An Extrusion Strategy for On-demand SF_5Cl Gas Generation from a Commercial Disulfide

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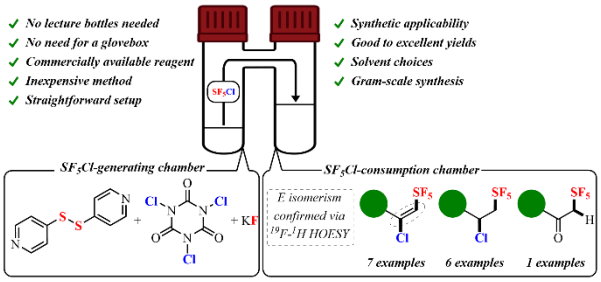
Supporting Information Placeholder

ABSTRACT: Herein, we report a novel methodology for the ex-situ generation of SF_5Cl by employing 4,4′-dipyridyl disulfide as a safe commercial reagent obviating the need for lecture bottles. The method is applicable to certain SF_5Cl-involving transformations using a two-chamber reactor. Moreover, easily applying SF_5Cl in both polar and non-polar media is rendered feasible while avoiding the use of glove-box techniques. This report also suggests ^1H-^{19}F HOESY as a simple and fast stereochemistry indication for chloropentafluorosulfanylated olefins.

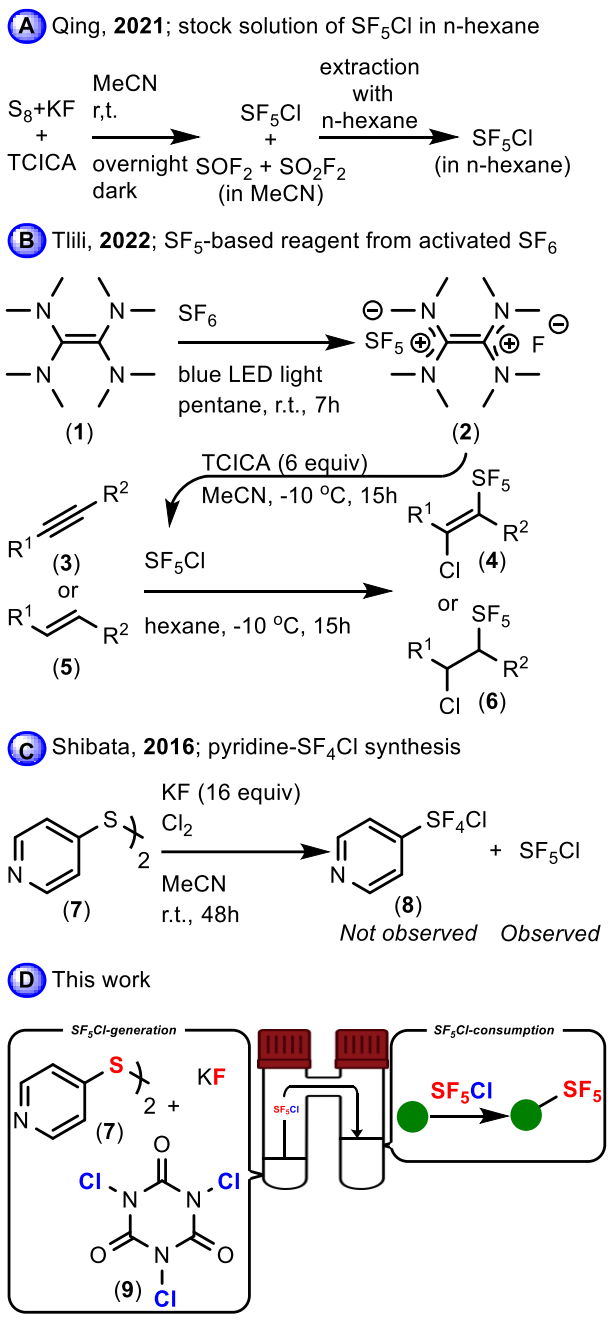


Enriching the fields of medicinal chemistry, materials science and agrochemistry, fluorine has presented itself as a privileged functionality.[1] In this regard and amongst the pioneering fluorinated substituents, the pentafluorosulfanyl group (-SF_5) stands out as a shining gem. The rapid popularization is a result of the discovery of the distinctive and peculiar set of molecular characteristics - such as high electronegativity and yet high lipophilicity, bulkiness as well as thermal, hydrolytic and chemical stabilities - brought about by the incorporation of the SF_5 group onto organic molecules.[2]

Evidently, broad applications of SF_5-containing compounds revolve around their synthetic accessibility. The prominent approaches towards SF_5-containing compounds include (i) C-SF_5 bond formation (typically via SF_5Cl) and (ii) S-F bond formation.[2] Regarding the former, in the past few years, major progress was made in rendering SF_5Cl more readily accessible to the scientific community alleviating a previously unaddressed synthetic bottleneck (Scheme 1, A and B). The group of Qing reported a new way to access stock solutions of SF_5Cl, by performing the KF/TCICA-mediated chloropentafluorination of elemental sulfur in MeCN, followed by an organic-organic extraction with n-hexane (Scheme 1, A).[3] Notwithstanding the notable improvements, the methodology suffers from certain drawbacks. Firstly, a preparative step is involved, requiring amounts of chemicals, solvents and time for the preparation of the solution. The second issue is that the solvent of the final solution is n-hexane; this clearly means that the methodology is restricted to more non-polar starting materials. Lastly, in the described procedure, a glovebox is required which is not accessible to all groups. In an alternative approach to rendering SF_5Cl available to the synthetic community, the group of Tlili applied ex-situ generation of SF_5Cl in a two chamber reactor (Scheme 1, B).[4] Aiming to take advantage of the setup, Tlili and colleagues developed an elegant SF_5Cl precursor (**2**) via blue LED light induced activation of SF_6 in the presence of the organic reductant tetrakis(dimethylamino)ethylene (TDAE, **1**). While this is a valuable discovery and the first example of on-demand SF_5Cl generation, the need for glovebox handling and the high cost of the air-sensitive TDAE reductant (**1**) in the preparation of the non-commercial precursor **2** form a possible hurdle for general implementation.

Inspired by the abovementioned examples, we sought an alternative procedure applicable for ex-situ generation of SF_5Cl relying solely on stable and commercially available precursors. Based on our recent experience with oxidative halogenation of sulfur containing precursors[5] and further confirmed in a 2016 report by Shibata and co-workers,[6] we realized that 4,4′-dipyridyl disulfide (DPDS, **7**) was a potential candidate precursor for ex-situ SF_5Cl generation. This was based on the finding that DPDS (**7**), in a chlorotetrafluorosulfanylation attempt with Cl_2 and KF, did not yield the anticipated 4-(chlorotetrafluoro-λ⁶-sulfanyl)pyridine (**8**). Instead, a release of SF_5Cl was detected (Scheme 1, C).

Scheme 1. Background and Hypothesis



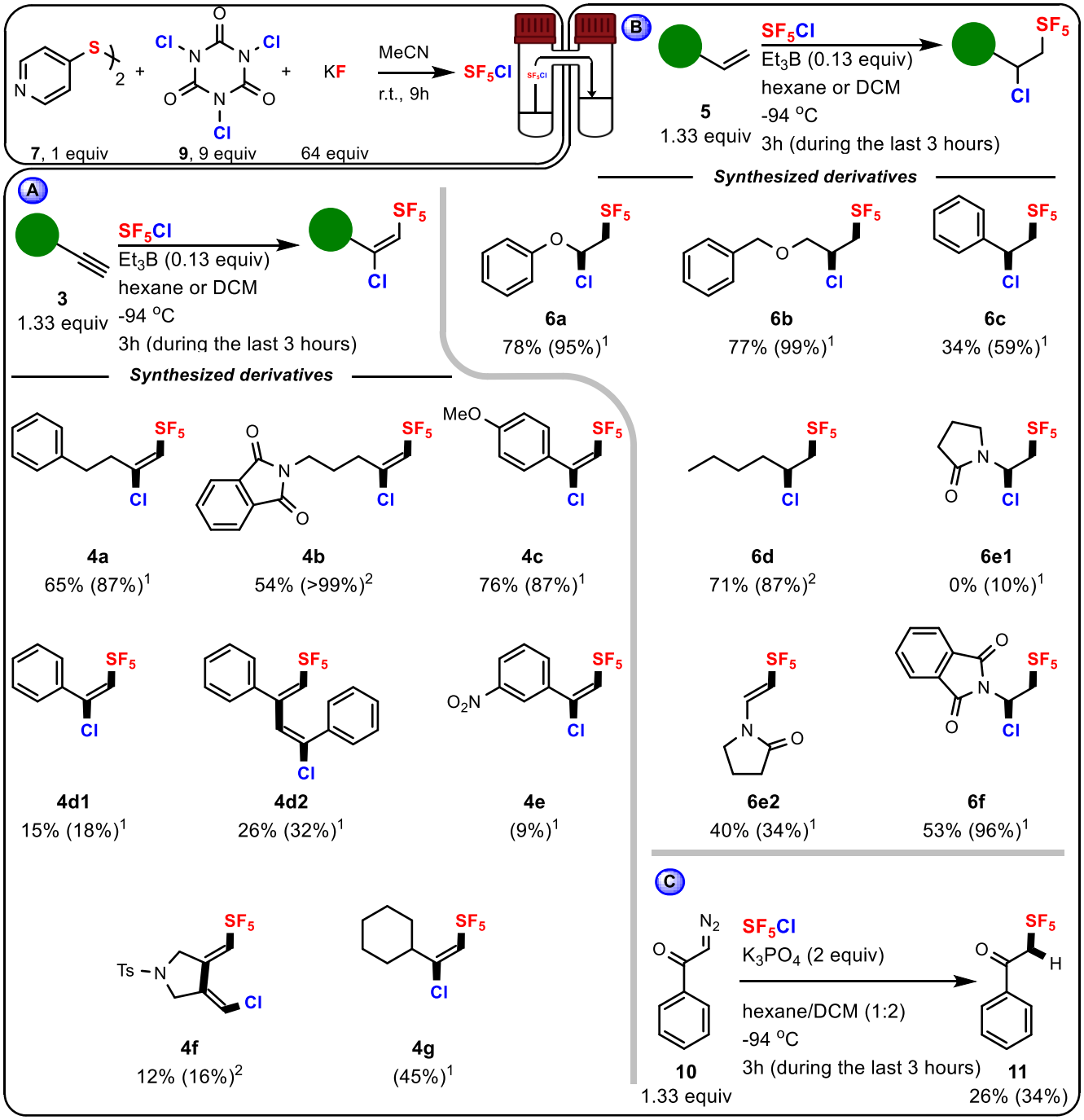
From a practical point of view, the use of chlorine gas for ex-situ generation of SF_5Cl was not desired since it is likely to give rise to ample side reactions with substrates present in the gas consumption chamber. For that reason, we turned to TCICA (**9**), a chlorine source for chlorotetrafluorosulfanylation recently introduced by the group of Togni.[7] We examined the reaction mixture of DPDS (**7**, 1 equiv) with TCICA (**9**, 18 equiv) and KF (32 equiv) after 18 hours stirring under a nitrogen atmosphere. Reassuringly, SF_5Cl (10%) was observed in the filtered crude mixture and again no 4-(chlorotetrafluoro-λ⁶-sulfanyl)pyridine (**8**) was detected via ^{19}F NMR spectroscopy.

Next, we set to employ DPDS (**7**) for ex-situ generation/consumption of SF_5Cl in a two-chamber reactor. For that purpose, the reaction of 4-phenylbutyne (**3a**) with SF_5Cl generated from the reaction of DPDS (**7**) with TCICA (**9**) and KF was selected as the model reaction. An extensive optimization evaluating the impact of various factors in both gas-generating as well as gas-consuming chambers was performed. Following the acquired results, we were satisfied to observe an ^{19}F NMR yield of 87% could be obtained for **4a** employing DPDS (**7**, 1 equiv), TCICA (**9**, 9 equiv) and KF (64 equiv) in dry MeCN at room temperature in the gas generation chamber and using 4-phenylbutyne (**3a**, 1.0 equiv), Et_3B (0.13 equiv) in dry n-hexane at -94 °C in the gas consumption chamber. Under these conditions, a far shorter reaction time (9 h) gave superior results compared to the typical reaction times (18-48 h) for an optimal KF/TCICA-mediated chlorotetrafluorosulfanylation established in the literature.[7-8] Moreover, the method is compatible with both polar (DCM and Et_2O) and non-polar (n-hexane) solvents for the SF_5Cl radical addition, creating a suitable solubility profile for the employment of a wider range of starting materials. Fully detailed results and description of the optimization can be found in the supporting information.

With the encouraging optimization results in hand, we sought to explore the applicability of the method to previously reported transformations involving SF_5Cl gas. We commenced with the radical addition of SF_5Cl onto alkynes (**3**) as the same transformation was chosen for the optimization (Scheme 2, A). To our delight, both aliphatic and aromatic substitution on the triple bond were perfectly tolerated, giving good to excellent ^{19}F NMR yields for the adducts (**4a-g**). For instance, a 99% ^{19}F NMR yield was achieved for the more complex **4b**. Similar to the pattern the literature,[9] the yield obtained for SF_5-olefins (**4c-e**), proved to be significantly substituent-oriented. In this regard, it was noted that the reaction progress is ruled by the availability of the π electrons of the triple bond. Consequently, ^{19}F NMR yields for phenylacetylenes increase when there is an electron-donating group present and vice versa. For instance, a very low yield (impossible to isolate) for product (**4e**) was detected. When using phenylacetylene (**3d**), a moderate yield for **4d1** was achieved. In this case, however, the 2:1 (phenylacetylene/SF_5Cl) dimer (**4d2**) was a major byproduct. On the other hand, a significantly high yield was acquired for the 4-methoxy-adduct (**4c**). Another interesting result was obtained when *N*,*N*-di(propargyl)toluenesulfonamide (**3f**) was subjected to the optimized conditions. The major product **4f** was the results of an intramolecular cyclization. Unfortunately, product **4g** could not be isolated. For more information on the assignment of the stereochemistry, see below.

We next set out to extrapolate the methodology to the addition of SF_5Cl onto double bonds (Scheme 2, B). Pleasingly, moderate to excellent yields were achieved starting from versatile substrates (**5a-f**). Phenyl vinyl ether (**5a**) as well as allyl benzyl ether (**5b**) were smoothly transformed to the corresponding SF_5-adducts with near-perfect yields (95% for **6a** and 99% **6b**). Additionally, styrene (**5c**) could be well accommodated. Gratifyingly, we also managed to easily forge and purify an aliphatic chain-SF_5 (**6d**). A somewhat unexpected observation was made when *N*-vinyl pyrrolidone (**5e**) was used as the substrate. While two prominent SF_5-containing products (**6e1** and **6e2**) were detected in ^{19}F NMR spectrum of the crude mixture of the gas consumption chamber, only one product eluted from column chromatography (carried out the day after the reaction). The emerging product after characterization turned out to be compound 6e2 with an isolated yield (40%) that was higher than the expected yield estimated based on ^{19}F NMR

Scheme 2 Substrate scope



Isolated yields are given and ^{19}F NMR yields are in parentheses. [1] The reaction solvent is n-hexane. [2] The reaction solvent is DCM.

(34%) in the crude. We assume that the obtained product (**6e2**) could be best rationalized by the self-promoted dehydrochlorination of the expected SF_5Cl-adduct (**6e1**). Conversely, *N*-vinylphthalimide (**5f**), excellently yielding the expected adduct (**6f**, 96%), does not seem to undergo the self-promoted dehydrochlorination.

Finally, we chose aryl SF_5-methylene ketones as reaction partners in our system as, to the best of our knowledge, these compounds have only been synthesized using the storable SF_5Cl solution method. Herein, we find the method applicable to the same transformation, albeit with a reduced but still synthetically useful yield for **11** (Scheme 2, C).

To examine the synthetic utility of the method, a larger-scale synthesis of product **4a** (starting with 5 mmol of **3a**) was carried out under the optimized conditions. After isolation, a 69% (1.010 g) yield could be achieved rendering the gram-scale synthesis possible.

Mechanistic studies on the gas generating chamber are under investigation and will be reported in due course.

Conventionally, SF_5-olefins synthesized via the radical addition of SF_5Cl onto triple bonds are assumed to end up with the *E* orientation around the double bond. The use of X-ray crystallography to determine the stereochemistry of each product, albeit it would be optimally accurate, seems very challenging. First of all, this technique is quite costly and unavailable to many research groups. To make the matter more complicated, the majority of SF_5-compounds are liquid at room temperature due to which it is practically impossible to grow their crystals for X-ray crystallography. Very recently the group of Tlili provided a ^1H-^1H NOESY spectrum recorded on the SF_5Cl-adduct of 4-bromophenylacetylene implying that the absence of through-space correlation between the vinylic and ortho hydrogen atoms signifies the *E* isomerism.[4] However, the absence of NOE effects does not necessarily result from the absence of dipolar coupling and only the presence of NOE effects should be considered. Therefore, we assumed that ^1H-^{19}F HOESY experiments could provide extra information to shed light on the matter. For that purpose, compounds **4d1** and **4b** were selected. Optimized geometries in computational models suggested that the equatorial fluorine atoms on the SF_5 group and either the ortho aryl protons (for compound **4d1**) or the allylic protons (for compound **4b**) hydrogen atoms in the *E*-isomers would be able to show a heteronuclear NOE as shown in Figure 1, A. These interactions would not be possible in the alternative *Z*-isomers of the compounds. In line with our hypothesis, the aforementioned through-space correlations were detected by the ^1H-^{19}F HOESY technique, directly demonstrating that the *E* orientation exists around the double bond (Figure 1, B, the signals highlighted by red circles). However, through-space correlations for compound **4b** were also detected between equatorial fluorine atoms on the SF_5 group and the hydrogens of the other two methylene moieties. To further validate our claim, we also performed single-crystal X-ray diffraction studies for one representative compound **4b** (Figure 1, C). In perfect alignment with the ^1H-^{19}F HOESY spectrum, the crystal structure reveals the *E* isomerism for the double bond. Hence, ^1H-^{19}F HOESY spectroscopy seems to be an adequate tool for the confirmation of the stereochemistry around the double bond in similar compounds.

To sum up, we have introduced a new reagent to generate SF_5Cl ex situ, eliminating the need for any type gas bottles. The reagent has the advantage of being readily available as it is inexpensive and commercial. Moreover, it does not impose particular risks. The system enabled facile harness of the generated SF_5Cl in certain SF_5Cl-involving transformations. Satisfying yields were achieved for most of the compounds synthesized applying the described SF_5Cl generation methodology showcasing the applicability of the system. In addition, the methodology allowed for the use of both polar and non-polar solvents. Furthermore, the method appeared to work effectively in gram scale demonstrating its scalability. Based on the merits offered, we believe this method is of practical utility for research-scale synthesis and has the potential to become a key tool in other reactions that typically require SF_5Cl gas. Additionally, determination of the *E* isomerism of SF_5-olefines prepared via radical chloropentafluorosulfanylation of alkynes was shown to be possible employing ^1H-^{19}F HOESY spectroscopy.

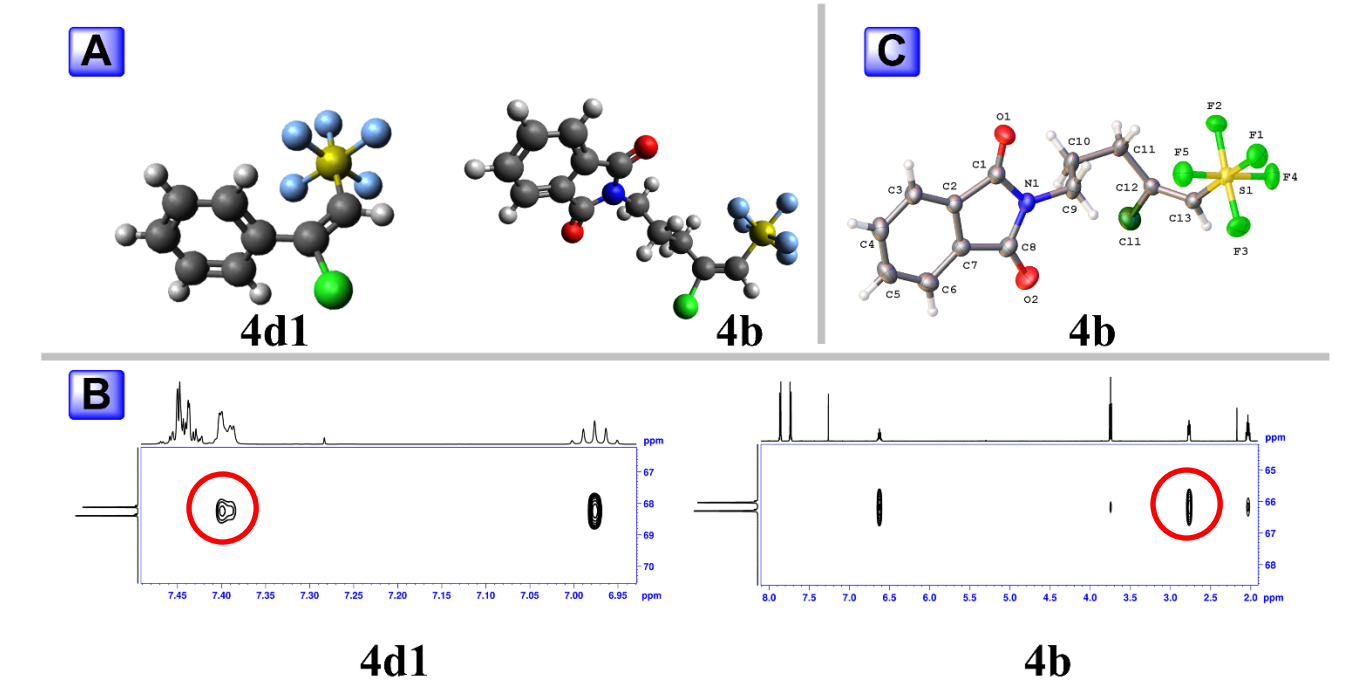


Figure 1. A) Optimized molecular geometries of compounds **4d1** and **4b** B) ^1H-^{19}F HOESY spectra of compounds **4d1** and **4b** C) Crystal structure of compound **4b**, showing atom labelling and thermal ellipsoids drawn at the 30% probability level.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

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