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Metal-free di- and tri-fluoromethylation of alkenes realized by visible-light-induced perylene photoredox catalysis†

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Regioselective amino-difluoromethylation of aromatic alkenes via C(sp³)-CF₂H and C(sp³)-N bond formation with the C=C moiety has been achieved in a single operation by visible-light photoredox catalysis. The combination of a shelf-stable and easy-to-handle sulfonium salt, *S*-difluoromethyl-*S*-di(*p*-xylyl)sulfonium tetrafluoroborate, and perylene catalysis is the key to the successful transformation. Furthermore, this noble metal-free protocol allows for the photocatalytic trifluoromethylation of alkenes.

Introduction

The trifluoromethyl (CF₃) and difluoromethyl (CF₂H) groups have prevailed as key structural motifs of drugs and agrochemicals.¹ In particular, the CF₂H group is regarded as a unique fluorinated group because it acts as a bioisostere to hydroxyl and thiol units as well as a lipophilic hydrogen donor. Recently, practical trifluoromethylation has been realized by the action of appropriate catalysis to a variety of CF₃ sources.² In contrast, versatile strategies for the direct difluoromethylation of various carbon skeletons are still underdeveloped.³

In the past several years, visible-light photoredox catalysis with metal catalysts such as [Ru(bpy)₃]²⁺ and *fac*-[Ir(ppy)₃] (bpy = 2,2'-bipyridine, ppy = 2-phenylpyridyl) has emerged as a useful tool for radical trifluoromethylation.⁴ In particular, shelf-stable and solid sulfonium salts such as Umemoto A⁵ and Yagupolskii B⁶ reagents readily undergo single-electron transfer (SET) from photoactivated catalysts to serve as excellent CF₃ radical precursors (Fig. 1).^{7,8} More recently several groups, including us, have developed novel strategies for generation of the CF₂H radical from well-designed CF₂H sources such as sulfonyl derivatives (C-E) and phosphonium salts F.⁹ Remarkably, the subtle change in the number of fluorine atoms in the CF₂X reagents (X = F, H) causes significant differences in their chemical properties such as redox performance and stability. For example, generation of the CF₂H radical from electrophilic CF₂H sources as presented herein demands a stronger reductant compared with the CF₃ radical. In general, the Ir

photocatalyst, *fac*-[Ir(ppy)₃], is regarded as a strong 1e⁻reductant when excited by visible light irradiation. But from the viewpoint of the elements strategy initiative¹⁰ and green chemistry, development of organic photocatalytic systems has attracted great interest.¹¹ However, the design of visible-light organic photoredox catalysts with stronger reduction power still leaves room for further development. In 2014, König and co-workers developed the consecutive photoinduced electron transfer (conPET) of perylene diimide, but it requires sacrificial electron donors.¹² The groups of Hawker and Miyake reported that phenylphenothiazine and diaryl dihydrophenazine serve as strong reductants, respectively.¹³ Then, simple polycyclic aromatic hydrocarbons (PAHs) attracted our attention. It is known that some PAHs exhibit high excited state energies

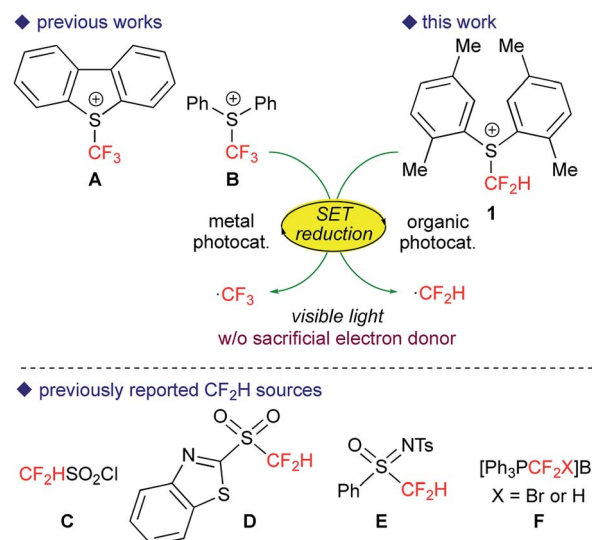


Fig. 1 Reductive generation of fluoroalkyl radicals by SET photoredox catalysis. Ts = *p*-toluenesulfonyl.

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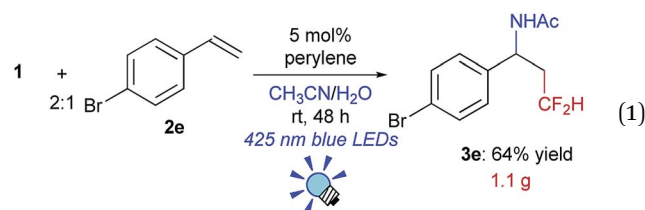
accompanied by relatively high HOMO levels,¹⁴ suggesting that they can serve as efficient and economical photoredox catalysts without extra reductants. Herein, we disclose that perylene can serve as an excellent visible-light organic photocatalyst for amino-difluoromethylation of aromatic alkenes in a single operation. The present noble metal-free photocatalytic system also allows trifluoromethylation of alkenes.

Results and discussion

We first tackled the synthesis of a shelf-stable and easy-to-handle electrophilic CF₂H source. In 2007, Prakash, Olah and co-workers reported on the synthesis of the *S*-difluoromethyl-*S*-phenyl-*S*-2,3,4,5-tetramethylphenylsulfonium reagent **G**,¹⁵ which reacted with various hetero-atom-nucleophiles resulting in the formation of X–CF₂H bonds (X = N, O, P), but construction of a C(sp³)–CF₂H bond has not been reported. In addition, the reagent **G** is semi-solid and not very stable, and so decomposes by ~10% after three months even when stored at –20 °C. Therefore, we designed the *S*-(difluoromethyl)sulfonium reagent (**1**), where the two methyl groups of the *p*-xylyl substituents in the proximity of the sulfur atom may hinder decomposition *via* ionic and carbenoid reactions due to steric and electronic effects. The reagent **1** was easily synthesized according to the procedures modified from the original ones^{15,16} and characterized by ¹H, ¹³C and ¹⁹F NMR spectroscopy and elemental analysis. The structure of **1** was confirmed by single crystal X-ray analysis (Scheme 1).¹⁷ Compound **1** is a stable, crystalline white solid. It is worth noting that no decomposition was observed of a solid sample on a shelf for three months at ambient temperature, while a CH₃CN solution partially decomposed (~10%) when left for 24 h at ambient temperature. In addition, a cyclic voltammogram of **1** exhibited a broad irreversible reduction wave at around –1.70 V *vs.* [Cp₂Fe].

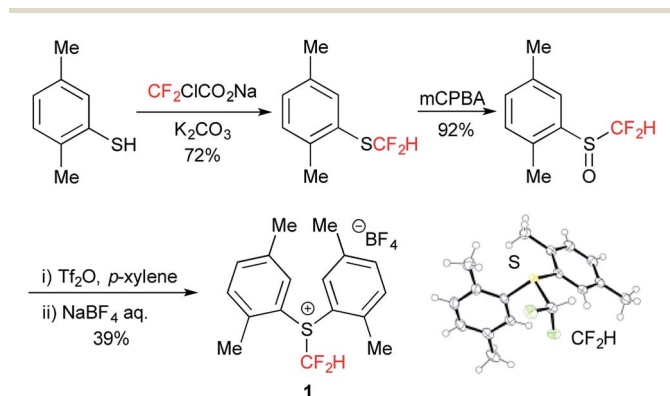
With this new reagent in hand, we explored the photoredox-catalyzed amino-difluoromethylation of styrene **2a**, which would lead to potentially useful β-CF₂H substituted amines.¹⁸ To design an organic photocatalytic system under visible light irradiation, absorption bands in the visible light region are vital. Pale-colored PAHs with large π-conjugated systems may work as visible-light catalysts. We commenced the reaction of **2a**

in the presence of 10 mol% perylene (absorption maxima: 434, 407 nm) in CD₃CN containing an equimolar amount of D₂O, under visible light irradiation with 425 nm blue LEDs. To our delight, deuterated *N*-(3,3-difluoro-1-phenylpropyl)acetamide **3a-d₄** was obtained in a 96% yield (entry 1 in Table 1). In contrast, analogous PAHs such as anthracene and pyrene were totally ineffective, presumably because of a lack of a visible absorption band, while 9,10-dimethylantracene worked to some extent (entries 2–4). It is worth noting that the Ir photocatalyst, *fac*-[Ir(ppy)₃], was sluggish (entry 5). The estimated reduction potential of the photoexcited perylene was remarkably high (–2.23 V *vs.* [Cp₂Fe] in CH₃CN, see the ESI†) and even higher than that of *fac*-[Ir(ppy)₃] (–2.14 V (ref. 19)), which has been regarded as the most strongly reducing visible-light photoredox catalyst. The quantum yield of the emission of *perylene (94% (ref. 14)) is far superior to that of *[*fac*-[Ir(ppy)₃]] (38% (ref. 19)), but the emissive excited state of perylene has a very short lifetime (8.2 ns). Thus, perylene has been studied extensively as a fluorescent molecule, but less attention has been paid to it as a photoredox catalyst.²⁰ Using 1.1 equivalents of **1** decreased the yield (entry 6). The reaction did not proceed at all either in the dark or in the absence of perylene (entries 7 and 8).



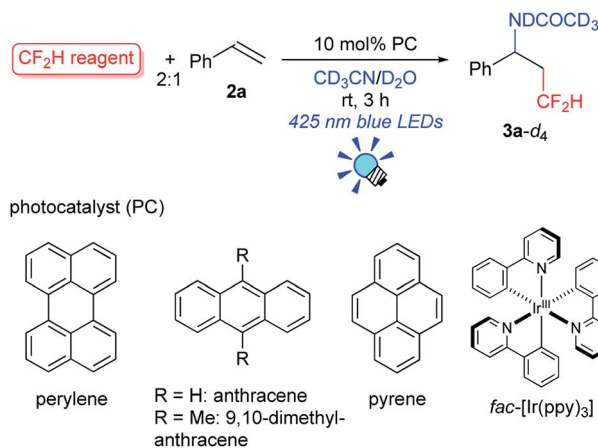
Furthermore, the reactions of neutral halogen-free sulfonyl derivatives (**D** and **E**) and sulfonium reagent **G** were conducted under optimized conditions (entries 9–11). It should be noted that the sulfonium reagents (**1** and **G**) are superior to **D** and **E** in this photocatalytic reaction. The sulfonium reagent **G** also served as an effective CF₂H source (entry 11), but the stability and handling of reagent **1** were significantly improved.

We further investigated the scope of this reaction (Table 2) and found that the catalyst loading could be reduced to 5 mol%. The reaction of styrene derivatives with a variety of functional groups such as Me (**2b**), F (**2c**),¹⁷ Cl (**2d**), Br (**2e**), AcO (**2f**), Bpin (**2g**) and aldehyde (**2h**) groups afforded the corresponding β-CF₂H substituted amino compounds (**3b–g**) in 30–76% yields in a regioselective manner. To demonstrate the scalability of this organic photocatalytic system, the amino-difluoromethylation of **2e** was carried out on a gram scale, and the product **3e** was isolated in a 64% yield (1.1 g) (eqn (1)). It is worth noting that this reaction could be applied to a structurally more complex estrone derivative (**2i**) (**3i**: 38%). An alkene with a bulky mesityl substituent (**2j**) was also a substrate suitable for this transformation (**3j**: 52%), but 1,1-diphenylethylene (**2k**) afforded the substituted CF₂H-alkene (**4**) in a 55% yield *via* deprotonation from the carbocationic intermediate (*vide infra*). Furthermore, the system was amenable to the regioselective reaction of the internal alkenes. The reactions of *trans*-β-methylstyrene (**2l**),



Scheme 1 Synthesis and an ORTEP drawing (BF₄ anion: omitted) of **1**.



Table 1 Optimization of the photocatalytic amino-difluoromethylation of **2a**^a

Entry	CF ₂ H reagent	PC	λ _{max} , nm	Yield of 3a-d₄ ^b , %
1	1	Perylene	434, 407	96
2	1	Anthracene	376, 357	0
3	1	9,10-Dimethyl-anthracene	398, 377	34
4	1	Pyrene	334, 319	0
5 ^c	1	<i>fac</i> -[Ir(ppy) ₃]	375 (ref. 19)	29
6 ^d	1	Perylene	—	68
7 ^e	1	Perylene	—	0
8	1	—	—	0
9	D	Perylene	—	0
10	E	Perylene	—	Trace
11	G	Perylene	—	88

^a The reaction was carried out under N₂ atmosphere and irradiation of 425 nm blue LEDs at room temperature using the photocatalyst (2.5 μmol), CF₂H reagent (50 μmol), **2a** (25 μmol), and CD₃CN (0.50 mL; containing 25 μmol of D₂O) in an NMR tube. ^b Yields were determined by ¹H NMR spectroscopy using SiEt₄ as an internal standard. ^c A 71% NMR yield of **3a-d₄** was obtained in 24 h. ^d The ratio of **1** : **2a** is 1.1 : 1. ^e In the dark. LED = light-emitting diode, ppy = 2-phenylpyridyl.

trans-stilbene (**2m**), and 1,2-dihydronaphthalene (**2n**) provided the CF₂H-substituted amino products (**3l-n**) in 44–64% yields but as mixtures of diastereomers. Remarkably, cinnamic acid ester (**2o**) could also be used for this transformation, resulting in the production of a CF₂H-substituted β-amino acid derivative (**3o**: 60%). These results showed that this metal-free photocatalytic system with the CF₂H reagent **1** is useful for regioselective and simultaneous construction of C(sp³)-CF₂H and C(sp³)-N bonds onto a C=C moiety regardless of the functionalities.

Next, to examine the scope with respect to fluoroalkylation, the perylene-catalyzed system was applied to trifluoromethylation (Scheme 2). The reaction of styrene **2a** with the reagent **B** afforded the amino-trifluoromethylated product **5** in a 66% yield.^{7b} Perylene also promoted chlorotrifluoromethylation of the aliphatic alkene **2p** with CF₃SO₂Cl to give the product **6** in a 57% yield.²¹

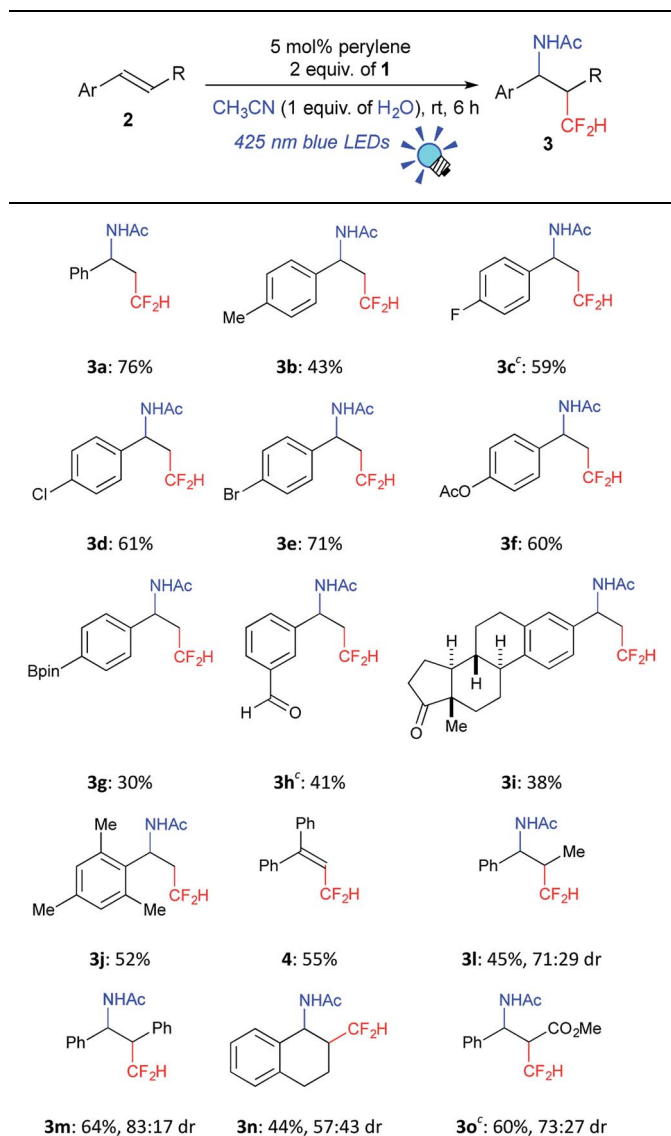
To gain insight into the reaction mechanism we conducted some experiments. The reaction of 1-phenyl-2-(1-phenylethenyl)cyclopropane (**2q**) afforded the difluoromethylated, ring-opened product **7** (23% yield), indicating the involvement of radical processes in the photocatalytic reaction

(Scheme 3). Moreover, the reaction of **2a** with **1** required continuous visible light irradiation for steady conversion (see the ESI[†]), suggesting that a radical chain mechanism was not the main reaction pathway.

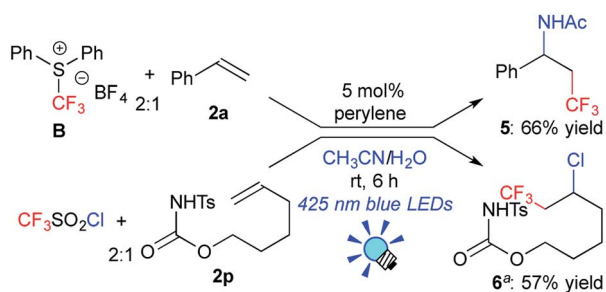
On the basis of the above-mentioned observations, a possible reaction mechanism for perylene-catalyzed difluoromethylation is depicted in Scheme 4. Perylene excited by visible light irradiation (*perylene) undergoes SET to the electrophilic CF₂H reagent **1** to form the difluoromethyl radical [•]CF₂H via C-S bond cleavage, and the radical cation of perylene ([perylene]^{•+}). The very short lifetime of *perylene may be compensated by its highly emissive quantum yield to promote the SET process. Fluorescence quenching experiments support the SET process (see the ESI[†]). The generated [•]CF₂H radical reacts with alkene **2** to form the adduct **8**, which is oxidized by [perylene]^{•+} to provide the carbocationic intermediate **8**⁺. Subsequent Ritter amination²² of **8**⁺ with CH₃CN/H₂O affords the amino-difluoromethylated product **3**. When an α-substituted styrene **2k** is used as a substrate, deprotonation of **8**⁺ gives the CF₂H-alkene **4**.



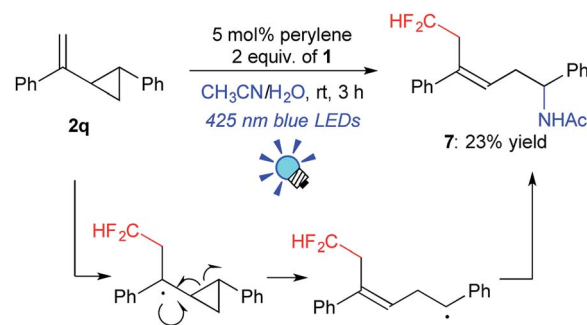
Table 2 Scope of the perylene-catalyzed amino-difluoromethylation of alkenes^{ab}



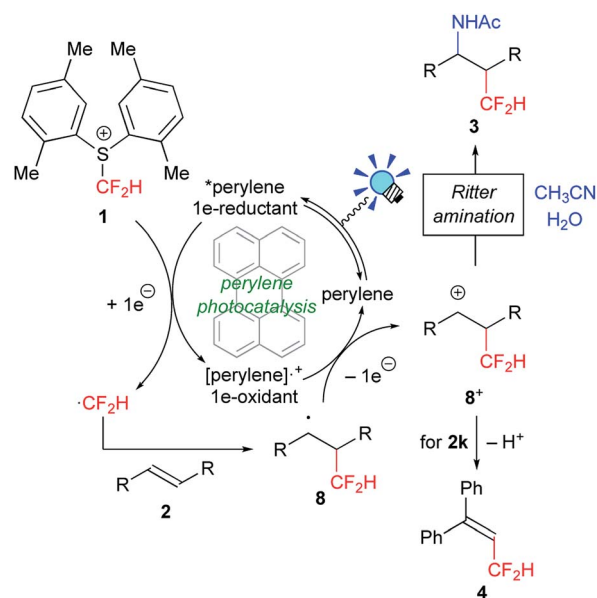
^a For detailed reaction conditions, see the ESI.† ^b Yields of the isolated products are lower than those before purification. The purification processes decreased the isolated yields. The diastereomer ratios (dr) were determined using ¹H NMR spectra of crude reaction mixtures. ^c 12 h. Ac = acetyl, Bpin = boronic acid pinacol ester.



Scheme 2 Perylene-catalyzed trifluoromethylation. ^aAnhydrous CH₃CN was used as a solvent.



Scheme 3 Control experiment for radical difluoromethylation.



Scheme 4 A plausible reaction mechanism.

Conclusions

In conclusion, we have developed noble metal-free photocatalytic di- and tri-fluoromethylation of alkenes using a perylene catalyst. The combination of the new *S*-(difluoromethyl) sulfonium salt (**1**) and perylene catalysis allows for facile amino-difluoromethylation of aromatic alkenes through radical processes, for which the Ir photocatalyst works much less efficiently. Thus, the unprecedented simple synthesis of β-CF₂H-substituted amines from alkenes has now become feasible. Further development of perylene-catalyzed reactions is currently under way in our laboratory.

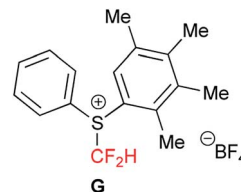
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