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Visible-Light Photoredox Difluoromethylation of Phenols and Thiophenols with Commercially Available Difluorobromoacetic Acid

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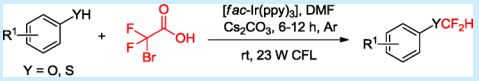
Supporting Information

ABSTRACT: A simple and efficient visible-light photoredox one-pot method for difluoromethylation of phenols and thiophenols has been developed. The protocol uses commercially available, inexpensive, and easy handling difluorobromoacetic acid as the difluoromethylating agent, and the diverse *O*- and *S*-difluoromethylated products were prepared in good yields with tolerance of many functional groups.



The discovery of new drugs with fluorine molecules has great potential because more than 20% of the pharmaceuticals and agrochemicals on the market, including a couple of top-10 drugs, are organofluorines.[1,2] Therefore, the fluorination of organic compounds has become an important strategy in drug development. Among the fluorinated molecules, difluoromethyl ethers are increasingly found in various fields.[3] Aryl difluoromethyl ethers are especially widely used as medicinally important compounds. For example, they are applied as anti-HIV agents,[4] enzyme inhibitors,[5] and antimicrobial agents.[6] Pantoprazole (Protonix) with a difluoromethyl ether as a proton-pump inhibitor is among the top 100 pharmaceuticals.[7] The most popular strategy for the synthesis of difluoromethylated products is based on the reaction of nucleophilic reagents with difluorocarbene, so organic and medicinal chemists have been devoted to explore new methods and/or reagents for generation of reactive difluorocarbene types. In the past decades, various difluorocarbene precursors such as HCF_2Cl, HCF_3, CHF_2I, $PhSO_2CF_2Cl$, $ArCOCF_2Cl$, $ClCF_2CO_2Na$, $FSO_2CF_2CO_2H$, $BrCF_2P(O)(OEt)_2$, $TMSCF_2Br$, HCF_2OTf, and $PhS(O)(NTs)CF_2H$ have been developed in the difluoromethylation of phenols[8] and thiophenols.[9] However, some drawbacks of the difluorocarbene precursors hamper their wide application such as the use of the ozone-depleting compounds,[10] difficult to handle gaseous reagents, commercially unavailable chemicals, and a requirement for harsh reaction conditions.[9g] Therefore, it is highly desirable to develop an efficient method with a broad substrate scope under relatively mild conditions by using an operationally simple and environmentally benign difluorocarbene precursor. Recently, photoredox methods with visible light as a renewable energy source have become a powerful strategy under mild conditions,[11] As part of our continuing study on the visible-light photoredox organic reactions,[12] we report herein the use of commercially available and easy handling difluorobromoacetic acid as a general difluorocarbene precursor for the difluoromethylenation of phenols and thiophenols under visible-light photocatalysis at room temperature.

At first, visible-light photoredox reaction of 2-naphthol (**1m**) with difluorobromoacetic acid (**2**) was used as the model to optimize conditions including photocatalysts, solvents, bases, and reaction time under an atmosphere of argon and irradiation of visible light with a 23 W compact fluorescent light (CFL). As shown in Table 1, three common photocatalysts, $[Ru(bpy)_3]Cl_2$ (**A**), [*fac*-Ir(ppy)$_3$] (**B**), and $[Ir(dFCF_3ppy)_2](dtbbpy)PF_6$ (**C**), were screened using DMF as the solvent and Cs_2CO_3 as the base for 12 h (entries 1−3), and [*fac*-Ir(ppy)$_3$] (**B**) provided the highest yield (entry 2). We investigated reaction time (compare entries 2, 4, and 5), and a 12 h reaction was suitable. Several solvents were tested (entries 6−9), and DMF gave the best result (compare entries 2 and 6−9). Other bases were attempted (entries 10−13), and they were inferior to Cs_2CO_3. Only a trace amount of product **3m** was observed in the absence of photocatalyst (entry 14) or visible light (entry 15). A 78% yield was obtained when two 3 W blue LEDs replaced 23 W CFL as the light source (entry 16), which showed that the reaction was performed with visible light rather than UV light.

After determination of the optimized process above, the substrate scope for the visible-light difluoromethylation of phenols with difluorobromoacetic acid (**2**) was investigated. As shown in Table 2, different phenols (**1**) were tested, and the results showed that the phenols containing electron-withdrawing groups on the aromatic rings exhibited higher reactivity than those containing electron-donating groups. *O*-Difluoromethylation of 7-hydroxycoumarin with **2** was successfully realized, and **3p** was obtained in 76% yield. We attempted visible-light-promoted coupling of 2,7-naphthalenediol with 2 equiv of **2**, and *O*,*O*′-difluoromethylation product **3q** was prepared in 89% yield. The difluoromethylation of phenols tolerated various functional groups, including C−Cl bonds (**3c** and **3d**), C−Br bonds (**3d** and **3e**), C−I bonds (**3f** and **3g**), acetyl (**3h**), cyano (**3i**), nitro (**3j** and **3k**), naphthyl (**3m** and **3n**), ether (**3o**), and ester (**3p**) groups. Interestingly, the one-pot *O*-difluoromethylation of phenols (**1**) used readily available, easy handling, and inexpensive difluorobromoacetic acid (**2**) as

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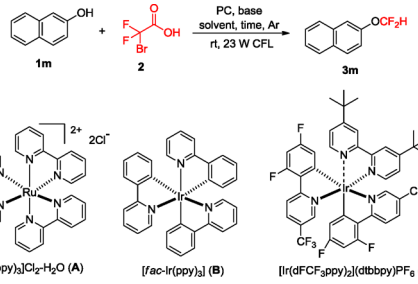
Table 1. Optimization of Conditions for Visible-Light Photoredox Reaction of 2-Naphthol (1m) with Difluorobromoacetic Acid (2)[a]



entry	PC	solvent	base	time (h)	yield[b] (%)
1	**A**	DMF	Cs_2CO_3	12	68
2	**B**	DMF	Cs_2CO_3	12	86
3	**C**	DMF	Cs_2CO_3	12	81
4	**B**	DMF	Cs_2CO_3	9	76
5	**B**	DMF	Cs_2CO_3	6	60
6	**B**	DMA	Cs_2CO_3	12	63
7	**B**	DCE	Cs_2CO_3	12	NR
8	**B**	MeCN	Cs_2CO_3	12	40
9	**B**	toluene	Cs_2CO_3	12	trace
10	**B**	DMF	K_2CO_3	12	75
11	**B**	DMF	Na_2CO_3	12	23
12	**B**	DMF	K_3PO_4	12	44
13	**B**	DMF	KOH	12	64
14[c]	-	DMF	Cs_2CO_3	12	trace
15[d]	**B**	DMF	Cs_2CO_3	12	trace
16[e]	**B**	DMF	Cs_2CO_3	24	78

[a]Reaction conditions: argon atmosphere and irradiation of visible light, photocatalyst (PC) (3 μmol), 2-naphthol (**1m**) (0.3 mmol), difluorobromoacetic acid (**2**) (0.3 mmol), solvent (2.5 mL), base (0.9 mmol), temperature (rt, ~25 °C), time (6−12 h) in a sealed Schlenk tube. [b]Isolated yield. [c]In the absence of photocatalyst. [d]The reaction was carried out in the dark. [e]The reaction was carried out under irradiation of two 3 W blue LED light bulbs. CFL = compact fluorescent light. DMA = *N*,*N*-dimethylacetamide. DCE = 1,2-dichloroethane. NR = no reaction.

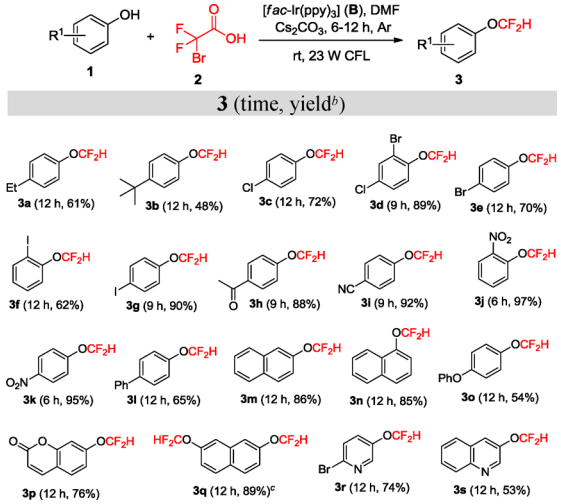
the difluoromethylating reagent, and the reaction was performed well at room temperature. Therefore, this is a convenient and practical method. *O*-Difluoromethylation of aliphatic alcohols was attempted under the present conditions, but the reaction did not work.

Reaction of [1,1′-biphenyl]-2,2′-diol (BINOL) (**1t**) with **2** under the standard conditions provided 4-fluorodinaphtho[2,1-*d*:1′,2′-*f*][1,3]dioxepine (**3t**) in 50% yield. The reaction underwent a sequential two-step process, including visible-light-promoted intermolecular *O*-monodifluoromethylation of BINOL leading to **3t′** and base-mediated intramolecular cyclization affording **3t** (Scheme 1).

Inspired by the results above, we surveyed visible-light photoredox difluoromethylation of thiophenols (**4**) under the standard conditions (Table 3), and similar results were provided as those in Table 2. Therefore, the present visible-light photoredox difluoromethylation displayed wide universality.

We explored the mechanism on the visible-light photoredox difluoromethylation of phenols (**1**) and thiophenols (**4**). After treatment of 2-naphthol (**1m**) with difluorobromoacetic acid (**2**) in the absence of photocatalyst at room temperature for 12 h followed with 1 N HCl, no product **6** was found (Scheme 2a). Meanwhile, compound **7** was prepared according to the previous procedures,[13] but decarboxylation was not performed

Table 2. Substrate Scope for the Visible-Light Photoredox Difluoromethylation of Phenols 1[a]



[a]Reaction conditions: argon atmosphere and irradiation of visible light, [*fac*-Ir(ppy)$_3$] (**B**) (3 μmol), substituted phenol (**1**) (0.3 mmol), difluorobromoacetic acid (**2**) (0.3 mmol), DMF (2.5 mL), Cs_2CO_3 (0.9 mmol), temperature (rt, ~25 °C), time (6−12 h) in a sealed Schlenk tube. [b]Isolated yield. [c]In the presence of **2** (0.6 mmol) and Cs_2CO_3 (1.2 mmol).

Scheme 1. Reaction of [1,1′-Biphenyl]-2,2′-diol (BINOL) (1t) with 2 under the Standard Conditions

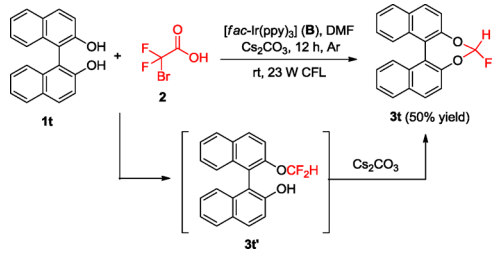
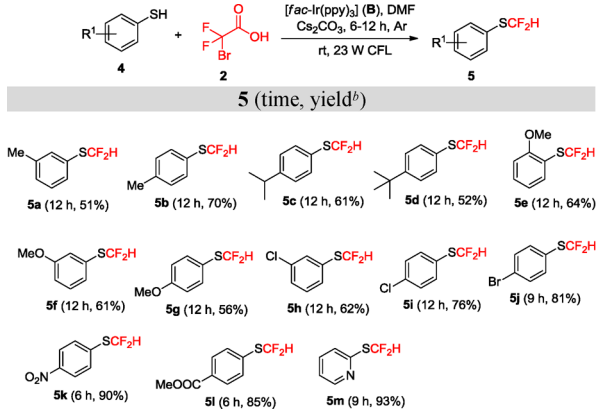


Table 3. Substrate Scope for the Visible-Light Photoredox Difluoromethylation of Thiophenols (4)[a]



[a]Reaction conditions: argon atmosphere and irradiation of visible light, [*fac*-Ir(ppy)$_3$] (**B**) (3 μmol), substituted thiophenol (**1**) (0.3 mmol), difluorobromoacetic acid (**2**) (0.3 mmol), DMF (2.5 mL), Cs_2CO_3 (0.9 mmol), temperature (rt, ~25 °C), time (6−12 h) in a sealed Schlenk tube. [b]Isolated yield.

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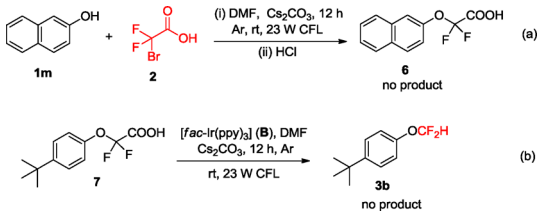
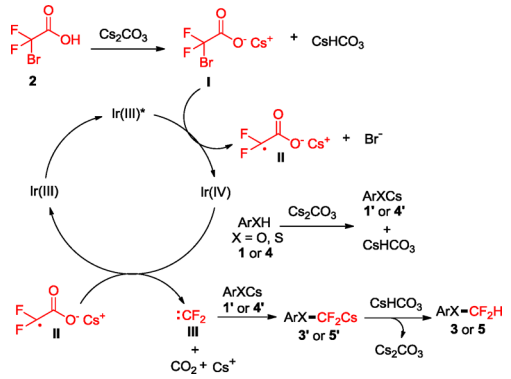
Scheme 2. (a) Treatment of 2-Naphthol (1m) with Difluorobromoacetic Acid (2) in the Absence of Photocatalyst. (b) Treatment of Compound 7 under the Standard Conditions



under the standard photoredox conditions (Scheme 2b). The results showed that the difluoromethylation in Tables 2 and 3 did not produce intermediates **6** and **7**. The reduction potential for the reductive dehalogenation of $BrCF_2COOCs$ (**I**) was detected, $E_{1/2}^{red} = -1.29$ V vs SCE (see Figure S1), so *fac*-$Ir(ppy)_3$ was a strong electron donor to reduce **I** in Scheme 3

Scheme 3. Plausible Mechanism on the Visible-Light Photoredox Difluoromethylation



from its photoexcited state ($E_{1/2}^{IV/*III} = -1.73$ V vs SCE[11a]). Fluorescence-quenching experiments also confirmed this result (see Figures S2–S4). Therefore, a plausible mechanism is suggested in Scheme 3. Treatment of **2** with Cs_2CO_3 gives carboxylate **I** and $CsHCO_3$. Similarly, reaction of **1** or **4** with Cs_2CO_3 provides **1′** or **4′** and $CsHCO_3$. Irradiation of photocatalyst Ir(III) with visible light gives the excited-state [Ir(III)]*, and a single electron transfer (SET) from [Ir(III)]* to **I** leads to Ir(IV) and carbon-centered radical **II** leaving Br^-. A SET of carboxylate anion in **II** to Ir(IV) regenerates the photocatalyst Ir(III), freeing difluorocarbene **III**, CO_2, and Cs^+. Reaction of **III** with **1′** or **4′** donates **3′** or **5′**, and subsequent treatment of **3′** or **5′** with $CsHCO_3$ affords the desired difluoromethylation product **3** or **5**.

In summary, we have developed a simple and efficient one-pot method for the difluoromethylation of phenols and thiophenols. The protocol uses commercially available, inexpensive, and easy to handle difluorobromoacetic acid as the difluoromethylating agent. The reaction underwent the formation of difluorocarbene under visible-light photocatalysis, and the difluorocarbene was trapped with a variety of phenols and thiophenols to obtain the target products in good yields with tolerance of numerous functional groups. We believe that the present method will find wide application.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b01118.

Experimental details; NMR data (PDF)

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Notes

The authors declare no competing financial interest.

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