

# Photoredox Catalytic Pentafluorosulfanylative Domino Cyclization of $\alpha$ -Substituted Alkenes to Oxaheterocycles by Using $SF_6$

David Rombach,<sup>\*,[a]</sup> Bernhard Birenheide,<sup>[b]</sup> and Hans-Achim Wagenknecht<sup>\*,[c]</sup>

Dedicated to Professor Antonio Togni on the occasion of his 65th birthday.

**Abstract:** Virtually inert sulfur hexafluoride becomes a precious pentafluorosulfanylation agent, if properly activated by photoredox catalysis, to access  $\alpha$ -fluoro and  $\alpha$ -alkoxy  $SF_5$ -compounds. This advanced protocol converts  $SF_6$  in the presence of alkynols as bifunctional C–C- and C–O-bond forming reagents directly into pentafluorosulfanylated oxygen-containing heterocycles in a single step from  $\alpha$ -substituted alkenes. The proposed mechanism is supported by theoretical calculations and gives insights not only in the pentafluorosulfanylation step but also into formation of the carbon-carbon bond and is in full agreement with Baldwin's cyclization rules. The key step is a radical type 5-, 6- respectively 7-exo-dig-cyclization. The synthesized oxaheterocycles cannot be simply prepared by other synthetic methods, show a high level of structural complexity and significantly expand the scope of pentafluorosulfanylated building blocks valuable for medicinal and material chemistry.

Since the initial report on the preparation of the first organic pentafluorosulfanyl compounds  $SF_5CF_3$  using excessive fluorination of  $CS_2$  by Cady in 1950,<sup>[1]</sup> the pentafluorosulfanyl ( $SF_5$ ) group has found increasing interest in agro- und medicinal

chemistry as well as in functional materials due to its unique steric and electronic properties.<sup>[2–9]</sup> However, this research field was hampered by the very limited accessibility of pentafluorosulfanylated compounds for about 60 years. In particular, the highly toxic sulfur fluorides  $SF_5Cl$ ,  $SF_5Br$  and  $S_2F_{10}$  have been the only preparative sources of the  $SF_5$  radical. However, these reagents are extremely toxic, and their commercial availability is limited. Dolbier<sup>[10–12]</sup> and Umemoto<sup>[13]</sup> reported independently methods to access  $SF_5$ -arenes from disulfides by oxidation with  $AgF_2$  or chlorine in the presence of  $KF$  and  $ZnF_2$ . Recently, Togni further turned this method into a gas-free approach by in-situ chlorine formation from trichloroisocyanuric acid.<sup>[14]</sup> In contrast, sulfur hexafluoride ( $SF_6$ ) so far is only rarely considered as a reagent in organic synthesis<sup>[15–21]</sup> due to its intrinsic inertness; its potential usefulness as pentafluorosulfanylation agent has even been negatively evaluated.<sup>[16]</sup> In contrast,  $SF_6$  was applied for three deoxyfluorination methods developed independently by Jamison, Rueping and Dielmann.<sup>[17–19]</sup> The pentafluorosulfanylation activity of  $SF_6$  in photoredox catalysis could only recently be unlocked in our lab (Figure 1).<sup>[20,21]</sup> We showed that the photoredox catalytic activation of  $SF_6$  allows the preparation of pentafluorosulfanylated styrenes and their ethers.<sup>[21]</sup> Herein, we establish an advanced one-step pentafluorosulfanylative C–C bond forming protocol based on previous work using a radical cascade sequence. Alkynols are used as bifunctional C–C- and C–O-bond forming reagents to prepare oxaheterocyclic compounds, namely oxepans, tetrahydropyrans and tetrahydrofurans. Following up our previous work on the activation of sulfur hexafluoride to access new chemical space,<sup>[20,21]</sup> this new method expands the scope of accessible pentafluorosulfany-

[a] Dr. D. Rombach

Laboratory of Inorganic Chemistry  
Swiss Federal Institute of Technology (ETH)  
Vladimir-Prelog-Weg 1–5/10, 8093 Zürich (Switzerland)  
E-mail: drombach@ethz.ch

[b] B. Birenheide

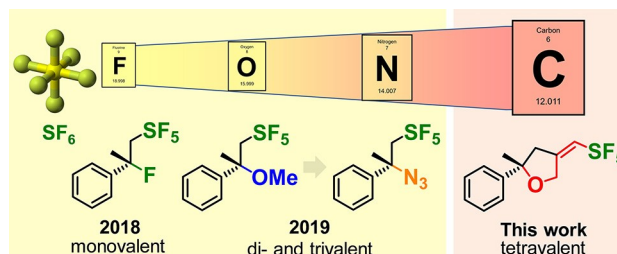
Institute of Inorganic Chemistry  
Karlsruhe Institute of Technology (KIT)  
Engesserstr. 15, 76131 Karlsruhe (Germany)

[c] Prof. H.-A. Wagenknecht

Institute of Organic Chemistry  
Karlsruhe Institute of Technology (KIT)  
Fritz-Haber-Weg 6, 76131 Karlsruhe (Germany)  
E-mail: Wagenknecht@kit.edu

Supporting information for this article is available on the WWW under <https://doi.org/10.1002/chem.202100767>

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**Figure 1.** The recent advancement of photoredox catalytic methods to convert  $SF_6$  into pentafluorosulfanylated organic compounds as valuable synthesis building blocks.

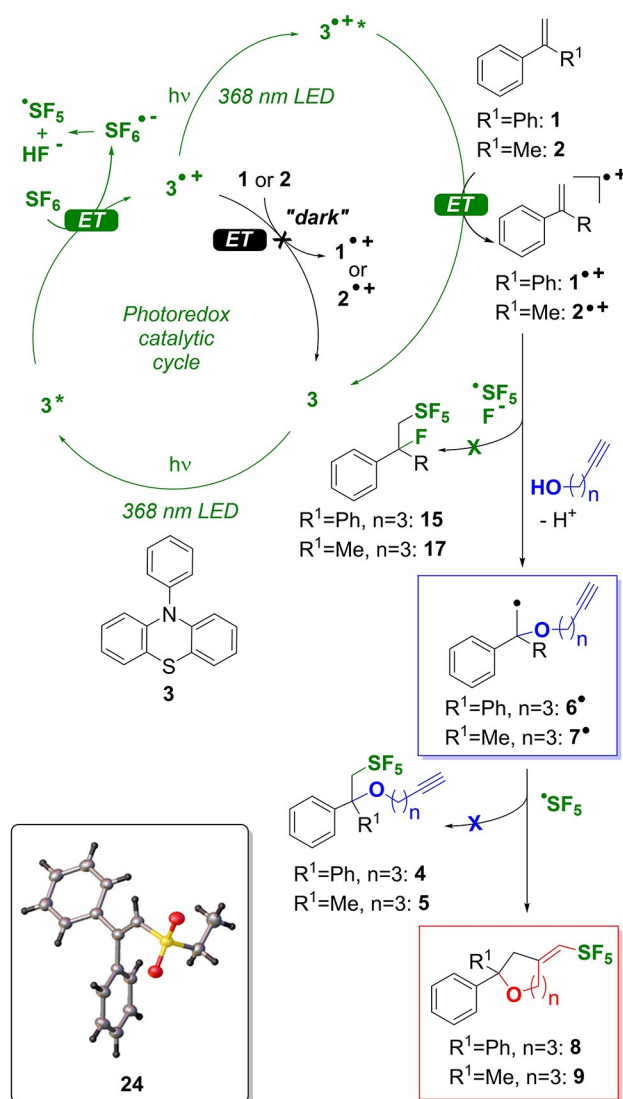
lated products with high complexity that is characteristic for natural products or advanced pharmaceuticals (Figure 1).

In particular, oxaheterocycles play a key role in medicinal chemistry. Tetrahydropyrans and tetrahydrofurans are the 6<sup>th</sup> and 11<sup>th</sup>, respectively, most frequently used ring substructures listed in the FDA Orange Book in 2014.<sup>[22]</sup> Moreover, tetrahydropyrans are highly important structural motifs in marine toxins and other natural products with often cytotoxic activity.<sup>[23–25]</sup> Oxepanes are not yet quite important in medicinal chemistry although they often show cytotoxic activity<sup>[26]</sup> and they are found in several classes of natural compounds isolated from marine organisms like algae, fungi or corals.<sup>[27,28]</sup> Our method to activate SF<sub>6</sub> uses N-phenylphenothiazine **3** as organic photoredox catalyst.<sup>[20,29–31]</sup> The estimated strong reduction potential of –2.5 V (vs. SCE) in the excited state is crucial for the desired fragmentation channel of SF<sub>6</sub> into the SF<sub>5</sub> radical.<sup>[29,32–37]</sup>

Such single electron reduction of SF<sub>6</sub> was previously accomplished by a thermal reaction with TEMPO lithium in order to pentafluorosulfanyl alkenes.<sup>[15]</sup> We recently investigated the addition of both SF<sub>5</sub> and 5-pentyn-1-ol to 1,1-diphenylethylene **1**. After irradiation (368 nm LED) of **1** (0.20 M) in the presence of 3 equiv. of 4-pentynol, 10 mol% photoredox catalyst **3** and 10 mol% of triethylborane as radical stabilizer and fluoride trap, we found not only the expected acyclic ether **4** in 26% yield, but also the new reaction product **8** in 14% yield. According to <sup>1</sup>H-, <sup>13</sup>C and <sup>19</sup>F-NMR spectroscopy as well as XRD structure and mass spectrometry this product is oxepane **8** that carries the SF<sub>5</sub>-substituent in the remote vinylic position. It is remarkable with respect to its complex structure that it could be prepared from the  $\alpha$ -substituted alkene **1** in just one step.

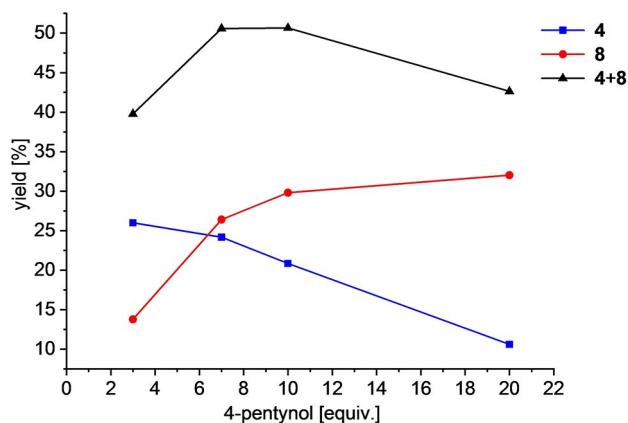
The fundamental steps of photoredox catalytic activation of SF<sub>6</sub> by N-phenylphenothiazine were spectroscopically investigated (Figure 2) and include two consecutive electron transfer steps<sup>[38]</sup> to activate both SF<sub>6</sub> and the substrate **1**. The first electron transfer forms radical cation 3<sup>•+</sup> and generates the SF<sub>5</sub> radical. After excitation of 3<sup>•+</sup> the back electron transfer closes the photoredox catalytic cycle and generates the key radical cation 1<sup>•+</sup> which can be trapped either by the in-situ generated fluoride anion<sup>[20]</sup> or by alcohols as external nucleophiles to yield product **4**. The fluoride trapping is suppressed by triethylborane as additive. We propose an intramolecular radical-alkyne addition for the cyclization reaction to the new product **8**.<sup>[21]</sup> In particular, we postulate a competitive trapping of the spin center of the substrate radical cation 1<sup>•+</sup> after photoredox catalytic activation by the free SF<sub>5</sub> radical or the alkynol.

To get more insight into the reaction mechanism and to optimize the reaction towards cyclization product **8** we varied the concentration of 4-pentynol with substrate **1**. Based on our mechanistic proposal we expected that an increase of the alcohol concentration causes the faster trapping of the radical cation 1<sup>•+</sup> and preferential formation of the cyclic product **8** and vice versa for the acyclic product **4**. This assumption could be experimentally confirmed by increasing the amount of alcohol in the solution from 3 equiv. to 20 equiv. Indeed, the ratio of the two competing reaction products **4**:**8** changed from 1:1 to 3:1 while forming 32% of product **8** (Figure 3). The total yields of 40–51% are in good agreement of the yields



**Figure 2.** Overview of reaction pathways after photoredox catalytic activation of SF<sub>6</sub> by irradiation at 368 nm and pentafluorosulfanylation of  $\alpha$ -methyl (**1**) and  $\alpha$ -phenyl styrene (**2**) with novel intramolecular radical-alkyne addition to cyclization products **8** and **9**. Insert: Structure of the isolated sulfone **24**.

previously reported for acyclic SF<sub>5</sub> compounds.<sup>[20,21]</sup> The best total yield of 51% for both products was achieved with 7–10 equiv. 4-pentynol. The relatively constant total yield of products **4** and **8** over the whole range of different 4-pentynol concentrations indicates a high stability of the SF<sub>5</sub>-radical in the presence of relatively high alcohol concentrations. Similar results were obtained using  $\alpha$ -methyl styrene **2** as the second substrate. Here the relative yields of products **5**:**9** could be changed from more than 3:1 using 3 equiv. of 4-pentynole to 1:1 using 10 equiv. (Figure S91). Due to the quite aggressive reaction conditions paired with the sensitivity of the radicals involved, the yields could not be further increased due to several side reactions and photocatalyst decomposition as reported in previous studies.<sup>[20,21]</sup> Higher photocatalyst concentrations lower the product yields likely due to overreduction of



**Figure 3.** Yields of **4** and **8** and the total yields of both products depending on the concentration of 4-pentynol. The yields were determined by  $^{19}\text{F}$  NMR spectroscopy. Reaction conditions: 0.20 M **1**, 10 mol%  $\text{BET}_3$ , 10 mol% **3**, 22 h, 20 °C, MeCN, 368 nm LED. 2.8 bar  $\text{SF}_6$ .

the transients. This hypothesis is supported by formation of sulfone **24** that we isolated as a side-product during the synthesis of **8** (see Figure 2, insert).

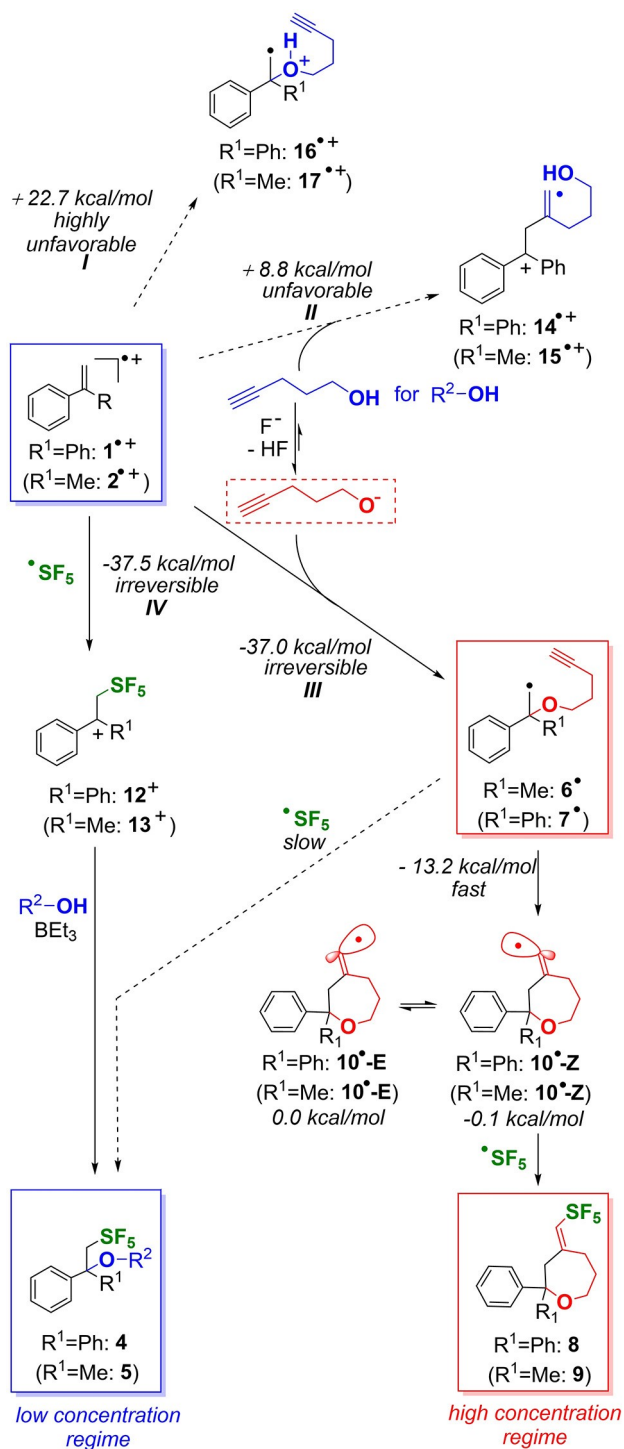
At first glance, the observed concentration dependence hints a competitive trapping of radical cation  $1^{*\dagger}$  by either 4-pentynole as nucleophile or the  $\text{SF}_5$  radical. In this scenario, the relative rate of formation of the methylene-type radical  $6^\bullet$  and cation  $12^\dagger$  decide on the formation of the cyclic product **8** vs. the acyclic product **4**. However, this reaction pathway does not seem to be reasonable due to the initial formation of the oxonium-type radical cation  $16^{*\dagger}$ . Therefore, we performed theoretical investigations applying DFT on the level of the M06-2X functional as well as DLPNO-CCSD(T) to shine light on the mechanism.<sup>[39–47]</sup> All investigated levels of theory are in qualitative alignment on each single reaction step except for the almost isoenergetic isomers of vinyl radical cation  $14^\dagger$ . As expected, only trapping of  $1^\dagger$  by the  $\text{SF}_5$  radical forming  $12^\dagger$  is thermodynamically strongly favored (–37.5 kcal/mol), whereas the direct addition of the alkyne under formation of  $16^{*\dagger}$  is strongly endergonic, which has been confirmed by theory (+22.7 kcal/mol). These results strongly support the proposed reaction pathway to the open chain product **4** but cannot explain the concentration dependence of both reaction products. To explain the observed behavior one needs to take into consideration the strong basicity of anhydrous fluoride which has been shown previously in several reports; its  $\text{pK}_a$  (HF) in MeCN has been estimated to be 25.2.<sup>[48]</sup> We therefore propose a protolytic pre-equilibrium between the in-situ generated anhydrous fluoride anion (from  $\text{SF}_6$ ) and 4-pentynol that could fully explain the observed concentration dependence of the reaction outcome. Indeed, the Gibbs free energy for the addition of the 4-pentoxide anion generating the methylene-type radical  $6^\bullet$  is about –37.0 kcal/mol, clearly exergonic, and the reaction therefore fully irreversible. Furthermore,  $6^\bullet$  is rapidly converted into the intermediate  $10^\bullet$  by 7-exo-dig-cyclisation according to Baldwin's rules.<sup>[49–51]</sup> The calculated Gibbs free energy difference between  $6^\bullet$  and  $10^\bullet$  is –13.2 kcal/mol indicates a strongly

exergonic cyclisation forming the seven-membered ring  $10^\bullet$ . This result is in qualitative alignment with similar radical cyclization reactions reported in literature.<sup>[52,53]</sup> It is therefore unreasonable that a bimolecular trapping by the  $\text{SF}_5$  radical can compete with the ring closure reaction, but it cannot be fully excluded. We therefore propose the vinyl radical  $10^\bullet$  as key intermediate to the cyclization product. To rule out the direct alkyne addition to radical cation  $1^{*\dagger}$  we carried out a control reaction using 1-octyne as substrate lacking the tethered hydroxyl function for intramolecular cyclization.

This reaction does not show significant amounts of any pentafluorosulfanylation product. It agrees well with our theoretical prediction that this step to  $14^\dagger$  is entropically highly unfavourable by  $T\Delta S_R = -14.3$  kcal/mol. This clearly indicates that the tethering of the hydroxy function of 4-pentynol onto the radical cation  $1^{*\dagger}$  is required *prior* to the alkyne addition reaction. Furthermore, this result also confirms the effective abstraction of the fluoride anion by triethylborane preventing the formation of the competing addition products of  $\text{SF}_6$  to **15** and **17**, respectively. We assume that this reaction mechanism applies also for substrate **2**.

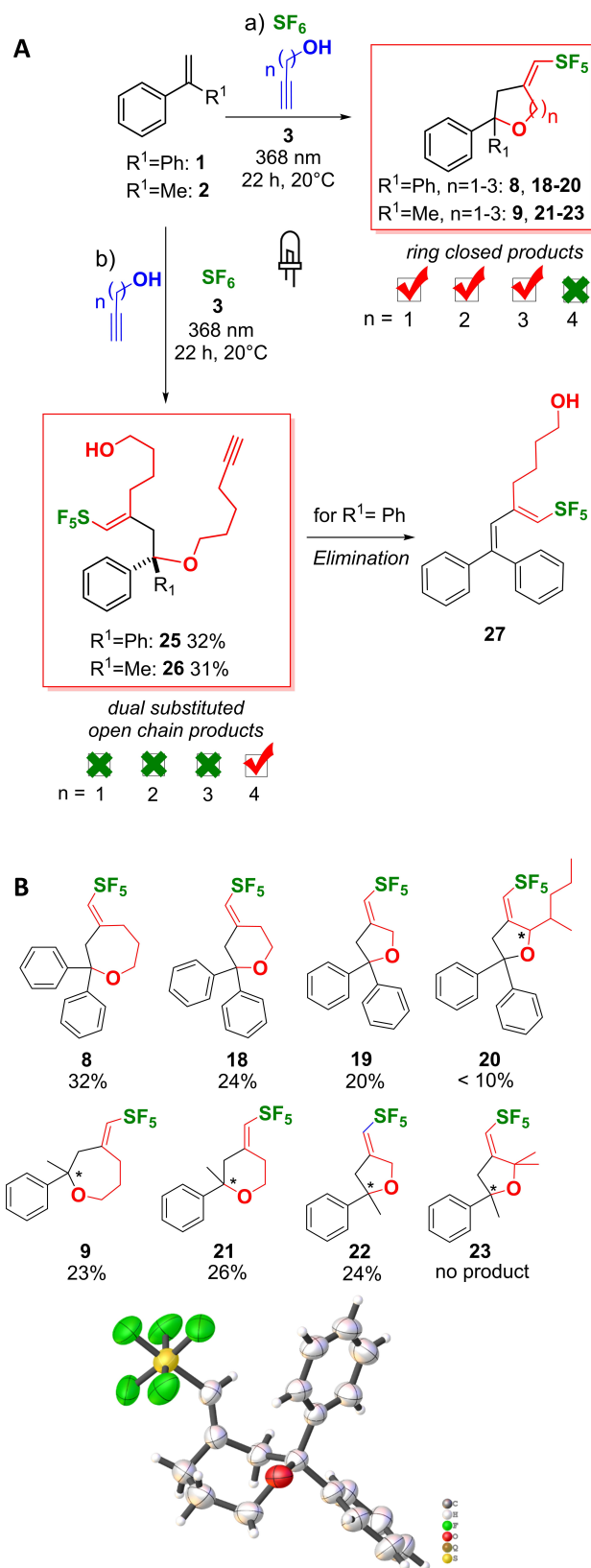
The configuration of the pentafluorosulfanylated double bond was investigated by NOE measurements as well as by XRD analysis of **8**. Remarkably, all products showed exclusively (*E*)-configuration of the double bond. To investigate the reason for the pronounced stereoselectivity minimum energies of both intermediate radicals have been calculated. Both configurations, (*E*)-isomer  $10^\bullet\text{-E}$  and (*Z*)-isomer  $10^\bullet\text{-Z}$ , differ only by about 0.1 kcal/mol in energy. Hence, the stereoselectivity cannot be attributed to thermodynamic control by the vinyl radical intermediate  $10^\bullet$ . Regarding the trajectories of the radical-radical recombination, the selectivity could be attributed to pure kinetic differences caused by the steric bulk of the quaternary carbon center (Figure 4).

The yields were generally determined by  $^{19}\text{F}$  NMR spectroscopy due to the fact that the fluorinated compounds are hard to purify. However, to validate our  $^{19}\text{F}$ -NMR quantification protocol we recently could show a good alignment of the isolated yield of a representative  $\text{SF}_5$ -product with the yield determined by  $^{19}\text{F}$  NMR spectroscopy.<sup>[21]</sup> The substrate scope of this reaction was elucidated with different 1-alkynols, and the corresponding products are formed according to Baldwin's cyclization rules. 5-, 6- and 7-exo-dig ring closures were obtained (Figure 5). Our method is not restricted to the formation of the achiral oxepane **8**, but was also used to prepare the chiral oxepane **9** as racemic mixture. The variation of the chain length of the 1-alkynol yielded differently sized heterocycles, including tetrahydropyranes **18** and **21**, as well as tetrahydrofurans **19** and **22**. A significant decrease in the product yields was observed by introducing  $\alpha$ -substitution to the 1-alkynol, shutting down the reaction by quaternization of the  $\alpha$ -carbon due to excess steric bulk and rigidity. While the monosubstituted 4-methylheptyn-3-ol reduced the yield of product **20** to below 10%, the use of 2-methylbut-3-yn-2-ol generated only the addition product of  $\text{SF}_6$  instead of **23**. This effect could be attributed to the steric bulk and decreased nucleophilicity. Our attempts to further expand the substrate



**Figure 4.** Proposed mechanism controlling the formation of the acyclic products 4 and 5 vs. the ring closed products 8 and 9 during photoredox catalytic pentafluorosulfanylation of substrates 1 and 2, respectively, in the presence of 1-pentynol. Geometry optimizations and frequency calculations: DFT/def2-TZVP/M06-2X, 293 K, CPCM (MeCN). Refinement of electronic energies: DLPNO-CCSD(T)/def2-TZVP/CPCM (MeCN).

scope by 5-hexyn-1-ol as reagent towards oxocanes yielded a different and unexpected product. We isolated only the labile double substitution products 25 and 26 that are formed after



**Figure 5.** A: Overview of reactions: a) 0.20 mmol 1 or 2 (0.2 M in MeCN), 20.0 equiv. 1-alkynol, 10 mol%  $\text{BEt}_3$ , 10 mol%  $3$ , MeCN,  $20^\circ\text{C}$ , 368 nm, 2.8 bar  $\text{SF}_6$ . b) 1.00 mmol 1 or 2 (0.2 M in MeCN), 20.0 eq. 1-hexynol, 10 mol%  $\text{BEt}_3$ , 10 mol%  $3$ , MeCN,  $20^\circ\text{C}$ , 368 nm, 2.8 bar  $\text{SF}_6$ . B: Substrate scope. Image: XRD structure of the isolated product 8. Volume corrections (alcohol volume) neglected except for optimization process of the lead compound to facilitate the protocol. The yields were determined by  $^{19}\text{F}$  NMR spectroscopy.

ring opening of the unfavorably strained ring and consecutive trapping of the cation by a second 5-hexynole.

Furthermore, formation of the elimination product **27** was observed after storage for several days or during purification of **25** on silica. Remarkably, during this study we also isolated sulfone **24** as side product that was identified by XRD, NMR spectroscopy and FAB-MS (Figure S41–S44, S79–S80, Table S2). This is an important result because the formation of **24** hints for the first time at the “overreduction” of the primarily formed SF<sub>5</sub> species, however the detailed mechanism of formation is not clear yet.

In conclusion, we present a new protocol to synthesize pentafluorosulfanylated and oxygen-containing heterocyclic compounds ranging from five- to seven-membered rings in a one-step protocol by photoredox catalysis. Although the yields are only in the range of 20% to 32%, it is important to point out that this advanced method shows proof of concept that even complex transformations could be realized under SF<sub>6</sub> activating conditions by precise finetuning of the kinetics. The method therefore expands the scope of accessible SF<sub>5</sub> containing chemical space. However, the method suffers from catalyst decomposition under the highly aggressive reaction conditions and further improvements of substrate scope and -tolerance need to be carried out in the future. The method utilizes SF<sub>6</sub> as non-toxic pentafluorosulfanylation reagent and could be applied to the preparation of pentafluorosulfanylated achiral and chiral products with remarkable structural complexity, in particular including precious 5-, 6- and 7-membered heterocycles. The corresponding eight-membered cyclic product is not formed due to significant ring strain; instead, ring-opened products have been formed in comparable yields. We support, for the first time, the proposed reaction pathways after photoredox SF<sub>6</sub> activation by extensive theoretical calculations. While the method today is still limited to the use of  $\alpha$ -substituted styrenes, the substrate scope is broad with respect to the alcohols as external nucleophiles and can potentially be broadened in the future by tackling the highly reactive reaction conditions. Our photoredox catalytic method combines the disposal of SF<sub>6</sub> (after any technical applications) and completely avoids the highly toxic “conventional” SF<sub>5</sub>-transfer reagents SF<sub>5</sub>Cl, SF<sub>5</sub>Br and S<sub>2</sub>F<sub>10</sub>. The combined experimental and computational approach allowed to gain important insights into the operating reaction mechanism, indicating that the addition of the nucleophile precedes the spin trapping step to yield the heterocyclic products. These pentafluorosulfanylated products of high structural complexity cannot be simply synthesized by other methods and shows once more that SF<sub>6</sub> can act as a precious pentafluorosulfanylation reagent. We hope that this work will encourage further investigations on the use of SF<sub>6</sub> in pentafluorosulfanylation chemistry pushing the frontiers towards the development of less aggressive and more selective protocols in the future.

## 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 “Chemical photocatalysis” for participation in their qualification program. D. R. acknowledges the Swiss National Science Foundation (SNSF, CRSK-2 195863) for financial support of this research and thanks Prof. Antonio Togni for fruitful discussions and continuous support. D. R. further thanks Prof. Erick. M. Carreira for his support. Furthermore, we thank Prof. Frank Breher and Prof. Michael A. R. Meier for sharing parts of their infrastructure and ETH Zurich for providing access to the Euler HPC Cluster. Open access funding enabled and organized by Projekt DEAL.

## Conflict of Interest

The authors declare no conflict of interest.

**Keywords:** electron transfer · pentafluorosulfanylation · phenothiazine · photocatalysis · photochemistry · sulfur hexafluoride

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Manuscript received: March 2, 2021  
Accepted manuscript online: April 8, 2021  
Version of record online: May 11, 2021