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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* $C(sp^3)–CF_2H$ and $C(sp^3)–N$ 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 (CF_3) and difluoromethyl (CF_2H) groups have prevailed as key structural motifs of drugs and agrochemicals.[1] In particular, the CF_2H 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 CF_3 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 **A**[5] and Yagupolskii **B**[6] reagents readily undergo single-electron transfer (SET) from photoactivated catalysts to serve as excellent CF_3 radical precursors (Fig. 1).[7,8] More recently several groups, including us, have developed novel strategies for generation of the CF_2H radical from well-designed CF_2H sources such as sulfonyl derivatives (**C**–**E**) and phosphonium salts **F**.[9] Remarkably, the subtle change in the number of fluorine atoms in the CF_2X reagents (X = F, H) causes significant differences in their chemical properties such as redox performance and stability. For example, generation of the CF_2H radical from electrophilic CF_2H sources as presented herein demands a stronger reductant compared with the CF_3 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 initiative[10] 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

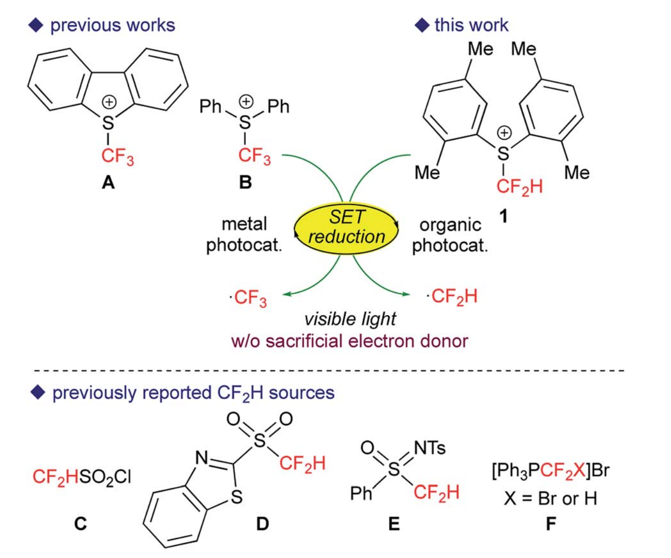

Fig. 1 Reductive generation of fluoroalkyl radicals by SET photoredox catalysis. Ts = *p*-toluenesulfonyl.

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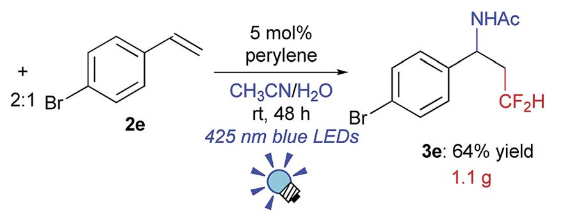
accompanied by relatively high HOMO levels,[14] suggesting that they can serve as efficient and economical photoredox catalysts without extra reductants. Herein, we disclose that perylene can serve as an excellent visible-light organic photocatalyst for amino-difluoromethylation of aromatic alkenes in 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 CF_2H 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–CF_2H bonds (X = N, O, P), but construction of a C(sp^3)–CF_2H 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 ^{1}H, ^{13}C and ^{19}F 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 CH_3CN 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.* [Cp_2Fe].

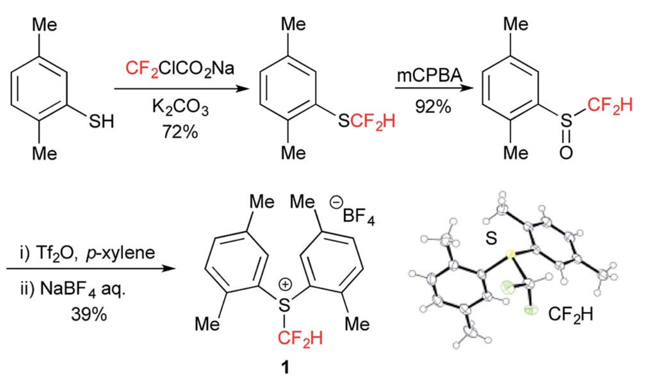
With this new reagent in hand, we explored the photoredox-catalyzed amino-difluoromethylation of styrene **2a**, which would lead to potentially useful β-CF_2H substituted amines.[18] To design an organic photocatalytic system under visible light irradiation, absorption bands in the visible light region 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 CD_3CN containing an equimolar amount of D_2O, under visible light irradiation with 425 nm blue LEDs. To our delight, deuterated *N*-(3,3-difluoro-1-phenylpropyl)acetamide **3a**-d_4 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-dimethylanthracene 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.* [Cp_2Fe] in CH_3CN, 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).



(1)

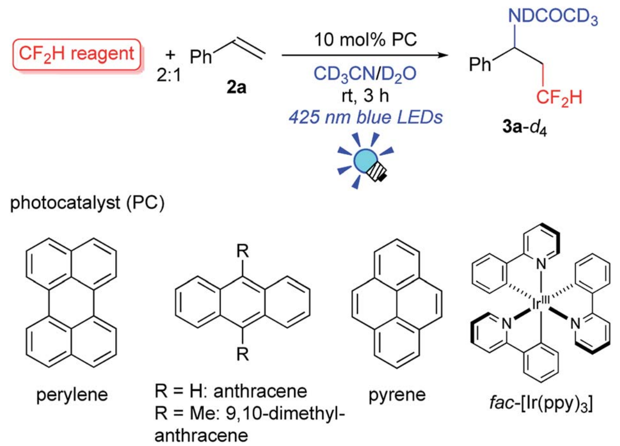
Furthermore, the reactions of neutral halogen-free sulfonyl derivatives (**D** and **E**) and sulfonium reagent **G** were conducted under optimized conditions (entries 9–11). It should be noted that the sulfonium reagents (**1** and **G**) are superior to **D** and **E** in this photocatalytic reaction. The sulfonium reagent **G** also served as an effective CF_2H 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-CF_2H 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 CF_2H–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 (BF_4 anion: omitted) of **1**.

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



Entry	CF_2H reagent	PC	λ_{max}, nm	Yield of **3a**-d_4[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**	*fac*-[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 N_2 atmosphere and irradiation of 425 nm blue LEDs at room temperature using the photocatalyst (2.5 μmol), CF_2H reagent (50 μmol), **2a** (25 μmol), and CD_3CN (0.50 mL: containing 25 μmol of D_2O) in an NMR tube. [b] Yields were determined by ^1H NMR spectroscopy using $SiEt_4$ as an internal standard. [c] A 71% NMR yield of **3a**-d_4 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.

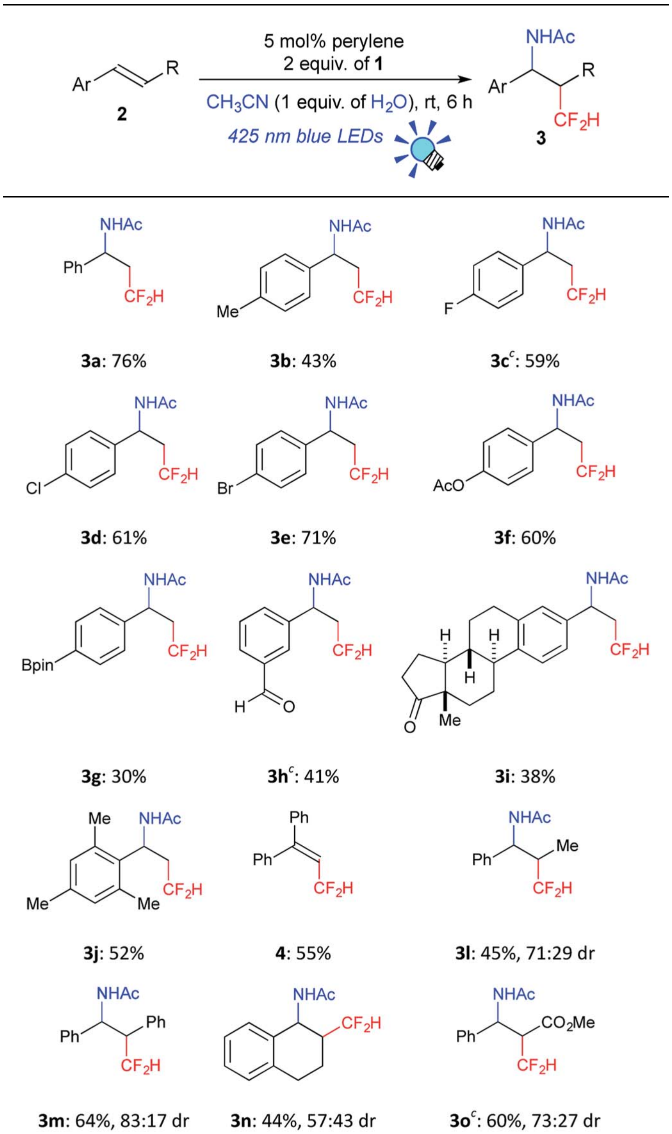
trans-stilbene (**2m**), and 1,2-dihydronaphthalene (**2n**) provided the CF_2H-substituted amino products (**3l–n**) in 44–64% yields but as mixtures of diastereomers. Remarkably, cinnamic acid ester (**2o**) could also be used for this transformation, resulting in the production of a CF_2H-substituted β-amino acid derivative (**3o**: 60%). These results showed that this metal-free photocatalytic system with the CF_2H reagent **1** is useful for regioselective and simultaneous construction of C(sp^3)–CF_2H and C(sp^3)–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 CF_3SO_2Cl to give the product **6** in a 57% yield.[21]

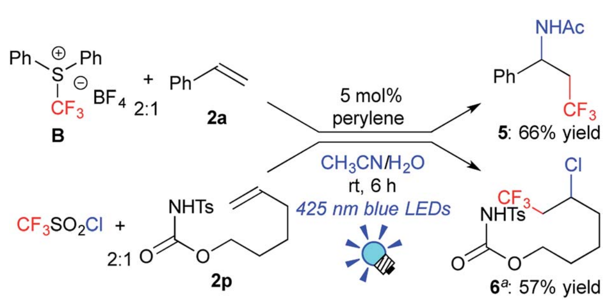
To gain insight into the reaction mechanism we conducted some experiments. The reaction of 1-phenyl-2-(1-phenylethenyl)cyclopropane (**2q**) afforded the difluoromethylated, ring-opened product **7** (23% yield), indicating the involvement of radical processes in the photocatalytic reaction (Scheme 3). 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 CF_2H reagent **1** to form the difluoromethyl radical $^{\bullet}CF_2H$ *via* C–S bond cleavage, and the radical cation of perylene ([perylene]$^{\bullet+}$). 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 $^{\bullet}CF_2H$ radical reacts with alkene **2** to form the adduct **8**, which is oxidized by [perylene]$^{\bullet+}$ to provide the carbocationic intermediate **8**$^+$. Subsequent Ritter amination[22] of **8**$^+$ with CH_3CN/H_2O affords the amino-difluoromethylated product **3**. When an α-substituted styrene **2k** is used as a substrate, deprotonation of **8**$^+$ gives the CF_2H–alkene **4**.

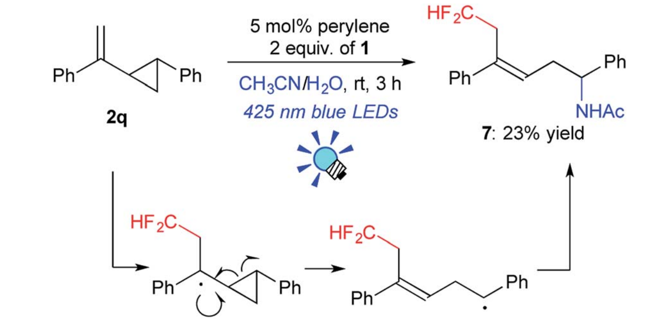
Table 2 Scope of the perylene-catalyzed amino-difluoromethylation of alkenes[ab]



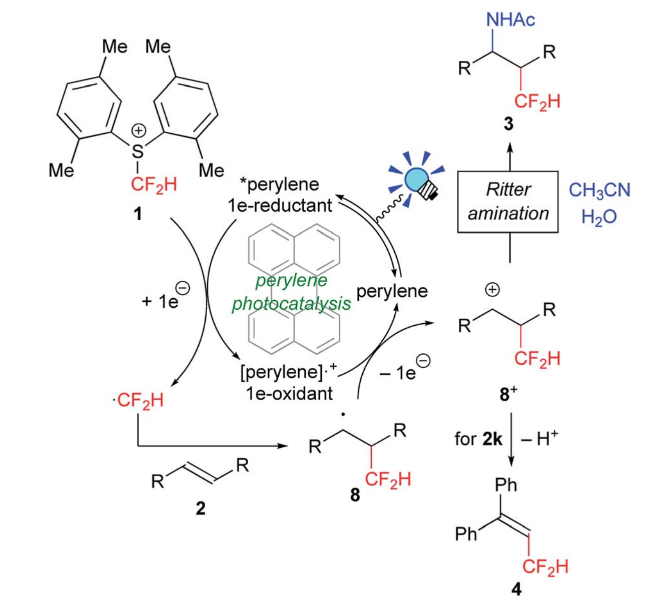
[a] For detailed reaction conditions, see the ESI.† [b] Yields of the isolated products are lower than those before purification. The purification processes decreased the isolated yields. The diastereomer ratios (dr) were determined using ^{1}H NMR spectra of crude reaction mixtures. [c] 12 h. Ac = acetyl,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



Scheme 2 Perylene-catalyzed trifluoromethylation. [a]Anhydrous CH_3CN 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-CF_2H-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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Notes and references

1 (*a*) *Fluorine in Medicinal Chemistry and Chemical Biology*, ed. I. Ojima, Wiley-Blackwell, Chichester, 2009; (*b*) N. A. J. Meanwell, *Med. Chem.*, 2011, **54**, 2529; (*c*) *Modern Fluoroorganic Chemistry*, ed. P. Kirsch, Wiley-VCH, Weinheim, 2013.

2 For recent selected reviews on catalytic trifluoromethylation, see: (*a*) A. Studer, *Angew. Chem., Int. Ed.*, 2012, **51**, 8950; (*b*) H. Egami and M. Sodeoka, *Angew. Chem., Int. Ed.*, 2014, **53**, 8294; (*c*) J. Charpentier, N. Früh and A. Togni, *Chem. Rev.*, 2015, **115**, 650; (*d*) C. Alonso, E. M. de Marigorta, G. Rubiales and F. Palacios, *Chem. Rev.*, 2015, **115**, 1847.

3 (*a*) J. Hu, W. Zhang and F. Wang, *Chem. Commun.*, 2009, 7465; (*b*) M.-C. Belhomme, T. Besset, T. Poisson and X. Pannecoucke, *Chem.–Eur. J.*, 2015, **21**, 12836; (*c*) J. Rong, C. Ni and J. Hu, *Asian J. Org. Chem.*, 2017, **6**, 139.

4 (*a*) T. Koike and M. Akita, *Top. Catal.*, 2014, **57**, 967; (*b*) S. Barata-Vallejo, S. M. Bonsei and A. Postigo, *Org. Biomol. Chem.*, 2015, **13**, 11153; (*c*) X. Pan, H. Xia and J. Wu, *Org. Chem. Front.*, 2016, **3**, 1163; (*d*) T. Chatterjee, N. Iqbal, Y. You and E. J. Cho, *Acc. Chem. Res.*, 2016, **49**, 2284; (*e*) T. Koike and M. Akita, *Acc. Chem. Res.*, 2016, **49**, 1937.

5 T. Umemoto and S. Ishihara, *J. Am. Chem. Soc.*, 1993, **115**, 2156–2164.

6 (*a*) V. V. Lyalin, V. V. Orda, L. A. Alekseeva and L. M. Yagupolskii, *Zh. Org. Khim.*, 1984, **20**, 115; (*b*) J.-J. Yang, R. L. Kirchmeier and J. M. Shreeve, *J. Org. Chem.*, 1998, **63**, 2656.

7 (*a*) Y. Yasu, T. Koike and M. Akita, *Angew. Chem., Int. Ed.*, 2012, **51**, 9567; (*b*) Y. Yasu, T. Koike and M. Akita, *Org. Lett.*, 2013, **15**, 2136; (*c*) N. Noto, K. Miyazawa, T. Koike and M. Akita, *Org. Lett.*, 2015, **17**, 3710; (*d*) R. Tomita, T. Koike and M. Akita, *Angew. Chem., Int. Ed.*, 2015, **54**, 12923.

8 M. Li, Y. Wang, X.-S. Xue and J.-P. Cheng, *Asian J. Org. Chem.*, 2017, **6**, 235.

9 For selected examples of photocatalytic incorporation of the CF_2H group, see: (*a*) X.-J. Tang and W. R. Dolbier Jr, *Angew. Chem., Int. Ed.*, 2015, **54**, 4246; (*b*) Z. Zhang, X. Tang, C. S. Thomoson and W. R. Dolbier Jr, *Org. Lett.*, 2015, **17**, 3528; (*c*) W. Fu, X. Han, M. Zhu, C. Xu, Z. Wang, B. Ji, X.-Q. Hao and M.-P. Song, *Chem. Commun.*, 2016, **52**, 13413; (*d*) Q.-Y. Lin, X.-H. Xu, K. Zhang and F.-L. Qing, *Angew. Chem., Int. Ed.*, 2016, **55**, 1479; (*e*) J. Rong, L. Deng, P. Tan, C. Ni, Y. Gu and J. Hu, *Angew. Chem., Int. Ed.*, 2016, **55**, 2743; (*f*) Y. Arai, R. Tomita, G. Ando, T. Koike and M. Akita, *Chem.–Eur. J.*, 2016, **22**, 1262; (*g*) Q.-Y. Lin, Y. Ran, X.-H. Xu and F.-L. Qing, *Org. Lett.*, 2016, **18**, 2419.

10 E. Nakamura and K. Sato, *Nat. Mater.*, 2011, **10**, 158.

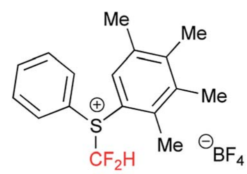
11 (*a*) D. Ravelli, M. Fagnoni and A. Albini, *Chem. Soc. Rev.*, 2013, **42**, 97; (*b*) S. Fukuzumi and K. Ohkubo, *Chem. Sci.*, 2013, **4**, 561; (*c*) D. P. Hari and B. König, *Chem. Commun.*, 2014, **50**, 6688; (*d*) N. A. Romero and D. A. Nicewicz, *Chem. Rev.*, 2016, **116**, 10075.

12 I. Ghosh, T. Ghosh, J. I. Bardagi and B. König, *Science*, 2014, **346**, 725.

13 (*a*) N. J. Treat, H. Sprafke, J. W. Kramer, P. G. Clark, B. E. Barton, J. R. de Alaniz, B. P. Fors and C. J. Hawker, *J. Am. Chem. Soc.*, 2014, **136**, 16096; (*b*) J. C. Theriot, C.-H. Lim, H. Yang, M. D. Ryan, C. B. Musgrave and G. M. Miyake, *Science*, 2016, **352**, 1082.

14 (*a*) S. A. Ruetten and J. K. Thomas, *J. Phys. Chem. B*, 1998, **102**, 598; (*b*) C. Koper, M. Sarobe and L. W. Jenneskens, *Phys. Chem. Chem. Phys.*, 2004, **6**, 319; (*c*) *Molecular Fluorescence*, ed. B. Valeur and M. N. Berberan-Santos, Wiley-VCH, Weinheim, 2012.

15 G. K. S. Prakash, C. Weber, S. Chacko and G. A. Olah, *Org. Lett.*, 2007, **9**, 1863.



G

16 V. P. Mehta and M. F. Greaney, *Org. Lett.*, 2013, **15**, 5036.

17 CCDC 1533276 for **1** and CCDC 1533274 for **3c** contain the supplementary crystallographic data, respectively†

18 C. Ni, J. Liu, L. Zhang and J. Hu, *Angew. Chem., Int. Ed.*, 2007, **46**, 786. We conducted deprotection of the acetyl group in the amino-difluoromethylated product **3e** to give the corresponding primary amine with the CF_2H group (see the ESI†).

19 L. Flamigni, A. Barbieri, C. Sabatini, B. Ventura and F. Barigelletti, *Top. Curr. Chem.*, 2007, **281**, 143.

20 (*a*) G. M. Miyake and J. C. Theriot, *Macromolecules*, 2014, **47**, 8255; (*b*) S. Okamoto, K. Kojiyama, H. Tsujioka and A. Sudo, *Chem. Commun.*, 2016, **52**, 11339.

21 For chlorotrifluoromethylation mediated by a Ru photocatalyst, see: S. H. Oh, Y. R. Malpani, N. Ha, Y.-S. Jung and S. B. Han, *Org. Lett.*, 2014, **16**, 1310.

22 J. J. Ritter and P. P. Minieri, *J. Am. Chem. Soc.*, 1948, **70**, 4045.