Metal-Free Direct C–H Perfluoroalkylation of Arenes and Heteroarenes Using a Photoredox Organocatalyst

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Abstract: We report the visible-light-induced trifluoromethylation of arenes and heteroarenes using sodium trifluoromethanesulfinate catalyzed by anthraquinone-2-carboxylic acid. This reaction is a metal-free trifluoromethylation of arenes and heteroarenes catalyzed by a photoredox organocatalyst. Perfluoroalkylated arenes were also produced using sodium perfluoroalkylsulfinates.

Keywords: C–H activation; electron transfer; organocatalysis; photochemistry; radical reactions

The introduction of a CF₃ group can change the physical properties of a compound, such as solubility and lipophilicity, and gives the compound better membrane permeability and increased bioavailability than its non-fluorinated analogues.^[1] Therefore, the development of new methods for the synthesis of compounds with a CF₃ group is one of the most important areas of research in organic synthesis. Thus, many studies have been published that investigate various methods of trifluoromethylation. Although cross-coupling reactions catalyzed by transition metals have been reliable methods for the synthesis of trifluoromethylated arenes, they require prefunctionalized arenes incorporating halides, boronic acids, or directing groups.^[2] Thus, the direct radical trifluoromethylation of arene C-H moieties has received much attention,^[3] and useful methods include CF_3I/Δ ,^[4] $CF_3I/$ uon,⁽⁻⁾ and userul methods include CF_3I/Δ ,⁽⁴⁾ $CF_3I/$ FeSO₄/H₂O₂/DMSO,^[5] $CF_3Br/Na_2S_2O_4$,^[6] $(CF_3)_2Te$,^[7] $(CF_3CO_2)_2$,^[8] CF_3CO_2H/XeF_2 ,^[9] $CF_3SO_2Na/Cu(OTf)_2/$ *t*-BuOOH,^[10] CF_3SO_2Na/t -BuOOH,^[11] $(CF_3SO_2)_2Zn/t$ -BuOOH,^[12] $CF_3SO_2CI/[RuCl_2(PPh)_3]$,^[13] $CF_3SiMe_3/$ Ag(OTf)/KF,^[14] $CF_3I(III)/MeReO_3$,^[15] and $CF_3SiMe_3/$ PhI(OAc)₂/BQ.^[16] These methods are advantageous for the synthesis of trifluoromethylated for the synthesis of trifluoromethylated compounds because prefunctionalized substrates are not required;

however, these methods do require transition metal catalysts, stoichiometric reagents, highly reactive reagents, potentially explosive reagents, or harsh reaction conditions [Scheme 1, Eq. (1)].

On the other hand, light is an important factor in many reactions; therefore, it can be considered as a type of reagent. Because this clean reagent exudes no residues and has neither shape nor weight, it is an important component in developing environmentally benign processes. Consequently, photoinduced radical trifluoromethylations have also been reported.^[17] In 2011, MacMillan's group showed an impressive direct trifluoromethylation through a radical-mediated mechanism using polypyridyl organometallic complexes such as Ru(phen)₃Cl₂ as a photoredoxcatalyst and CF₃SO₂Cl as a source of the trifluoromethyl

Previous work

without photo-irradiation

$$R_{ll}^{II} \xrightarrow{H} R_{ll}^{II} \xrightarrow{H} R_{ll}^{II} \xrightarrow{(1)} R_{ll}^{II} \xrightarrow{(1)} R_{ll}^{II} \xrightarrow{(1)} (1)$$

photoredox metal catalysis

$$R_{\overline{U}}^{\underline{f_1}} \xrightarrow{H} \underbrace{\text{transition metal catalyst}}_{H_{\overline{U}}} R_{\overline{U}}^{\underline{f_1}} \xrightarrow{CF_3} (2)$$

This work

photoredox organo catalysis

$$R_{I}^{f, hv}(VIS)$$

$$R_{I}^{fSO_2Na}$$

$$cat. AQN-2-CO_2H$$

$$R_{I}^{f} = CF_3, C_2F_5$$

$$R_{I}^{f} = CF_{13}, C_8F_{17}$$

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Scheme 1. Trifluoromethylation of arenes and heteroarenes.

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Table 1. Study of the reaction conditions.^[a]



Entry	Solvent	Catalyst	Additive	Yield $[\%]^{[b]}$ (2-CF ₃ , 4-CF ₃)
1	CH ₃ CN	MB	TFA	25 (8, 17)
2	CH ₃ CN	9,10-DCA	TFA	61 (21, 40)
3	CH ₃ CN	Acid Red 94	TFA	36 (11, 25)
4	CH ₃ CN	AQN	TFA	73 (21, 52)
5	CH ₃ CN	AQN-2-CO ₂ H	TFA	79 (25, 54)
6	EtOAc	AQN-2-CO ₂ H	TFA	46 (14, 32)
7	acetone	AQN-2-CO ₂ H	TFA	45 (15, 30)
8	hexane	AQN-2-CO ₂ H	TFA	0
9	MeOH	AQN-2-CO ₂ H	TFA	9 (3, 6)
10	CH ₃ CN	AQN-2-CO ₂ H	AcOH	60 (20, 40)
11	CH ₃ CN	AQN-2-CO ₂ H	H_2SO_4	70 (21, 49)
12	CH ₃ CN	AQN-2-CO ₂ H	AlCl ₃	56 (17, 39)
13	CH ₃ CN	AQN-2-CO ₂ H	_	49 (15, 34)
14	CH ₃ CN	_	TFA	0
15 ^[c]	CH ₃ CN	AQN-2-CO ₂ H	TFA	0
16 ^[d]	CH ₃ CN	AQN-2-CO ₂ H	TFA	0
17 ^[e]	CH ₃ CN	AQN-2-CO ₂ H	TFA	43 (14, 29)
18 ^[f]	CH ₃ CN	AQN-2-CO ₂ H	TFA	84 (28, 56)
19 ^[g]	CH ₃ CN	AQN-2-CO ₂ H	TFA	71 (22, 49)
20 ^[h]	CH ₃ CN	AQN-2-CO ₂ H	TFA	0

[a] Reaction conditions: 1a (0.15 mmol), CF₃SO₂Na (4.0 equiv.), catalyst (0.05 equiv.), and additive (0.06 equiv.) in solvent (3 mL) under an argon atmosphere were stirred and irradiated with four fluorescent lamps at room temperature.
 [b] Violds datamined by ¹H NMP

^[b] Yields determined by ¹H NMR.

^[c] The reaction was carried out in the dark.

^[d] Galvinoxyl (1 equiv.) was added.

^[e] The reaction was carried out for 10 h.

^[f] The reaction was carried out for 30 h.

^[g] The reaction was carried out with one fluorescent lamp for 30 h.

^[h] CF₃SO₂Cl was used instead of CF₃SO₂Na.

group under visible light irradiation at room temperature. Notably, this reaction uses no potentially explosive oxidant [Scheme 1, Eq. (2)].^[18a] However, to the best of our knowledge, the metal-free photoredox trifluoromethylation of arenes and heteroarenes *via* a trifluoromethyl radical intermediate has not been reported.^[19] In the course of our study with organophotocatalysts,^[20] we examined metal-free photoredox reactions and successfully found that using CF₃SO₂Na as a source of the trifluoromethyl group and a catalytic amount of anthraquinone-2-carboxylic acid (AQN-2-CO₂H) allowed us to perform the direct trifluorome-

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thylation of arenes and heteroarenes under visible light irradiation from a general-purpose fluorescent lamp.

On the other hand, fluorous tag techniques have been extensively developed in the field of organic chemistry; however, methods for the introduction of fluorous chain groups, such as perfluoroalkyl groups, are limited on account of the specific reactivity of fluorous compounds.^[21] Therefore, the development of synthetic methods that can effectively introduce fluorous groups is highly desirable. We now report the details of a trifluoromethylation and perfluoroalkylation process catalyzed by a photoredox organocatalyst [Scheme 1, Eq. (3)].

Table 1 shows the results of an investigation of the reaction conditions for trifluoromethylation of 1,3-dimethoxybenzene (1a) under visible light irradiation from four fluorescent lamps. Among the typical photosensitizers and solvents examined (entries 1-9), we determined AQN-2-CO₂H^[22] and acetonitrile to be the most effective for this reaction (entry 5). In addition, acids accelerate the reaction rate (entries 5 and 10-13), and TFA is the most effective. However, we cannot explain yet why the addition of TFA accelerates the reaction rate. It is noted that light irradiation and AON-2-CO₂H were necessary for this reaction (entries 14 and 15). Since no product could be obtained in the presence of galvinoxyl, we believe that this reaction could proceed through a radical mechanism (entry 16). In addition, we extended the reaction time to 30 h, which gave the best result (entry 18). When the number of fluorescent lamps was reduced to one, **2a** was also obtained in good yield (entry 19). It was also noted that CF₃SO₂Cl was an inactive reagent under our conditions (entry 20).

Using the optimized reaction conditions for trifluoromethylation, the scope and limitations of the reaction were explored (Scheme 2). Electron-rich arenes gave the corresponding products in good yields (**2a**, **2b**, **2c**, **2d**, **2e**, **2f**, and **2g**). In addition, some substituted heteroarenes were also obtained in good yields (**2h**, **2i**, and **2j**). In contrast, we got trace amounts of product when benzene was used as substrate, and nitrobenzene did not react at all. For further studies, we used various sodium perfluoroalkylsulfinates and found that pentafluoroethyl (C_2F_5) and heptafluoropropyl (C_3F_7) groups could be substituted on 1,3,5-trimethoxybenzene in good yields (**2k** and **2l**). Furthermore, $C_6F_{13}SO_2Na$ and $C_8F_{17}SO_2Na$ also



reacted with **1e** to give the corresponding products in good to high yields (**2m** and **2n**).

The experimental (Figure 1) results suggest the following catalytic cycle, as shown in Scheme 3: the



Figure 1. Oxidation-reduction potential determined by cyclic voltammetry.

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Scheme 3. Plausible reaction mechanism.

ground and excited redox states of AQN, an electrontransfer mediator, are important for the formation of the electron deficient trifluoromethyl radical (CF_3), which functioned as an oxidant of the substrate and an active species for the formation of trifluoromethylarenes. The photoinduced downhill electron transfer from $CF_3SO_2^-$ to the excited state of AQN (AQN*) is expected to efficiently generate CF₃SO₂ and AQN⁻⁻ radicals on the basis of their redox potentials. Facile oxidation of AQN⁻⁻ by SO₂ produced by cleavage of CF_3SO_2 regenerates the ground state of AQN. The expectation that an electron from $CF_3SO_2^-$ is turned over during the photocatalytic electron-transfer cycle based solely on the driving force predicted by the redox potentials. At this stage, no detailed mechanistic data on the two-fold reaction of an arene with $\cdot CF_3$ are available, but it is rationally considered that a likely reaction pathway includes the radical addition of $\cdot CF_3$ to an electron-rich position of the aromatic ring, which is followed by oxidation of the generated radical 3 to cation 4 by $\cdot CF_3$ followed by deprotonation.^[23] The later reaction may be considered as a hydrogen abstraction reaction of 3 by CF_3 rather than an electron-transfer reaction facilitated by proton transfer, as is shown in Scheme 3. At present we are not able to differentiate between these two possibilities.

In conclusion, we have developed a convenient photoredox-based method for the direct trifluoromethylation of arenes and heteroarenes using an organocatalyst. This method is a metal-free, direct trifluoromethylation using a photoredox-based process under visible light irradiation. Furthermore, perfluoroalkylated arenes can also be effectively obtained under similar conditions. Therefore, this method is of great value from both green chemistry and organic synthesis perspectives because of its use of visible light irradiation and its application to the design and synthesis of compounds with trifluoromethyl groups and fluorous tags.

Experimental Section

General Procedure

TFA (0.06 equiv., 0.15 M MeCN solution) was added to a solution of substrate (0.15 mmol), CF₃SO₂Na (4 equiv.), AQN-2-CO₂H (0.05 equiv.) in MeCN (3 mL) in a Pyrex test tube. The reaction mixture under an argon balloon was stirred and irradiated externally with four of 22 W fluorescent lamps for the indicated time. Then the solution was basified with saturated aqueous NaHCO₃ and brine, the product was extracted with EtOAc and washed with brine, followed by MgSO₄ drying. The product was purified by PTLC.

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6 Metal-Free Direct C-H Perfluoroalkylation of Arenes and Heteroarenes Using a Photoredox Organocatalyst

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Ar, hv (VIS) RfSO₂Na н cat. AQN-2-CO2H, TFA MeCN $Rf = CF_3, C_2F_5$ up to 92% yield arene or heteroarene C₆F₁₃, C₈F₁₇

Rf

6