

Photoredox Catalytic Hydropentafluorosulfanylation of Alkynes by Sulfur Hexafluoride

Max Flügge,[§] Sven Klehenz,[§] Silas Leidenheimer, David Rombach,* and Hans-Achim Wagenknecht*



Cite This: *JACS Au* 2026, 6, 965–972



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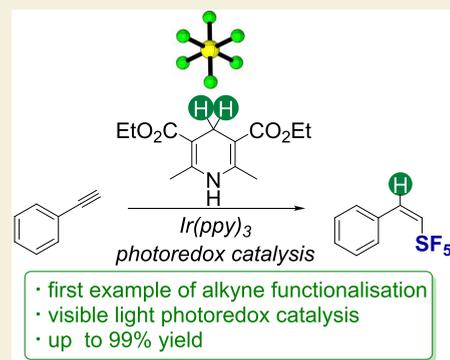
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ABSTRACT: The interest in organic compounds bearing the pentafluorosulfanyl (SF_5) group has increased significantly. The photocatalytic utilization of the cheap and nontoxic sulfur hexafluoride (SF_6) as an SF_5 -donating motif is an extremely valuable and still underdeveloped pathway in comparison to the well-established methodology employing the highly toxic SF_5Cl gas. However, due to the high stability and associated low redox potential of SF_6 , paired with the ambiphilicity of the SF_5 radical, the development of catalytic systems to gain SF_5 -bearing organic molecules from SF_6 is particularly challenging. We hereby present the first photocatalytic hydropentafluorosulfanylation of aryl alkynes by SF_6 using $\text{Ir}(\text{ppy})_3$ as a visible-light photoredox catalyst and Hantzsch ester as a sacrificial reductant as well as a hydrogen atom transfer (HAT) reagent. The method delivers the corresponding pentafluorosulfanylated alkenes in good to excellent yields.

KEYWORDS: photochemistry, photocatalysis, fluorine, electron transfer



INTRODUCTION

Recently, the pentafluorosulfanyl ($-\text{SF}_5$) group experienced a tremendous increase in research interest.^{1–3} The introduction of fluorinated motifs in organic molecules has gained significant momentum during the last decades through their gradual expansion in the fields of agrochemistry,^{4,5} optoelectronics,^{6–8} and pharmaceutical chemistry.⁹ However, the development of fluorinated non-PFAS motifs (per- and polyfluorinated alkyl substances) is a pressing need in contemporary organofluorine chemistry.^{9–13} Besides the well-established trifluoromethyl ($-\text{CF}_3$) and trifluoromethoxy ($-\text{OCF}_3$) groups in medicinal chemistry,^{14–16} the $-\text{SF}_5$ group has been shown to modify the properties of active pharmaceutical ingredients (API), agrochemicals, but also optoelectronic materials and catalysts.^{17–20} In comparison to the widely explored $-\text{CF}_3$ group, the $-\text{SF}_5$ group has been suggested as a bioisosteric replacement of $-t\text{Bu}$, $-\text{NO}_2$, halogens, or $-\text{CF}_3$.²¹ Additionally, it significantly exceeds electronegativity (3.65 vs 3.3) and lipophilicity of $-\text{CF}_3$ as reflected by its Hansch π parameters ($\pi = 1.23$ vs 0.88).^{22–24} Furthermore, aromatic SF_5 compounds possess a high hydrolytic stability.²⁵ The latter properties render it a useful substituent for being used in pharmaceuticals and agrochemical industries.^{9,10,26–28} In contrast, synthetic access in particular to SF_5 -functionalized aliphatic and vinyl compounds is still a central challenge and limits the knowledge about these fundamental motifs.²⁹ Conventionally, the synthesis of aliphatic SF_5 -organic compounds requires the use of SF_5Cl , which is a highly toxic gas.^{30,31} Recently, several groundbreaking strategies have been developed to overcome this restriction.

These comprise the *in situ* or *ex situ* preparation of SF_5Cl , the development of SF_5 -transfer reagents based on β -fragmentation or N- SF_5 bonds (Figure 1A), as well as the development of prefunctionalized platform reagents rendering the *on-site* use of SF_5Cl obsolete.^{2,32–40} Sulfur hexafluoride (SF_6) is a nontoxic, but highly potent greenhouse gas, for a long time indispensable in high-voltage switch gear insulation and only most recently replaced by alternative materials.^{23,41} Its inertness is caused by its unique electronic structure. First, all bonding and nonbonding orbitals are fully occupied. Second, two additional weak contributions contribute to the overall bonding situation: (i) Weak interaction of the e_g set of the nonbonding orbitals located at the fluoride substituents with the e_g subset of sulfur 3d-orbitals. (ii) Back-bonding from highly charged fluorine substituents of t_2 symmetry to the FSF σ_p bonds. This unique bonding situation and tight fluorine shielding around the comparably small sulfur atom result in significantly reduced reactivity and render the application of SF_6 as a synthetically useful reagent, an unsolved problem for decades.¹³ Nagorny et al. were able to fluorinate glycosides via the photocatalytic activation of SF_6 .⁴² Other examples include deoxyfluorinations using SF_6 reported by Jamison and co-

Received: October 22, 2025

Revised: January 8, 2026

Accepted: January 9, 2026

Published: February 10, 2026



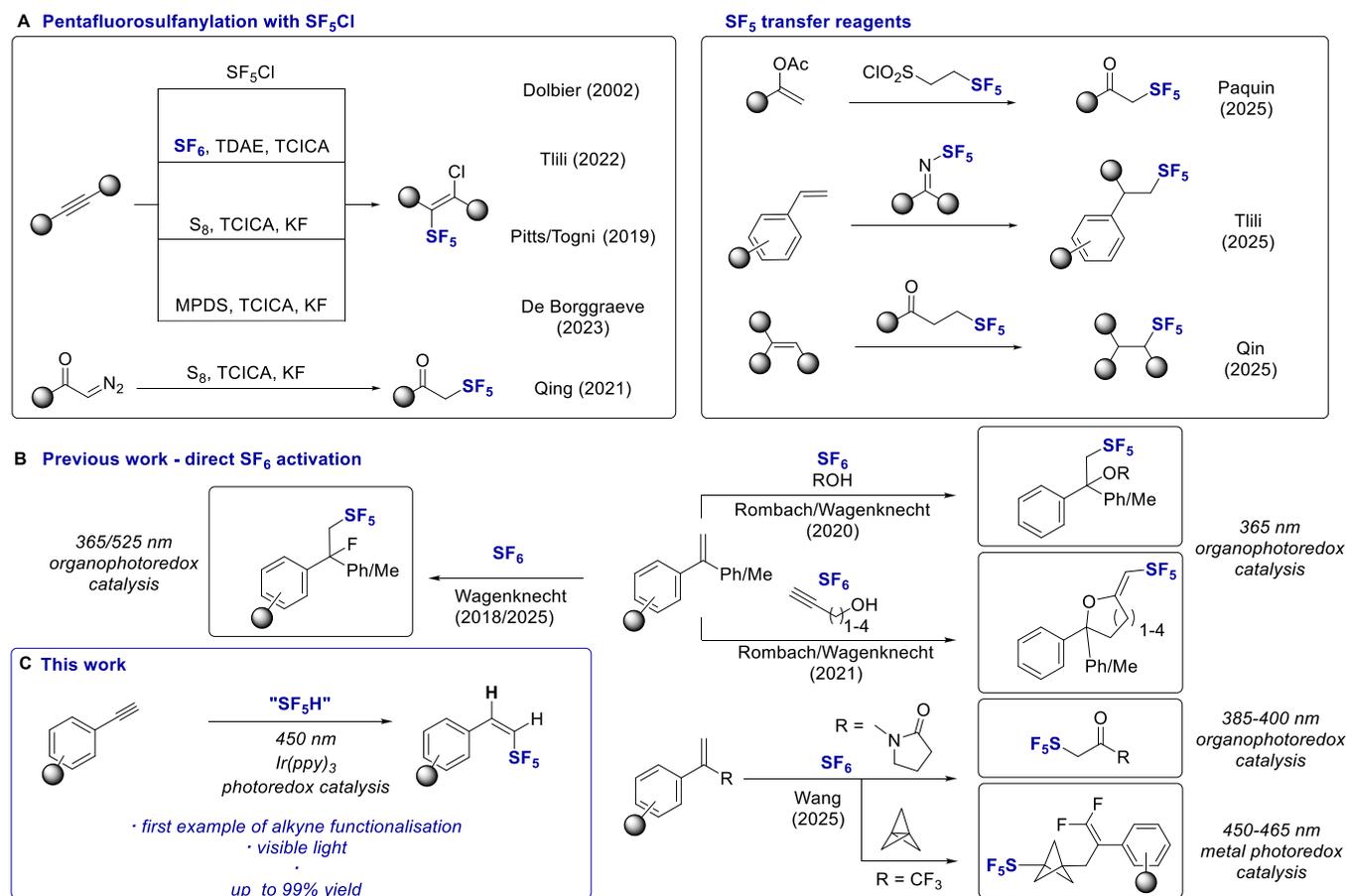


Figure 1. (A) Overview of pentafluorosulfanylation reactions from previous work.^{39,60–63} (B) Examples of direct SF₆ activation.^{32,33,34} (C) This work, the direct SF₆ activation for hydropentafluorosulfanylation of terminal alkynes.

workers and Xie et al.⁴³ The application of SF₆ as an nucleophilic fluorination reagent was shown by Wang and co-workers.⁴⁴ However, these cases focus only on the degradation of SF₆ to generate new C–F bonds, whereas the selective linkage of the SF₅ group to organic compounds would be much more valuable.

While its activation by transition metals or as a fluorination or deoxyfluorination reagent has been previously reported by Ernst, Braun, and many more,^{45–47} selective activation modes maintaining the SF₅ scaffold, adding a significant amount of sustainability, have only recently been unlocked. In 2015, the first selective photocatalytic activation of SF₆ was a proof-of-principle study describing the addition of SF₆ to styrenes.⁴⁸ While the initial method was limited to the concomitant formation of a C–F bond, we could expand the versatility of this approach to concomitant C–O and C–C bond formation, yielding SF₅-substituted oxo-heterocycles (Figure 1B).^{49,50} Moreover, we developed the concept of redox-convertible groups to expand the pentafluorosulfanylation substrate scope.⁵¹ The major limitation of this approach is the consecutive two-photon photoredox cycle being operative, striving potentials of –2.1 to 2.1 V (vs SCE),⁶⁴ therefore dictating a tight redox corridor to substrates. The quest for simplifying the initially reported method to mitigate this problem led us to reinvestigate potential catalysts without critical radical–radical recombination. The previously required necessity of re-excitation of the primary oxidation product was rendered impossible by shifting to a d⁷-Ir^{II} species. Capping the oxidative manifold of the process at E_{ox}(Ir(III)/Ir(II)) = +0.77

V allowed to turn to alkynes as competent substrates for the addition of SF₅ radicals in the absence of a possibility for single electron oxidation. The change of substrates allowed us to enter a new photocatalytic approach without a conPET: Herein, we report a new protocol for pentafluorosulfanylation of alkynes based on the application of Ir(ppy)₃ as a photoredox catalyst and the Hantzsch ester as a sacrificial reductant and a hydrogen atom transfer (HAT) reagent proceeding via a single excitation cycle. During the preparation of this manuscript, a related approach was reported by Wang et al. using DIPEA as the reducing agent to access SF₅–BCP cores.⁵⁵

RESULTS AND DISCUSSION

Activation of SF₆ Using Ir(ppy)₃

The reduction potential of SF₆ has been determined to be –1.90 V (vs SCE), or –2.17 V (vs Fc/Fc⁺), respectively.^{42,52} Our previous studies show that a reduction potential of –2.1 V vs SCE is crucial for the cleavage of SF₆ into the open-shell SF₅ radical, instead of the closed-shell SF₅ anion. This can be achieved by using the highly reductive *N*-phenyl phenothiazine as an organophotoredox catalyst.⁴⁸ Tris(2-phenylpyridine)-iridium (Ir(ppy)₃) is commonly used as a photoredox catalyst engaging in oxidative or reductive quenching cycles.^{53,54} However, the reduction has a potential of E_{1/2}(Ir^{IV}/Ir^{III}) = –1.73 V vs SCE, which is not sufficient for the desired activation of SF₆ under the formation of SF₅ radicals.⁵⁵ Therefore, any attempts to use direct photoinduced electron transfer (ET) from Ir(ppy)₃ to SF₆ failed to deliver

pentafluorosulfanylated reaction products. Reductive quenching of the catalyst forming an Ir^{II} is thermodynamically not feasible due to the reduction potential of $E_{1/2}(\text{Ir}^{\text{III}*}/\text{Ir}^{\text{II}}) = 0.31$ V vs SCE.⁵⁵

However, thermal back ET of Ir(II) to Ir(III) seems to be thermodynamically accessible ($E_{1/2\text{Red}} = -2.20$ V vs SCE), which should be sufficient for the generation of SF₅ radicals. To access the Ir^{II} species efficiently, the addition of a sacrificial reductant is required. While only few reports investigate the chemistry of Ir^{II}, Hantzsch ester **1** has been reported to be able to act as a reducing agent.⁵⁶ Following the previously outlined mechanistic assumptions (Figure 2), Ir^{III} is reductively

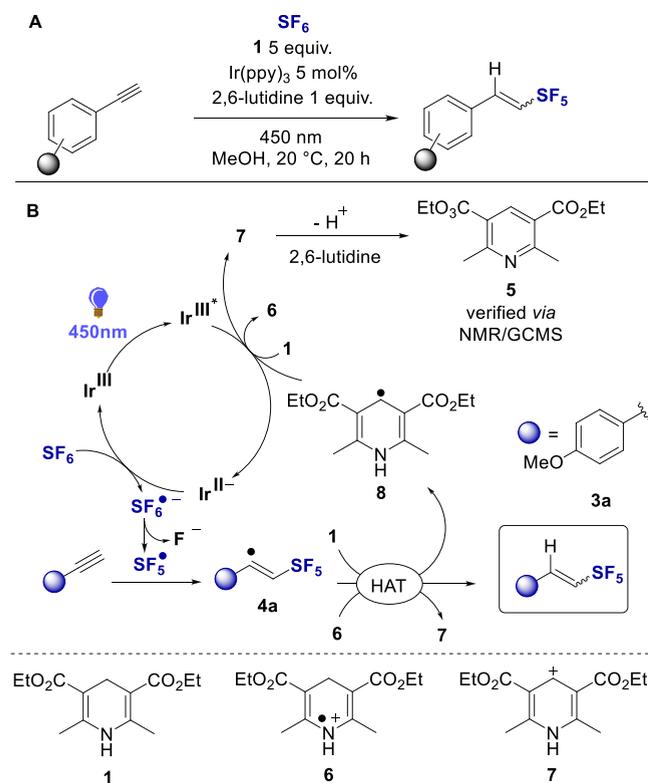


Figure 2. (A) General reaction scheme of the SF₆ activation with optimized parameters for model substrate **2a** and the synthesis of **3a**. (B) Proposed photoredox catalytic mechanism for the pentafluorosulfanylation of **2a** using irradiation at 450 nm (LED).

quenched by Hantzsch ester **1** forming Ir^{II}. Based on this mechanistic proposal, 4-methoxy-phenylacetylene **2a** was chosen as a substrate bearing an electron-rich alkyne moiety, allowing the electron-deficient SF₅ radical to attack the triple bond at low stationary SF₅ radical concentrations. The substrate was converted into the SF₅H adduct **3a** by SF₆ (2.8 bar) in the presence of Ir(ppy)₃ (5 mol %) and the Hantzsch ester **1** as the photocatalyst upon irradiation at 450 nm (LED). No product formation and no SF₆ activation were observed in the absence of the Hantzsch ester **1**, without Ir(ppy)₃, and without inert conditions (Table 1, entries 2–4). Addition of 1.2 equiv of **1** to the reaction mixture yielded 12% of the SF₅H adduct **3a** (Table 1, entry 5). Increasing the amount of **1** to 5 equiv to ensure fast quenching of the photoredox catalyst and HAT caused an increase of the yield of **3a** from 12% to 20% (Table 1, entry 6). At this point, due to the limited solubility of **1** in MeCN, the solvent was changed to MeOH, which not only improves the solubility of **1** but also

Table 1. Optimization of SF₅H Addition of Substrate **2a** to Product **3a**^a

entry	deviation from standard conditions	solvent	yield of 3a /%
1	-	MeOH	78
2	no inert conditions	MeCN	-
3	No Ir(ppy) ₃ , no 1	MeCN	-
4	No 1	MeCN	-
5	1.2 equiv of 1	MeCN	12
6	5 equiv of 1	MeCN	20
7	No 2,6-lutidine	MeOH	25
8	T = 10 °C	MeOH	26
9	T = 35 °C	MeOH	31
10	0.5 equiv of 2,6-lutidine	MeOH	20
11	2.0 equiv of 2,6-lutidine	MeOH	28
12	65 h	MeOH	>99

^aStandard conditions are given in the reaction scheme. All yields are given as the sum of the E- and Z-isomer mixture (10:1).

slightly improves the solubility of SF₆, which increases the yield from 12% to 25% (Table 1, entry 7).⁵⁷ Both elevating and lowering the temperature to 35 and 10 °C decrease the yield to 31% and 26%, in comparison to the standard conditions, respectively (Table 1, entries 8 and 9). During the initial reduction of the Ir photocatalyst, Hantzsch ester **1** undergoes a single ET step, while another Hantzsch ester undergoes a HAT reaction with the open-shell SF₅ adduct species **4a**. In order to generate the observed pyridine species **5**, a proton (H⁺) is released as a byproduct. Therefore, the addition of a base might be required as a proton scavenger.⁵⁸ In fact, adding 1 equiv of 2,6-lutidine increased the yield from 25% to 78% (Table 1, entry 1). Lowering (0.5 equiv) or increasing (2.0 equiv) the amount of 2,6-lutidine reduces the yield of **3a** to 20% and 28%, respectively (Table 1, entries 10 and 11). It is not entirely clear in which step of the mechanism the deprotonation of the Hantzsch ester **1** or its radical intermediate **6** or **7** takes place, as the deprotonation of both **6** and **7** is considered a possible reaction pathway. However, the drastic yield increase due to the addition of 2,6-lutidine would suggest that the abstraction of the amino proton is crucial. Ultimately, increasing the irradiation time from 20 to 65 h led to the formation of **3a** in quantitative yield (>99%, Table 1, entry 12). A time-dependent study utilizing the phenylacetylene (**2b**) showed a linear increase from 10 to 65 h, revealing the necessity of the increased irradiation time (see Supporting Information (SI) Figure S26).

With respect to the electrophilic character of the SF₅ radical, investigation of the substrate scope revealed the method to be highly versatile for the conversion of electron-rich substrates (Figure 3). This observation might also be caused by competing photoreduction of the electron-deficient alkynes by Ir^{II} or thermal reduction by Ir^{II}. For example, the electron-deficient 4-ethynylbenzotrile (**2f**) showcases no hydro-pentasulfanylation under the standard conditions. This is possibly due to the higher reduction potential of -1.26 V vs SCE in comparison to **2a** (-2.94 V vs SCE) and **2b** (-2.75 V vs SCE). Translating the standard conditions onto the less

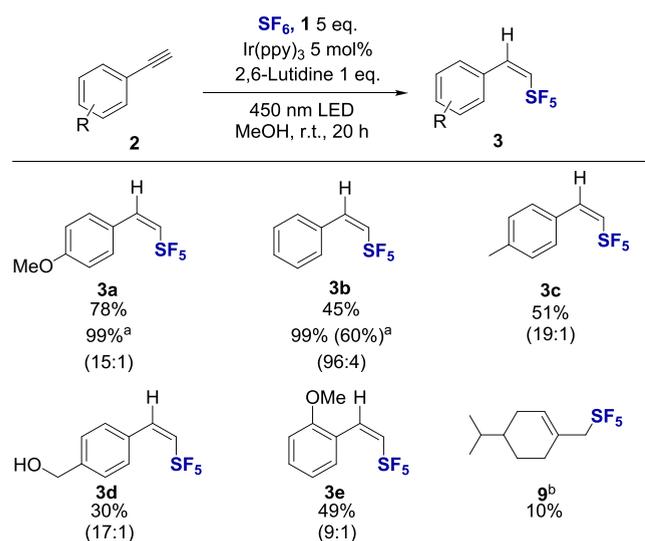


Figure 3. Scope for hydro-pentafluorosulfanylated products. Yields determined via ^{19}F NMR spectroscopy. Isolated yield is given in brackets. Ratio of *Z*-Isomer and *E*-Isomer in lower brackets (*Z*:*E*). ^aYield after 65 h reaction time. ^bFrom β -Pinene 10.

electron-rich phenylacetylene **2b** showcases a yield of 45% for product **3b** in the ^{19}F NMR spectrum. However, increasing the reaction time to 65 h again leads to a quantitative yield.

Mechanistic Investigation

To shine light on the operating reaction mechanism, we carried out mechanistic studies. Initially, Stern–Volmer fluorescence quenching studies indicated quenching of $\text{Ir}(\text{ppy})_3$ by **1** with a Stern–Volmer constant of $K_{\text{SV}} = 8.21 \text{ L/mol}$ (Figure 4A), confirming an initial photoinduced ET generating the Ir^{II} -complex. To further prove a potential ET

from Ir^{II} to SF_6 , we ran a comprehensive study using ^{19}F NMR spectroscopy and photocyclovoltammetry (Figure 4B). While **1** was found to be stable in MeOH over a period of 45 min at room temperature in the dark, irradiation at 450 nm caused unproductive reduction of the solvent MeOH under the formation of pyridine **5** by putative direct excitation of **1**. The $\text{Ir}^{\text{III}}/\text{Ir}^{\text{II}}$ half-wave was monitored by cyclovoltammetry under irradiation at 450 nm. In the presence of **1**, the half-wave $\text{Ir}^{\text{III}}/\text{Ir}^{\text{II}}$ was depleted in solution. This result aligns with the Stern–Volmer experiments and ^{19}F NMR studies, indicating reduction of Ir^{III} by **1**. Addition of SF_6 to the pre-reduced catalyst restores the $\text{Ir}^{\text{III}}/\text{Ir}^{\text{II}}$ half-wave indicating reduction of SF_6 by Ir^{II} in this case. This agrees again with the ^{19}F NMR experiments, indicating the formation of fluorinated reaction products under the same conditions (Figure 4C). No activation of SF_6 was observed in the absence of the Ir catalyst, excluding unproductive side product formation due to the rise of a reactive species caused by the background oxidation of **1** (see SI Figure S15). Furthermore, ^2D labeling studies were carried out subjecting a set of deuterated Hantzsch ester species (**1**- D_1 - D_3) to the reaction conditions in the presence of **2a**. Analysis by GC/MS revealed that only species **1**- D_2 and **1**- D_3 were able to generate the deuterated **3a-D** species efficiently. Therefore, it is viable to assume that the CH_2 bridge between the ester moieties of **1** partakes in the HAT (Figure 4D). In contrast, no deuterium transfer was observed using N-D derivative **1**- D_1 . Control experiments in the presence of $\text{MeOD-}d_4$ did not show any incorporation of deuterium into the substrate, excluding the solvent from engaging in the HAT process.

To compare the observed reaction outcome with the previous report using SF_5Cl by Paquin⁵⁹ and to shine light on the operating reaction mechanism, we turned to a theoretical description of the catalytic cycle on the level of

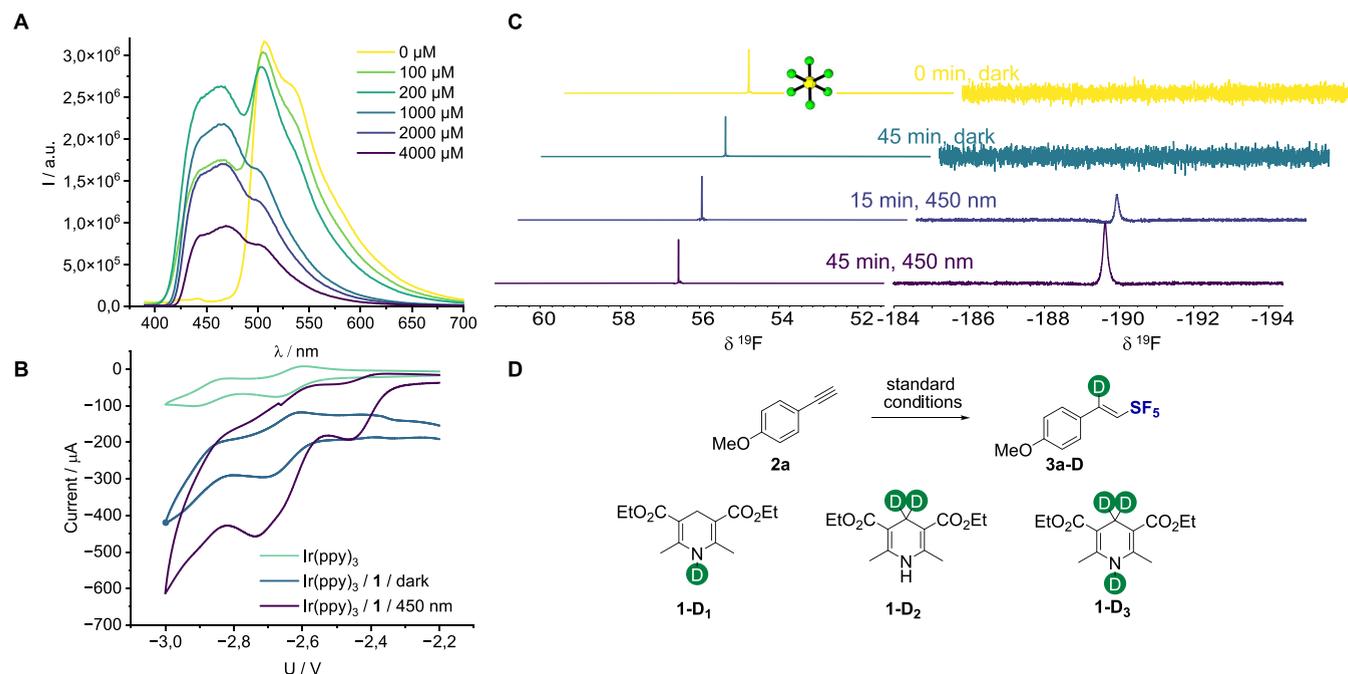


Figure 4. Mechanistic investigations. (A) Stern–Volmer quenching experiment of $\text{Ir}(\text{ppy})_3$ with Hantzsch ester **1**. (B) Cyclic voltammograms of $\text{Ir}(\text{ppy})_3$, $\text{Ir}(\text{ppy})_3$ with **1** in darkness and under irradiation at 450 nm, respectively. (C) Time-resolved ^{19}F NMR spectroscopy with $\text{Ir}(\text{ppy})_3$, **1** and SF_6 in CD_3OD , showcasing only degradation of SF_6 under irradiation at 450 nm. The ^{19}F NMR spectra show an unidentified side product of the SF_6 degradation. (D) Deuterium studies, using different deuterated Hantzsch esters (**1**- D_1 , **1**- D_2 , **1**- D_3).

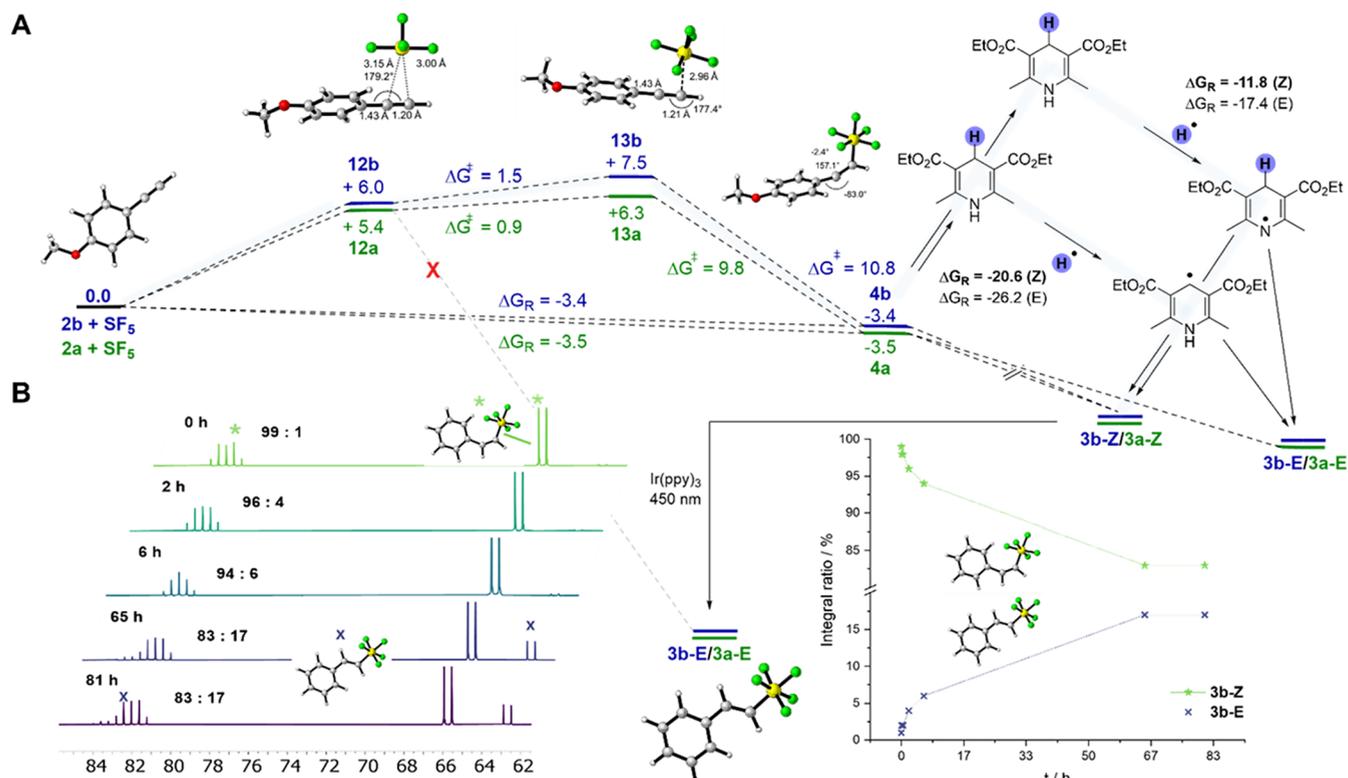


Figure 5. (A) Energy profile of the proposed reaction mechanism on the level of DLPNO-CCSD(T)/ccp-VTZ/CPCM in MeOH. All energies are given in kcal/mol. (B) Isomerization of primary product **3a-Z** by Ir(ppy)₃ under triplet sensitization conditions.

RI/CPCM/DLPNO-CCSD(T)/ccp-VTZ//RI/CPCM/DFT/M062X/dhf-TZVP/D3(0). The obtained Gibbs free energy change of the addition step on **2a** was found to be in very good agreement with previous results on the level of QICSD obtained by Paquin ($\Delta G_R = -3.2$ kcal/mol vs -3.5 kcal/mol, $\Delta G^\ddagger = 6.3$ kcal/mol in both cases). However, in MeOH, we observe a very flat minimum corresponding to a slightly endergonic π -complex **12a** or **12b**, respectively, whose formation is slightly endergonic ($\Delta G = 6.0$ or 5.4 kcal/mol). A more detailed analysis of the geometry of these π -complexes revealed a distance of the S-center of the SF₅ radical to the π -system of 3.00 Å (**2a**) and 3.06 Å (**2b**), fairly close to the transition state for an addition to the acetylene forming the vinyl radical **13b** (2.96 Å) and **13a** (2.79 Å), respectively, indicating an early starting material like transition state for the addition step and explains the determined very low barriers for addition of 0.9 or 1.5 kcal/mol, for the respective species (Figure 5).

The intermediate vinyl radicals are only slightly more stable than the starting materials, while the barrier for back reaction to the π -complex is only 9.8 and 10.8 kcal/mol, respectively, indicating a dynamic equilibrium with the starting material and the radical adduct species **4b**. Interestingly, all attempts to optimize a transition state leading to the diastereomeric *E*-configured SF₅ radical failed; as soon as constraints on the preoptimized structure were lifted, structure optimization converged to the *Z*-configured radicals **4a** and **4b**, indicating that there is no corresponding minimum for *E*-configured radical **4b-E**. In the photocatalytic experiments, a ratio between *E*- and *Z*-product **3b-Z:3b-E** of $94:6$ is obtained. Previous calculations by Paquin et al. have determined a difference between the barrier for the HAT of 2.7 kcal/mol as

the last step of the reaction mechanism explaining the preferred formation of the *Z*-product.⁵⁹ However, we found an indication that the observed *E/Z* ratio might be a superposition between the primary reaction pathway controlled by the HAT and subsequent photoisomerization forming **3b-E**. Subjecting pure **3b-Z** to irradiation at 450 nm in CD₃OD in the absence of the Ir complex yields the *E*- and *Z*-isomers in a photostationary state of $96:4$ (**3a-Z:3a-E**) (see SI Figure S25). Interestingly, in the presence of Ir(ppy)₃ (5.8 mol %, 2.0 mM), the photoisomerization at 450 nm gave an *E*-enriched ratio of $83:17$ (**3a-Z:3a-E**). Therefore, a potential pathway yielding an enrichment of the product **3a-E** is proposed by the secondary photoisomerization induced by sensitization of the primary reaction product **3b-Z** by Ir(ppy)₃. Accumulation of spin density on the β -SF₅-carbon was confirmed by the observation of ring opening of the bicyclic system of β -pinene **10** forming product **9** in a yield of 10% (see Figure 3, lower right). Therefore, trapping of the vinyl radical **13a** or **13b**, respectively, is most likely induced by HAT from the 4-position of **1** in accordance with a calculated driving force of $\Delta G = -20.6$ kcal/mol.

CONCLUSION

Vinylic SF₅ compounds are conventionally synthesized via the addition of highly toxic SF₅Cl gas to alkynes. We report a novel method for the synthesis of vinyl-SF₅ species, representatively shown for **3a**, utilizing cheap and nontoxic SF₆ as an SF₅-donating motif. For the first time, the hydropentafluorosulfanylation of alkynes was realized via the photocatalytic activation of SF₆ using *in situ*-generated, highly reducing Ir^{II} as a photocatalyst. The generated open-shell SF₅ species resulting from the reduction undergoes an addition onto 4-

methoxyacetylene (2a). We assume that the initially formed open-shell adduct **4b** is trapped by a HAT process to form 1,2-substituted SF₅H styrene adduct **3a**. Hantzsch ester **1** is employed both as a sacrificial reductant to access Ir^{II} and as the HAT donor. Detailed mechanistic studies by Stern–Volmer quenching, photocyclovoltammetry, and ¹H and ¹⁹F NMR spectroscopy support the proposed reaction mechanism. This method, for the first time, allows the hydropentafluorosulfanylation of alkynes with several advantages: (i) It relieves from the detrimental effects of a conPET-like cycle, (ii) it allows to shift the photoredox catalysis to the visible light range, and (iii) it overcomes the inefficient radical addition to a triple bond by the use of the HAT mechanism. At the same time, the strongly reducing nature of Ir^{II} limits the substrate scope to electron-rich substrates.

■ ASSOCIATED CONTENT

SI Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/jacsau.5c01407>.

All experiments and the results; Emission spectra of the used LED LED450-03 (450 nm, 80 mW); The used irradiation setup with a magnetic stirrer, vial block with a cooling element, 450 nm LED array; Deuterium experiment (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

David Rombach – Department of Chemistry, University of Zurich, 8057 Zurich, Switzerland; Email: david.rombach@chem.uzh.ch

Hans-Achim Wagenknecht – Institute of Organic Chemistry, Karlsruhe Institute of Technology (KIT), 76131 Karlsruhe, Germany; orcid.org/0000-0003-4849-2887; Email: wagenknecht@kit.edu

Authors

Max Flügge – Institute of Organic Chemistry, Karlsruhe Institute of Technology (KIT), 76131 Karlsruhe, Germany

Sven Klehenz – Institute of Organic Chemistry, Karlsruhe Institute of Technology (KIT), 76131 Karlsruhe, Germany

Silas Leidenheimer – Institute of Organic Chemistry, Karlsruhe Institute of Technology (KIT), 76131 Karlsruhe, Germany

Complete contact information is available at: <https://pubs.acs.org/doi/10.1021/jacsau.5c01407>

Author Contributions

§M.F. and S.K. contributed equally to this work.

Funding

This work was financially supported by the Deutsche Forschungsgemeinschaft (DFG, grant Wa 1386/23–1) and the Swiss National Science Foundation (SNSF, grant PZ00P2_209115). KIT and the University of Zurich are gratefully acknowledged.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank Mathis Mitha, Sophia Abou El Mirate, and Jacqueline Lehner for experimental support, proof reading, and scientific discussion. The authors acknowledge the support by the state of Baden-Württemberg through bwHPC and the German Research Foundation (DFG) through grant no INST 40/575-1 FUGG (JUSTUS 2 cluster).

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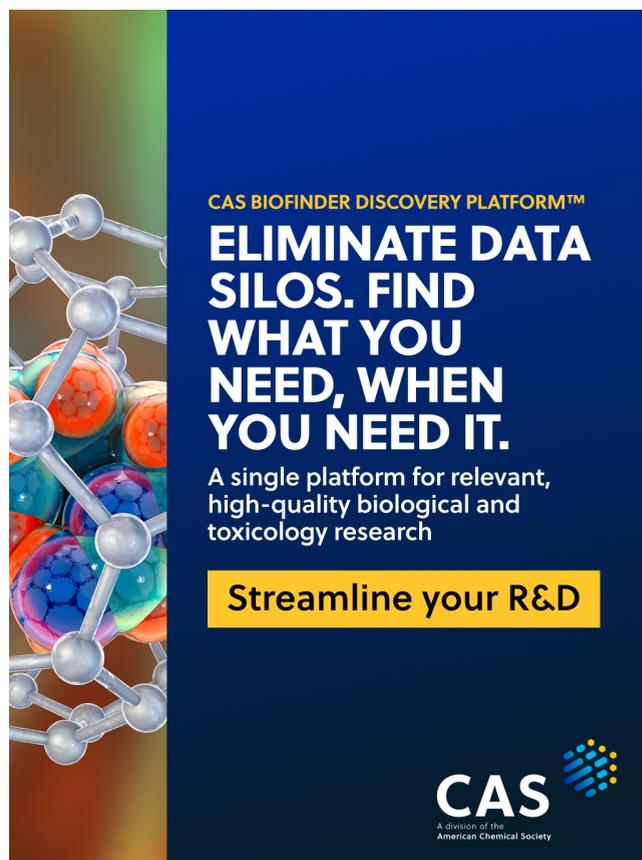
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