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Naoki Noto, Takashi Koike, and Munetaka Akita

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Visible Light-Triggered Monofluoromethylation of Alkenes by Strongly Reducing 1,4-Bis(diphenylamino)naphthalene Photoredox Catalysis

Naoki Noto,‡ Takashi Koike,*†,‡ Munetaka Akita*†,‡

†Laboratory for Chemistry and Life Science, Institute of Innovative Research, ‡School of Materials and Chemical Technology, Tokyo Institute of Technology, R1-27, 4259 Nagatsuta-cho, Midori-ku, Yokohama 226-8503, Japan.

ABSTRACT: Monofluoromethyl (CH_2F) radical can be easily generated from a sulfoximine-based precursor (CH_2F-S(=O)(=NTs)-Ph) by the action of visible light metal-free photoredox catalysis with readily accessible 1,4-bis(diphenylamino)naphthalene. The catalyst design based on the high excitation energy ($E_{0,0}$) and interchromophoric conjugation features a strong reducing power and a high quantum yield of emission of the photocatalyst. In addition, their photophysical properties are preserved in various polar solvents. The present system is amenable to oxy-monofluoromethylation of alkenes with high functional-group tolerance, *i.e.*, single-step synthesis of γ-fluoroalcohol scaffolds from various alkenes. Applications to late-stage functionalization of potentially bioactive molecules are also shown.

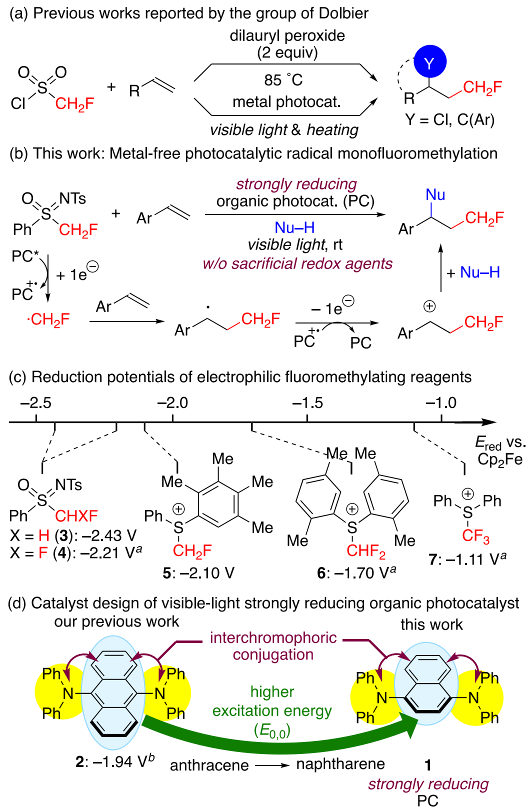
photoredox catalysis, organic photocatalyst, monofluoromethylation, radical reaction, alkene difunctionalization.

Development of methodologies for synthesis of organofluorine compounds attracts increasing attention of synthetic chemists because of their unique properties as pharmaceuticals, agrochemicals, and functional materials.[1] Recently, various methods for fluorination and introduction of fluorinated organic units have been developed.[2] However, compared to a large number of successful examples for tri- and di-fluoromethylation reactions, strategies for direct incorporation of a monofluoromethyl (CH_2F) group into carbon skeletons, *i.e.*, fluorinative homologation, are still underdeveloped.[3,4] In particular, monofluoromethylation of alkenes is limited to the two types of radical reactions with CH_2FSO_2Cl reported by the group of Dolbier, and they require harsh conditions or a stoichiometric amount of a peroxide, leading to halo- and intramolecular carbo-monofluoromethylation (Scheme 1a).[4]

For the past several years, our group has revealed that a combination of photoredox catalysis and shelf-stable electrophilic fluoroalkylating reagents such as sulfonium- and sulfoximine-based tri- and di-fluoromethylating reagents (**4**, **6**, **7**) is a reliable way for fluoroalkylation of unsaturated carbon–carbon bonds.[5] This catalytic system is triggered by 1e-reduction of the electrophilic reagents by the excited photocatalyst (PC*). Finally, unsaturated bonds are functionalized with fluoroalkyl and nucleophilic groups to furnish various difunctionalized products bearing a fluoroalkyl group under mild conditions without sacrificial redox agents. In the case of monofluoromethylation, single-step synthesis of various γ-fluoro substiuted products from alkenes is enabled, which are not always easy to be accessed by simple fluorination.

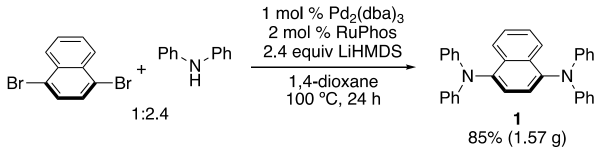
Herein we disclose *photocatalytic monofluoromethylative difunctionalization of alkenes under mild and metal-free conditions* (Scheme 1b). A major obstacle of reductive monofluoromethylation is due to the reduction potentials of the sulfonium-

Scheme 1. Strategy for Radical Monofluoromethylation of Alkenes by Organic Photoredox Catalysis.



[a]The potentials are those reported in the literatures.[5b,c,e,6] [b]The reducing power is that reported in the literature.[8]

Scheme 2. Gram-Scale Synthesis of Photocatalyst 1



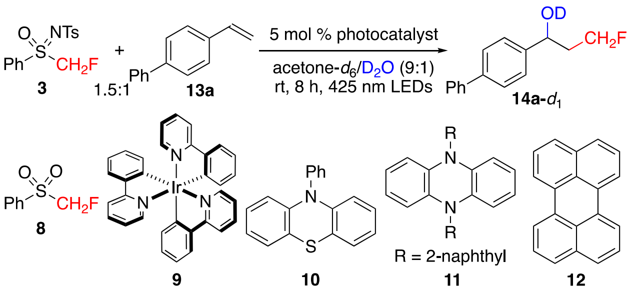
and sulfoximine-based CH_2F precursors (**3**, **5**), which are significantly lower than those of the corresponding di- and tri-fluoromethylating reagents (**4**, **6**, **7**) to make the 1e-reduction of them difficult (Scheme 1c).[6] Therefore, development of a strongly reducing catalyst is essential to achieve the reaction.

Most of the previous photoredox catalysts have relied on use of their triplet excited species with longer lifetimes because they may have more chances to interact with reactants.[7] But the triplet species in general show the significant downward trend in energy compared to the singlet species, resulting in disadvantage as reductants. To explore a strongly reducing photocatalyst, we turned our attention to energetically favorable design of molecules.

Recently, we reported that 9,10-bis(diphenylamino)anthracene **2** serves as an efficient organophotocatalyst for radical fluoroalkylative difunctionalization under visible light irradiation.[8] Catalyst **2** exhibits a visible light absorption band and excellent emission properties derived from interchromophoric conjugation,[9] but it is not strong enough to reduce the CH_2F precursors (**3**, **5**) (Scheme 1c and 1d). The reducing power of a catalyst in the photo-excited state (E^*_{ox}) can be estimated according to the equation, $E^*_{ox} = E_{ox} - E_{0,0}$ (E_{ox}: oxidation potential in the ground state, $E_{0,0}$: excitation energy).[10] In addition, emission energy (λ_{em}) is strongly connected to excitation energy ($E_{0,0} \approx hc/\lambda_{em}$, h: Planck constant, c: speed of light). In brief, naphthalene derivatives with higher emission energy are expected to show stronger reducing power than anthracene derivatives (emission (λ_{em}): λ_{em}(naphthalene) = 338 nm, λ_{em}(anthracene) = 403 nm).[11] Therefore, we designed 1,4-bis(diphenylamino)naphthalene **1** (Scheme 1d), which was easily prepared in a good yield and in a gram scale by the palladium-catalyzed Buchwald-Hartwig amination reaction (Scheme 2: 85%, 1.57 g).[12]

We commenced hydroxy-monofluoromethylation of alkenes with sulfoximine-based CH_2F-reagent **3**[13] (E_{red} = –2.43 V) in the presence of photocatalyst **1**. To our delight, visible light irradiation (λ = 425 nm) of a mixture of *p*-vinylbiphenyl **13a** and 1.5 equivalents of **3** dissolved in acetone-d_6/D_2O in the presence of 5 mol % of **1** afforded the expected monofluoromethylated alcohol **14a**-d_1 in an 83% NMR yield (Table 1, entry 1). Then, we scrutinized the reaction system. For the CH_2F reagent, the sulfonium-type reagent **5**[3b] (E_{red} = –2.10 V) afforded **14a**-d_1 in a lower yield because a considerable amount of ArS–CH_2F was formed from **5** through cleavage of the S–Ar bonds rather than the desired S–CH_2F bond (entry 2, see the Supporting Information). The sulfone-type reagent **8**[14] turned out to be sluggish presumably due to its very low reduction potential (E_{red} = –2.64 V) (entry 3). For the photocatalyst, several strongly reducing ones such as *fac*-[Ir(ppy)$_3$] (**9**), phenothiazine (**10**)[15] and 5,10-dihydrophenazine (**11**) derivatives,[16] perylene (**12**),[5e,17] and **2**[8] were examined, but they turned out to be much less effective than **1** (entries 4–9). The higher catalytic performance of **1** may be ascribed to compatibility of the stronger reducing power (E^*_{ox}), the visible light absorption ability, and its robustness.

Table 1. Optimization of Photocatalytic Hydroxy-Monofluoromethylation of *p*-Vinylbiphenyl (13a)



Entry	Photocat.	CH_2F-reagent	Yield of **14a**-d_1,%
1	**1**	**3**	83
2	**1**	**5**	36
3	**1**	**8**	<5
4	**2**	**3**	0

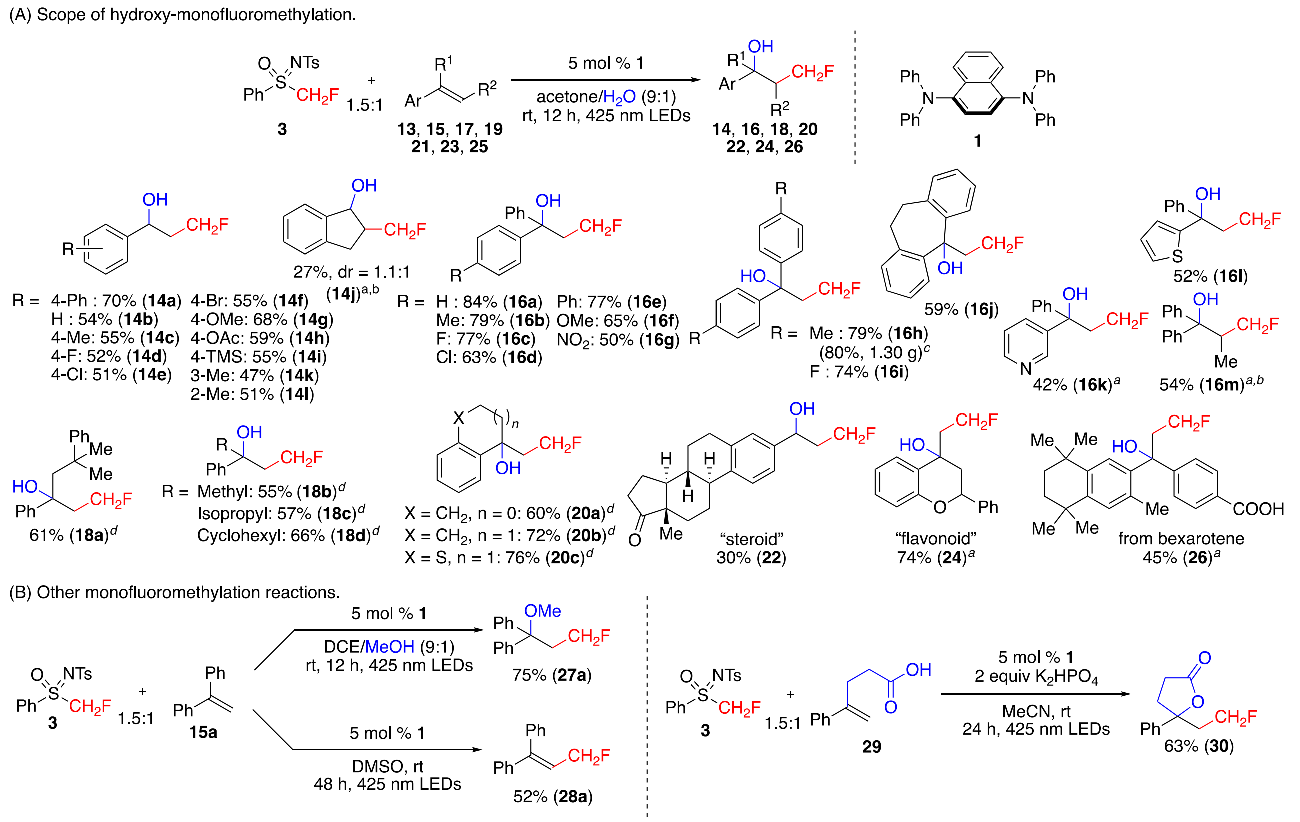
5	**9** (E^*_{ox} = –1.98 V)	3	29
6	**10** (E^*_{ox} = –2.52 V)^a	3	12
7^b	**10**	3	19
8	**11** (E^*_{ox} = –2.10 V)^a	3	6
9	**12** (E^*_{ox} = –2.23 V)^a	3	9
10	-	3	0
11^c	**1**	3	0
12^d	**1**	3	0
13^e	**1**	3	53
14^f	**1**	3	77

Yields were determined by ^{1}H NMR spectroscopy using tetraethylsilane as an internal standard. Typically, the reaction was performed with *p*-vinylbiphenyl **13a** (0.0250 mmol), **3** (0.0375 mmol), and photoredox catalyst (1.25 µmol) in a mixture of acetone-d_6 (0.45 mL) and D_2O (0.05 mL) under irradiation with blue LEDs (λ = 425 nm) at room temperature. The reducing powers (E^*_{ox} V vs. Cp_2Fe) are values reported in the literatures except **9**. [a][E^*_{ox} vs. Cp_2Fe] = [E^*_{ox} vs. SCE] – 0.41.[15b,16b,5e] [b]LED (λ = 380 nm) was used. [c]Reaction was performed in the dark. [d]TEMPO (3 equiv.) was added. [e]Reaction was performed under air. [f]1,3,5,7-Cyclooctatetraene (1 equiv.) was added.

Notably, the catalytic activity of **1** is drastically changed compared to **2** by the alternation of the anthracene core to naphthalene. Visible light irradiation and the photoredox catalyst are essential to the reaction (entries 10 and 11). In the presence of TEMPO, TEMPO-CH_2F was formed instead of **14a**-d_1 (entry 12). In the presence of triplet quenchers such as O_2 and 1,3,5,7-cyclooctatetraene, the reaction was retarded but afforded **14a**-d_1 in 53% and 77% NMR yields, respectively (entries 13 and14).

With the optimized reaction conditions in hand, we next examined the reactions of various alkenes (Chart 1A). Styrene derivatives with a variety of functional groups such as Ph, Me, F, Cl, Br, OMe, OAc and TMS groups (**13a**–**13i**, **13k**, **13l**) and indene **13j** afforded the corresponding 3-fluoropropanols **14a**–**14l** in 27–70% yields. Unfortunately, aliphatic alkenes such as 1-octene and 1,1-dicyclohexylethene did not provide the corresponding products under the present conditions. *gem*-Diarylalkenes (**15a**–**15m**) also afforded the corresponding alcohols **16a**–**16m** in moderate to good yields (42–84%).

Chart 1. Scope of the Present Photocatalytic Monofluoromethylation of Alkenes

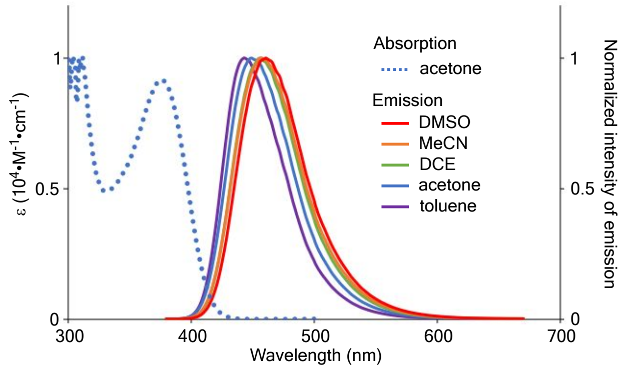


For the details of the conditions, see the Supporting Information. DCE = 1,2-dichloroethane. [a]Reaction time = 24 h. [b]8 mol% of **1** was used. [c]Gram-scale synthesis. [d]Reaction time = 18 h.

It is noteworthy that functionalities such as NO_2 (**16g**: 50%), pyridyl (**16k**: 42%), and thienyl (**16l**: 52%) groups were also tolerated with the reaction. In addition, the gram-scale synthesis of **16h** was performed in an 80% yield (1.30 g), demonstrating the scalability of the present organic photocatalytic system. The reactions of α-alkylstyrene derivatives (**17a**–**17d**) and methylidene substrates (**19a**–**19c**) were relatively slow but afforded the products **18a**–**18d** and **20a**–**20c** in moderate yields (55–76%) after prolonged irradiation. Furthermore, functionalization of potentially bioactive alkenes such as steroid and flavonoid was also possible (**22**: 30%, **24**: 74%). Notably, a CH$_2$F group was successfully incorporated into an anti-cancer drug, bexarotene (**26**: 45%). In addition to the hydroxy-monofluoromethylation mentioned above, methoxy- (**27a**: 75%) and dehydro-monofluoromethylation (**28a**: 52%), and intramolecular monofluoromethylative lactonization (**30**: 63%) were also achieved (Chart 1B) in various solvents such as DCE, MeCN and DMSO.

To obtain insights into the efficient catalytic ability of **1**, its photophysical and electrochemical properties were examined (Figure 1a). Catalyst **1** (in acetone) shows an absorption band extended to the visible region (λ_{abs} = 375 nm) and a blue emission (λ_{em} = 449 nm) with a very high quantum yield of fluorescence (Φ = 0.99), whereas an excited state lifetime of **1** is very short (τ = 9 ns), indicating that the photo-excited species with a nanosecond span of lifetime causes efficient photoredox reaction. According to DFT and TD-DFT calculations, the visible absorption band is assigned to the HOMO–LUMO transition (Figure 1b). The distributions of the HOMO and LUMO partially overlap with each other. Delocalization of the HOMO over the whole molecule are caused by interchromophoric conjugation derived from the distorted (neither coplanar nor orthogonal) arrangements around the amino group with respect to the naphthalene core and phenyl groups. These features of the orbitals arouse the efficient intramolecular charge transfer (CT), leading to the characteristic extension of the absorption band to the visible region and the high quantum yield.[9]

(a) UV-vis and fluorescence spectra.



(b) Frontier orbitals & electronic transition around visible region

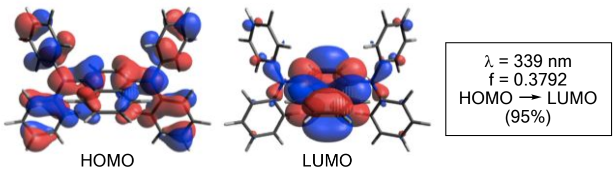


Figure 1. Photophysical Data for **1**. (a) UV-vis (in acetone) and fluorescence spectra (in various solvents). (b) Frontier orbitals & electronic transition calculated by DFT and TD-DFT calculations.

In contrast, the HOMOs and LUMOs of the previously reported strongly reducing organic photoredox catalysts such as **11** and the carbazole derivative (**31**)[18] are rather localized on the donor and acceptor moieties, respectively, and thus their distributions are separated. The separated orbital distributions of them might be connected to the long-lived excited states (**11**: 4.3 μs in DMA,[16b] **31**: 250 ns in THF[18]) but weaker absorption bands derived from intramolecular CT and lower quantum yields of emission. Furthermore, it is noteworthy that the photophysical properties of **1** is not significantly affected by solvents (Figure 1a). The difference between the emission maxima ($\Delta\lambda_{em}$) of **1** observed in toluene and DMSO is only 18 nm. Additionally, **1** also maintains the excited state lifetime (τ = 8–10 ns) and the quantum yield (Φ = 0.94–0.99) (see the Supporting Information). In contrast, for organic photocatalysts with the separated frontier orbital distributions such as **11** and **31**, large bathochromic shifts of emission ($\Delta\lambda_{em}$ = 100–200 nm)[16c,18] induced by solvents were reported, which are associated with decrease of the reducing power (E^*_{ox}).[10]

A cyclic voltammogram of **1** contains two reversible redox waves. The first oxidation potential determined by DPV analysis (E_{ox} = +0.36 V, see the Supporting Information) is comparable to those of the previously reported strongly reducing catalysts (**9**,[10,19] **10**[15b]). The reducing powers (E^*_{ox} vs. Cp$_2$Fe) of **1** in the excited state in various solvent are estimated as follows: −2.40 V (in acetone), −2.41 V (in 1,2-dichloroethane), −2.35 V (in acetonitrile), and −2.30 V (in DMSO).[10] These preserved strong reducing powers due to the insensitivity of the emission to solvents mentioned above make monofluoromethylation in various polar solvents successful.

Fluorescence quenching experiments revealed that **1*** was not quenched by alkene **13a** but by **3** (see the Supporting Information). Together with the result of the radical trapping experiment by TEMPO (Table 1, entry 12), the reductive ·CH$_2$F radical generation from **3** should trigger the reaction. In addition, from a result of the quantum yield measurement of the reaction (Φ = 8%), contribution of the radical chain mechanism in this reaction turned out to be minor component (see the Supporting Information). The high quantum yield of fluorescence implies that a considerable amount of the active excited species of **1** is allowed to take part in the reaction. The combination of (i) the strong reducing power caused by the high emission energy level and (ii) the high fluorescent quantum yield of **1** may compensate its short excited state lifetime.

In conclusion, we have developed a strongly reducing photoredox system with 1,4-bis(diphenylamino)naphthalene catalyst **1**, which is easily accessible and shelf-stable. The present system promotes metal-free hydroxy-monofluoromethylation of alkenes with the easy-to-handle sulfoximine-based CH$_2$F reagent under mild conditions, leading to facile synthesis of γ-fluoroalcohols from alkenes. Moreover, extension to other monofluoromethylation of alkenes is feasible due to the retention of the high reducing power in various solvents. The present work offers a new strategy for development of visible light organic photocatalysts with high reducing power but short excited state lifetime, which are useful for reactions elusive by the conventional Ir photocatalyst. Further development of reactions which require the higher reducing power is currently under way in our laboratory.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures, characterization, crystallographic data of **1**, photo- and electro-chemical experiments, control experiments, DFT calculations and ^{1}H, ^{13}C, and ^{19}F NMR spectra (PDF)

AUTHOR INFORMATION

Corresponding Authors

*E-mail: koike.t.ad@m.titech.ac.jp.
*E-mail: makita@res.titech.ac.jp.

Notes

The authors declare no competing financial interest.

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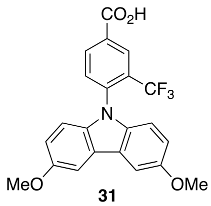

31

(19) The E^*_{ox} value of **9** (vs. Cp_2Fe in acetone) was determined to be −1.98 V on the basis of E_{ox} = 0.40 V and λ_{em} = 522 nm.

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