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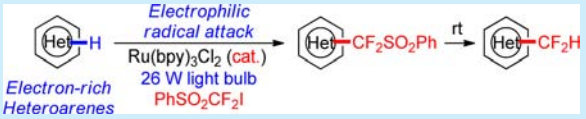
Visible Light-Mediated C−H Difluoromethylation of Electron-Rich Heteroarenes

Yi-Ming Su, Yu Hou, Feng Yin, Yue-Ming Xu, Yan Li, Xiaoqi Zheng, and Xi-Sheng Wang*

Department of Chemistry, University of Science and Technology of China, 96 Jinzhai Road, Hefei, Anhui 230026, China

Supporting Information

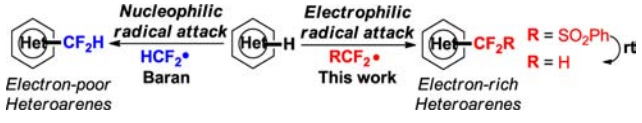
ABSTRACT: A novel method for visible-light photoredox-catalyzed difluoromethylation of electron-rich *N*-, *O*-, and *S*-containingheteroarenes under mild reaction conditions is developed. Mechanistic investigation indicates that the net C−H difluoromethylation proceeds through an electrophilic radical-type pathway.



The difluoromethyl moiety (CF_2H) is an intriguing structural motif that has special biological properties, such as enhancement of membrane permeability, binding affinity, and bioavailability.[1] Additionally, it can act as lipophilic hydrogen-bond donor and a bioisostere of alcohols and thiols.[2] As a result, the difluoromethyl moiety has been of extensive interest for use in pharmaceuticals, agrochemicals, and material sciences.[3] However, although a variety of methods for incorporating the closely related trifluoromethyl group into a diverse array of organic compounds have been reported,[4] there remain relatively few successful examples of difluoromethylation, particularly of (hetero)arenes.

Classically, the strategy of choice for synthesizing difluoromethylated (hetero)arenes has been deoxofluorination of aldehydes. However, these reactions generally suffered from harsh reaction conditions[5] and requirement of prefunctionalization. Recently, the Amii group reported a sequential copper-catalyzed cross-coupling/hydrolysis/decarboxylation route to difluoromethylarenes.[6] The Hartwig[7] and Prakash[8] groups reported direct copper-mediated nucleophilic difluoromethylation of iodoarenes with HCF_2M (M = TMS and *n*-Bu_3Sn, respectively). Although the difluoromethylatedarene products were obtained in excellent yields in these cases, successful examples of heterocycles to which this methodology was applied were quite limited, primarily to pyridine derivatives. Inspired by Minisci's early research,[9] Baran and co-workers recently reported an impressive approach for direct difluoromethylation of electron-deficient heterocycles with zinc difluoromethanesulfinate(DFMS) through a radical pathway, in which a nucleophilic CF_2H radical attack to an electron-deficient reactive site was claimed, and mainly electron-deficient heteroarenes were reported (Scheme 1).[10] We envision an electrophilic difluoromethyl radical might be triggered by replacing the acidic hydrogen on HCF_2 moiety with a removable electron-withdrawing group. Herein, we report a visible light photoredox difluoromethylation of electron-rich *N*-, *O*-, and *S*-containing electron-rich heteroarenes,[11,12] in which the net C−H difluoromethylation proceeds through an electrophilic radical-type path.

Scheme 1. C−H Difluoromethylation of Heteroarenes



Inspired by recent advances in visible-light photoredox catalysis,[13] which avoid the use of potential hazardous radical initiators, our study commenced with *N*-methylpyrrole (**1a**) as the pilot substrate and $PhSO_2CF_2I$, a well-established difluoromethylation reagent developed by Prakash and Hu,[14] as a difluoromethyl resource in the presence of catalytic $Ru(bpy)_3Cl_2{\cdot}6H_2O$ (1 mol %) at 40 °C. To our excitement, the desired difluoro(phenylsulfonyl)methylated product **2a** was obtained when DMF was used as the solvent, albeit in low yield (entry 1, Table 1). A careful survey of solvents was then performed, which revealed CH_2Cl_2 as optimal (entries 1−6). While most of the inorganic and organic bases were not compatible with this reaction (Table S2, Supporting Information), KOAc and NaOH afforded the best yields (entry 13 and 14) as well as K_2HPO_4 (entry 7). To further improve the yield, the reaction concentration was also investigated, which indicated a higher concentration gave the best yield while combination of CH_2Cl_2 as solvent (entry 15). Lastly, control experiments demonstrated that no desired product would be generated without light (entry 16), and the yield would be significantly reduced (26%) without $Ru(bpy)_3Cl_2{\cdot}6H_2O$ as catalyst (entry 17). To compare the different scope of application, *N*-methylpyrrole (**1a**) was also subjected to the standard conditions of Baran's method,[10] which showed no corresponding difluoromethylated product generated after checking by ^{19}F NMR (entry 18).[15]

With the optimized reaction conditions in hand, we examined the substrate scope. Gratifyingly, *N*-free pyrroles (**2b**, **2e**) were found to smoothly undergo difluoromethylation, giving the desired products in slightly reduced yields (Figure 1). The investigation of substituents effect showed both electron-

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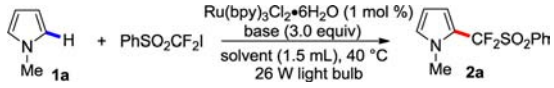
Table 1. Visible Light-Mediated Difluoromethylation of *N*-Methylpyrrole: Optimization of Reaction Conditions[a,b]



entry	solvent	base	yield (%)	entry	solvent	base	yield (%)
1	DMF	K_2HPO_4	10	10	CH_2Cl_2	$NaHCO_3$	21
2	DMSO	K_2HPO_4	22	11	CH_2Cl_2	Cs_2CO_3	50
3	MeCN	K_2HPO_4	21	12	CH_2Cl_2	NaOAc	32
4	MeOH	K_2HPO_4	21	13	CH_2Cl_2	KOAc	67 (80[c])
5	NMP	K_2HPO_4	11	14	CH_2Cl_2	NaOH	72 (60[c])
6	DCE	K_2HPO_4	30	15[c]	CH_2Cl_2	K_2HPO_4	91
7	CH_2Cl_2	K_2HPO_4	59	16[c,d]	CH_2Cl_2	K_2HPO_4	0
8	CH_2Cl_2	NEt_3	54	17[c,e]	CH_2Cl_2	K_2HPO_4	26
9	CH_2Cl_2	DABCO	17	18[f]			0

[a]Reaction conditions: **1a** (0.4 mmol, 2.0 equiv), $PhSO_2CF_2I$ (1.0 equiv), $Ru(bpy)_3Cl_2·6H_2O$ (1 mol %), base (3.0 equiv), solvent (1.5 mL), 40 °C, 24 h. [b]Isolated yield. [c]Solvent (0.5 mL). [d]No light. [e]No catalyst. [f]The reaction was performed under Baran's standard conditions.[10]

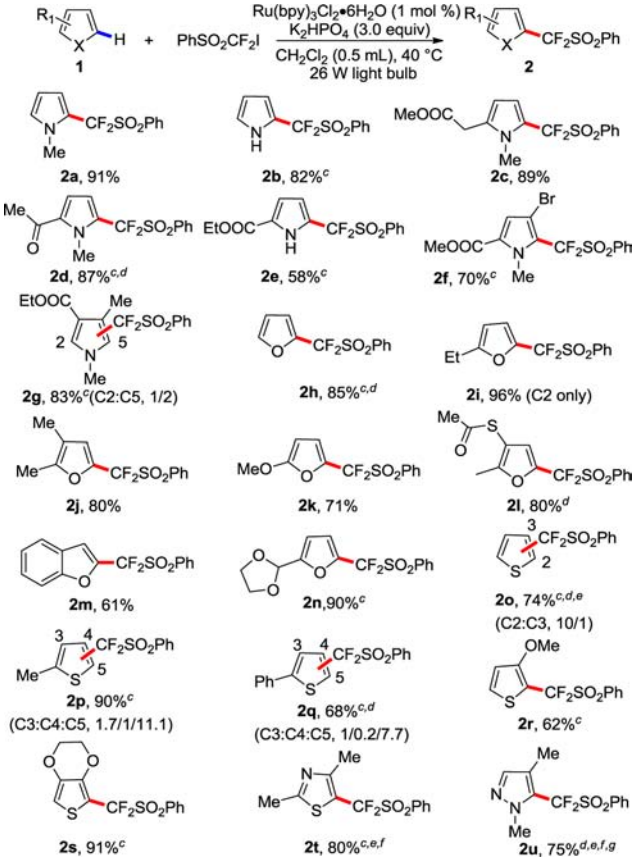


Figure 1. Scope of electron-rich heteroarene substrates. (a) Reaction conditions: $PhSO_2CF_2I$ (0.2 mmol, 1.0 equiv), **1** (2.0 equiv), $Ru(bpy)_3Cl_2·6H_2O$ (1 mol %), K_2HPO_4 (3.0 equiv), CH_2Cl_2 (0.5 mL), 40 °C, 24 h. (b) Isolated yield. (c) 48 h. (d) $Ru(bpy)_3Cl_2·6H_2O$ (3 mol %). (e) **1** (5.0 equiv). (f) 60 °C. (g) 72 h.

donating (**2c**) and electron-withdrawing groups (**2d**–**f**) on the pyrrole ring were compatible with this method. While 3- and 4-postion on pyrrole ring were substituted by different electron-withdrawing and electron-donating groups respectively, this transformation gave the difluoromethylated compounds at the electron-rich 5-position as major product (**2g**). Notably, *O*- and *S*-containing heteroarenes, such as furan and thiophene derivatives, could also be difluoro(phenylsulfonyl)methylated in satisfactory yields. Various substituted groups including Me, Et, Ph, MeO, and SAc on the furan and thiophene rings were also tolerated. Interestingly, 2,4-dimethylthiazole and 1,4-dimethylpyrazole, which contain two heteroatoms in their rings, also were found to give good yields (**2t**–**u**) but required a higher catalyst loading (3 mol %) for the later one (**2u**).

To test whether this method extended to other heteroarenes, we next examined a variety of electron-rich indoles, whose framework has been realized as a key motif in biological and medical chemistry. Unsurprisingly, a series of 3-substiuted indoles were difluoromethylated smoothly, giving the desired products in moderate to good yields (Figure 2). Additionally, while the *N*-free indole gave moderate yield, changing *N*-protecting group from Me to other electron-donating groups, such as Et or Bn, has almost no effect on the yields (**4c**,**d**). All indoles bearing primary (1°) or secondary (2°) alkyl groups or a phenyl group at the C3 position were proven to be effective substrates for this transformation (**4e**–**g**). A range of functional groups on the aryl ring of indoles, including both electron-donating groups, such as Me and OMe, and electron-withdrawing groups, such as F, Cl, and Br, were also tolerated (**4h**–**o**). Notably, the difluoro(phenylsulfonyl)methylation of simple indoles without C3 substitution also proceeded in good yields, albeit with low regioselectivities (**4p**–**r**).

To understand the site-selectivity patterns of this reaction with heterocyclic compounds that contain multiple potentially reactive sites, we applied our catalytic C–H difluoromethylation reaction to two select heteroarenes, **5** and **7**, in order to observe the product distributions (Scheme 2). Interestingly, compared with Baran's previous result with dihydroquinine, in which a nucleophilic radical addition mode was seen (functionalization of the electron-deficient C2 position adjacent to nitrogen atom of the pyridine ring),[10] our difluoromethylation reaction occurred at the most electron-rich C5 position with **5**. This suggests that the putative electrophilic difluoro(phenylsulfonyl)methyl radical generated by photoredox-catalyzed reduction of $PhSO_2CF_2I$ is more electrophilic than the $HCF_2^•$ radical implicated in Baran's case. Futhermore, the reaction with 4-methylthiazole (**7**) also predominantly gave functionalization at the electron-rich C5 position (C5:C2 = 3.3:1), further corroborating the preference of our new developed method for attack at the electron-rich position.

To understand the mechanism of this transformation, we carried out a series of experiments. First, we attempted to perform the reaction in the presence of 1.0 equiv TEMPO as a radical scavenger, and only 4% of the desired product was

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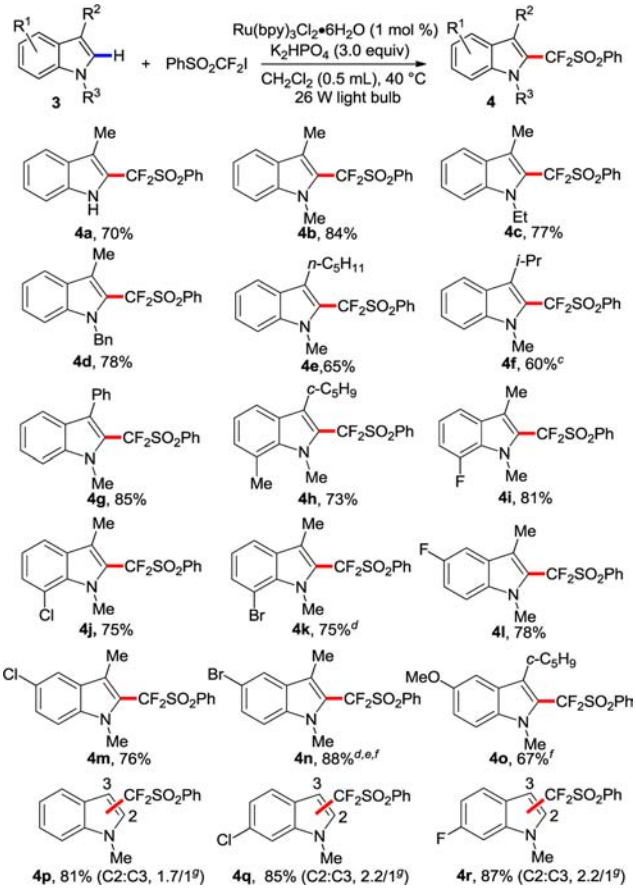
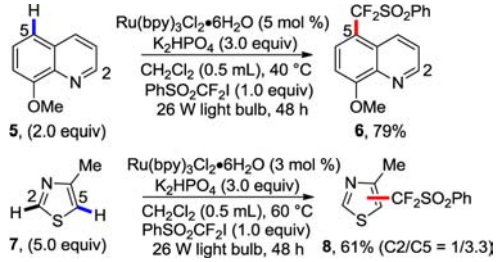


Figure 2. Scope of functional indoles. (a) Reaction conditions: **3** (0.2 mmol, 1.0 equiv), $PhSO_2CF_2I$ (1.4 equiv), $Ru(bpy)_3Cl_2{\cdot}6H_2O$ (1 mol %), K_2HPO_4 (3.0 equiv), CH_2Cl_2 (0.5 mL), 40 °C, 48 h. (b) Isolated yield. (c) 24 h. (d) $Ru(bpy)_3Cl_2{\cdot}6H_2O$ (3 mol %). (e) 58 h. (f) 60 °C. (g) **3** (1.6 equiv).

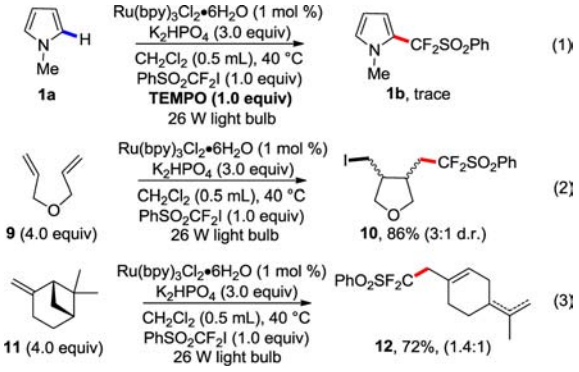
Scheme 2. Site-Selectivity of Difluoromethylation



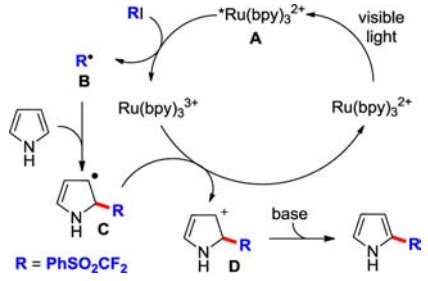
obtained (eq 1, Scheme 3). This observation was consistent with the established catalytic cycle that the photoredox catalysis proceeds via a radical path. While we failed to capture the coupling product of TEMPO with $PhSO_2CF_2I$ (eq 1, Scheme 3), we were able to employ two kinds of radical clocks to trap the $PhSO_2CF_2^{\bullet}$ radical. The reaction of $PhSO_2CF_2I$ with allyl ether **9** under the standard reaction conditions gave the cyclized product **10** in 86% yield (3:1 dr), and the reaction with *β*-pinene **11** provided the ring-opened diene **12** (isolated as an isomeric mixture) via rearrangement (eq 2 and 3, Scheme 3). Both results implicated the involvement of $PhSO_2CF_2^{\bullet}$ radical in this progress.

On the basis of these observations and the reported results on photoredox catalysis,[13] a plausible photoredox catalytic cycle was depicted in Scheme 4. Initially, the excitation of

Scheme 3. Radical-Trapping Experiments



Scheme 4. Possible Catalytic Cycle



photocatalyst $Ru(bpy)_3Cl_2{\cdot}6H_2O$ with visible light produced by a 26 W light bulb gives the exited state **A**, which sequentially followed a reduction of $PhSO_2CF_2I$ to afford Ru(III) and an electrophilic $PhSO_2CF_2^{\bullet}$ radical **B**. Addition of this radical species to the electron-rich arene results in the formation of radical intermediate **C**. Radical **C** is then oxidized to cation **D** by Ru(III) followed by base-mediated deprotonation to give the final difluoromethylated product.

Desulfonylation of **4p** mediated by Mg was found to proceed smoothly at room temperature,[16] affording the difluoromethylindole **13a** in 95% yield (Figure 3). While the indoles with electron-rich (**4b**) or -deficient groups (**4q**−**r**) were compatible with this method, *O*- (**2m**−**n**), *S*- (**2s**), and two heteroatoms (**2t**,**u**) containing (phenylsulfonyl)difluoromethylatedheterocycles were also desulfonylated smoothly to provide the desired

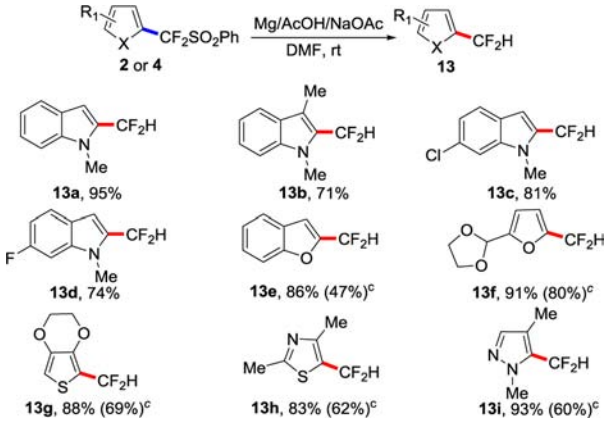


Figure 3. Reductive desulfonylation. (a) Reaction conditions: **2** or **4** (0.2 mmol, 1.0 equiv), Mg (4.7 mmol), buffer solution (2.0 mL), DMF (2.0 mL), rt. (b) Isolated yield. (c) Values in parentheses were yields of the one-pot process.

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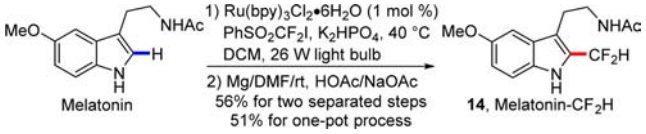
difluoromethylheterocycles in good to excellent yields. To our excitement, it was found that the one-pot process, in which only removal of solvent was required after difluoro(phenylsulfonyl)-methylation, worked pretty well with only slightly reduced yield (**2n,s–u**).

To demonstrate the potential and the functional groups tolerance of this methodology, we next attempted to difluoromethylate melatonin, a natural product with free indole ring and amide group, with our newly developed difluor-omethylation sequence (Scheme 5). To our excitement, the

Scheme 5. Difluoromethylation of Melatonin



difluoro(phenylsulfonyl)methylation of melatonin proceeded smoothly under the standard conditions, affording the difluoromethylated product **14** at 56% combined yield followed by desulfonylation with excess Mg (51% yield for one-pot process).

In summary, we have developed a novel method for visible light photoredox difluoromethylation of electron-rich hetero-arenes under mild conditions, in which the net C–H difluoromethylation proceeds through an electrophilic radical-type path. *N*-, *O*-, and *S*-containing heteroarenes were found to be compatible with this new transformation. Further application of this method to the modification of complex molecules is ongoing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization data (^{1}H NMR, ^{13}C NMR, HRMS). This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: xswang77@ustc.edu.cn.

Notes

The authors declare no competing financial interest.

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