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De-risking S–F bond formation: A gas cylinder-free strategy to access S(IV) and S(VI) fluorinated compounds.

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Abstract: The sulfur-fluorine partnership occupies a privileged position in fluorine chemistry given the functional versatility that it imparts to organic structures. Despite this, available methodologies to forge S–F bonds are limited compared to C–F bond formation. Here, we describe a synthetic protocol that selectively enables the oxidative halogenation of aliphatic, aromatic, and heteroaromatic thiols to their corresponding SF_4Cl, SO_2F and SF_3 derivatives. Selective oxidation of thiols to either S(IV)–F or S(VI)–F compounds is achieved by employing bench-stable calcium hypochlorite as chlorine surrogate (CLOgen), in the presence of KF as fluoride source. Density functional theory (DFT) calculations provided insight into the mechanistic aspects of the transformation and rationalized the observed isomeric preference towards the SF_4Cl derivatives. Ultimately, this glovebox-free method selectively dispatches three classes of compounds upon reaction condition fine-tuning. Furthermore, first-in-class transformations are reported, including the preparation of aliphatic SF_4Cl intermediates, their transformation into aliphatic sulfur pentafluoride analogs, and post-functionalizations that allow accessing highly complex SF_4-bridged scaffolds.

Introduction

Despite their modest presence in naturally-occurring organic compounds, fluorine occupies a privileged position in life and materials science.[1] For example, the impact of fluorine on medicinal chemistry and drug design is remarkable. Today, around 20% of marketed drugs contain one fluorine atom or a fluorinated group. However, it is important to point out that 86% of these scaffolds pivot on fluorinated and trifluoromethylated scaffolds.[2] This is in line with the synthetic accessibility of these two functionalities in comparison to more 'exotic' fluorinated groups, whose synthetic bottlenecks limited their applicability.

Currently, besides the undisputed carbon-fluorine partnership, sulfur-fluorine bond formation is increasingly gaining attention, owing to the versatility that characterizes prototype structures of this class. For instance, both S(IV)–F and S(VI)–F compounds are used as deoxyfluorinating agents.[3] Furthermore, S(VI)–F compounds are employed as covalent probes in chemical biology and drug discovery. Among the "SuFEx"-able warheads, sulfonyl fluoride[4] and fluorosulfate[5] groups are used as emerging reactive probes with tuned electrophilicity.

Similarly, SF_5-containing substrates and SF_4-bridged analogs span various research fields, including materials science, drug design, and organic chemistry.[6] For example, the "polar hydrophobic" character of SF_5 has been exploited to design liquid crystals,[7] luminescent materials,[8] and polymers[9] with improved properties. Furthermore, due to its high lipophilicity and enhanced size, SF_5 is considered as a bioisostere of common functional groups in drug design, including *t*-butyl, nitro, and trifluoromethyl.[10] For example, drug candidates that contain an SF_5 group have shown enhanced biological activities compared to their analogs,[11] with representative structures such as DSM265 reaching phase II clinical trials[12].

Long-standing efforts to forge S–F bonds hinged on oxidative fluorination methods in presence of difficult-to-handle F_2 gas, AgF_2 or XeF_2 as a fluorine source.[13] In a ground-breaking work, Umemoto et al. described the synthesis of arylsulfur trifluorides and aryl chlorotetrafluorosulfur intermediates by oxidative halogenation in the presence of Cl_2/KF.[14] Subsequently, the same method was successfully applied to heteroaromatic disulfides by the groups of Dolbier and Shibata.[15]

While Umemoto's approach has had an enormous impact on expanding the substrate scope and overcoming some of the drawbacks of the F_2/N_2 system (e.g. undesired ring fluorination), nevertheless it requires the use of specialty equipment such as pressurized Cl_2 gas cylinders, considerably restricting wider lab-scale use. A highly important modification was recently reported by Pitts, Santschi, Togni and co-workers,[16] who got similar and sometimes improved results by substituting Cl_2 for trichloroisocyanuric acid (TCICA) as a solid chlorine source. This gas-free method was further elaborated by Shibata[17] and Cornella[18] to significantly expand the scope of aromatic S(VI) fluorides. Notwithstanding the indisputable advantages, the TCICA/KF method still harbours some drawbacks. Firstly, this method has been described as moisture sensitive and requires glovebox handling, hence restricting its use to laboratories equipped with such costly and cumbersome instrument. Further complications, arise from the high excess of TCICA and use of highly expensive spray-dried KF as well as of disfulfides or

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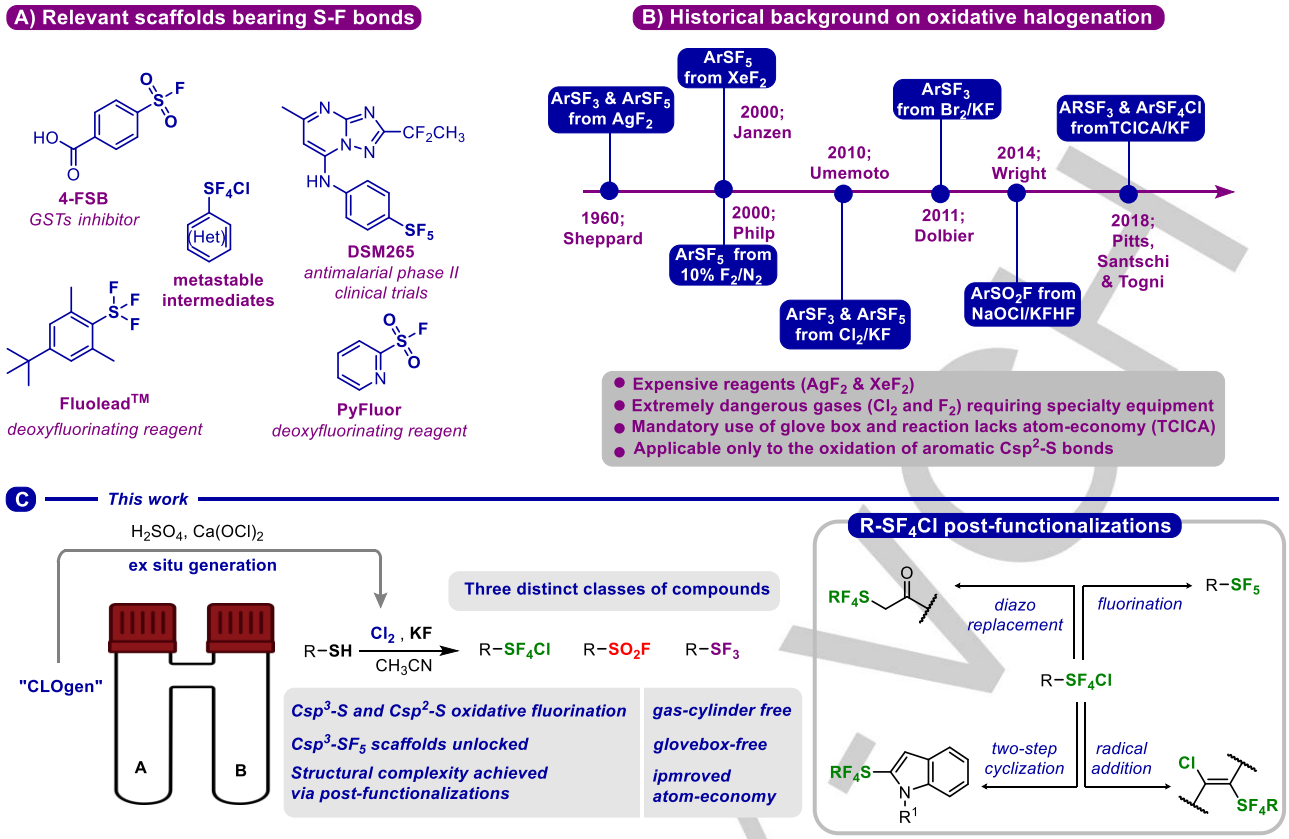


Figure 1 A) Relevant scaffolds bearing S-F bonds B) historical background on oxidative halogenation C) safe and facile preparation of three distinct S-F bearing compounds as well as post-functionalizations of SF_4Cl-bearing intermediates.

protected thiols. This not only negatively affects the atom economy but also increases solid material-to-solvent ratio that renders stirring of the reaction mixture very challenging.

In that respect, a gas-cylinder-free and glovebox-free approach that is capable of forging S–F bonds that simultaneously improves atom economy and endows functional group tolerance is highly desirable.

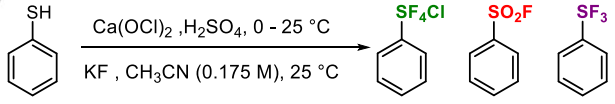
Results and Discussion

With this in mind, we devised a novel oxidative halogenation approach able to selectively deploy products **2**, **3** and **4** containing sulfur in the S(VI) and S(IV) oxidation state starting from readily available aliphatic and (hetero)aromatic thiols **1**. By exploiting the practicality of the two-chamber reactor, we envisaged a protocol that allows the ex situ formation of chlorine gas under CLOgen conditions, followed by its dissolution into the reaction mixture containing the corresponding thiol and KF in CH_3CN.

Calcium hypochlorite is the main active ingredient of chlorinated lime, a disinfectant that is widely used for water treatment, as well as for the sterilization of swimming pools and household facilities. Furthermore, it is safely used for the sanitization of fruits and vegetables dedicated to human consumption. Similarly to other hypochlorites, $Ca(OCl)_2$ is expected to form hypochlorous acid (HOCl) under acidic conditions, that will undergo chlorine speciation.[19]

In light of this, we reasoned that the addition of a Brønsted acid to $Ca(OCl)_2$ could generate chlorine, which once diffused in the other chamber would enable oxidative halogenation of thiols in presence of KF. And indeed we found that adding 0.5 ml of sulfuric acid to $Ca(OCl)_2$ in chamber A gives rise to the formation

Table 1 Oxidative halogenation of thiophenol selectively yielding chlorotetrafluorothiophenol **2a**, phenylsulfonyl fluoride **3a**, and phenyl sulfurtrifluoride **4a**.



1a 2a 3a 4a

Entry	$Ca(OCl)_2$[b] (equiv.)	Acid (ml)	KF (equiv.)	Time (h)	Yield [a] (2/3/4 %)
1	8	0.5	16	8	37/9/3
2	8	0.5	16	16	40/24/0
3	8	1	16	16	57/5/3
4	6	1	16	16	73/13/0
5 [c]	8	1	16	16	0/85/0
6	2	1	16	16	0/0/52

[a] Yields are determined by ^{19}F NMR spectroscopy in presence of α,α,α-trifluorotoluene as internal standard. [b] In entry 4 a fresh bottle of $Ca(OCl)_2$ was employed. [c] Reaction was run using non-anhydrous reagents.

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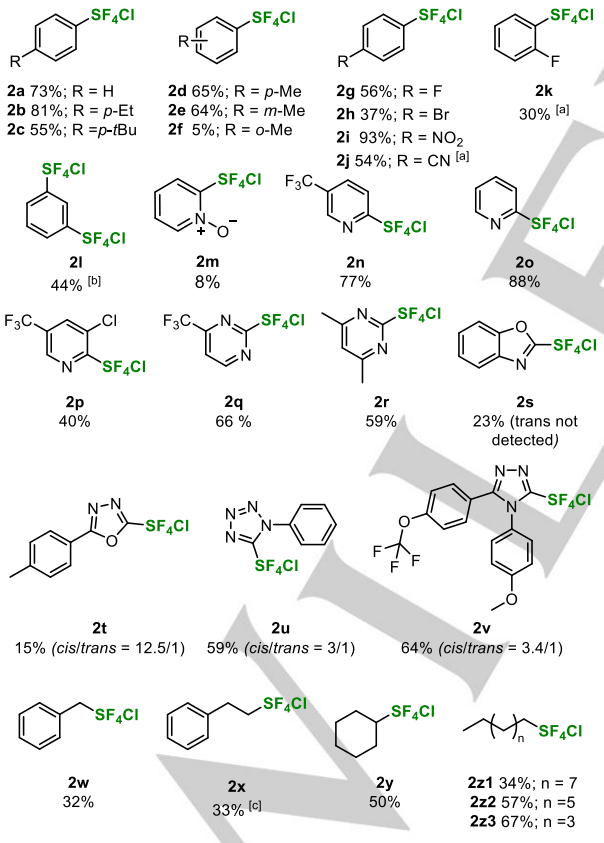
of chlorotetrafluorothiophenol **2a** in chamber B with an ^{19}F NMR yield of 37% after 8 hours (Table 1, entry 1). By increasing the reaction time to 16 hours, we mainly observed an increase in yield for the phenylsulfonyl fluoride **3a**, probably due to in situ hydrolysis of **2a**. To overcome the undesired hydrolysis, we increased the volume of sulfuric acid to 1 ml, obtaining a yield of 57%, probably owing to its known desiccating properties. Unexpectedly, by employing a new batch of $Ca(OCl)_2$ we observed an increase in yield of **3a** up to 73% even with a lower number of equivalents (8 vs. 6 equiv, Table 1, entry 3 vs. entry 4). Furthermore, by substituting oven-dried KF and anhydrous CH_3CN with "wet" reactants, thiophenol was selectively converted into the corresponding phenylsulfonyl fluoride **3a** with a yield of 73% (Table 1, entry 5). And finally, by decreasing the number of equivalents of calcium hypochlorite (Table 1, entry 6) we were able to arrest the reaction at the S(IV) oxidation state, selectively obtaining phenylsulfur trifluoride **4a.**

Under the optimized conditions (Table 1, entry 5) we converted a large scope of (hetero)aromatic and aliphatic thiols to their corresponding chlorotetrafluorosulfur adducts **2a**–**2z3** (Scheme 1). Both electron rich (**1b**–**1f**) and electron poor (**1g**-**1j**) starting materials successfully underwent oxidative halogenation, yielding the *meta*- and *para*-substituted compounds (**2a-2j**) in a modest to excellent yield (37-93%). In addition, as expected, *ortho*-substituted thiophenols gave compounds **2f** and **2k** in lower yields, 5% and 30% respectively, due to steric hindrance. Notable is the double oxidative halogenation of the dimercaptobenzene **1l** to the corresponding product **2l**, by doubling the number of equivalents



Scheme 1 Substrate scope for the synthesis of chlorotetrafluorosulfur compounds. Reactions were run on a 0.350-mmol scale. Yields shown are quantified via ^{19}F NMR. [a] 6 equivalents of $Ca(OCl)_2$ was used. [b] 16 equivalents of $Ca(OCl)_2$ was used [c] 32 equivalents of KF was used.

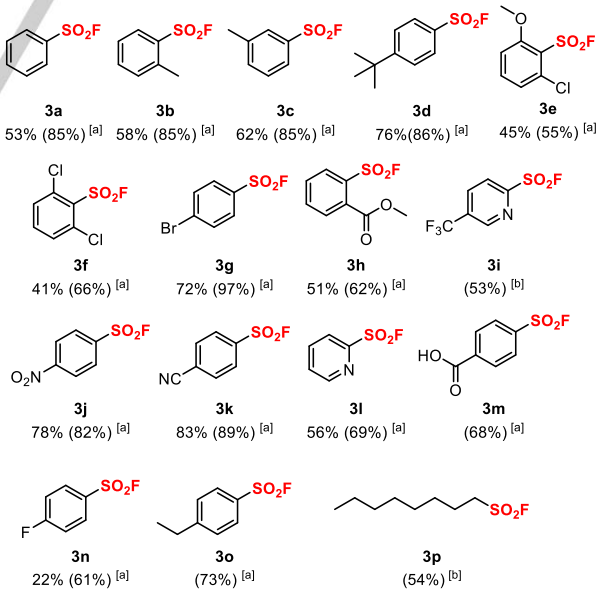
of reagents. Furthermore, heteroaromatic thiols containing a pyridine or pyrimidine ring were smoothly converted into the desired products **2m**–**2r**. In contrast to *o*-substituted thiophenols, the *ortho*-chlorine effect in **1p**, seems to have a lower impact on the reactivity, thus yielding **2p** in a 40% yield.

Five-membered heteroaromatic thiols yielded the corresponding compounds **2s**–**2v** in modest to good yields. Interestingly, unlike six-membered heteroaromatic thiols, compounds **2s**–**2v** are obtained as a mixture of *cis*/*trans* isomers. From an initial inspection it can be deduced that the presence of an oxygen atom as in the case of the benzoxazole or oxadiazole ring in compounds **2s** and **2t,** shifts the stereoselectivity more strongly towards the *cis*-isomer compared to nitrogen-containing five-membered rings.

Finally, our oxidative halogenation method was successfully extended to aliphatic thiols. Herein, we report for the first time the oxidative chlorotetrafluorination of $C(sp^3)$–S bonds. The method tolerates the conversion of benzylic, cycloalkyl and linear-chain alkyl thiols to their corresponding SF_4Cl adducts. Six different aliphatic thiols were smoothly converted into their corresponding aliphatic SF_4Cl-containing scaffolds (**2x**-**2z3**) in decent to good yields (32-67%).

Later, we directed our attention towards the synthesis of the highly versatile sulfonyl fluorides. Direct oxidation methods of sulfur(II) species to sulfonyl fluorides include the electrochemical oxidation[20] of disulfides, use of excess of Selectfluor[21] as an oxidizing and fluorinating agent, and oxidation of thiols in presence of sodium hypochlorite and KHF_2[22]. More recently, arylthiophtalimides were converted into their corresponding sulfonyl fluorides under glovebox conditions in presence of TCICA, KF and MeOH.[18a] Despite existing reports provide alternatives to access sulfonyl fluorides, they employ prefunctionalized sulfones, expensive oxidizing agents such as Selectfluor, or require anhydrous reaction conditions.

Herein, we were able to synthesize sulfonyl fluorides employing technical grade KF and CH_3CN. Under the previously optimized



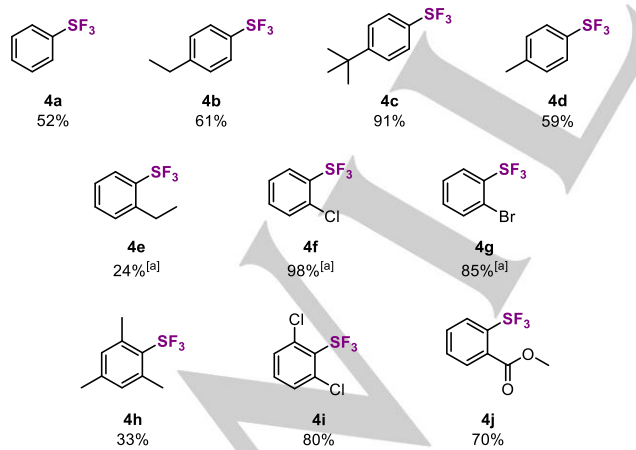
Scheme 2 Substrate scope for the synthesis of sulfonyl fluorides. Reactions were run on a 0.350-mmol scale. Isolated yields are given and ^{19}F NMR yields are in parentheses. [a] Compounds were prepared applying non-anhydrous conditions. [b] Compounds were prepared applying anhydrous conditions followed by hydrolysis.

conditions (Table 1, entry 6), we converted a series of thiols into sulfonyl fluorides **3a**–**3p** with good to excellent yields (Scheme 2). Nonetheless, for a few of the isolated products, yields are lower than expected probably due to their inherent reactivity. Electron-donating (**3b**–**3d**) and electron-withdrawing (**3f**–**3k**) substituents on the aromatic ring do not seem to affect the reaction outcome. Furthermore, unlike for the Ar–SF_4Cl products, the reactivity is not affected by the presence of bulkier substituents in *ortho* position of the thiol group (**3b** vs. **3c** in Scheme 2), and even bulkier or 2,5-disubstituted precursor were smoothly converted into the corresponding sulfonyl fluorides (**3f** in Scheme 2).

As expected, highly electron rich substrates such as 2–mercaptoanisole undergo ring chlorination. Compound **3e** could be considered of interest in view of further post-functionalization, given the use of chloroarenes in cross-coupling reactions. Additionally, we report the synthesis of two relevant scaffolds such as 4-(fluorosulfonyl)benzoic acid (4–FSB, **3m**) and 2-pyridinesulfonyl fluoride (PyFluor, **3l**). The 4–mercaptobenzoic acid and 2–mercaptopyridine were converted into the known glutathione inhibitor **3m** and deoxyfluorinating reagent **3l** with ^{19}F NMR yield of 68% and 69%, respectively. Worth highlighting is the synthesis of compound **3p**. In contrast to (hetero)aromatic sulfonyl fluorides, the aliphatic sulfonyl fluoride **3p** could not be synthesized under the optimized reaction conditions. Indeed, aliphatic thiols require anhydrous conditions and the reaction proceeds via the alkyl–SF_4Cl intermediate, followed by hydrolysis into their aliphatic sulfonyl fluoride analog. Unfortunately, **3p** could not be isolated.

Finally, we dedicated our attention to the synthesis of arylsulfur trifluorides, given their use as deoxyfluorinating agents. S(IV)–F bond forging was initially achieved via oxidative fluorination in presence of expensive AgF_2.[13a] Follow-up methodologies employed toxic and corrosive molecular bromine[23] or gaseous chlorine[24] as an oxidant in presence of KF.

Herein, under CLOgen conditions, we report the conversion of ten aromatic thiols into their corresponding arylsulfur trifluorides. Precursors bearing electron-rich as well as electron-poor substituents undergo oxidative fluorination to yield compounds **4a**–**4j** in moderate to excellent yields (31–99%). On the other hand, compounds **4e-4g** require a larger excess of $Ca(OCl)_2$



Scheme 3 Substrate scope for the synthesis of arylsulfur trifluorides. Reactions were run on a 0.350-mmol scale. [a] 6 equiv of $Ca(OCl)_2$ (instead of 2 equiv.) have been employed. Yields shown are quantified via ^{19}F NMR using α,α,α-trifuorotoluene as the internal standard.

(Scheme 3). Arylsulfur trifluorides are known to be reactive and therefore difficult to isolate.

Given the importance of R–SF_4Cl structures as key intermediates in downstream synthesis to access SF_4-bridged structures, we performed a series of post-functionalizations. Initially, we focused on the radical addition of chlorotetrafluorosulfanyl-containing intermediates on alkynes. Inspired by Dolbier's conditions,[25] catalytic amounts of triethylborane as radical initiator gave the desired products **5a-5d** in good yields (
Scheme 4-A). Furthermore, dehydrochlorination of **5b** gave the corresponding SF_4-alkyne **6** in presence of LiOH (
Scheme 4-B).

Similarly, **5c** could be converted into the novel SF_4-bridged indole **7** (
Scheme 4-C). Inspired by Blanchard and Bizet, this was achieved via a two-step base-mediated dehydrochlorination/ intramolecular cyclization procedure in presence of LiHMDS and K_3PO_4.[26] Another proof-of-concept transformation includes the one-step synthesis of α-SF_4R ketones (
Scheme 4-D). Hydrotetrafluorosulfanylation was carried out by reacting $ArSF_4Cl$ with the corresponding α-diazo ketone under basic conditions, and compounds **8a-b** were isolated in good yields. Up to date, α-SF_4R compounds could be accessed only via multiple step synthesis.[27] Finally, we dedicated our attention to the conversion of R–SF_4Cl into R–SF_5 (
Scheme 4-E). As a proof of concept, four aromatic–SF_4Cl precursors were converted into Ar–SF_5 either in presence of KHF_2 or $AgBF_4$ as a fluorinating agent. In our hands, the use of $AgBF_4$ gave higher yields than KHF_2. When KHF_2 is employed, 13% and 52% ^{19}F NMR yields were achieved for compounds **9a** and **9c**, respectively. In contrast, by using $AgBF_4$ compounds **9a** and **9c** gave 74% and 96% ^{19}F NMR yields, respectively. In addition, we report the first transformation of $C(sp^3)$–SF_4Cl into the corresponding alkyl–SF_5 using the optimized conditions. Unfortunately, **9a** could not be isolated due to the high volatility.

Intrigued by the *cis/trans* stereoselectivity, a DFT analysis was performed on a subset of 9 compounds (**2a**–**2c**, **2o**, **2r–2v**) to reveal if the isomeric preference towards the SF_4Cl adducts is steered by the thermodynamic stability of the products or rather the kinetics of the reaction. First, the most stable conformations of both the *trans*- and *cis* products were optimized at the PBE-D3BJ level of density functional theory in conjunction with the def2-TZVP basis set (full computational details are outlined in the supporting information).[28] Previous studies report the slow isomerization process from *trans* to *cis* SF_4Cl products, leading to the natural conclusion that the *cis* product is the thermodynamically most stable isomer.[14, 29] However, based on the computed Gibbs free energies ($\Delta G_{t\text{-}c} = G_{trans} - G_{cis}$) it is clear that for the 9 selected compounds there is a negligible difference in thermodynamic stability between the *cis* and *trans* stereoisomers (Figure 2).

Nevertheless, closer inspection of the optimized geometries do reveal notable structural differences between the different SF_4Cl adducts. This concerns the orientation of the –SF_4Cl group with respect to the aryl plane. The latter can be expressed by the absolute value of the torsion angle formed over one of the equatorial halogen atoms (F or Cl) towards the closest *ortho* atom (C, N or O). In most cases, this torsion angle is similar for the *trans* and *cis* adduct with a value close to 45° (Figure 2). However, when two heteroatoms are placed *ortho* with respect to the SF_4Cl adduct, one being an oxygen atom, the SF_4Cl rotates in the *cis*

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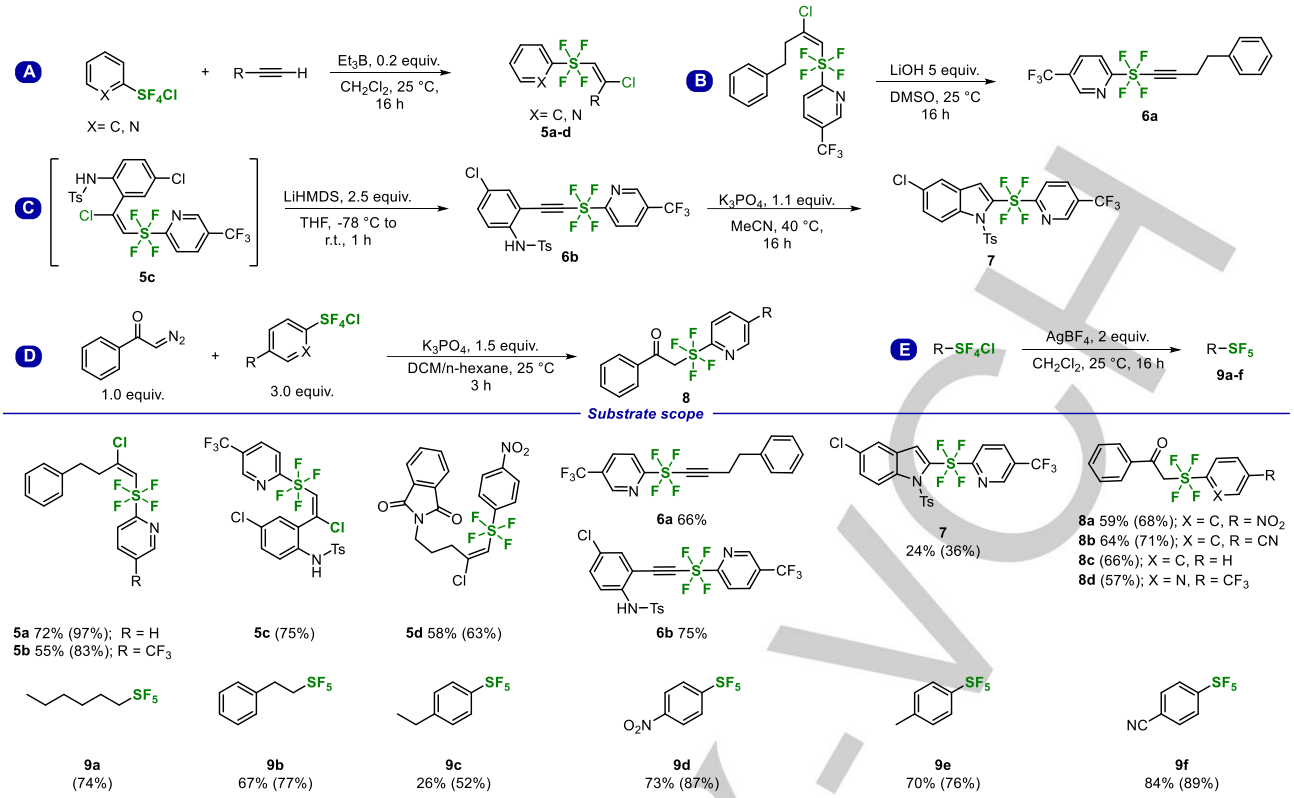

Scheme 4 Substrate scope for the post-functionalizations of chlorotetrafluorosulfur internediates into highly complex SF_4-bridged scaffolds. Isolated yields are given and ^{19}F NMR yields are in parentheses.

adduct to mitigate the repulsion between the larger Cl atom and the heteroatoms. This results in a torsion angle closer to 90° for **2s** and **2t**. Latter effect diminishes when the two *ortho* atoms are both nitrogen (**2u** and **2v**) or when they are part of a six-membered ring (**2r**). For the *trans* isomer the torsion angle remains close to 45°, as in this case the larger halogen is placed in the axial position.

As the relative thermodynamic stability of the products could not explain the experimentally observed stereoisomeric preference, we investigated the kinetic aspects of the reaction. Umemoto and co-workers proposed a mechanism in which the isomeric preference would be locked during the final addition of Cl_2 to the Ar–SF4$^-$K$^+$ complex.[14] For this reason, we focused our computational investigation at computing this step of the postulated reaction profile at the PBE0-D3BJ/def2-TZVP level of theory and with acetonitrile solvation effects implicitly included through the SMD model (see Supporting Information).[30] Furthermore, it was decided to investigate the reaction of **2a** and **2s**, as experiments indicate these reactions to yield the *trans* and *cis* isomer, respectively (Scheme 1). Our efforts resulted in plausible structures for the $SF_4^-K^+$ intermediate complex as well as a transition state that yields the SF_4Cl products. Importantly, for **2a**, the activation barrier of the chlorination step towards the *trans* adduct ($\Delta G^{\ddagger}$ = 7.9 kcal·mol^{-1}) is lower compared to the corresponding activation barrier that yields the *cis* adduct ($\Delta G^{\ddagger}$ = 10.1 kcal·mol^{-1}). In contrast, for **2s**, the activation barrier associated with the *cis* adduct ($\Delta G^{\ddagger}$ = 8.1 kcal·mol^{-1}) is substantially lower compared to the *trans* adduct ($\Delta G^{\ddagger}$ = 12.3 kcal·mol^{-1}) (Figure 3). These observations are in line with the experimentally observed stereoselectivities for **2a** and **2s**. By comparing the reaction profiles, it becomes apparent that for the *cis* pathway the difference in activation barriers between **2a** and **2s** can largely be explained by the relative height of the transition state complex. However, for the *trans* pathway the difference in activation barriers between **2a** and **2s** is accounted for by the relative stability of the $SF_4^-K^+$ intermediate. Indeed, upon scrutinizing the structure of the intermediate, a complexation between the potassium cation and the nitrogen in the *ortho* position of the substrate seemingly provides a significant stabilizing effect in the case of **2s**. Such stabilizing effect does not occur during the *cis* pathway nor in the absence of *ortho* heteroatoms (**2a**). Supported by this computational analysis, we propose the *cis*/*trans* isomeric preference of the reaction to be driven by the kinetic aspects of the reaction rather than the thermodynamic stability of the product.

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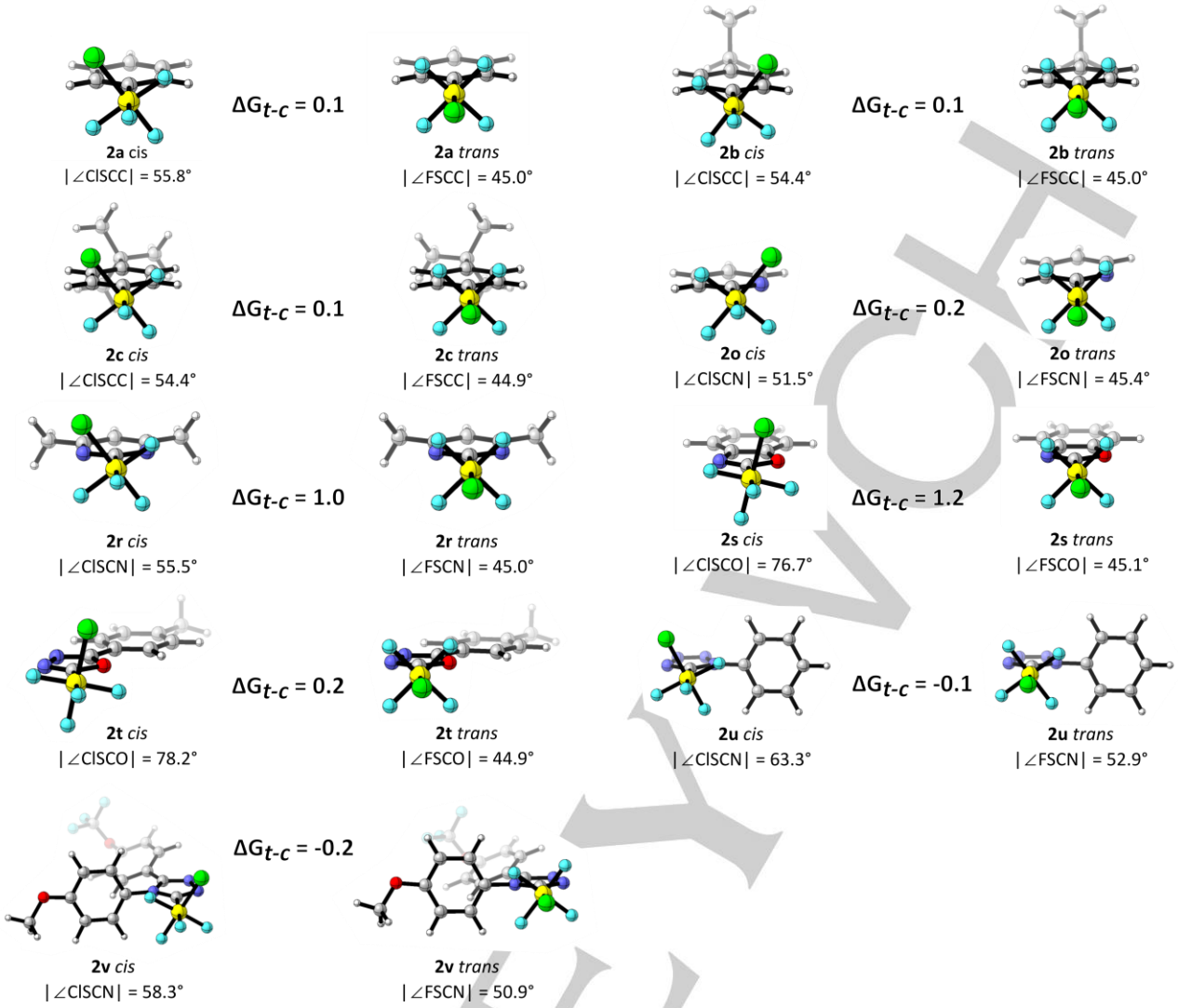

Figure 2 . Gas phase optimized geometries (PBE-D3BJ/def2-TZVP) of the *cis* and *trans* -SF_4Cl product of 9 selected compounds. Their respective absolute value of the torsional angle describing the rotation of the –SF_4Cl group with respect to the aryl ring is displayed below their label. The difference in Gibbs free energy between the *trans* and *cis* adduct (ΔG_{t-c}) is computed at the PBE-D3BJ/def2-TZVP level of theory and provided in kcal·mol^{-1}.

Conclusion

In summary, by harnessing ex situ chlorine gas generation ('CLOgen' conditions), we were able to develop an overarching oxidative halogenation approach. This safe and reliable method enabled the oxidative halogenation of a large library of thiols, dispatching chlorotetrafluorosulfanyl derivatives, aryl sulfonyl fluorides and arylsulfur trifluorides, only by fine-tuning reaction conditions. The method has large functional group tolerance and enabled the synthesis of first-in-class alkyl–SF_4Cl and corresponding SF_5 analogs. SF_4Cl derivatives were employed in post-functionalizations, including the conversion into the corresponding SF_5 analogs, two step-cyclization yielding a hitherto unknown SF_4-bridged indole, and the direct access to α-SF_4Ar ketones. Furthermore, DFT calculations over a subset of nine SF_4Cl substrates suggested that the stereoisomeric *cis* preference might not be driven by the thermodynamic stability of the product. From our data, it seems that such selectivity is rather of kinetic nature, owing to the interaction between the *ortho*-heteroatom and the potassium cation that increases the activation barrier for the *trans* isomer.

To conclude, the reported gas-cylinder-free and glovebox-free oxidative halogenation method represent a valuable approach to access starting materials of interest. In the future it could be applied to other potential transformations that require the use of chlorine gas.

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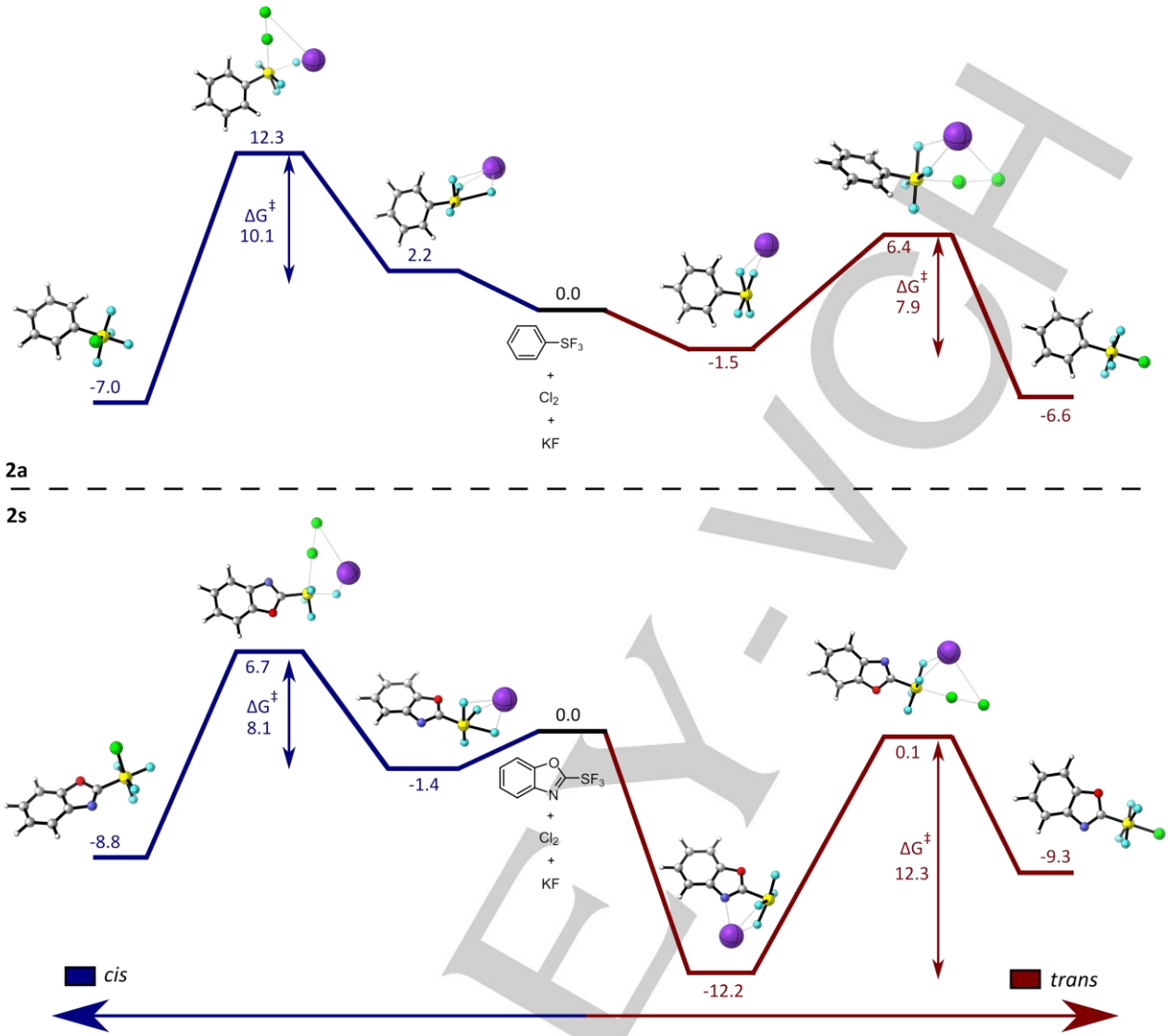

Figure 3. Schematic representation of potential energy surface going from the $SF_4^-K^+$ complex to the SF_4Cl product through chlorination with Cl_2. Left: *cis* pathway, right: *trans* pathway, top: profile of **2a**, bottom: profile of **2s**. All stationary points were computed at the PBE0-D3BJ/def2-TZVP level of theory (SMD=acetonitrile). The Gibbs free energy levels are expressed in kcal·mol^{-1} and relative to the isolated reactants. For the first intermediate isolated Cl_2 is taken into consideration, while for the product isolated KCl is taken into consideration when calculating the relative free energy levels.

Experimental Section

General procedure for the synthesis of SF_4Cl-bearing compounds

In an oven- and Schlenk-dried two-chamber reactor, calcium hypochlorite (0.404 g, 2.800 mmol, 8 or 6 equiv.) was added to the gas-generating chamber (A) and the main chamber (B) was charged with the thiol (0.350 mmol, 1 equiv.) – only in case the thiol is solid –, finely-crushed oven-dried potassium fluoride (0.329 g, 5.600 mmol, 16 equiv.), and then immediately vacuum-N_2 cycles were performed. Then, dry acetonitrile (2 mL) and the thiol – in case the thiol is liquid – were injected in chamber A. After that, an excess amount of sulfuric acid (1 mL, 17.990 mmol, 51.4 equiv.) was gently injected into the gas-generating chamber at 0 °C to generate Cl_2 gas and the temperature was allowed to rise back to room temperature. The reaction was stirred at room temperature for 16 hours. Subsequently, the remaining chlorine gas was slowly neutralized by ventilating the atmosphere of the reactor into a concentrated solution of sodium hydroxide. In order to measure the ^{19}F NMR yield, α,α,α-trifluorotoluene, as an internal standard, was added to the reaction mixture and an aliquot of the reaction mixture was filtered (0.4 ml) via a PTFE syringe filter straight into an NMR tube followed by the addition of 0.1 ml of deuterated chloroform. To acquire a crude product 2 for the next step(s), the NMR sample was added to the rection mixture which has been filtered via a PTFE syringe filter into a polyethylene centrifuge tube and the solvent was evaporated in vacuo at 0 °C.

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Author contribution

WMDB, EI, and JD secured funding. EI and WMDB conceived the project and EI coordinated the work. JD proposed the chlorine generation method. RK, AZ, CB, and EI performed the synthesis. RVL performed the computational part. EI and RVL drafted the manuscript. All authors agree with the content.

Keywords: chlorine • organofluorine • pentafluorosulfanyl • synthetic methodology • two-chamber

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RESEARCH ARTICLE

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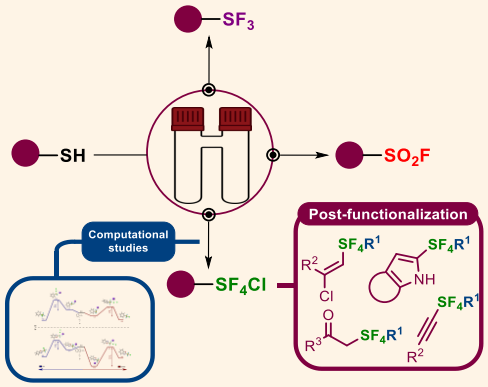

Herein we report the oxidative halogenation of thiols via the ex-situ generation of chlorine by employing calcium hypochorite as solid bench-stable precursor. This approach enables the synthesis of three distinct classes of compounds (R-SF_3, RSO_2F and RSF_4Cl). Metastable R-SF_4Cl intermediates are further postfunctionalized to access structures of higher complexity, and computational analysis elucidate potential pathways that leads to *cis*-selectivity for certain heteroaromatic SF_4Cl structures.

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