1-yl)-λ^6-sulfane (**201**) in high yields in two steps from 3,3,3-trifluoropropyne (**199**) by the addition of SF_5Br followed by a dehydrobromination reaction (Scheme 35B).[83] This compound was demonstrated to be a good dienophile in Diels–Alder reactions, as shown by its reaction with pyranone. Importantly, this procedure permits the introduction of the SF_5 group at the *ortho* position of arenes (**202**). Carreira and co-workers reported a synthetic strategy for preparing SF_5-containing N-heterocyclic building blocks, such as quinolinones, quinolines, and pyridines (Scheme 35C).[84] Benzyl SF_5-acetate (**204**) proved to be an excellent candidate to participate in aldol reactions, providing a wide range of 3-SF_5-quinolinones in good to excellent yields. These compounds can be rapidly converted into the corresponding quinolines **205** using either $POCl_3$ or $POBr_3$.

Since the SF_5 group is considered a bioisostere of the CF_3 and ^{t}Bu groups, the authors compared the physicochemical properties of 3-SF_5-quinolinone with its CF_3 and ^{t}Bu analogues. Preliminary collected data showed that SF_5 exhibits higher lipophilicity than CF_3, but lower than the ^{t}Bu group. The membrane permeability increases in the order $SF_5 < {}^t\text{Bu} < CF_3$. In terms of p$K_a$ values, the SF_5-quinolinone was the most acidic. Concerning the solubility, both the CF_3 and SF_5 compounds are considerably more soluble than the ^{t}Bu counterpart.

Kanishchev and Dolbier generated *ortho*-SF_5-benzyne (**208**) by a lithiation/elimination sequence starting from 2-



Scheme 35. Synthesis of different aryl-SF_5 and heteroaryl-SF_5 compounds.

fluoro-SF_5-benzene **207** (Scheme 35D).[85] The highly reactive SF_5-benzyne intermediate underwent Diels–Alder cyclization with furan in situ, and the product **209** was subjected to a series of further chemical transformations en route to **210** and **211**.

All these synthetic alternatives allow access to *ortho*-substituted aryl-SF_5 compounds in good yields, in contrast to direct oxidative fluorination (Section 5.1), where the *ortho*-substituted diaryldisulfides are still the main limitation to expand the substrate scope.

6. Conclusion and Outlook

This Minireview highlights different approaches toward the synthesis aryl-S^{VI} fluorides, where the central S atom is substituted with 2, 3, 4, or 5 F atoms, thus defining the fluorination level. Level 2 fluorinated compounds have been successfully prepared by using XeF_2/Et_3NCl as an oxidative fluorinating system, a method that still remains in use nowadays. Remarkably, these compounds have gained much attention recently, as the corresponding sulfoxonium cations have been shown to be super-Lewis acids for organic transformations.

Level 3 fluorination is still an underdeveloped platform, with untapped potential for synthesis. It is clear that $ArSOF_3$ compounds are good linchpin reagents for the synthesis of sulfonimidoyl fluorides.

Whereas levels 2 and 3 are still underdeveloped, their higher fluorinated analogues (levels 4 and 5) have been widely studied and their synthesis widely explored. In this regard, recent advances in the use of $Ar–SF_4Cl$ compounds have shown that strong oxidants such as F_2 and Cl_2 can be replaced by the safer and easy-to-handle TCCA/KF system.

Finally, the synthesis of arylsulfanyl pentafluorides have been the most studied and improved, as a result of the recent interest of $Ar–SF_5$ compounds in medicinal chemistry. The current synthetic approaches rely on the Cl–F exchange from the corresponding $Ar–SF_4Cl$ compounds. Alternatively, other synthetic procedures that employ SF_5Cl gas as a precursor to the SF_5 group have also been successful, although the synthesis of the aryl ring is required.

Despite the excellent advances in the synthesis of (hetero)arylsulfur(VI) fluorides and their successful applications, the reported approaches still suffer from several disadvantages, such as narrow substrate scope and harsh reaction conditions. Thus, we envision that innovative work in this area is likely to arise from new greener and milder synthetic methods. Moreover, as a result of the high interest in the SF_5 group in medicinal chemistry and biology, this area will also evolve to avoid the use of toxic SF_5Cl as a SF_5 radical precursor, and the use of the greener, but less reactive, SF_6 gas. The very few examples of this latter approach already show the promising synthetic utility of SF_6 gas as a building block for sulfur(VI) fluoride synthesis.[86]

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: Fluorine · Pentafluorosulfanyl Arenes · Sulfinyl Trifluorides · Sulfur · Tetrafluorosulfanyl Chlorides

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