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Photoredox Catalytic α-Alkoxypentafluorosulfanylation of α-methyl- and α-phenylstyrene using SF_6

David Rombach[a] and Hans-Achim Wagenknecht*[a]

Abstract: SF_6 is applied as pentafluorosulfanylation reagent to prepare ethers with vicinal SF_5 substituent by a one-step protocol applying photoredox catalysis. This method shows a broad substrate scope with respect to applicable alcohols for the conversion of α-methyl and α-phenyl styrenes. The products bear a new structural motif with two functional groups installed in one step. The alkoxy group allows elimination and azidation as further transformations into valuable pentafluorosulfanylated compounds. These results confirm that non-toxic SF_6 is a useful SF_5 transfer reagent, if properly activated by photoredox catalysis, and toxic reagents are completely avoided. In combination with light as energy source, a high level of sustainability is achieved. By this synthetic access, the proposed potential of the SF_5 substituent in medicinal, agro and material chemistry may be exploited in the future.

Pentafluorosulfanylation (SF_5) chemistry is still a challenge and difficult task since the initial report about CF_3SF_5 by Cady in 1950.[1] This lack of modern methods is even more astonishing considering the proposed physicochemical profile of the SF_5 substituent added to small organic molecules.[2,3] For example, exchange of the widely used CF_3 substituent that is bioisosteric to CH_3 by a SF_5 substituent in anoretic Norfenfluramin, induces a dramatic change in the pharmacological profile.[4] Further first evidence for a benign profile of organic SF_5 compounds was reported.[5] These features predict a thrilling future of this functional group in chemistry.[6] However, the accessibility of SF_5-compounds is still rather difficult even if a mild synthesis starting from disulfides has been established by Umemoto in 2012[7] and further facilitated by Pitts and Togni quite recently.[8] However, formation of the C-S bond still requires the use of extraordinarily toxic reagents, like S_2F_{10}, and the mixed sulfur halogenides SF_5Cl and SF_5Br. In contrast, reports on non-toxic SF_6 in synthesis are rare although it has strong environmental implications.[9-15] SF_6 is still indispensable as insulating gas in technical applications, like high voltage gears, and as protecting gas in the production of metals. SF_6 has an extraordinary potential as greenhouse gas.[16] The use of SF_6 as chemical reagent would be sustainable, because the gas would be converted into potentially valuable chemical building blocks.

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In general, the use of SF_6 as SF_5 transfer reagent is difficult due to its alternating bond dissociation enthalpies.[17] In particular the electron excess dependent fragmentation channels of the SF_6 radical anion hampered the proper activation by photoinduced single electron transfer.[18-23] The dominant channel of activation at low electron energies is the fragmentation into SF_4 and the fluoride anion.[18,22,23] This mode of reactivity was explored recently by Jamison and also by Rueping, reporting deoxyfluorination-type chemistry under photoredox conditions (Figure 1).[12,13]

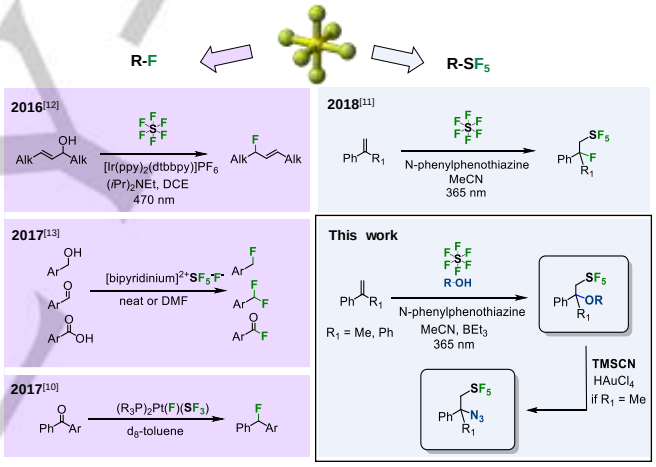

Figure 1. Overview of recent photochemical and chemical activation of SF_6 for deoxyfluorinations (left) and pentafluorosulfanylations (right).

Photoredox catalysis applies light as energy source for organic reactions.[24-35] Herein, we report on an advanced photoredox catalytic activation of SF_6, which does not only pentafluorosulfanylate α-methyl (**1**) and α-phenyl styrenes (**2**) but additionally forms a C-O-bond, which significantly broadens the synthetic scope and opens the way for functionalization of the SF_5-building blocks. In contrast to fluorinations,[12,13] our approach precisely controls the local reductivity by N-phenylphenothiazine (**3**) as strong photoredox catalyst[36] in order to transfer the SF_5 group to α-methyl- (**1**) and α-phenylstyrene (**2**) to yield **4** and **5**.[11] Mechanistic investigations revealed a twofold excitation process (Figure 2), similar to the conPET process reported by König.[37] The quenching of the excited state of **3** by SF_6 generates $SF_6^{\bullet-}$ that fragments by the electron excess energy into the SF_5 radical. The second electron transfer activates the substrates by formation of their radical cations $\mathbf{1}^{\bullet+}$ and $\mathbf{2}^{\bullet+}$, respectively. This process seems to be critical for successful pentafluorosulfanylation due to the high oxidation power of the

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SF_5 radical. The simple addition of MeOH to the reaction mixture consisting of **1** or **2**, catalyst **3** and SF_6 in MeCN yielded the SF_5-methyl ethers **8** or **9.** The previously observed dimerization of **2**[11] was almost completely suppressed which makes the fast trapping of $\mathbf{2}^{\bullet+}$ by MeOH very likely. The final step for pentafluorosulfanylation is the simple trapping of the resulting captodatively stabilized radicals $\mathbf{6}^{\bullet}$ or $\mathbf{7}^{\bullet}$, respectively, by the remaining SF_5 radical. The competing nucleophilic attack by in situ generated fluoride anions could be reduced by addition of Lewis acid. The addition of 10-20 mol% BEt_3 almost completely suppressed the formation of the vicinal fluoride **5** by trapping available fluoride anions in the solution. This is important for the preparation of a broader variety of SF_5 compounds by alcohols as external nucleophiles. Further functional groups in the side chains of these alcohols give access to versatile SF_5-building blocks.

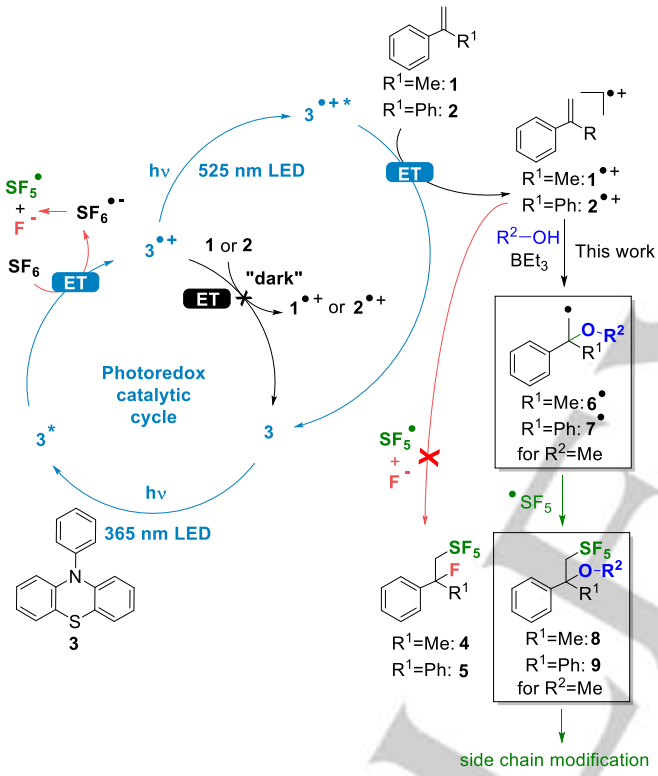

Figure 2. Proposed mechanism of photoredox catalytic activation of SF_6 by N-phenylphenothiazine (**3**) for pentafluorosulfanylation of α-methyl (**1**) and α-phenyl styrene (**2**) and addition by fluoride as internal nucleophile to **4** and **5** or alcohols (R^2-OH) as external nucleophiles to products **8** and **9** (shown for R^2=Me).

We optimized reaction conditions representatively for **2** (Table 1). The initial yield of 29% of **9** (determined by GC-FID) was achieved with 10 mol% photocatalyst **3** and 5 equiv. of MeOH in a 0.1 M solution of **2**. The pressure of SF_6 was adjusted to 2.8 bar (3.1 mmol) by a gas measure apparatus. A higher amount of MeOH (10 equiv.) increased the yield to 44%. Reducing the catalyst load to 5 mol% **3** decreased the yield to 35%. While the dilution of the reaction mixture to 0.05 M decreased also the yield, an optimized yield of 53% was observed using 0.2 M solution of **2**. Higher concentrations did not further increase the yield. Additional control experiments were carried out before a broader substrate scope was investigated. The use of methoxide as strongly basic nucleophile caused the collapse of reactivity and **9** not was observed. As expected, no product was observed during control reactions in the absence of light or the catalyst **3**, nor in the absence of MeOH. Finally, we explored the effect of BEt_3 While the selectivity was dramatically increased by BEt_3 (see above), the yield of **9** could not further be increased by the investigated range of 0-40 mol% BEt_3. This indicated a passive interaction in the mechanism and deactivation of the generated fluoride anion by the Lewis acidic boron. The precise active species could not be identified while the formation of an intermediate alcohol coordination complex is likely based on Renaud.[38] The model reaction was also performed on a scale of 1.00 mmol of **2** which gave a yield of 45% for **9** with a higher pressure of SF_6 (5.5 bar) while the excess of SF_6 could be reduced to 6.1 equiv. The preparative isolation of **9** in 40% yield gave a pure product sample and allowed us to validate both the structure by NMR and XRD (Figure 3) and the applied ^{19}F-NMR quantification method. It is important to mention here, that **8** or **9** cannot be yielded by the reaction of the fluoride addition products **4** or **5** with methoxides, including $Ca(OMe)_2$, KOMe and LiOMe, and with BEt_3 (Figures S167-S174).

Table 1. Photoredox catalytic pentafluorosulfanylations of **2** to the methoxylated **9**.

entry	conditions[a]	[**2**] (M)	MeOH (equiv.)	yield (%)
1	365 nm	0.10	5	29
2	365 nm	0.10	10	44
3	365 nm	0.20	10	53
4	no light	0.10	10	no reaction
5	no catalyst	0.10	10	no reaction

[a]General reaction conditions: 20 mol% BEt_3, 20°C, 2.8 bar SF_6, 368 nm, 22 h in MeCN. Yields determined by GC-FID.

The substrate scope for the conversion of **1** and **2** is broad since a variety of functionalized alcohols, like branched alkohols, alkenols, internal and terminal alkynols, sterically demanding cyclopentanols, cyanoalcohols and even allenes, were tolerated to obtain **8**, **10**-**18** and **19**-**27** (Figure 3).

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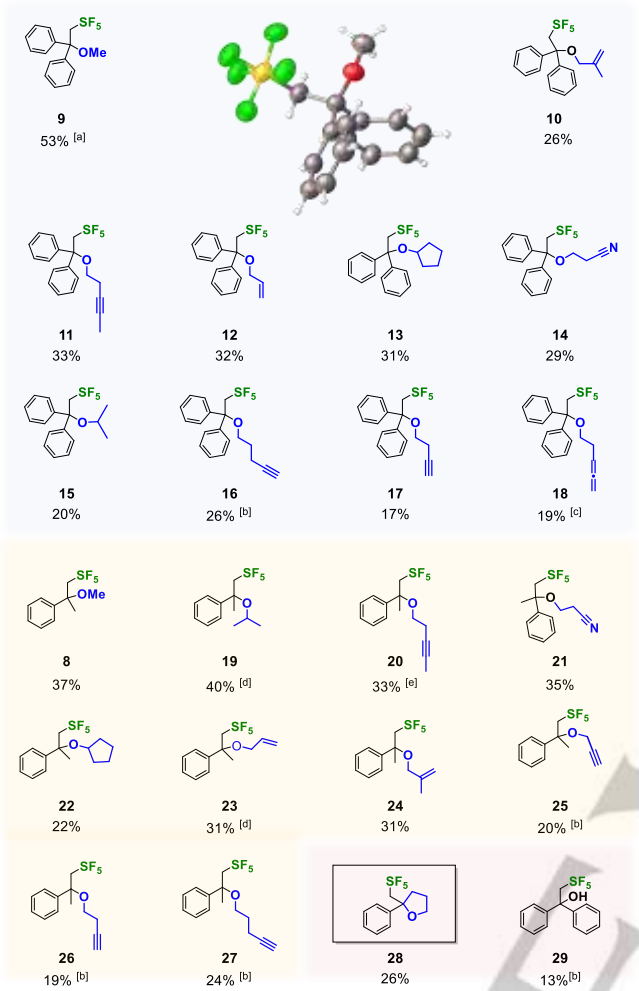

Figure 3. Substrate scope for the for the pentafluorosulfanylation of **1** and **2** and XRD structure of product **9**. Yields were determined by ^{19}F-NMR spectroscopy in the crude reaction mixture. General reaction conditions: 0.20 mmol, 0.20 M in MeCN, 10 mol% **3**, 10 mol% BEt_3, 22 h, 20°C, 2.8 bar (15 equiv.) SF_6, 368 nm. [a] yield determined by GC-FID, 20 mol% BEt_3 used. [b] 3.0 equiv. alkynol. [c] 0.15 M, 14 eq. allene. [d] 1.00 mmol scale. [e] 0.090 mmol scale, 11 mol% **3**, 11 mol% BEt_3. [f] Prepared with ethinylcyclopentanol.

The photoredox catalytic method is limited, of course, to the use of non-oxidizable alcohols. Phenyl alcohols were not accepted likely due to predominant oxidation by the catalyst **3**. Even more complex molecules like spiroethers were obtained via an intramolecular addition yielding **29** in 26% yield. Full conversion of the starting materials, however, is problematic due to the agressive reaction conditions and photocatalyst decomposition. Increased photocatalyst concentrations cause overreduction of the transients. Another competing reaction is the direct addition of alcohols to the substrates as well as in-situ hydrolysis of the products probably due to the formation of oxophilic sulfur species. Nevertheless, we found a remarkably broad acceptance of various alcohols for the alkoxylation of **1** and **2**, and the obtained yields between 13% and 53% should be regarded with respect to the fact that the compounds **10**-**28** were not yet synthetically accessible and bear a new and doubly functionalized structural motif. Additionally, our results show an orthogonal reactivity by the SF_5-radical pathway, which allows the use a large excess (10.0 equiv.) of alcohol without fully quenching of the reactive transient by deoxyfluorination.[12,13] While the use of water as nucleophile shut down the reaction, the use of sterically demanding alcohols favored formation of alcohol **29**.

DSC experiments revealed a boiling point of **8** of about 18 °C (Figure S159) and a melting point of **9** at 125 °C (Figures S160 and S161). **8** and **9** were photochemically stable during irradiation (365 nm, 24 mM in DMSO, Figures S163 to S166) for at least 62 h. **8** and **9** were stable at 75 °C in DMSO (24 mM), at 125 °C **8** showed a half-life of 68 min and **9** a half-life of 84 min under air (Figures S162) which proves a sufficient stability for further chemical transformations, which we investigated: (i) The methoxylated **8** and **9** were successfully converted to the vinylic and allylic SF_5 compounds **30** and **31** by the oxophilic Lewis acid $BF_3{\cdot}Et_2O$ (10 equiv.) in $CDCl_3$. The ^{19}F-NMR kinetic measurements showed in both cases remarkably fast conversion into the elimination products **30** and **31** with yields > 98% in less than 30 min. (Figure 4, top). (ii) Finally, we broadened the versatility of our method by conversion of the benzylic ether **8** into the corresponding azide **32**. This reaction required $HAuCl_4$ as catalyst.[39] Instead of the expected acidification of the vicinal methylene group the ^{19}F NMR spectra evidenced a clean an efficient conversion of 98% after 5 h (Figure 4, bottom). **32** showed the characteristic IR signatures of both the azide stretch mode at 2109 cm^{-1} as well as the SF_5 signatures at around 813 cm^{-1} (Figure S157). It is important to mention here, that such vicinal SF_5 azides could potentially be used for “click”-type cycloadditions or could serve as precursors for the corresponding amino acids.

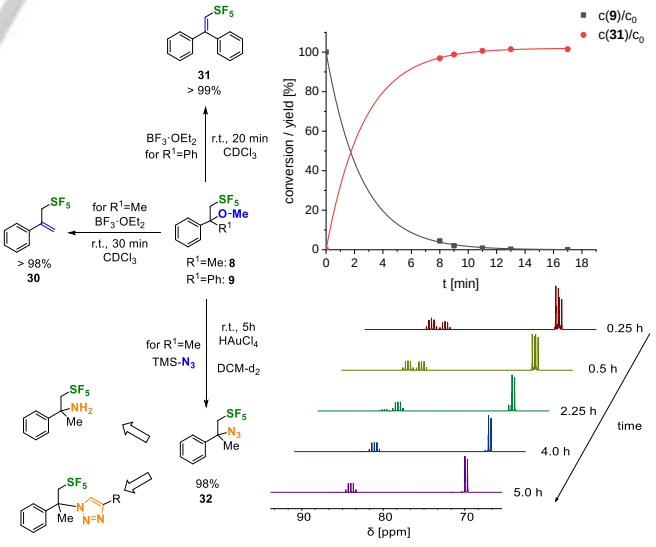

Figure 4. Top: Elimination of the methoxy substituent of **8** and **9** by 10.0 equiv. $BF_3{\cdot}Et_2O$, and representative ^{19}F-NMR kinetics for the conversion of **9** to **31**. Bottom: Azidation of **8** to **32** (with potential following chemistry) and time resolved ^{19}F-NMR spectroscopy analysis for the conversion of **8** to **32**.

In conclusion, we report herein a novel method to synthesize ethers with vicinal SF_5 substituent by a one-step protocol including photoredox catalysis. The products described herein bear a new structural motif with two functional groups, the SF_5 and the alkoxy substituents, and thereby represent important new SF_5-building blocks. Moreover, the alkoxy substituents allow further transformation by elimination and azidation. Our results complement the closed-shell deoxyfluorination type photoredox chemistry of SF_6 and pave the way to use SF_6 as a highly valuable SF_5-transfer reagent if properly activated by highly reducing photoredox catalysts. Our method does not only tolerate protic groups and high concentrations of alcohols, but uses them as nucleophiles. Unfortunately, the presence of water as nucleophile is strictly prohibited by irreversible sulfoxidation of the photoredox catalyst. Despite this resctriction, the corresponding SF_5-alcohol can be pepared by the use of sterically demanding alcohols. Toxic reagents are completely avoided, and instead, non-toxic SF_6 is applied as chemical reagent. Our vision is to reuse SF_6 after technical applications for chemical synthesis of valuable SF_5-molecules, instead of simply destroying it. Thereby, the proposed benign potential of the SF_5 substituent in medicinal, agro- and material chemistry may be exploited in the future. In combination with light as energy source, the basis for a high level of sustainability is set.

Experimental Section

All experimental details are described in the Supporting Information.

Acknowledgements

Financial support by the Deutsche Forschungsgemeinschaft (grant Wa 1386/16-2) and KIT is gratefully acknowledged. D.R. thanks the Landesgraduiertenstiftung Baden-Württemberg for a doctoral fellowship and the GRK 1626 for their qualification program. Further we thank Prof. Dr. Frank Breher and Prof. Dr. Michael A. R. Meier as well as Prof. Dr. M. Wilhelm for sharing parts of their infrastructure. We kindly thank M. Sc. Bernhard Birenheide for solving the XRD structure of **9**.

Conflicts of interest

D. R. and H.A.W. filed a patent application of the reported method.

Keywords: photochemistry • addition • photocatalysis • electron transfer • phenothiazine.

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Layout 1:

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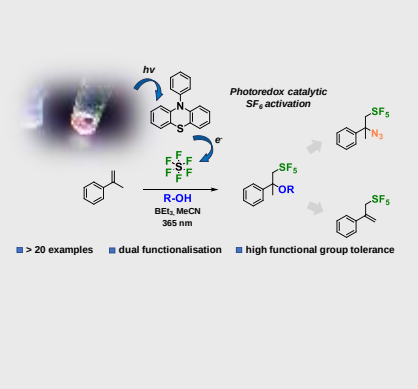
Dual functionalization by light: The pentafluorosulfanyl and the alkoxy substituents are introduced to styrenes by a one-step protocol.



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Photoredox Catalytic α-Alkoxypentafluorosulfanylation of α-methyl- and α-phenylstyrene using SF_6