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Photo-induced hydroxypentafluorosulfanylation of alkenes with SF_5Cl and oxygen gas and their further derivatization

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Fluorinated or fluoroalkylated alcohols are common structural motifs in biologically active molecules, natural products, and pharmaceuticals. However, pentafluorosulfanyl (SF_5) alcohols, a unique class of SF_5 compounds that serve as synthetically valuable building blocks, are difficult to prepare with current methodologies. In this article, we present a single-step, metal-free, and photo-induced hydroxypentafluorosulfanylation of styrenes or α,β-unsaturated esters/amide, producing a series of structurally diverse pentafluorosulfanyl alcohols with up to 89% yields. This reaction is mild and operationally simple, using molecular oxygen as the hydroxy source. The protocol is suitable for a wide range of alkenes, including natural products and drug molecule derivatives. The formed SF_5 alcohol units can be readily converted into diverse functionalized SF_5 compounds, such as α-SF_5 ketones, SF_5 diols, and SF_5 cyclic carbonates. The potential applications of these SF_5 compounds in pharmaceutical and material sciences are vast, making this research a step forward in the field.

Recently, the pentafluorosulfanyl (SF_5) group[1–8], an emerging organic fluorinated functional group, has attracted significant attention in the fields of medicine, pesticides and materials[9–15]. Compared with its structurally analogous CF_3 group, SF_5 group has higher lipophilicity (similar to *t*-Bu group) and electron-absorbing properties (similar to nitro group)[16,17]. Therefore, the installation of an SF_5 group to an organic molecule significantly affects its physical and chemical properties. Consequently, molecules bearing an SF_5 functional group could potentially be excellent pharmaceutical compounds[1,4,18]. Despite the similarity between SF_5 and CF_3, there are still a limited number of reactions to introduce SF_5 group, in contrast to the well-established chemistry of CF_3. For aromatic or heteroaromatic SF_5 compounds, the methods include the direct fluorination of aryl disulfides in the presence of an alkali metal fluoride, as well as the chlorine to fluorine exchange of pre-synthesized chlorotetrafluorosulfanyl intermediates using a fluoride source such as AgF, IF_5, HgO/HF or PPHF, KHF_2, Ag_2CO_3, $AgBF_4$ etc[19–29]. In the case of aliphatic SF_5 compounds, the predominant strategy involves the addition of SF_5Cl or SF_5Br to alkenes and alkynes under mild free radical conditions[30–33]. However, the synthesis and storage of SF_5Cl reagents have long been challenging due to their high reactivity and low boiling point; it wasn't until 2019 that Togni and Pitts et al. discovered a gas-free method for synthesizing SF_5Cl using molecular sulfur, trichloroisocyanuric acid (TCICA), and potassium fluoride (KF)[34]. Based upon it, the Qing group in 2021 developed a more practical approach to produce an easy-to-handle solution of SF_5Cl in *n*-hexane[35]. Accordingly, SF_5Cl has been emerging as a popular SF_5 donor in a variety of radical pentafluorosulfanylation reactions[36–40]. For instance, Qing's group reports hydro(chloro)pentafluoro-sulfanylation of diazo compounds[35], iodopentafluorosulfanylation of [1.1.1] propellane as well as three-component radical addition reaction of SF_5Cl[41], alkene and diazo compounds[42]. Shortly thereafter, they developed a one-step method to synthesize SF_5-substituted alkynes from ethynylbenziodoxolones (EBX)[43]. Pitts et al. synthesized

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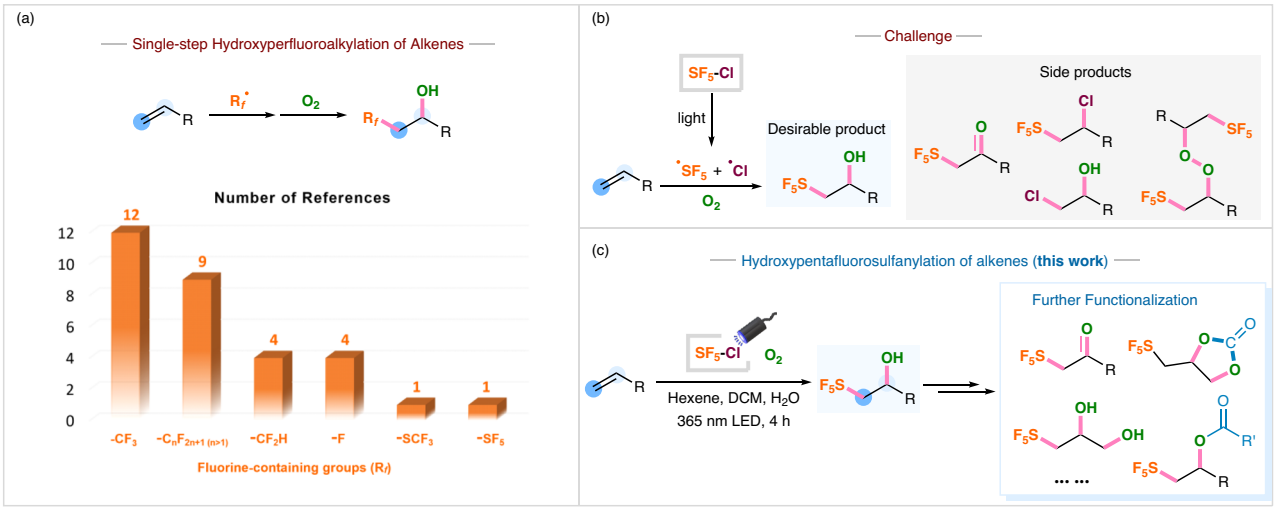
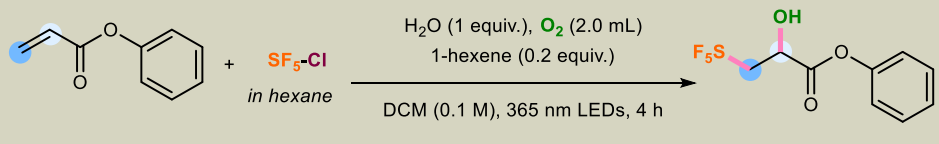


Fig. 1 | Radical-mediated hydroxyfluoroalkylation of alkene and this work. a Literature statistics of the advancements in hydroxyfluoroalkylation of alkenes. **b** The challenge posed by radical hydroxypentafluorosulfanylation of alkenes. **c** Hydroxypentafluorosulfanylation of alkenes with SF_5Cl and oxygen gas.

Table 1 | Optimization of reaction conditions[a]



1a (0.05 mmol) **2** (2 equiv.) **Standard Conditions** **3a**

Entry	Deviation from the standard conditions	Yield [%][b]
1	None	89
2	No 1-hexene	52
3	No H_2O	69
4	No O_2	N. D.
5	$CHCl_3$ instead of DCM	60
6	CCl_4 instead of DCM	54
7	THF instead of DCM	<5
8	Acetonitrile instead of DCM	<5
9	427 nm LEDs instead of 365 nm LEDs	61
10	390 nm LEDs instead of 365 nm LEDs	64
11	1 equiv. SF_5Cl instead of 2 equiv.	57
12	DCM (0.2 M) instead of DCM (0.1 M)	65

N.D. denotes not detected.
[a]Reaction conditions (unless otherwise specified): 1 (0.05 mmol), 2 (0.1 mmol, ~0.3 M in *n*-hexane), H_2O (0.05 mmol), O_2 (0.09 mmol), 1-hexene (0.01 mmol), DCM (0.5 mL), 365 nm LEDs, r.t., 4 h, N_2 atmosphere.
[b]Yields were determined based on the isolated products.

structurally diversified SF_5-bicyclopentanes (SF_5-BCPs) and SF_5-cyclobutanes (SF_5-CBs) via a strain-release pentafluorosulfanylated process[36,38]. Champagne and Paquin et al. discover photoinitiated *anti*-hydropentafluorosulfanylation of terminal alkynes[44]. Cahard and co-workers utilized a combination of SF_5Cl, KI, and 18-crown-6 ether to produce SF_5I and successfully synthesized (*E*)−1-iodo-2-(pentafluoro-λ⁶-sulfanyl) alkenes[45]. Moreover, the direct activation of the highly inert sulfur hexafluoride (SF_6) as a pentafluorosulfanylating reagent offers an alternative source of SF_5• for photoredox catalysis[46–48]. However, to date, this method has been limited to reactions with styrene derivatives. Concurrently, the synthetic applications and derivatizations of SF_5-substituted building blocks facilitate the efficient construction of complex SF_5-containing molecules that are otherwise challenging to synthesize[49–51]. Despite these advancements, the formation of Cl radicals during the radical chemistry of SF_5Cl with alkenes often leads to the production of chlorinated SF_5-products, limiting the development of SF_5Cl as a reagent[33,42,52–61]. Therefore, developing a more practical and efficient method for synthesizing novel SF_5-substituted compounds is highly desirable.

Alkenes are key building blocks in organic chemistry. The radical bifunctionalization of alkenes is an efficient and practical synthetic protocol, enabling the simultaneous introduction of two pivotal functional groups. Fluorinated alkyl radicals, renowned for their

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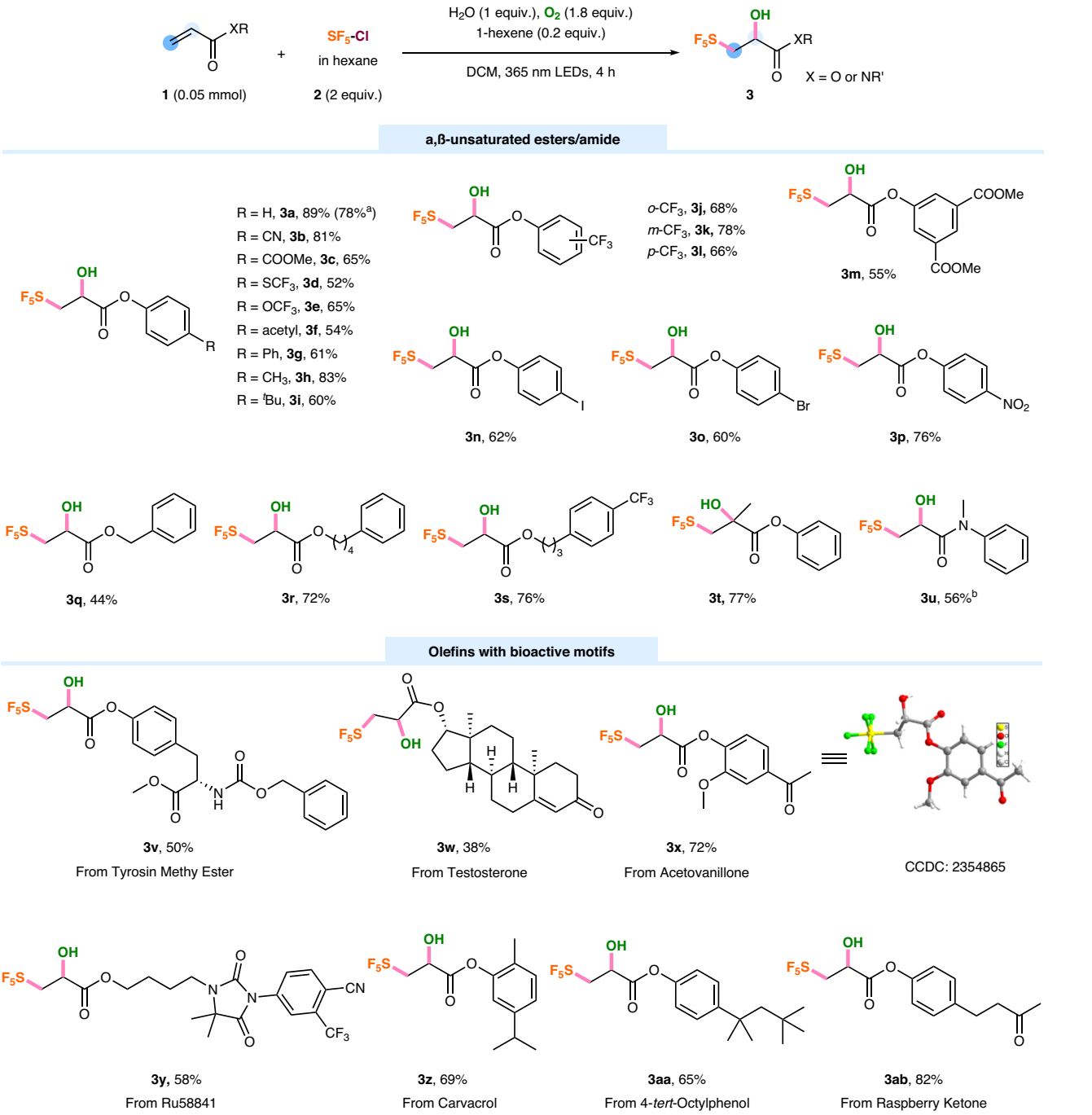

Fig. 2 | Substrate scope of hydroxypentafluorosulfanylation of alkenes. Reaction conditions: 1 (0.05 mmol), 2 (0.1 mmol, ~0.3 M in *n*-hexane), H_2O (0.05 mmol), O_2 (0.09 mmol), 1-hexene (0.01 mmol), DCM (0.5 mL), 365 nm LEDs, r.t., 4 h, N_2 atmosphere, isolated yields. [a]Reaction was scaled up to 0.5 mmol scale; [b]White LEDs, 12 h instead of 365 nm LEDs, 4 h.

robust electrophilic nature, readily engage in radical addition reactions with alkenes. Additionally, the hydroxyl functional group, as a valuable synthetic building block, could be introduced by oxygen gas and enable further diverse functionalizations[62,63]. To date, such a strategy has been widely utilized in various fluorinated functional groups, including CF_3[64–75], C_nF_{2n+1}[76–84], CF_2H[85–88], F[89–92] and SCF_3[93] (Fig. 1a). However, the single-step method for the simultaneous introduction of SF_5 and hydroxyl groups to alkenes has only been reported by the Wagenknecht group[47]. More commonly, the currently existing methods to synthesize pentafluorosulfanyl alcohols utilize indirect methods via multi-step reactions[94], or direct methods but using alcohol-containing starting materials[52,59]. Nevertheless, current reactions generally lack broad substrate scopes, with only a few reports of pentafluorosulfanyl alcohols. We hypothesize that a direct method where two functional groups could be introduced would have great potential in late-stage drug development, especially in complex and bioactive complex molecules. However, recent synthetic progress has significant limitations. For instance, in an oxidizing environment, alcohols are prone to further oxidation, forming their ketone derivatives[66,68]. Moreover, other radical additions, such as the chlorohydroxylation[95,96] and chloropentafluorosulfanylation[33,42,52–61] of olefins, can occur, leading to uncontrollable and undesired products (Fig. 1b). Herein, through our meticulous design, we present the photo-induced hydroxypentafluorosulfanylation of alkenes using SF_5Cl

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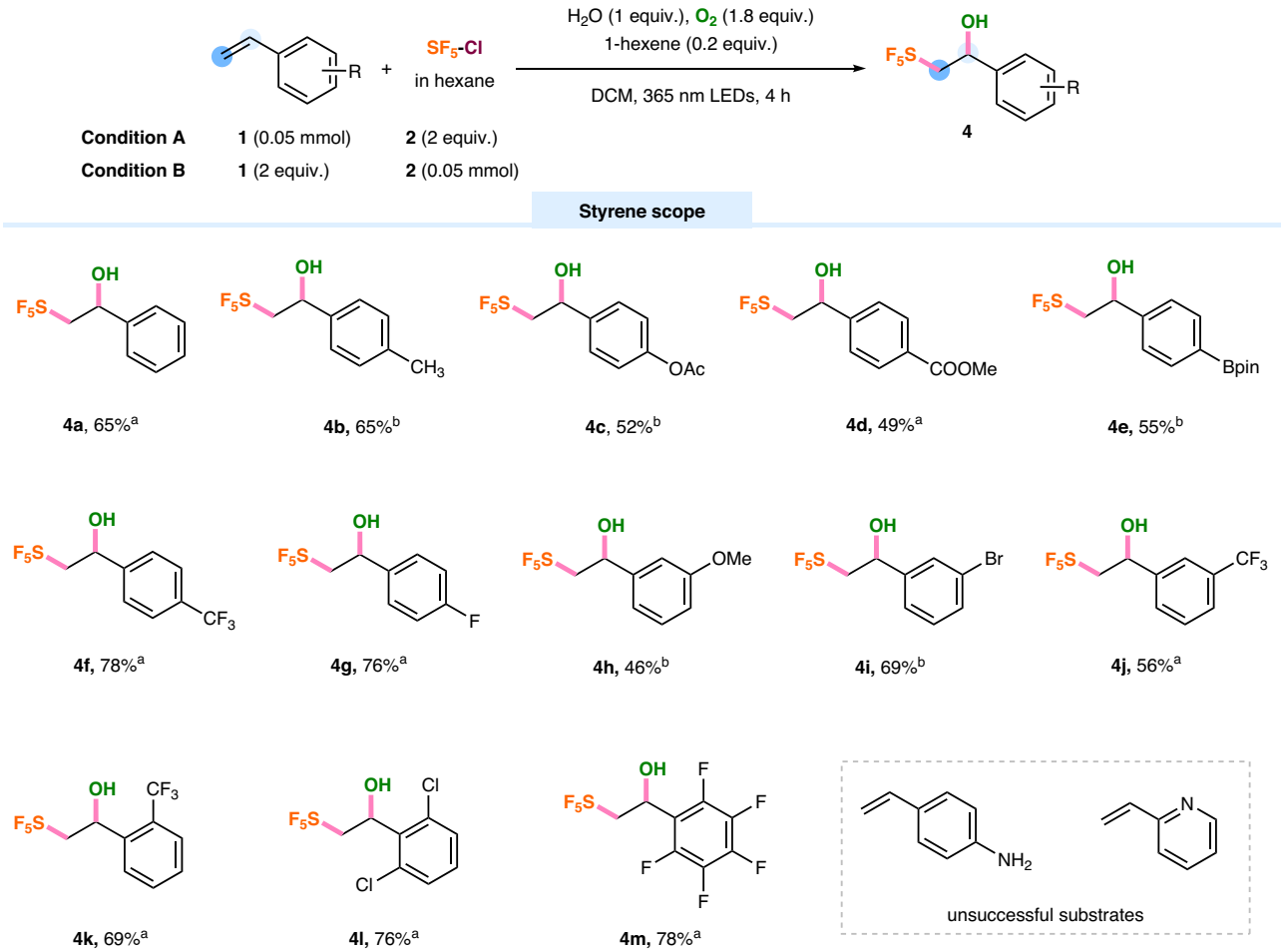

Fig. 3 | Substrate scope of hydroxypentafluorosulfanylation of styrenes. [a]Condition A: **1** (0.05 mmol), **2** (0.1 mmol, ~0.3 M in *n*-hexane), H_2O (0.05 mmol), O_2 (0.09 mmol), 1-hexene (0.01 mmol), DCM (0.5 mL), 365 nm LEDs, r.t., 4 h, N_2 atmosphere, isolated yields; [b]Condition B: **1** (0.1 mmol), **2** (0.05 mmol), H_2O (0.05 mmol), O_2 (0.09 mmol), 1-hexene (0.01 mmol), DCM (0.5 mL), 365 nm LEDs, r.t., 4 h, N_2 atmosphere, isolated yields.

and oxygen gas as the oxidant. Importantly, we demonstrate that these SF_5-alcohol scaffolds not only serve as suitable platforms for synthesizing α-SF_5-ketones, SF_5-diols, SF_5-cyclic carbonates, but also hold promise for the development of potential SF_5-substituted medicinal drugs (Fig. 1c).

Results

Method optimization

To optimize reaction conditions, α,β-unsaturated ester 1a was chosen as the template alkene substrate to react with SF_5Cl. Under optimal conditions, 0.1 M DCM was used as the solvent, and 1a (0.05 mmol) and SF_5Cl (0.1 mmol) were exposed to oxygen gas in the presence of 1 equivalent of H_2O and 0.2 equivalents of 1-hexene for 4 h at room temperature under 365 nm LEDs light. Product 3a was produced with an 89% isolated yield (Table 1, entry 1). We found that the addition of 1-hexene significantly increased the yield by inhibiting the formation of chlorinated byproducts (entry 2 and vide infra). Additionally, oxygen gas was critical for the transformation; no reaction was detected in its absence (entry 4). When halogenated solvents such as $CHCl_3$ and CCl_4 were used for the reaction (entries 5 and 6), diminishing yields were observed. Non-chlorinated solvents, including THF and acetonitrile, also resulted in much lower yields (entries 7 and 8). Additionally, using 427 nm or 390 nm LEDs as the excitation light source led to sluggish reactions and lower yields (entries 9 and 10). Using less than two equivalents of SF_5Cl or increasing the reaction concentration resulted in reduced yields (entries 11 and 12).

Substrate scope

With the optimized reaction conditions in hand, we examined the functional group tolerance of olefinic substrates. We were pleased to find that a variety of electron-donating and electron-withdrawing functional groups on the aryl ring were well tolerated in this transformation (3a-3p, Fig. 2). Electron-withdrawing groups such as cyano, ester, trifluoromethoxy, trifluoromethylthio and acetyl were well tolerated, furnishing products 3b-3f in 52–81% yield. Furthermore, trifluoromethyl groups on aryl ring were tolerated under the reaction conditions with positional insignificance (3j-3l). Additionally, the transformation also tolerated electron-neutral and electron-donating groups. Products with phenyl (3g), methyl (3h), and *tert*-butyl (3i) groups were obtained in 60–83% yield. Substrates with halogen groups on the aromatic rings also performed well, delivering products 3n and 3o in 62% and 60% yields, respectively, which are more conducive to subsequent coupling derivatization. The nitro group (3p) with strong polarity was also well tolerated, yielding 76%. When the ester group is attached to aliphatic groups (3q-3s), the hydroxypentafluorosulfanylation of the alkene achieved yields of 44–76%. It was gratifying to observe that a tertiary alcohol featuring the SF_5 motif (3t) could be generated in 77% yield, indicating the potential of our strategy to overcome steric hindrance in substrates. Further exploration revealed that both single substituted (3c) and multiple substituted (3m) substrates are suitable for this transformation, with the desired products obtained in moderate yields. To further demonstrate the synthetic applications of this protocol, we explored the late-stage

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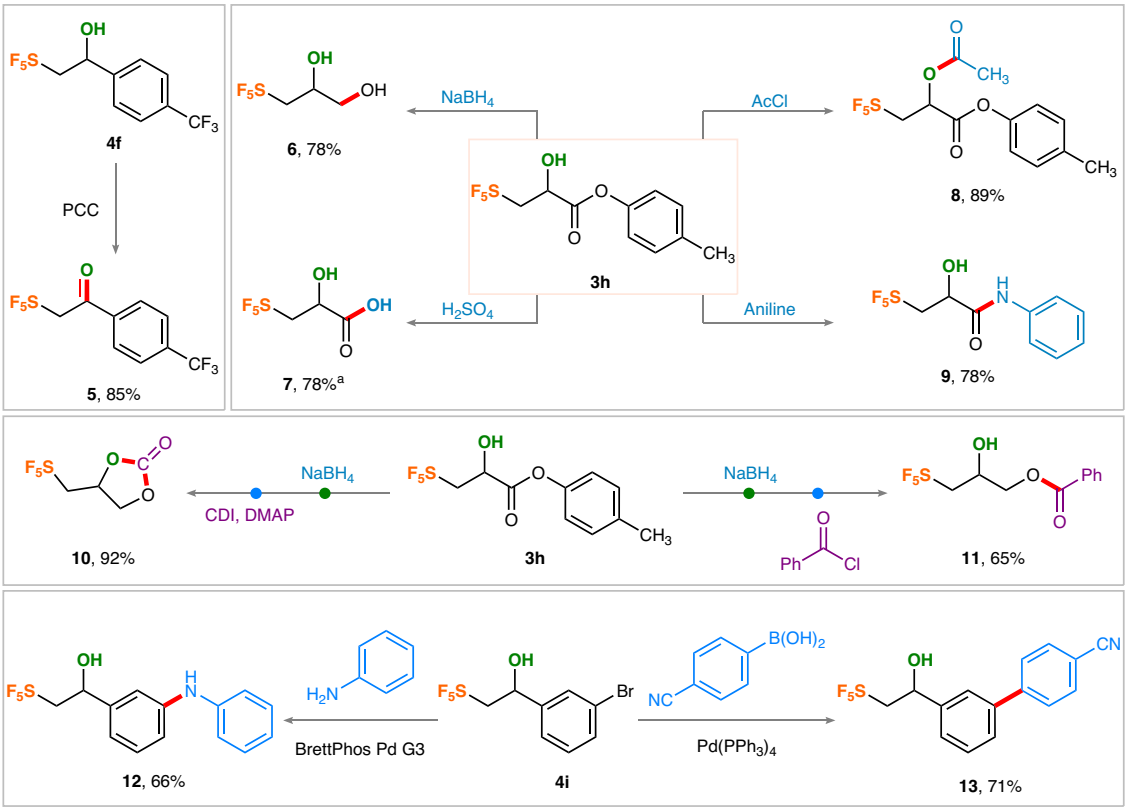

Fig. 4 | Further transformation of pentafluorosulfanyl alcohols. Reaction conditions: See the Supporting Information Section 2.6 for full experimental details, isolated yields. [a]Yield was determined by ^{19}F NMR spectroscopy using trifluoroacetic acid as the internal standard.

elaboration of natural product derivatives and pharmaceutical molecules, achieving synthetically useful yields. For example, the amino acid derivative tyrosine methyl ester (3v) was produced in 50% yield. The corresponding product 3w was also obtained in the reaction with the natural androgen estrone. We unequivocally verified the desired hydroxypentafluorosulfanylation product 3x from an acetovanillone-based olefin via X-ray crystallographic analysis. Additionally, the androgen receptor antagonist Ru58841 (3y) participated in the reaction with a yield of 58%. Selected pharmaceutically active compounds, including carvacrol (3z), 4-tert-octylphenol (3aa), and raspberry ketone (3ab), smoothly proceeded to deliver the corresponding products, highlighting the capacity for late-stage modification of complex natural or pharmaceutical molecules. These experimental results further demonstrate the advantages of our strategy in late-stage transformations to derive biologically relevant pentafluorosulfanylated molecules. Due to the lipophilic properties of the SF_5 group, these molecules could potentially have unique biological activities in medicinal development, even with the protected alcohol functional groups of bioactive compounds.

We next sought to broaden the substrate scope of the transformation to include styrenes (Fig. 3). To our delight, the target product 4a was obtained in 65% yield when styrene was used. However, when electron-donating groups were attached to the phenyl rings, almost no products were generated under standard conditions. Further investigation indicated that the formation of an electron-donor-acceptor (EDA) complex between the electron-donating group substrates and pentafluorothiochloride resulted in the consumption of the substrate, as evidenced by UV-visible spectroscopy experiments (see Supporting Information Section 2.5.1 for details). We hypothesized that an increased amount of substrate would be necessary for an effective reaction. To our delight, switching the ratio of electron-donating substrates to SF_5Cl to 2:1 uneventfully furnished 4b, 4c, and 4h albeit somewhat diminished yields, showcasing the generality of the reaction. We then tested substrates with electron-withdrawing groups. In the case of using a substrate with an ester motif, the reaction occurred smoothly, with the ester remaining intact (4d). Halogen atom (F, Br) substituents on the aryl ring (4g and 4i) had little influence on the reaction efficiency. The effect of substituents at different positions was determined using trifluoromethyl substrates (4f, 4j and 4k). Even in cases with the trifluoromethyl group in the *ortho* position, the reaction yield was still good (4k). For substrates with multiple halogens, the corresponding products (4l and 4m) were obtained with good yields of 76% and 78%. Unfortunately, further examination of styrene derivatives revealed that based-derived structures, such as pyridine or aniline (See Supporting Information Section 2.3 for details), still remained unsuitable for this reaction.

Further derivatization

The synthetic utility of this approach has also been demonstrated by the transformations of the resulting hydroxypentafluorosulfanylated compounds. First, as described in previous literature, the SF_5-substituted ketone is significant[35,50,55,97]. As shown in Fig. 4, oxidation of pentafluorosulfanyl alcohol 4f using PCC reagent afforded ketone 5 in 85% yield. We can also use $NaBH_4$ to reduce 3h to give the desired diol 6 in 78% yield. The resulting diol product 6 can be further transformed. For example, when reacting with CDI and DMAP, it could be converted to SF_5-substituted cyclic carbonate 10 in 92% yield. In addition, the diol product 6 could undergo selective protection of alcohols to give product 11. Gratifyingly, the resulting SF_5-substituted α-hydroxy acids (AHAs), as the potential cosmetics, were obtained under the acidity condition. In addition, 3h could be transformed into 8 in the presence of acetyl chloride, which also demonstrated the utility of our method. Treatment of product 3h with aniline afforded acylation product 9 successfully in 78% yield. Moreover, cross-coupling transformations are among the most common and powerful reactions in the synthesis and development of SF_5 compounds[97–99], the bromo-substituted SF_5

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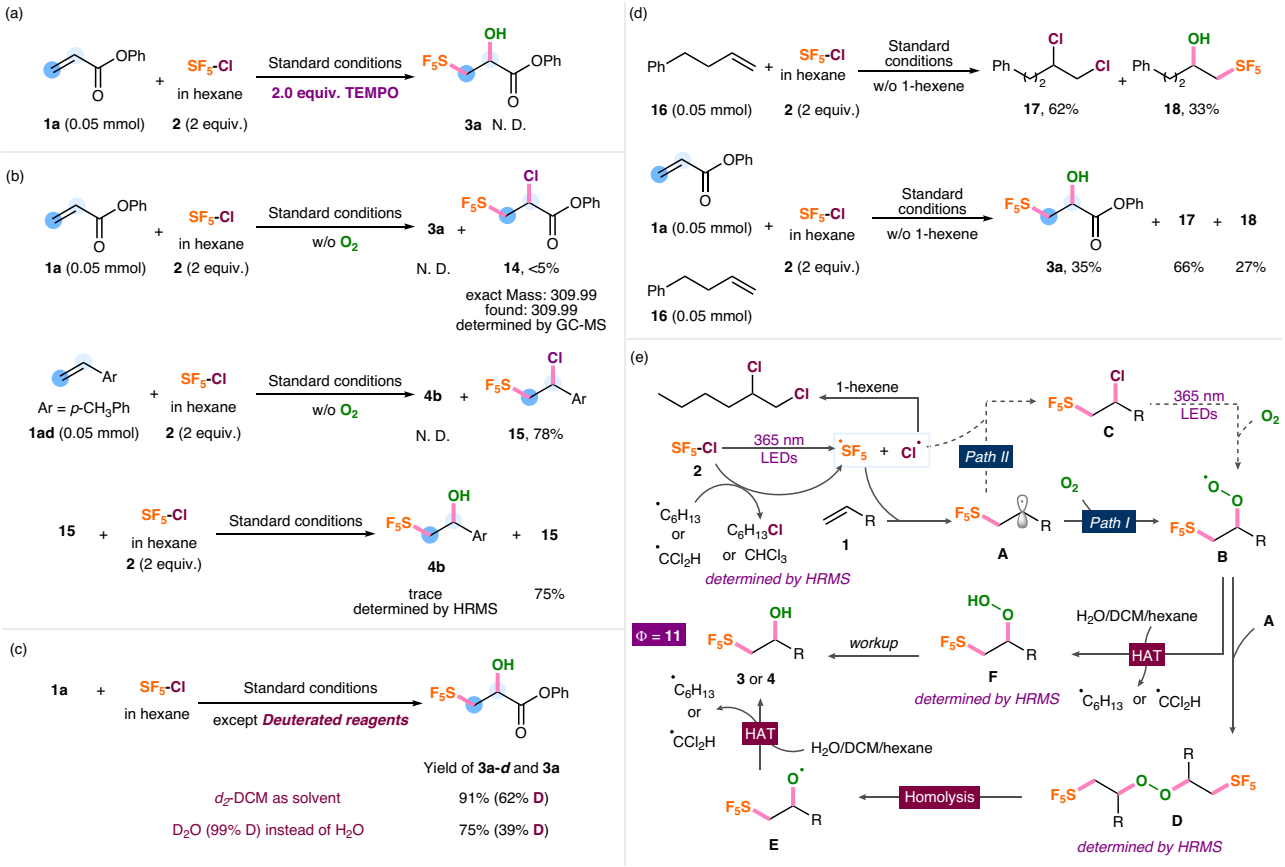

Fig. 5 | Mechanistic investigations and proposed mechanism for hydroxypentafluorosulfanylation of alkenes. a Radical capture experiment. **b** Control experiment of chloropentafluorosulfanylated product. **c** Deuteration experiment. **d** Control experiment of aliphatic alkene. **e** Proposed mechanism. Reaction conditions: 1 (0.05 mmol), 2 (0.1 mmol, ~0.3 M in *n*-hexane), H_2O (0.05 mmol), O_2 (0.09 mmol), 1-hexene (0.01 mmol), DCM (0.5 mL), 365 nm LEDs, r.t., 4 h, N_2 atmosphere, isolated yields. N. D. denotes not detected.

alcohols 4i could function as a coupling reagent to generate the desired arylation or animation products (12 and 13) through either Suzuki or Buchwald-Hartwig cross-coupling reaction, without any protecting groups on the substrates. Our strategy to develop hydroxypentafluorosulfanyl products would be synthetically valuable and powerful to expand the pharmaceutical drug pools containing the SF_5 group.

Mechanistic investigations

Control experiments were conducted to gain mechanistic insights into the reaction. Under standard conditions, the reaction was entirely suppressed by 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO), and no products were formed, suggesting the involvement of a radical process (Fig. 5a). Subsequently, in the absence of oxygen, the reaction with alkenes, whether acrylic acid ester or styrene, failed to produce the desired product 3a or 4b, instead yielding the chloropentafluorosulfanylated products 14 or 15 (Fig. 5b). Notably, when the chloropentafluorosulfanylated product 15 was directly subjected to the standard conditions, almost no hydroxypentafluorosulfanylated product 4b were obtained, with the starting material largely unreacted. Therefore, formation of chloropentafluorosulfanylated product is not the primary pathway in the overall mechanism (*vide infra*; Path II). To further clarify the source of hydrogen at the hydroxyl site of the product, control experiments were performed under the standard conditions while using d_2-DCM as the reaction solvent and D_2O as proton reagents respectively (Fig. 5c, Supporting Information Section 2.5.2). When d_2-DCM were used, 3a-*d* could be obtained in 62% D. By contrast, when D_2O was used, only 39% D was observed. This result clearly demonstrated that the proton of H_2O and solvent (DCM) were transferred to the product. As shown in Fig. 5d, the unactivated olefin (4-phenyl-1-butene 16) instead of 1-hexene was used to react with two equivalents of SF_5Cl, and dichlorinated addition product 17 was successfully obtained as the main product and a few hydroxypentafluorosulfanylated product 18, which demonstrated that aliphatic alkene (1-hexene) used in this experiment was a favorable chlorine radical trapping agent. However, when 4-phenyl-1-butene and an acrylic acid ester were used as substrates, a competition reaction occurred, resulting in a mixture of the corresponding hydroxypentafluorosulfanylated products (3a and 18), also along with the formation of a dichlorinated addition product of 4-phenyl-1-butene. Based on our control experiments and previous studies, we propose the following reaction mechanism (Fig. 5e). The reaction is initiated by the excitation of SF_5Cl using a 365 nm UV lamp. The S-Cl bond undergoes homolytic cleavage to form a Cl radical and an SF_5 radical, with the Cl radical being trapped by 1-hexene to afford 1,2-dichlorohexane. Of note, the quantum yield studies[100] indicate that this is a radical-chain process as evidenced by the calculation ($\Phi = 11$, see Supporting Information Section 2.5.3 for details). Therefore, an alternative pathway involves the trapping of SF_5Cl by the C_6H_{13} radical or $CHCl_2$ radical, derived from the solvent (hexane or DCM), leading to the formation of the corresponding aliphatic chlorides, $C_6H_{13}Cl$ or $CHCl_3$. These products were confirmed by HRMS (Supporting Information Section 2.5.3 for details) and are consistent with previous literature[35]. The generated SF_5 radicals are added to the olefin substrate 1, resulting in the formation of radical intermediate A (Path I), which is immediately trapped by oxygen gas to generate peroxide radical B. In contrast, Path II, which proposes chloropentafluorosulfanylated product C as the intermediate, is not supported by the control experiments presented in

Fig. 5b. When C was employed under standard conditions, the desired product 4 was scarcely obtained. The peroxide radical B is then converted into the desired product via two distinct pathways. In one pathway, the hydrogen is extracted from water or solvent, followed by cleavage of the peroxide bond to yield product 3 or 4. Alternatively, the peroxide radical B undergoes direct radical-radical coupling to produce the dimer D. Subsequent homolysis of dimer D forms radical intermediate E, ultimately affording the desired hydroxypentafluorosulfanylation product 3 or 4.

Discussion

In summary, we have disclosed an efficient and practical methodology for the hydroxypentafluorosulfanylation of olefins, which occurs under mild conditions and has been successfully applied to both styrene and electron-withdrawing alkenes. Using the widely available reagent SF_5Cl, this method enables the rapid synthesis of β-pentafluorosulfanyl alcohols. Of note, the reaction substrates are highly universal, rendering them suitable for the synthesis of complex SF_5-substituted molecules. Furthermore, the post-functionalization reactions of β-pentafluorosulfanyl alcohols could provide rapid avenues to construct complex molecules containing the SF_5 group. We believe that this hydroxypentafluorosulfanylation protocol will provide opportunities for applications in medicinal chemistry.

Methods

In a N_2 glovebox, to alkene 1 (0.05 mmol, 1.0 equiv.) was added 1-hexene (0.01 mmol, 0.20 equiv.) in a 10 mL sealed vial tube. Seal the bottle cap and then transfer it out of the glovebox. DCM (0.5 mL, 0.1 M), H_2O (0.05 mmol, 1.0 equiv.), O_2 (2 mL) and SF_5Cl (dissolved in *n*-hexane, ~0.3 M, 0.1 mmol, 2.0 equiv.) were injected through a syringe into the reaction, and the resulting mixture was stirred for 4 h at room temperature under the 365 nm LEDs. Then, the reaction was diluted with DCM. The filtrate was concentrated *in vacuo* and the residue was purified by flash column chromatography with developing agent of petroleum ether and ethyl acetate to afford product 3 or 4.

Data availability

Data relating to the characterization data of materials and products, general methods, optimization studies, experimental procedures, mechanistic studies and NMR spectra are available in the Supplementary Information. All data are also available from the corresponding author upon request. Crystallographic data for the structures reported in this Article have been deposited at the Cambridge Crystallographic Data Centre, under deposition numbers 2354865 (3x). This data can be obtained free of charge via www.ccdc.cam.ac.uk/structures/. Source data are provided with this paper.

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Author contributions

S. Guo conceived the project. Y. Y. Jiang, X. L. Meng, J. S. Zhang, G. Wu and X. J. Lin performed the experiments and analyzed the experimental data. All the authors discussed the results and contributed to the preparation of the final manuscript.

Competing interests

The authors declare no competing interests.

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