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# Direct and Regioselective C−H Oxidative Difluoromethylation of Heteroarenes

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Supporting Information

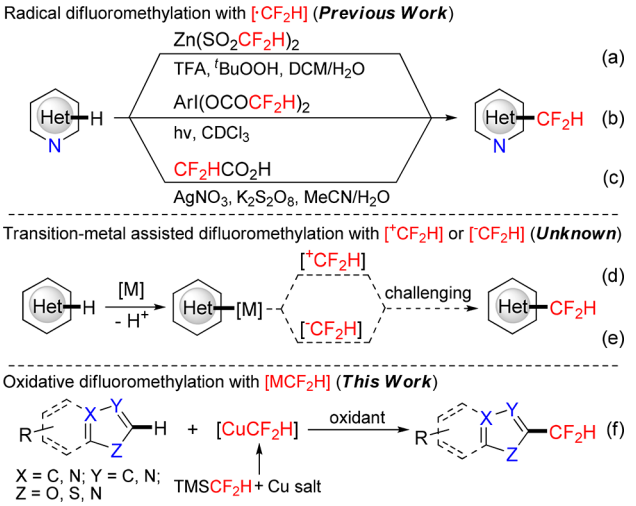
**ABSTRACT:** The difluoromethyl group ($CF_2H$) is of great interest in the area of medicinal chemistry. However, the investigation of molecular scaffolds containing this group has been hampered by the limitation of synthetic methods for the introduction of $CF_2H$ into heteroarenes. Herein we disclose a new strategy for the direct introduction of a difluoromethyl group into heteroarenes via the copper-mediated C−H oxidative difluoromethylation of heteroarenes with $TMSCF_2H$. This mild and regioselective method enables the convenient synthesis of a range of difluoromethylated heteroarenes in high yields. The usage of 9,10-phenanthrenequinone (PQ) as an oxidant is critical to the success of this new difluoromethylation reaction.



It is well-recognized that the introduction of fluoroalkyl groups into heteroarenes frequently has a dramatic impact on their physical, chemical, and biological properties.[1] Consequently, the fluorinated heteroarenes have attracted increasing interest in drug discovery.[2] Among them, the difluoromethylated heteroarenes such as thiazopyr (herbicide),[3a] fluxapyroxad (fungicide),[3b] and deracoxib (anti-inflammatory drug)[3c] have shown promising biological activities, probably because the difluoromethyl group ($CF_2H$) is normally considered as a lipophilic and metabolically stable hydrogen-bond donor.[4] Traditional approaches to difluoromethylated heteroarenes mainly include deoxyfluorination of heteroaromatic aldehydes,[5] difluorination of benzylic C−H bonds,[6] construction of heteroaromatic systems from $CF_2H$-containing building blocks,[7] and transformation of $CF_2R$-containing heteroarene precursors.[8] Recently, transition-metal-assisted difluoromethylation of heteroaromatic compounds (halides,[9] boronic acids,[10] zinc reagents,[11] and diazonium salts[12]) has been developed for the synthesis of difluoromethylated heteroarenes. But these protocols rely on prefunctionalized substrates.

Over the past decade, the direct transformation of ubiquitous C−H bonds has emerged as a straightforward and atom-economical functionalization method.[13] In 2012, Baran and co-workers reported a direct C−H difluoromethylation of heteroarenes with $Zn(SO_2CF_2H)_2$ through a radical pathway (Scheme 1a).[14a] Very recently, Maruoka[14b] and Nielsen[14c] disclosed the radical difluoromethylation of heteroarenes using

**Scheme 1. C−H Difluoromethylation of Heteroarenes**




$ArI(OCOCF_2H)_2$ (Scheme 1b) or $CF_2HCO_2H$ (Scheme 1c) as $CF_2H$ sources, respectively. However, these radical processes mainly focused on N-containing heteroaromatic substrates (pyridines, pyrroles, pyrimidines, pyrazines, purines, etc.), and in some cases a mixture of regioisomers was formed. Thus, the development of new C−H regioselective difluoromethylation of other heteroaromatic compounds (O- or S-containing heterocycles) is highly desirable.

Normally, transition-metal-assisted C−H functionalization involves, first, the formation of the metal intermediate followed by reaction with electrophilic[15] or nucleophilic[16] coupling partners. However, to the best of our knowledge, transition-metal-assisted C−H difluoromethylation has not been reported yet. We reasoned that the following two problems might make C−H difluoromethylation challenging: (1) the lack of practical electrophilic difluoromethylating reagents[17] hampers the development of electrophilic coupling pathway (Scheme 1d); (2) the relative instability of the $CF_2H$ anion[18] results in the difficult transmetalation of metal intermediates with nucleophilic difluoromethylating reagents (Scheme 1e). As difluoromethyl metal complexes ($L_nMCF_2H$, M = Zn, Ag, Cu) are involved in difluoromethylation reactions,[9a−c,f,i,12] we envi-

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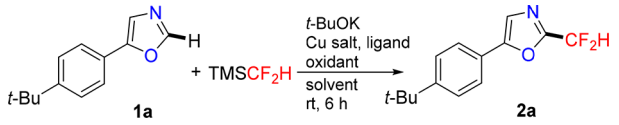
sioned that the cross-coupling of heteroarenes and $L_nMCF_2H$ under oxidative conditions might be feasible. In continuation of our research interest in oxidative fluoroalkylation reactions,[19] we disclose here the oxidative C−H difluoromethylation of heteroarenes with $[CuCF_2H]$ complexes generated *in situ* from $TMSCF_2H$ and copper salt (Scheme 1f). This protocol provides a convenient and regioselective access to a variety of difluoromethylated N- and/or O(S)-containing heteroarenes, which are not easy to obtain by radical difluoromethylation.

We initiated our studies by exploring the oxidative difluoromethylation of oxazoles. The oxazole motif is widely found in pharmaceuticals.[20] However, no method is available for the direct introduction of a $-CF_2H$ group into oxazoles. Thus, we chose 5-(4-(*tert*-butyl)phenyl)oxazole (**1a**) as the model substrate to optimize the reaction conditions (Table 1).

**Table 1. Optimization of Reaction Conditions**[a]



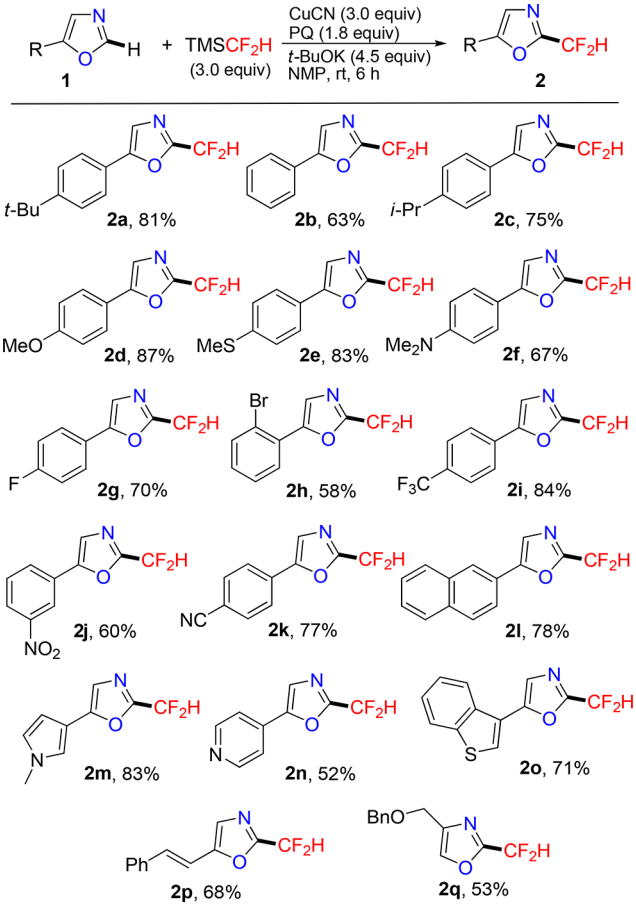

| entry | Cu salt | ligand | oxidant | solvent | yield (%)[b] |
|---|---|---|---|---|---|
| 1 | CuCl | phen | DTBP | DMF | 0 |
| 2 | CuCl | phen | $Ag_2CO_3$ | DMF | 0 |
| 3 | CuCl | | DTBP | DMF | trace |
| 4 | CuCl | | $Ag_2CO_3$ | DMF | 0 |
| 5 | CuCl | | $PhI(OAc)_2$ | DMF | trace |
| 6 | CuCl | | PQ | DMF | 45 |
| 7 | CuI | | PQ | DMF | 38 |
| 8 | CuTc | | PQ | DMF | 39 |
| 9 | CuCN | | PQ | DMF | 54 |
| 10 | CuSCN | | PQ | DMF | 46 |
| 11 | CuCN | | PQ | NMP | 75 |
| 12 | CuCN | | PQ | DMA | 63 |
| 13[c] | CuCN | | PQ | NMP | 68 |
| 14[d] | CuCN | | PQ | NMP | 71 |
| 15 | CuCN | phen | PQ | NMP | 18 |
| 16[e] | CuCN | | PQ | NMP | 89 |

[a]Reaction conditions: **1a** (0.1 mmol), $TMSCF_2H$ (0.2 mmol), *t*-BuOK (0.3 mmol), Cu salt (0.2 mmol), ligand (0.2 mmol), oxidant (0.12 mmol), solvent (2.0 mL), under Ar, rt, 6 h. [b]Yields determined by $^{19}F$ NMR spectroscopy using trifluoromethylbenzene as an internal standard. [c]0 °C. [d]50 °C. [e]$TMSCF_2H$ (0.3 mmol), *t*-BuOK (0.45 mmol), CuCN (0.3 mmol), PQ (0.18 mmol).

The oxidative difluoromethylation reaction was first conducted with **1a** and $TMSCF_2H$ in the presence of CuCl, phen(1,10-phenanthroline), and an oxidant (DTBP (di-*tert*-butyl peroxide) or $Ag_2CO_3$). To our disappointment, the reactions failed to deliver the desired product **2a** (entries 1 and 2). Only a trace of **2a** was detected in the absence of phen (entry 3). Further screening of the oxidants showed that the oxidant was crucial, and only 9,10-phenanthrenequinone (PQ) could promote the desired reaction in 45% yield (entry 6).The use of different copper salts revealed that CuCN was optimal (entries 7−10). Subsequently, switching dimethylformamide (DMF) to *N*-methylpyrrolidone (NMP) or dimethylacetamide (DMA) resulted in higher yields (entries 11 and 12). When the reaction was performed at lower or higher temperature, no better results were achieved (entries 13 and 14). To our surprise, the addition of phen led to a significantly diminished yield (entry 15). Finally, the yield of **2a** was improved to 89% by increasing the amounts of $TMSCF_2H$, *t*-BuOK, CuCN, and PQ (entry 16).

With the optimized reaction conditions in hand, we then evaluated the scope of copper-mediated direct difluoromethylation of oxazoles (Table 2). The mild reaction conditions

**Table 2. Substrate Scope of C−H Difluoromethylation of Oxazoles**[a]




[a]Reaction conditions: **1** (0.2 mmol), $TMSCF_2H$ (0.6 mmol), CuCN (0.6 mmol), *t*BuOK (0.9 mmol), 9,10-phenanthrenequinone (0.36 mmol), NMP (4.0 mL), under Ar, rt, 6 h, isolated yields.

allow the tolerance of electronically diverse functionalities, including alkyl, methoxy, methylthio, dimethylamino, halide, trifluoromethyl, nitro, and cyano substituents (**1c−k**). 5-Naphthyloxazole **1l** underwent this transformation smoothly, affording **2l** in high yield. Importantly, oxazoles (**1m−o**) bearing a heteroaryl ring were suitable to give the desired products (**2m−o**) in good yields and excellent chemoselectivites. Besides aryl-substituted oxazoles, alkenyl- and alkyl-substituted oxazoles (**1p** and **1q**) could also be employed in this protocol.

This oxidative C−H difluoromethylation was extended to other heteroarenes. As shown in Table 3, a series of heteroarenes including thiazole (**3**), imidazole (**4**), 1,3,4-oxadiazole (**5**), benzo[*d*]oxazole (**6**), benzo[*d*]thiazole (**7**), benzo[*b*]thiophene (**8**), pyridine (**9**), and thiophene (**10**) were all compatible to afford the corresponding difluoromethylated products **13−20**. It is noteworthy that the $CF_2H$ group was regioselectively attached to the more acidic carbon


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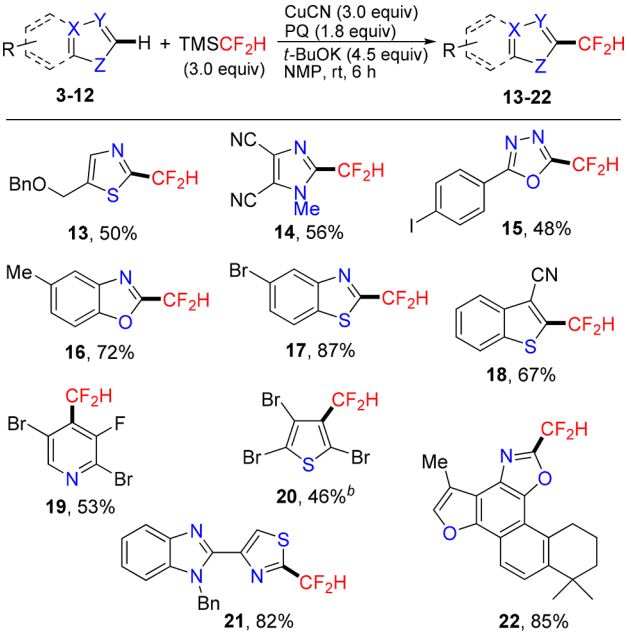
**Table 3. C−H Difluoromethylation of Other Heteroarenes**[a]

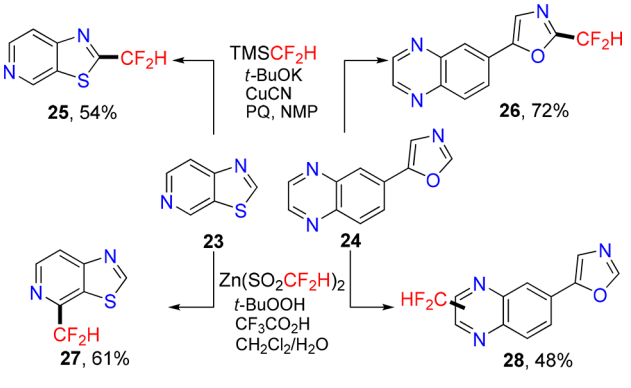



[a]Reaction conditions: **3**−**12** (0.2 mmol), $TMSCF_2H$ (0.6 mmol), CuCN (0.6 mmol), *t*-BuOK (0.9 mmol), 9,10-phenanthrenequinone (0.36 mmol), NMP (4.0 mL), under Ar, rt, 6 h, isolated yields. [b]Yields determined by $^{19}F$ NMR spectroscopy using trifluoromethylbenzene as an internal standard.

of the heteroaromatic ring. In the cases of imidazole (**4**), benzo[*b*]thiophene (**8**), pyridine (**9**), and thiophene (**10**), the substitution of electron-withdrawing groups is necessary for these transformations. Remarkably, this procedure is also applicable for the late-stage C−H difluoromethylation of biologically relevant compounds. For example, thiabendazole (fungicide and parasiticide)[21] derivative **11** was converted to product **21** in 82% yield. Furthermore, neosalvianen (natural product isolated from *Salvia miltiorrhiza*)[22] analogue **12** underwent this oxidative difluoromethylation reaction to give compound **22** in 85% yield. Unfortunately, other types of heteroarenes including caffeine, pyrimidine, and 1,3,5-triazine only afforded trace amounts of the desired products.

To further understand the scope and limitation of this protocol, the C−H difluoromethylation of the same heteroarenes under these oxidative and Baran's radical[14a] reaction conditions was investigated. As shown in Scheme 2, the

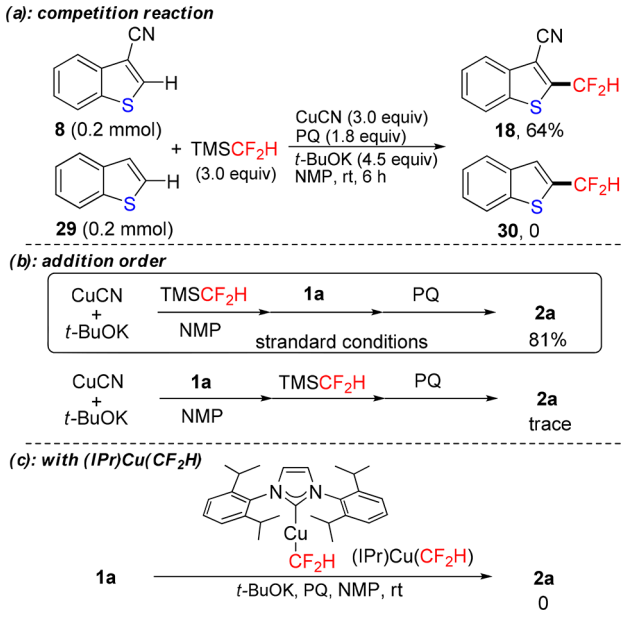
**Scheme 2. Comparison with Oxidative and Radical C−H Difluoromethylation**




oxidative difluoromethylation of thiazolo[5,4-*c*]pyridine (**23**) and 5-(quinoxalin-6-yl)oxazole (**24**) bearing several potential reactive sites took place exclusively on the more acidic carbon of azole rings, affording the difluoromethylated products **25** and **26**. On the other hand, compounds **23** and **24** underwent radical difluoromethylation to give products **27** and **28**, in which the $CF_2H$ group was connected to the more electron-poor carbon adjacent to the nitrogen atoms of the heteroarenes. These results clearly demonstrated the complementarity and orthogonality of oxidative and radical difluoromethylation reactions.

To gain insight into the reaction mechanism of the C−H oxidative difluoromethylation, a competition reaction was conducted with an equivalent amount of compounds **8** and **29** (Scheme 3a). The difluoromethylation of **8** took place

**Scheme 3. Mechanistic Investigation**




exclusively to afford product **18** in 64% yield, and no conversion was observed for less acidic substrate **29**. This experimental result showed that the deprotonation of the acidic C−H bond of herteroarene with base was crucial to the oxidative difluoromethylation. Furthermore, the addition order of the substrates was important for this reaction. Under the standard procedures, $TMSCF_2H$, **1a**, and PQ must be successively added to the mixture of *t*-BuOK and CuCN in NMP (Scheme 3b). If **1a** was added before $TMSCF_2H$, only a trace of **2a** was observed. These result demonstrated that difluoromethylcopper complex must be generated first. Finally, the oxidative coupling of **1a** with the isolated (IPr)Cu-$(CF_2H)$[9i] failed to give the desired product **2a** (Scheme 3c). We assumed that the bulky IPr ligand might deactivate the $CuCF_2H$ species for this reaction, which was consistent with the experimental observation (Table 1, entry 15). On the basis of the above experimental results and reported mechanisms for similar reactions,[19e,23] a preliminary reaction mechanism was proposed (Scheme 4). First, treatment of $TMSCF_2H$ with *t*-BuOK and CuCN gave $CuCF_2H$ and $Cu(CF_2H)_2^-$.[9b,c] Then, deprotonation of hereroarene with *t*-BuOK and transmetalation delivered intermediate **A**. Finally, oxidation of inter-



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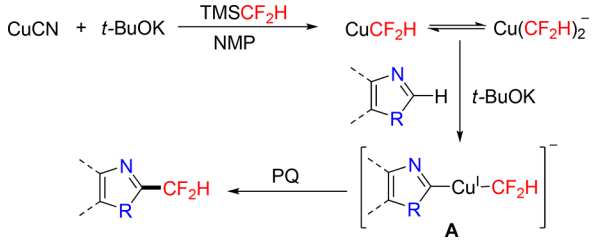
**Scheme 4. Proposed Reaction Mechanism**




mediate **A** with PQ[24] followed by reductive elimination afforded the desired product.

In conclusion, we have developed a copper-mediated oxidative C−H difluoromethylation of a variety of heteroarenes including oxazloe, thiazole, imidazole, 1,3,4-oxadiazole, benzo[*d*]oxazole, benzo[*d*]thiazole, benzo[*b*]thiophene, pyridine, thiophene, and thiazolo[5,4-*c*]pyridine. This protocol provides a new method for selective synthesis of the difluoromethylated heteroarenes that were not accessible by the reported reactions.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.8b08135.

Detailed experimental procedures and spectral data for all compounds (PDF)

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### Notes

The authors declare no competing financial interest.

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