Photoredox Catalytic α-Alkoxypentafluorosulfanylation of α-Methyl- and α-Phenylstyrene Using SF₆

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Abstract: SF₆ was applied as pentafluorosulfanylation reagent to prepare ethers with a vicinal SF₆ substituent through a one-step method involving 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 alkoxysulfanylwol let avoids elimination and azidation as further transformations into valuable pentafluorosulfanylated compounds. These results confirm that non-toxic SF₆ is a useful SF₆ transfer reagent if properly activated by photoredox catalysis, and toxic reagents are completely avoided. In combination with light as an energy source, a high level of sustainability is achieved. Through this method, the use of SF₆ in medicinal chemistry, agrochemistry, and materials chemistry may be exploited in the future.

Pentafluorosulfanylation (SF₆) chemistry has remained a challenging and difficult task since the initial report on CF₃SF by Cady in 1950. This lack of modern methods is astonishing considering the proposed physicochemical profile of the SF₆ substituent when added to small organic molecules. For example, exchange of the widely used CF₃ substituent that is biosacrificed to CH₃ with a SF₆ substituent in the anorectic norfenfluramine induces a dramatic change in the pharmacological profile. Further evidence for a benign profile of organic SF₆ compounds has been reported. These features predict great potential for this functional group in chemistry. However, the accessibility of SF₆ compounds is still rather difficult even though a mild synthesis starting from disulphides has been established by Umemo and co-workers in 2012 and further facilitated by Pits, Togni, and co-workers quite recently. However, formation of the C–S bond still requires the use of extraordinarily toxic reagents, like S₂F₁₈, and the mixed-sulfur halogenides SF₅Cl and SF₅Br. In contrast, reports on non-toxic SF₆ in synthesis are rare although this would have strong environmental advantages.

In particular the electron-excess-dependent fragmentation channels of the SF₆ radical anion have hampered proper activation by photoinduced single-electron transfer. This mode of reactivity was explored recently by Jamison and McTeague, as well as by Rueping and co-workers, who reported deoxyfluorination-type chemistry under photoredox conditions (Figure 1). We unlocked the complementary mode of activation of SF₆ for pentafluorosulfanylation of α-substituted styrenes. Photoredox catalysis applies light as an energy source for organic reactions. Herein, we report an advanced photoredox catalytic method for the activation of SF₆, which not only pentafluorosulfanylates α-methyl- and α-phenyl- styrenes but additionally forms a C–O bond, which significantly broadens the synthetic scope and opens the way for the functionalization of SF₆ building blocks. In contrast to fluorination and azidation as further transformations into useful building blocks. In contrast to fluorination and azidation as further transformations into useful building blocks.
redox catalyst\textsuperscript{[10]} in order to transfer the SF$_5$ group to \(\alpha\)-methyl- (1) and \(\alpha\)-phenyl- (2) styrenes, and addition by fluoride as an internal nucleophile to give 4 and 5 or alcohols (R-OH) as external nucleophiles to give products 8 and 9 (shown for \(R^2=Me\)).

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 loading to 5 mol\% 3 decreased the yield to 35\%. While dilution of the reaction mixture to 0.05 M also decreased 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 a strongly basic nucleophile caused a collapse in reactivity and 9 was not observed. As expected, no product was observed during control reactions in the absence of light or 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 although the formation of an intermediate alcohol coordination complex is likely based on previous observations by Renaud and coworkers.\textsuperscript{[80]} 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$_5$ (5.5 bar), while the excess of SF$_5$ 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 are not produced 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 S166–S173).

The substrate scope for the conversion of 1 and 2 is broad since a variety of functionalized alcohols, like branched alcohols, alkenols, internal and terminal alkenyls, sterically demanding cyclopanetolans, cyanohaloethers, and even allenes, were tolerated to give products 8, 10–18 and 19–27 (Figure 3).

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 through an intramolecular addition, yielding 29 in 26\% yield. Full conversion of the starting materials, however, is problematic due to the aggressive reaction conditions and photocatalyst decomposition. Increased photocatalyst concentrations cause overreduction of the transients. Another competing reaction is the direct addition of alcohols to the

![Figure 2. Proposed mechanism of photoredox catalytic activation of SF$_5$ by N-phenylphenothiazine (3) for pentafluorosulfanylation of \(\alpha\)-methyl (1) and \(\alpha\)-phenyl (2) styrenes, and addition by fluoride as an internal nucleophile to give 4 and 5 or alcohols (R-OH) as external nucleophiles to give products 8 and 9 (shown for \(R^2=Me\)).](image)

| 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$^\circ$C, 2.8 bar SF$_5$, 368 nm, 22 h in MeCN. Yields determined by GC-FID.
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 viewed in the context of the fact that compounds 10–28 were not previously 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 of tertiary alcohols for the conversion products 30 and 31 with yields of more than 98% in under 30 min (Figure 4, top).

Finally, we broadened the versatility of our method by conversion of the benzyl ether 8 into the corresponding azide 32. This reaction required HAuCl$_4$ as the catalyst.[39] Instead of the favored elimination reaction (by considering acidity), the $^{19}$F-NMR spectra evidenced an efficient conversion of 98% after 5 h (Figure 4, bottom). Compound 32 showed the characteristic IR signatures of both the azide stretch mode at 2109 cm$^{-1}$ and the SF$_5$ signatures at around 813 cm$^{-1}$ (Figure S156). 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.

In conclusion, we report herein a novel method to synthesize ethers with vicinal SF$_5$ substituent through a one-step method 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$_5$ as a highly valuable SF$_5$-transfer reagent if properly activated by highly reducing substrates as well as in situ hydrolysis of the products.
photoredox catalysts. Our method not only tolerates protic groups and high concentrations of alcohols, but uses them as nucleophiles. Unfortunately, the presence of water as a nucleophile is strictly prohibited by irreversible sulfoxidation of the photooxidation catalyst. Despite this restriction, the corresponding SF₃ alcohol can be prepared by the use of tertiary alcohols. Toxic reagents are completely avoided, and instead, non-toxic SF₃ is applied as a chemical reagent. Our vision is to reuse SF₆ after technical applications for chemical synthesis of valuable SF₃ molecules instead of simply destroying it, thereby enabling the proposed benign potential of the SF₃ substituent in medicinal, agricultural, and materials chemistry to be exploited in the future. In combination with light as an energy source, the basis for a high level of sustainability is set.

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Conflict of interest

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

Keywords: addition reactions · electron transfer · phenothiazine · photocatalysis · photochemistry

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