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# Photochemical Activation of Sulfur Hexafluoride: A Tool for Fluorination and Pentafluorosulfanylation Reactions

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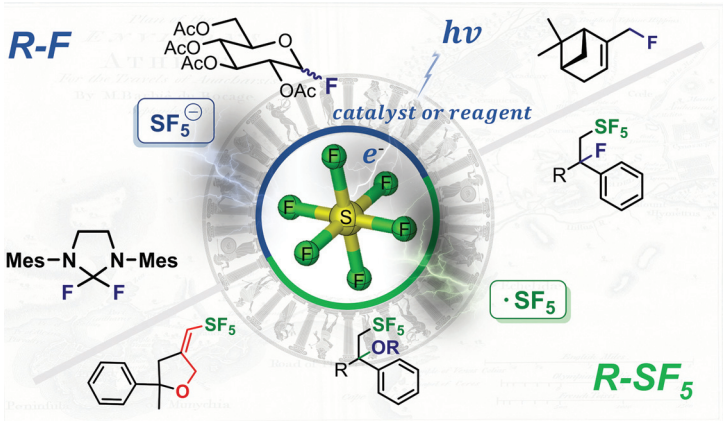


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**Abstract** The photoactivation of notoriously inert sulfur hexafluoride represents a challenge for photochemistry. This short review summarizes recently published efforts and the corresponding photochemical mechanisms for switching between the fluorination and pentafluorosulfanylation reactivity of organic substrates.



**Key words** photochemistry, photocatalysis, fluorination, electron transfer, light, sulfur hexafluoride, pentafluorosulfanylation

## 1 Introduction

Over the last decade, photoredox catalysis has become a powerful method in modern synthetic organic chemistry. Since 2018, between 900 and 1,000 publications appeared each year on the topic 'photoredox catalysis'. Light, preferably in the UV-A or visible range, provides enough energy to overcome the activation barriers of reactions that cannot be passed under thermal conditions by employing excited state reactivity.[1] Photoredox catalysis complements the current synthetic methodology of so far unknown transformations and allows the limits of available methods to be overcome.[2,3] Thus, photoredox catalysis is an important addition to the repertoire of transformations involved in the total synthesis of natural products[4] and late-stage functionalization of pharmaceutically active compounds.[5] Currently, the majority of methods developed use transition-metal catalysts, mainly based on ruthenium and iridium, due to their advantageous photophysical properties and their (photo)chemical robustness.[6] The concept of photoredox catalysis implies a certain degree of inherent sustainability using sunlight or energy-saving LEDs. Furthermore, generating redox active species in low concentrations and under spatiotemporal control allows the reactivity to be precisely controlled by suppression of competing side reactions. In order to enhance sustainability by combining photodriven reactions with organic (in the sense of non-metalated) photoredox catalysts, dyes have become important alternatives to metal catalysts, for instance, eosin y,[7] rhodamine 6G,[8] mesityl-[9] and aminoacridinium,[10] naphthochromenones,[11] phenones[12] and 4,6-dicyanobenzenes.[13] It is also worth mentioning here that both photoredox catalytic as well as stochiometric reactions can be performed even in the absence of any dye by exciting *in situ* formed donor–acceptor complexes.[3] Organic photoredox catalysts span a broad variety of molecular scaffolds that can easily be tuned by core modifications, a crucial prerequisite to adjust a particular catalyst system to be most effective in a distinct transformation.[14]

While divergent photochemical synthesis has become an important tool in modern photocatalysis,[15] the photoactivation of notoriously inert sulfur hexafluoride ($SF_6$) and switching between its fluorination and pentafluorosulfanylation reactivity illustrate recent challenges in photochemistry. In contrast to its smaller fluorinated analogues bearing a dipole moment along the elongated C–X bond, namely a simple fluorine substituent and the $CF_3$ group, the late-stage introduction of the $SF_5$ group is still a major challenge and its chemistry is highly underdeveloped.[16,17] While

a variety of nucleophilic and electrophilic fluorination or trifluoromethylation reagents today allow the routine introduction of fluorine in standard organic chemical laboratories under conventional inert conditions, the introduction of the $SF_5$ group is still restricted to the use of highly reactive and highly toxic gaseous mixed sulfur fluorides, requiring special equipment and allowances to handle these reagents, depending on the location of the laboratories.[18] Interestingly, the $SF_5$ group represents a special substituent out of a collection of chemically stable S(VI)-based functional groups, the chemistry of which has only been scarcely explored to date. Sulfoximines, sulfonediimines, sulfurimidoylfluorides and sulfonimidamides have been seriously neglected for quite some time in drug discovery programs. Only recently have these 'forgotten' S(IV) motifs experienced a tremendous increase in research interest, having been shown to uniquely contribute to modern medicinal chemistry, whilst offering novel modes of catalysis or being applicable in inverse drug discovery approaches.[19,20]

## 2 Sulfur Hexafluoride ($SF_6$)

In contrast to the high reactivity of sulfur fluorides in lower oxidation states or partly fluorinated sulfur fluorides, sulfur hexafluoride ($SF_6$) is a highly inert gas (bp –63.9 °C). It is non-flammable, odorless, colorless, tasteless and non-toxic.[21] Its inertness towards almost any chemical agent is mainly due to its fully symmetric octahedral fluorine shield that causes the lack of availability of a low-lying unoccupied orbital at the S(VI) center or the fluorine atoms for interaction with nucleophiles.[22] Furthermore, it is the strongest greenhouse gas known to mankind today; it displays a 22,800- to 23,500-fold higher greenhouse potential than carbon dioxide and has a mean lifetime in the atmosphere of about 3,200 years.[23] However, $SF_6$ remains indispensable in many applications, especially in the context of high-voltage switchgears, plasma-etching in semiconductor manufacturing and metallurgy, and needs to be destroyed after use.[24] Due to its widespread technical applications, $SF_6$ is produced on large scale (~10,000 tons/a), is quite cheap (44–54 €/kg) and easily available.[19] In contrast to lower sulfur fluorides such as $SF_4$ (including $SF_3$-$NR_2$ and $F_2S$=N), $SF_5$-Cl and $SF_5Br$, which have found widespread use as pentafluorosulfanylation and fluorination reagents,[16,25] $SF_6$ was virtually discounted as a reagent in organic synthesis due to its intrinsic inertness; its ability to serve as a pentafluorosulfanylation agent[26] for routine applications has even been excluded.[17]

## 3 The Pentafluorosulfanyl ($SF_5$) Group

The incorporation of fluorinated substituents into organic molecules significantly affects their physical, chemical, biological and pharmaceutical properties. Fluorinated compounds not only play an important role in pharmaceu-

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tical chemistry,[27,28] but also in agrochemistry,[29] dye chemistry,[30] and materials chemistry including optoelectronics.[28,31] Fluorination of a lead structure often increases metabolic stability and bioavailability and reduces the p$K_a$ of acidic groups in the surroundings.[32] The most routinely used fluorinated motif is the trifluoromethyl ($CF_3$) group.[33] Each individual fluorinated motif has a unique set of properties, including metabolic stability, steric demand, acidity, lipophilicity and polarity, which need to be matched with the requirements of the target and the desired mechanism of action during the optimization process to reach an optimized binding situation with the target and optimal pharmacological properties. Hence, it is an important task to search for more effective and stable fluorinated groups. Among the arsenal of commercially available fluorinated motifs like $SCF_3$, $OCF_3$ and $CF_3$, the pentafluorosulfanyl ($SF_5$) group is the most underexplored, often designated a 'forgotten functional group'. This arsenal is complemented by some more exotic emerging fluorinated motifs for which there is a lack of almost any synthetic accessibility today, for example, $SF_4$-bridged motifs, -$NRCF_3$ or -$OSF_5$.[34]

$SF_5$ compounds behave as promising analogues of $CF_3$ motifs in drugs and other functional organic compounds like agrochemicals and liquid crystals, which connect high lipophilicity with low rotational barriers and steric bulk. Highly beneficial properties have been proposed for the $SF_5$ group in pharmaceutically active drugs,[35,36] functional materials,[37,38] metal complexes,[38,39] biologically active compounds,[40] or for $^{19}F$ MRI by improving the signal-to-noise ratio (SNR) in combination with an ultrashort echo-time (UTE).[41] For instance, trifluoralin has a 5-fold enhanced activity against quackgrass and crabgrass if the $CF_3$ group is replaced by $SF_5$, whilst fenfluramine (an appetite suppressant) shows 10-fold strong binding to the receptor.[40a,42,43] Moreover, the $SF_5$ group is both thermally and widely chemically stable and not prone to hydrolysis under physiological conditions. After initial metabolic processing, it has recently been shown for some compounds that the $SF_5$ substituent can finally be metabolized with formation of fluoride anions.[42,44] The $SF_5$ substituent on phenyl rings shows a group electronegativity of 3.65 in contrast to 3.35 for $CF_3$, as well as a Hammett parameter of $\sigma_p = 0.68$, between $CF_3$ ($\sigma_p = 0.54$) and $NO_2$ ($\sigma_p = 0.78$) (Figure 1), and is highly lipophilic (Hansch parameter $\pi = 1.23$, between $SCF_3$: $\pi = 1.44$ and $OCF_3$: $\pi = 1.04$).[45] The $SF_5$ group has been discussed as a bioisosteric replacement not only for the $CF_3$ group but also for *t*Bu, $NO_2$ and halogen substituents.[35] The first organic pentafluorosulfanyl compound was described by Cady in 1950 who prepared $SF_5CF_3$ by excessive fluorination of $CS_2$.[46]

Triggered by the pronounced interest in the $SF_5$ group during the last decade, major progress has been made in developing new protocols to access $SF_5$-containing small molecules.[26,48] In principle, two general strategies can be distinguished that rely either on the formation of (i) S–F bonds

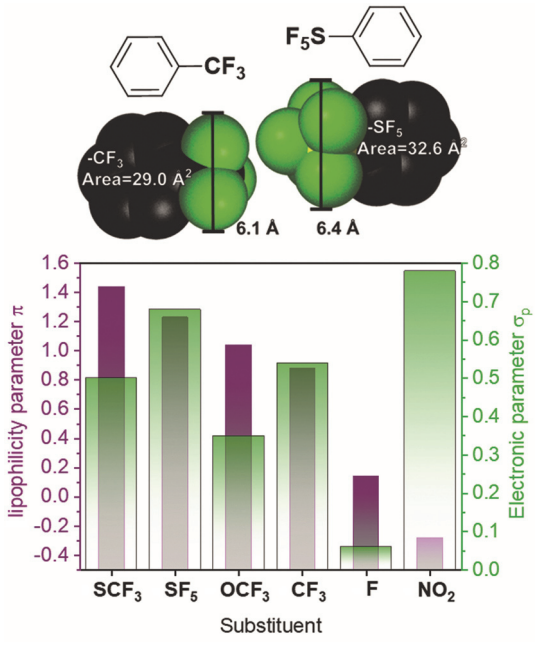



**Figure 1** Steric size of the $SF_5$ group in comparison to the $CF_3$ group (top) and the Hammett/Hansch parameters ($\pi$ and $\sigma_p$)[47] for a variety of fluorinated substituents and the $NO_2$ group in comparison (bottom)

(oxidative fluorination), or (ii) the C–S bond (direct pentafluorosulfanylation). The first approach has contributed majorly to a routine access to $SF_5$-substituted arenes to be employed as building blocks in early synthetic steps or divergent synthetic routes. In 1997, Ou et al. reported a chloride-supported, $XeF_2$-based strategy to access $ArSF_3$, $ArSF_4Cl$ and $ArSF_5$ compounds.[49] Mechanistic studies strongly point to the relevance of the presence of chloride as a halogen donor during an anion-radical transition during the course of the reaction.

A major breakthrough finally enabling the large-scale preparation of pentafluorosulfanylated arenes was reported by Umemoto in 2012 by employing $Cl_2$ as the oxidizing agent in the presence of KF to access $SF_4Cl$-substituted arenes that could finally be converted into the $SF_5$ compounds by treatment with HF, $ZnF_2$ or AgF.[50] Ultimately, in 2018, Togni reported a modified protocol enabling a gas-free synthesis of $SF_5$ arenes by employing trichloroisocyanuric acid as the oxidizing agent.[51] However, these synthetically highly valuable approaches do not transfer the desired functional group, but rather require prefunctionalized disulfides or thiophenols as starting materials. Limitations are posed by the rather aggressive reaction conditions, restricting the application of these methods mainly to the introduction of the $SF_5$ group in early synthetic steps. Arylphosphorothiolates have been demonstrated as convergent substrates for Ar-$SF_4Cl$ and Ar-$SF_5$ synthesis.[52] Furthermore, today this strategy cannot be applied to aliphatic substrates.

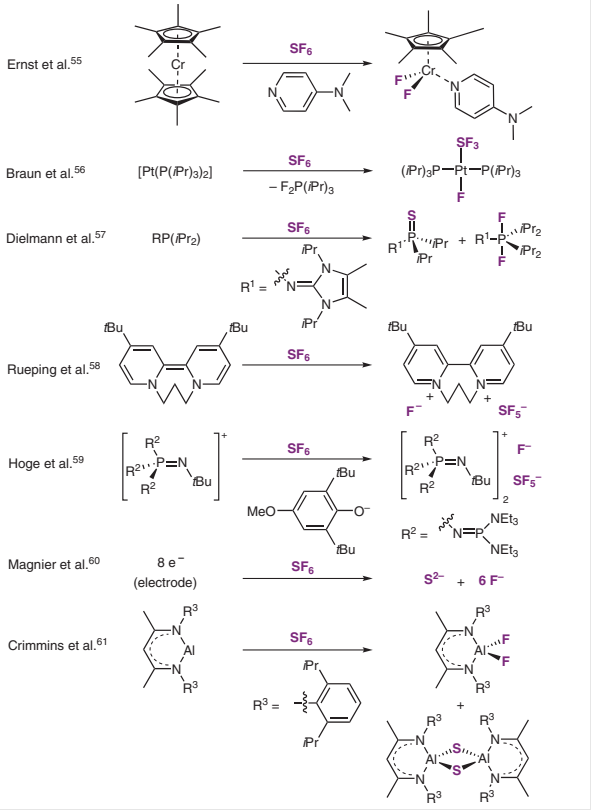
The above-mentioned approach of forming the C–S bond is currently limited to aliphatic substrates, and is by far more underdeveloped than the oxidative fluorination methodology. It fully depends on the generation of the $SF_5$ radical by application of the mixed sulfur fluorides $SF_5Cl$, $SF_5Br$ and $S_2F_{10}$. Alternative pathways that employ the corresponding charged $SF_5$ species suffer from the low nucleophilicity and lability of the $SF_5$ anion or the very high energy of the $SF_5$ cation. However, the extraordinary toxicity of the available pentafluorosulfanylation reagents excludes their use in standard research laboratories and renders the broad industrial use of these methodologies nearly impossible.[16,17] Taken together, the exploration and use of the $SF_5$ group in organic compounds is still very limited because of a lack of synthetic accessibility. However, ramping up from 2016, several reports have described the photochemical activation of sulfur hexafluoride, finally harnessing it either as a fluorination or a pentafluorosulfanylation reagent. In particular, the recent progress in pentafluorosulfanylation chemistry will enable the significant future potential of this long time written-off molecule in modern organofluorine chemistry.

## 4 Photoredox Catalytic Activation of $SF_6$

The inertness of $SF_6$ poses a significant challenge to chemists attempting to harness it as a reagent in synthesis. Early examples of $SF_6$ activation involve extreme reaction conditions employing very high temperatures,[53] or UV irradiation at wavelengths of <190 nm.[54] Modern $SF_6$ chemistry in contrast allows the molecule to be activated under much milder reaction conditions. These methods (Scheme 1) comprise the fluorination of low-valent transition-metal complexes developed by Ernst et al.[55] or Pt catalysts allowing deoxyfluorination reactions described by Braun et al.[56] Dielmann and co-workers reported the nucleophilic activation of $SF_6$ by superbasic phosphines either resulting in complete degradation to phosphine sulfides and difluorophosphoranes or conversion into a bench-stable $SF_5$ anion.[57]

Rueping and co-workers used bipyridine compounds as two-electron donors for the metal-free activation of $SF_6$. The formed $SF_5$ anion dissociates into $SF_4$ and allows deoxyfluorinations of benzylic alcohols, aldehydes and carboxylic acids.[58] The activation of $SF_6$ by non-coordinated phenolate anions was reported in 2021 by Hoge and co-workers, resulting in the formation of phosphazenium pentafluorosulfanylide salts.[59] $SF_6$ can be completely deconstructed by electrochemical reduction (Magnier et al.),[60] or by an aluminum(I) compound according to Crimmins et al.[61] (Scheme 1).

While these thermal or electrochemical methods contribute significantly to the efficient destruction of $SF_6$, such approaches suffer from an inherent disadvantage. One strategy of activation is the reduction of the high barrier of

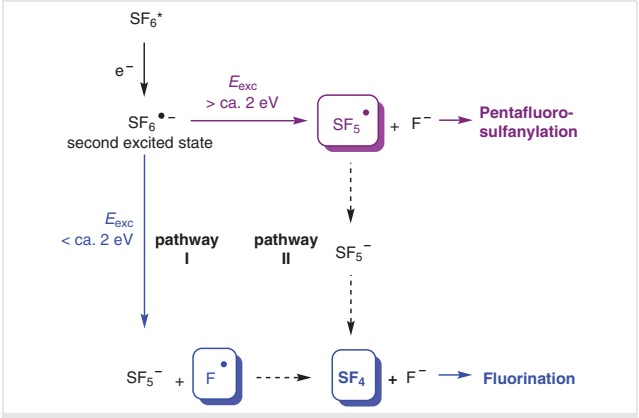



**Scheme 1** Overview of methods for the thermal/electrochemical activation of $SF_6$

activation by increasing the thermodynamic driving force of the reactions. However, these highly exergonic reactions tend to harm the selectivity and suffer from the alternating bond dissociation enthalpies of $SF_6$ and its partly defluorinated reaction products.[62] Thermal reaction approaches therefore tend to end up either in complex reaction mixtures or a thermodynamic sink generating either strong M–F bonds or inorganic fluoride as reaction products. These products cannot easily be applied in downstream fluorination reactions, and thus limit the versatility of these approaches. In general, photochemistry allows this problem to be circumvented by permitting a significant part of the reaction to progress on the potential energy surface of a particular excited state and only ultimately to cross-over to the ground state potential energy surface of the product. This product does not necessarily need to be the thermodynamic product of the ground state reaction, nor is it controlled by thermal reaction barriers connecting potential energy surfaces.

The reduction potential of $SF_6$ was determined to be –2.17 V vs $Fc^+/Fc$ (Magnier et al.),[60] being –1.8 V vs SCE, and –1.9 V vs SCE (Nargony et al.).[63] In the case of $SF_6$, one-electron reduction forms the radical anion $SF_6^{\bullet-}$, which can exist in at least four negative ion states. At least two of them can

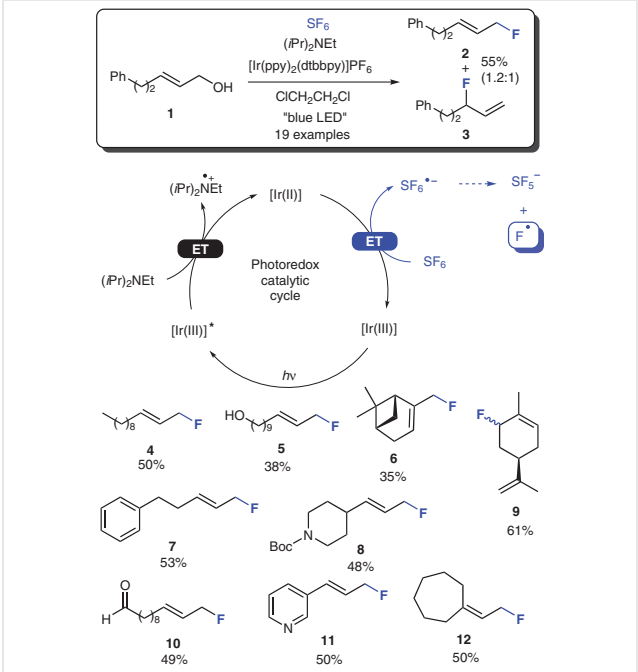
serve as synthetically relevant fragmentation pathways (Scheme 2) to form reactive species showing fundamentally different chemical reactivity.[64] The ground state of the radical anion $SF_6^{\bullet-}$ was proposed best to be described as an 'association complex $(SF_5^{\bullet}F)^{-}$', which is kept together by a very weak interaction of 1.35 ± 0.1 eV (~130 kJ/mol).[65] The first excited state leads to decomposition into the fluorine radical $F^{\bullet}$ and the anion $SF_5^-$ (pathway I), a formal Lewis acid–base adduct of $SF_4$ and the fluoride anion, which parallels exactly the reactivity of $SF_4$.[64] This state was successfully employed in fluorination- and deoxyfluorination-type reactions. However, it cannot serve as a pentafluorosulfanylation pathway due to its low stability and very weak nucleophilicity. To establish the ladder process for the fragmentation of the radical anion $SF_6^{\bullet-}$ into the pentafluorosulfanyl radical $SF_5^{\bullet}$ and a fluoride anion (pathway II), the second excited state of the radical anion $SF_6^{\bullet-}$ needs to be populated.[64] These considerations are aligned with mass spectrometric analysis as well as high-level theoretical calculations that have shown that different decomposition pathways of the radical anion $SF_6^{\bullet-}$ (in the gas phase) depend on the kinetic energy of the transferred electron for the preceding reduction from $SF_6$.[66] This also suggests internal conversion to effectively compete with the rates of dissociative relaxation of the initially populated negative ion state. Below approximately 2 eV excess electron energy, the radical anion $SF_6^{\bullet-}$ decomposes into the fluorine radical $F^{\bullet}$ and the anion $SF_5^-$.[67,68] In order to fragment into the radical $SF_5^{\bullet}$ this energy should be higher than a threshold of approximately 2 eV. Accordingly, Beier et al. showed that the one-electron reduction of $SF_6$ by TEMPOLi yielded aliphatic $SF_5$ compounds, and a mechanism employing the $SF_5$ radical was discussed.[69] These considerations are fully aligned with conventional pentafluorosulfanylation protocols relying on the use of $SF_5Cl$, $SF_5Br$ or $S_2F_{10}$, being the only identified sources of the $SF_5$ radical.[16,26,70]




**Scheme 2** The decomposition pathways of the $SF_6^{\bullet-}$ radical anion depend on the kinetic energy of the electron for the preceding reduction from $SF_6$.[41] Below approximately 2 eV, $SF_6^{\bullet-}$ decomposes into the fluorine radical $F^{\bullet}$, which gives access to fluorinations. Above 2 eV, $SF_6^{\bullet-}$ decomposes into the radical $SF_5^{\bullet}$, which allows pentafluorosulfanylations.

Based on these physical–chemical studies, a suitable photoredox catalyst for the activation of $SF_6$ by one-electron reduction firstly should be able to generate the $SF_6$ radical anion as a primary condition. To switch between its modes of reactivity, namely fluorination or pentafluorosulfanylation, the data suggests the requirement to gain control over the target negative ion state to induce the desired fragmentation of $SF_6^{\bullet-}$. To realize fragmentation to a $SF_5$ radical, higher reduction potentials (resulting in a higher contribution to electron excess energy) are suggested to be required compared to induce the formation of the $SF_5$ anion for fluorination purposes. This idea will be elaborated in the following parts of this short review.

In 2016, Jamison and co-workers developed the first method to activate $SF_6$ by photoredox catalysis employing the widely used and commercially available catalyst $Ir(ppy)_2(dtbppy)PF_6$ (excitation at 470 nm). This approach employs an oxidative quenching cycle that relies on a back-electron transfer by $(iPr)_2NEt$ as a sacrificial reductant (Scheme 3).[70] The oxidation potential of the Ir(III) center is $E_{ox}(Ir^{III}/Ir^{II})$ = –1.61 V (vs SCE).[71] The fragmentation of the formed radical anion $SF_6^{\bullet-}$ yields reactive fluoride radicals that under the strongly reducing reaction conditions most likely will be instantaneously reduced to fluoride and $SF_6^-$ anions to undergo deoxyfluorination-type reactions.[58] The suggested mechanism comprises activation of the alcohol by O–S bond formation to give a putative R–O–$SF_x$ intermediate. Interestingly, the observed retention of the configura-

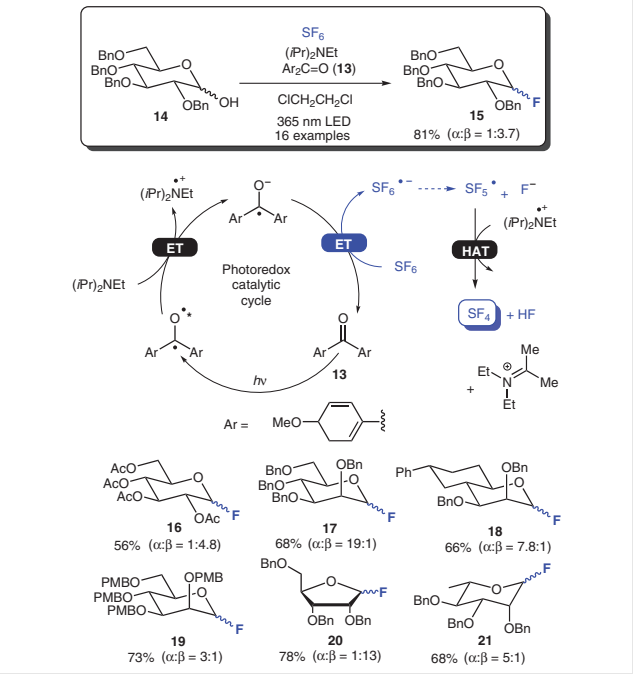



**Scheme 3** Photoredox catalytic activation of $SF_6$ by $Ir(ppy)_2(dtbpy)PF_6$ for the deoxyfluorination of allylic alcohols, e.g., **1** to allylic fluorides **2** and **3** (top), the proposed photoredox catalytic cycle (middle) and examples of the product scope **4**–**12** (bottom)

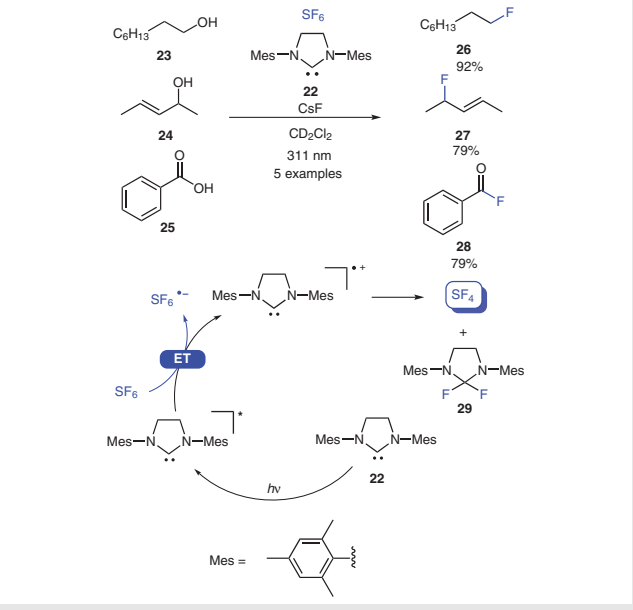
tion when *trans*- and *cis*-(–)-carveol are subjected to the reaction conditions hints at an $S_Ni$-type reaction mechanism, as has been observed in the case of deoxychlorination reactions employing $SOCl_2$.[72] The reaction tolerates a variety of functional groups, including the acid-labile Boc protecting group (**8**), vinylic sites (**9**) as well as aldehyde functions (**10**). The application of continuous-flow reactors gave products **4**, **6** and **12** on gram scale.

Later, Nagorny and co-workers applied a similar photocatalytic strategy to access glycosyl fluorides using $SF_6$ (Scheme 4) that more recently has also been translated into an electrochemical approach.[63,73] Here, 4,4′-dimethoxybenzophenone (**13**) served as an organic photoredox catalyst together with an amine as a sacrificial donor. This ketone was chosen as a photoredox catalyst due to its increased extinction coefficient at 365 nm, the long lifetime of its triplet state and its appropriate redox potential of $E_{red}(\mathbf{13}/\mathbf{13}^{\bullet-})$ = –2.20 V (vs SCE). It was hypothesized that the strong reducing agent causes $SF_6$ to mainly fragment into the radical $SF_5^{\bullet}$. It was further postulated that this radical undergoes a reaction with the previously oxidized aminyl radical cation to give $SF_4$, which was suggested to be the active fluorinating agent. The reaction conditions tolerate different protecting groups on the carbohydrate (Bn, **15** and **17**; Ac, **16**; benzylidene, **18**; PMB, **19**) and is applicable for a broad variety of monosaccharides (e.g., **20** and **21**). Even disaccharides were converted into the corresponding fluorides. Remarkably, flow chemistry allowed glycosyl fluoride **15** to be produced on gram scale.

Kemnitz and co-workers followed the idea of nucleophilic activation of $SF_6$ by envisioning N-heterocyclic carbenes being suitable nucleophiles. However, the incubation of various NHCs, e.g., **22**, with $SF_6$ showed only very weak activation under thermal reaction conditions (Scheme 5). Exploiting the excited state properties of NHC* under irradiation at 311 nm improved the efficacy of the desired activation remarkably.[74] The excited state reduction potential of NHC **22** has been determined as $E_{red}(\mathbf{22}^{*}/\mathbf{22}^{\bullet-})$ = –2.2 V (vs SCE), being sufficient to photoreduce $SF_6$ and induce a fragmentation of the radical anion $SF_6^{\bullet-}$ into the $SF_5^{\bullet}$ radical. After a second single-electron transfer, the $SF_5^-$ anion is formed which initiates the formation of $SF_4$ as a fluorinating agent able to deoxyfluorinate a variety of substrates including 1-octanol (**23**), allylic alcohol **24** and benzoic acid (**25**) to the corresponding products **26**–**28**. Recently, Huang et al. provided more detailed insights into the mechanism of the nucleophilic activation of $SF_6$ by NHCs through *in silico* experiments. This work proved comparably high barriers for the nucleophilic activation of $SF_6$ (43.4 and 33 kcal/mol) by a variety of NHCs. Furthermore, a linear correlation between the Gibbs free energies of activation and the HOMO energies of the NHC were observed. Following the same path, they predicted the thermodynamic and kinetic feasibility of the nucleophilic activation of $SF_6$ by NHCs.[75] Due to the requirement of stoichiometric amounts of carbene **22** that are converted into the difluorinated urea derivative, this method does not represent a photoredox catalytic approach.




**Scheme 4** Photoredox catalytic activation of $SF_6$ using ketone **13** for the deoxyfluorination of glycosides, e.g., **14**, to glycosyl fluoride **15** (top), the proposed photoredox catalytic cycle (middle) and examples of the product scope **16**–**21** (bottom)



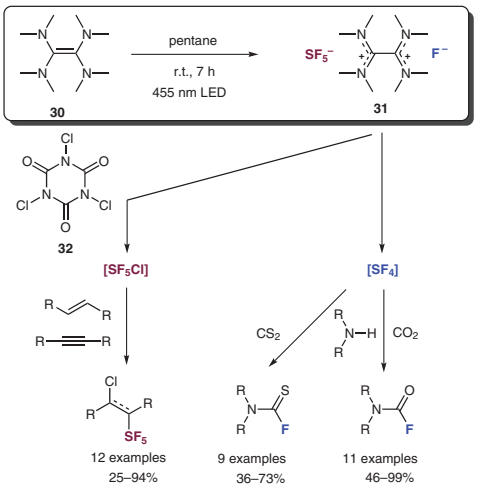

**Scheme 5** Photochemical activation of $SF_6$ by N-heterocyclic carbene **22** for the deoxyfluorination of substrates **23**–**25** to give the products **26**–**28**

The hitherto discussed literature starting from 2016 represent groundbreaking and pioneering work in overcoming the inertness of $SF_6$ for fluorination reactions. However, the work covered so far only represents one aspect of the *Janus-faced* reactivity of the $SF_6^{\bullet-}$ radical anion. In 2015, we became interested in the so far veiled *backward oriented face* of $SF_6$, i.e., its ability to undergo pentafluorosulfanylation reactions. For such a process neither thermal nor photochemical activation conditions had been reported previously. In this context it is noteworthy that the $SF_5$ radical, to a certain extent, resembles the F radical in its kinetic and its thermodynamic properties comprising its global electrophilicity index (ω = 3.7 eV vs 3.94 eV for F$^\bullet$), as well as its electron affinity.[76,77] The electron affinity of the $SF_5$ radical has been determined to be 3.8 ± 0.15 eV, which even exceeds that of a fluoride radical (3.42 eV) by about 0.4 eV.[64,73,78] Stabilization of the radical in solution in the presence of bulk reducing agents is therefore highly unlikely.

In 2002, Kirsch et al. filed a patent on the reaction of $SF_6$ with tetrakisdimethylamino(ethylene) (TDAE) (**30**) forming the mixed bisamidinium fluoride pentafluorosulfanylide **31**. The efficacy of the reaction could be enhanced by irradiating the reaction mixture with visible or UV light. Furthermore, the reagent was described as being a useful fluorinating and pentafluorosulfanylation reagent; however, only a somewhat general procedure was described.[79]

Recently, the group of Tlili resumed the exploration of this system, studying the metal-free activation of $SF_6$ by **30** to form reagent **31** under irradiation with blue light in pentane.[80] The versatile utility of **31** was demonstrated by the development of deoxy- and dethiofluorination reactions by subjecting $CO_2$ or $CS_2$ to the pentafluorosulfanylide species (Scheme 6). The deoxyfluorination of the primarily formed carbamic or thiocarbamic acids grants access to (thio)carbamoyl fluorides that can further be converted into precious *N*-trifluoromethylamines.[34d,e] $SF_4$ was proposed to be the reactive intermediate for fluorination reactivity. Interestingly, in the presence of trichloroisocyanuric acid (**32**), pentafluorosulfanylide **31** could be converted into $SF_5Cl$ *in situ*, which can add to alkenes or alkynes (Scheme 6). Furthermore, the mechanism of activation has been investigated. TEMPO trapping experiments revealed the transient occurrence of TDAE$^{\bullet+}$ as well as $SF_5$ radicals. However, a simple single-electron reduction of $SF_6$ by TDAE was ruled out based on electrochemical data; therefore the authors suggested an unknown intermediate to render the single-electron reduction of $SF_6$ thermodynamically possible.

We envisioned to gain control over the mode of reactivity, namely the *in situ* formation of a highly oxidizing $SF_5$ radical, that is *frightened away* by even weak electron donors by application of a photoredox catalytic approach. The rationale behind this was manifold. Firstly, the desired electron-transfer process could be tuned by excited state lifetimes, irradiation power, the emission spectrum of the light source as well as the concentrations of the reactants. Secondly, the amount of excess energy of the transferred electron needed to switch the mode of reaction of $SF_6$ should be able to be controlled by the energy difference between the acceptor state and the corresponding excited state energy of the photoredox catalyst. Ultimately, reducing the excited state density in the medium finally allowed destructive overreduction to be avoided, which is another stumbling stone of $SF_6$-based pentafluorosulfanylation chemistry as described above (see Scheme 1). A net neutral photoredox catalytic cycle in the absence of any sacrificial reductant could warrant for generating the $SF_5$ radical in a 'redox shelter', opening up a timeframe for transfer to an organic substrate before either colliding with another excited state of the catalyst or any reducing reaction intermediate.

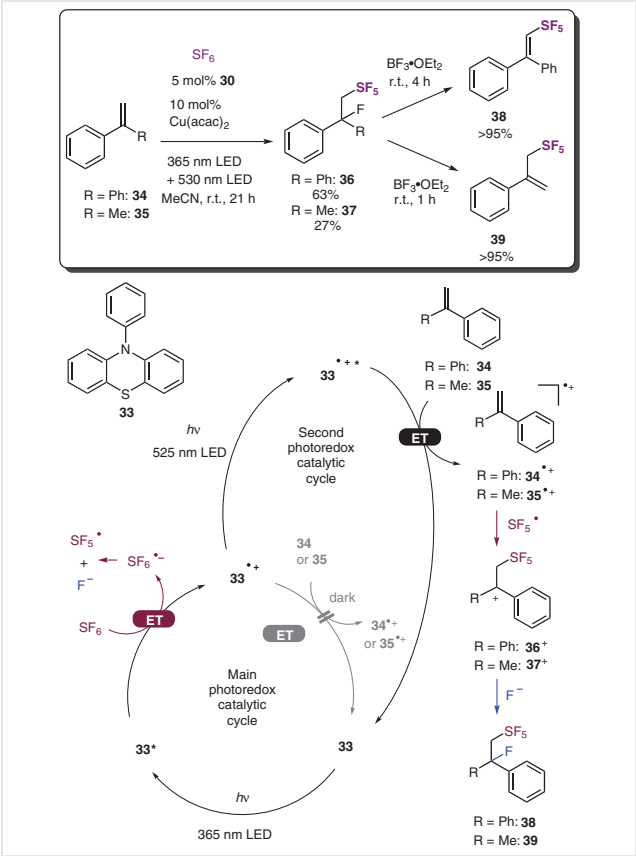



**Scheme 6** Photochemical and metal-free activation of $SF_6$ into the $SF_5$-based reagent **31** for both deoxyfluorinations and pentafluorosulfanylations

*N*-Phenylphenothiazines based on **33** are important photoredox catalysts because (i) they are synthetically well accessible, (ii) their modular structure allows the introduction of electron-donating or electron-withdrawing groups at the core or at the phenyl group to tune the optoelectronic properties, (iii) they are strongly reducing photoredox catalysts, and (iv) they are photochemically stable.[81] *N*,*N*-Diisobutylaminophenyl-phenothiazine is currently the most strongly reducing catalyst in this series that allows, for the first time, the photoredox catalytic alkoxylation of alkyl olefins, as non-activated substrates, to give products with Markovnikov selectivity. Such photocatalytic reductions do not require any additional reagent, tolerate other functional groups, including allyl, alkynyl, cyanide and even acid-labile Boc groups within the substrate scope, and allow *exo*-trig cyclizations.[82] Furthermore, *N*-phenylphenothiazines have been shown to form deeply colored stable radical cations, e.g., **33**$^{\bullet+}$, which can be excited in the near-infrared (NIR) or visible region to access a variety of strongly oxidizing doublet states $E_{ox}$(**33**$^{\bullet+*}$/**33**) ≥ 2.1 V (vs SCE).[83] Its participation

in chemical reactions was reported earlier by Moutet and Reverdy in 1979.[84] This class of catalysts therefore has the general prerequisites to be employed in oxidative 'conPET' (consecutive photoinduced electron transfer) processes spanning a potential range of operation of ca. 5 V.

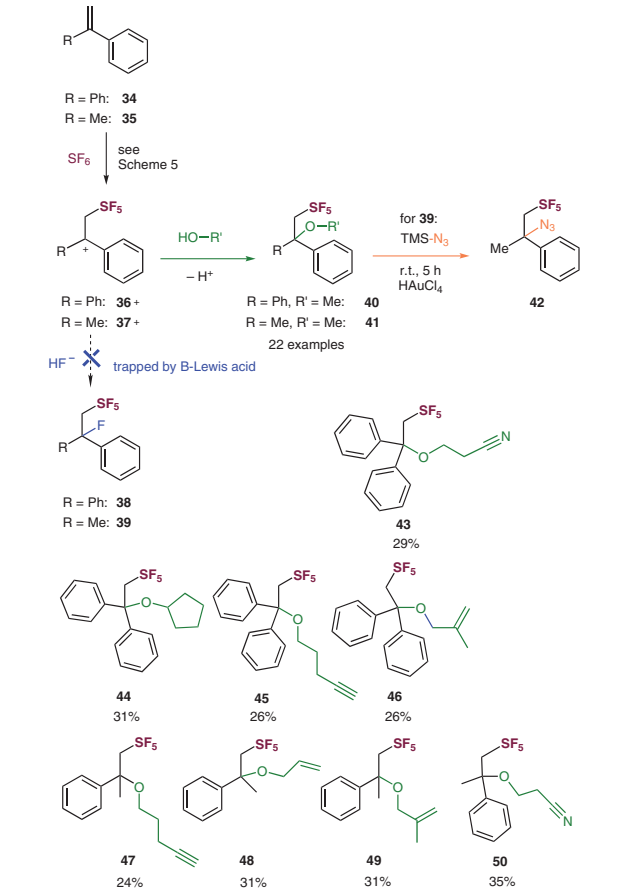
The first method to use $SF_6$ as a pentafluorosulfanylation reagent to yield valuable $SF_5$-containing organic compounds was therefore realized by a photoredox catalytic approach that precisely activates $SF_6$ using LED light at 365 nm and transfers the $SF_5$ group onto the organic substrates (see Scheme 5). In contrast to the mentioned photoredox catalytic activation of $SF_6$ for deoxyfluorination, our approach precisely controls the local reductivity by *N*-phenylphenothiazine (**33**) as a strong photoredox catalyst with an excited state potential of $E_{ox}(\mathbf{33}^*/\mathbf{33}^{\bullet+}) = -2.5$ V (vs SCE). It is able to transfer the $SF_5$ group from $SF_6$ to α-methyl- (**34**) and α-phenylstyrene (**35**) to yield compounds **36** and **37** (Scheme 7).[77] Furthermore, the vicinal fluoride anion can be abstracted to give the pentafluorosulfanylated vinyl and allyl compounds **38** and **39**, respectively. Additionally, the low loading of photocatalyst **33** in these experiments prohibits a potential overreduction that would yield the unpreferred $SF_5$ anion. Surprisingly, initial mechanistic investigations hinted at a reaction mechanism that is not based, as initially proposed, on a simple Giese-type addition to the styrene.[85] Instead, more detailed mechanistic studies revealed the participation of the radical cation in a twofold excitation process, mirroring the anionic 'conPET' process reported by König and co-workers.[8] Quenching of the excited state of **33** by $SF_6$ generates the correct negative ion state of the $SF_6$ radical anion, which fragments into the desired $SF_5$ radical. Radical cation $\mathbf{33}^{\bullet+}$ is not able to oxidize **34** or **35**, because back electron transfer, which would be required to close the photoredox cycle, is endergonic by about 100 kJ/mol according to electrochemical data and theoretical analysis. However, re-excitation of the radical cation $\mathbf{33}^{\bullet+}$ at 365 nm or 530 nm, allowing it to reach its highly oxidizing excited doublet states, allows for a second photoelectron transfer and activates the substrates by formation of their radical cations $\mathbf{34}^{\bullet+}$ and $\mathbf{35}^{\bullet+}$, respectively. This process is suggested to be critical in establishing an efficient pentafluorosulfanylation protocol due to its dual function. Firstly, it closes the photoredox catalytic cycle, and secondly it prepares the substrate by turning it into a strongly electron-deficient open-shell state that cannot be oxidized during the approach of the strongly oxidizing $SF_5$ radical before reaching the C–S bond-forming transition state. Such a process was detrimental to the reaction since it annihilates the reactive species by turning the *'Janus-faced'* coin to its fluorination side. This mechanistic proposal goes along with the suggested mechanism of fluorination by *Selectfluor*, including the formation of a radical cation and subsequent fluorine radical transfer.[86] The preproduct cations $\mathbf{36}^{+}$ and $\mathbf{37}^{+}$, respectively, can be trapped by in situ generated anhydrous fluoride anions to products **36** and **37**. Unfortunately, the substrate scope was limited to the styrenes **34** and **35**.




**Scheme 7** Photoredox catalytic activation of $SF_6$ by *N*-phenylphenothiazine (**33**) provides enough excitation energy into $SF_6$ to yield the pentafluorosulfanylated products **38**/**39**, and the photoredox catalytic mechanism

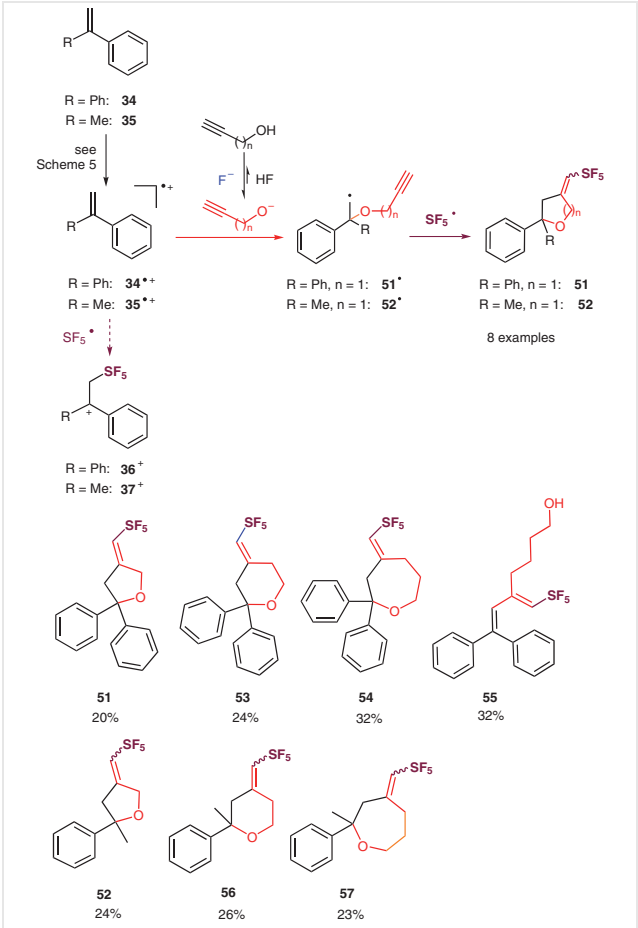
The interceptability of critical intermediates that we investigated in follow-up work corroborates the suggested reaction mechanism. Trapping of the intermediate cations $\mathbf{36}^{+}$ and $\mathbf{37}^{+}$ by alcohols as external nucleophiles not only allowed the scope of the reaction to be significantly enlarged, but also gave more precious insights into the operating reaction mechanism excluding a concerted addition of sulfur hexafluoride and installing both the $SF_5$ group and the vicinal fluoride substituent via a concerted reaction mode. In this variation of the reaction, the competing nucleophilic attack by *in situ* generated fluoride anions could be reduced by addition of 10–20 mol% of $BEt_3$. This almost completely suppressed the formation of the vicinal fluorides **38** and **39** by trapping available fluoride anions in the solution (Scheme 8). While we chose MeOH as our model compound to generate products **40** and **41** in moderate to good yields,

the method tolerated a broad variety of alcohols and functional groups, including vinyl, allyl, ethynyl and cyanide (**43**–**50**) on the side chain.[87] Furthermore, the isolated products could be subjected to follow-up transformations allowing Au(III)-catalyzed deoxyazidation to access the corresponding vinyl-, allyl- or azidopentafluorosulfanyl compounds **40**–**50**.




**Scheme 8** Proposed photoredox catalytic mechanism to pentafluorosulfanylated products **38** and **39** by trapping with alcohols as external nucleophiles instead of the internal fluoride anion, and examples of the product scope **40**–**50**

Further information regarding the proposed reaction mechanism could be acquired by another advance of this $SF_6$-based pentafluorosulfanylation protocol reported by our group in 2021. The discovery of a divergent reaction outcome when bifunctional alkynols were subjected to the reaction conditions led us to develop a domino-type reaction sequence to access the oxygen-containing heterocycles **51**–**54**, **56** and **57** in a single step, specifically tetrahydrofurans, tetrahydropyrans and oxepanes, starting from substrates **34** and **35** (Scheme 9).[88] This process is based on a cascade of C–O, C–C and terminal C–S bond-forming reactions with formation of one stereocenter starting from a styrene, an alkynol and $SF_6$ to generate a significantly high degree of complexity in a one-pot reaction. The proposed mechanism is in full agreement with Baldwin's cyclization rules and is supported by thermodynamic considerations and *in silico* studies. The key step is a radical type 5-, 6- or 7-*exo*-dig cyclization. Our mechanistic studies suggest a competitive trapping of $\mathbf{34}^{\bullet+}$ and $\mathbf{35}^{\bullet+}$ by the $SF_5$ radical or the *in situ* generated alkynol anion. The preformed equilibrium between the alkynol and the *in situ* formed anhydrous fluoride turned out to be critical to control the outcome of the reaction based on theoretical calculations. An alternative mechanism comprising an initial attack of the $SF_5$ radical on the alkyne was ruled out by a control experiment employing an alkyne lacking the hyxdroxy function and thermodynamic considerations. At high alkynol concentration the enriched alkoxide outcompetes the direct attack of the $SF_5$ radical forming the unusual terminal radical $\mathbf{51}^{\bullet}$. This quickly cyclizes to the corresponding vinyl radical that finally traps the $SF_5$ radical. However, the corresponding eight-membered oxocane product is not formed from substrate **34** due to significant ring strain; instead the ring-




**Scheme 9** Trapping of the intermediate substrate radical cations $\mathbf{34}^{\bullet+}$ and $\mathbf{35}^{\bullet+}$ by alkynols and the formation of oxaheterocyclic products **51**–**54**, **56** and **57**, and the acyclic product **55**

opened product **55** was formed in a comparable yield. With these heterocycles, the current $SF_5$ product scope shows a high level of structural complexity. The yields are rather low (20–32%), but it is important to keep in mind that these compounds cannot be synthesized by any other methods. Furthermore, the formation of remote $SF_5$-substituted reaction products **51**–**57** once more corroborates the existence of radical cations **34**$^{\bullet+}$ and **35**$^{\bullet+}$ as the key reaction intermediates of the reaction.

## 5 Conclusions

The application of photoredox catalysis is an important new approach to activate otherwise inert $SF_6$. For a long time, it has been believed that $SF_6$ is at the optimum of inertness. However, the energy of the attached electron that forms $SF_6^{\bullet-}$ in a particular negative ion state has been found to be the key parameter to control the fragmentation of the primarily formed $SF_6$ radical anion. This state decides the fate of the metastable radical anion, either forming a $SF_5$ anion or the corresponding $SF_5$ radical. This concept has recently been transferred from a physicochemical curiosity to powerful synthetic methods rendering the inert gas a precious reagent in synthesis, either shaping its fluorination or its pentafluorosulfanylation reactivity. $SF_6$ therefore not only adds a non-toxic alternative to highly toxic 'conventional' fluorination and deoxyfluorination reagents like DAST or $SF_4$, but also adds to the toolbox of $SF_5Cl$, $SF_5Br$ and $S_2F_{10}$ as the only non-toxic and non-corrosive reagent and paves the way to modern pentafluorosulfanylation chemistry, potentially completely avoiding toxic reagents in the future. Furthermore, the safety profile of the reactions is dramatically improved, forming reactive and highly toxic $SF_5$ transients in only very low stationary concentrations during the reaction. This methodology might combine the disposal of $SF_6$ (after any technical applications) with the formation of valuable pentafluorosulfanylated organic products and building blocks, thereby enhancing the sustainability profile of this strong greenhouse gas over its whole lifetime. The current state of the art should be considered as a proof-of-concept that $SF_6$ can serve as a precious reagent in organofluorine chemistry. Although the yields of the so far reported methods are rather low to moderate, the high degree of structural complexity of the reported products hints towards a widespread use of $SF_6$ in the future.[19] We expect further investigations on the use of $SF_6$ in pentafluorosulfanylation chemistry, pushing the frontiers towards the development of robust, less aggressive and more selective protocols in the future.

## Conflict of Interest

D.R. and H.A.W. have filed patent applications on the reported pentafluorosulfanation method.

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