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Copper-mediated difluoromethylation of electron-poor aryl iodides at room temperature†

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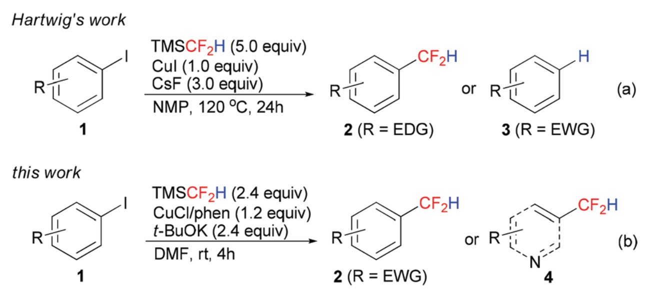
A convenient copper-mediated direct difluoromethylation of electron-deficient aryl iodides, as well as heteroaryl and β-styryl iodides, using $TMSCF_2H$ has been developed. This one-step protocol proceeded at room temperature, affording various difluoromethylated products in moderate to excellent yields.

As fluorinated organic molecules are widely applied in many fields, such as pharmaceuticals, agrochemicals and materials, extensive efforts have been devoted to incorporation of fluorinated functional groups into various compounds.[1] The difluoromethyl group (CF_2H) is isosteric and isopolar to a hydroxy (OH)[2] and thiol (SH)[3] unit, and also acts as lipophilic hydrogen bond donors.[4] Because of these unique properties, CF_2H-containing compounds are important components of pesticides and pharmaceuticals.[5] Up to now, different strategies have been developed for the synthesis of difluoromethylated compounds.[1,6] However, methods for preparation of difluoromethylated arenes are still limited. A traditional method for the preparation of these compounds is fluorination of different substrates, such as aldehydes.[7] Recently, transition-metal-mediated difluoroalkylation followed by further transformations has provided another efficient approach.[8] In 2012, Baran reported a direct introduction of the difluoromethyl moiety into heteroarenes with a new agent ($Zn(SO_2CF_2H)_2$, DFMS) *via* a radical process,[9] but mixtures of regioisomers were observed in some cases. Compared to the above methods, transition-metal-mediated direct difluoromethylation has some advantages such as shorter reaction steps and broader substrate scope. However, this strategy was not developed until two years ago,[10] probably because there were not so many stable and efficient difluoromethylation reagents.[6] Only two reagents have been applied in transition-metal-mediated direct difluoromethylation of aryl halides: Me_3SiCF_2H[10a] reported by Hartwig and n-Bu_3SnCF_2H[10b] reported by Prakash. Me_3SiCF_2H is easily accessible and less toxic than n-Bu_3SnCF_2H, which makes Me_3SiCF_2H the first choice in the lab and industry. However,



Scheme 1 Copper-mediated direct difluoromethylation with $TMSCF_2H$.

Hartwig's reaction system was only limited to electron-rich and electron-neutral iodoarenes **1** (Scheme 1a). Electron-poor substrates were transformed into the corresponding arenes **3**, and the reaction of heteroaryl iodides was not reported. These drawbacks hindered the wide application of Hartwig's method. In continuation of our research on transition-metal-mediated/catalyzed difluoroalkylation reactions,[11] we herein report an efficient copper-mediated difluoromethylation of electron-poor aryl iodides at room temperature (Scheme 1b). Difluoromethylated heteroarenes **4** can also be conveniently obtained in our reaction system. This work is an important complement to Hartwig's method.

Although the copper-mediated/catalysed trifluoromethylation using $TMSCF_3$ has been well established,[1e,f] the copper-mediated difluoromethylation with $TMSCF_2H$ is quite rare, probably because the Si–CF_2H bond is more inert[12] and difluoromethylcopper complexes are less stable.[13] Recently, Hu reported that an appropriate Lewis base and solvent was crucial in activating the Si–CF_2H bond,[14] and Prakash revealed that DMF was helpful to stabilize the $CuCF_2H$ by computer calculation.[10b] The above two results encouraged us to explore the copper-mediated difluoromethylation of electron-deficient aryl iodides with $TMSCF_2H$.

We initiated our investigation by reacting ethyl 4-iodobenzoate **1a** with $TMSCF_2H$ (2.0 equiv.) in the presence of KF (2.0 equiv.) and CuI (1.0 equiv.) in DMF (1.0 mL) at room

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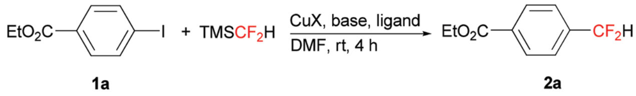
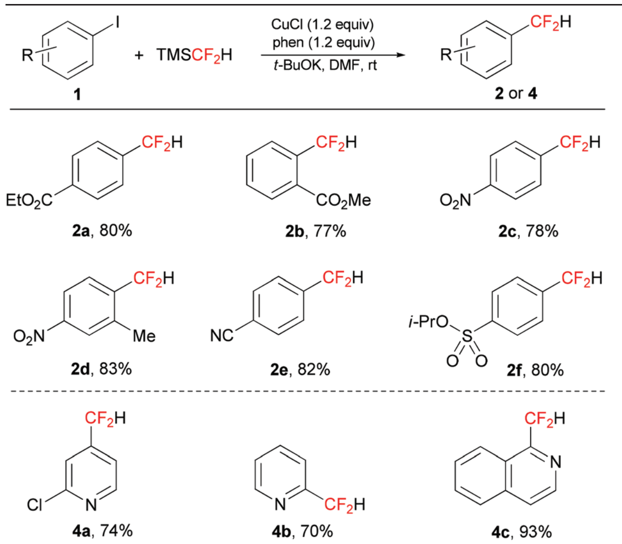
Table 1 Optimization of reaction conditions[a]



Entry	CuX	Base	Ligand	Yield[b] (%)
1	CuI	KF	—	NR
2	CuI	CsF	—	Trace
3	CuI	TBAT	—	NR
4	CuI	*t*-BuOK	—	25
5	CuI	*t*-BuONa	—	8
6	CuI	*t*-BuOLi	—	NR
7	CuCl	*t*-BuOK	—	35
8	CuBr	*t*-BuOK	—	31
9	CuOAc	*t*-BuOK	—	Trace
10	$Cu(OAc)_2$	*t*-BuOK	—	NR
11	CuCl	*t*-BuOK	Phen	70
12	CuCl	*t*-BuOK	Bipy	45
13	CuCl	*t*-BuOK	TMEDA	43
14	CuCl	*t*-BuOK	$Et_2NCH_2CH_2NEt_2$	30
15[c]	CuCl	*t*-BuOK	Phen	85
16[d]	CuCl	*t*-BuOK	Phen	84

[a] Reaction conditions: **1a** (0.2 mmol), $TMSCF_2H$ (2.0 equiv.), copper salt (1.0 equiv.), ligand (1.0 equiv.), base (2.0 equiv.), DMF (1.0 mL), rt. [b] Yield was determined by ^{19}F NMR using benzotrifluoride as an internal standard. [c] $TMSCF_2H$ (2.4 equiv.), CuCl (1.2 equiv.), phen (1.2 equiv.), base (2.4 equiv.). [d] $TMSCF_2H$ (3.0 equiv.), CuCl (1.5 equiv.), phen (1.5 equiv.), base (3.0 equiv.).

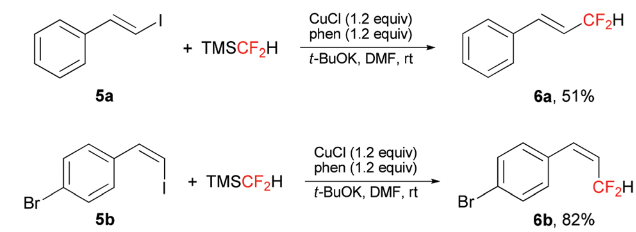
Table 2 Copper-mediated difluoromethylation of aryl and heteroaryl iodides[a,b]



[a] Reaction conditions: **1** (0.2 mmol), $TMSCF_2H$ (2.4 equiv.), CuCl (1.2 equiv.), phen (1.2 equiv.), *t*-BuOK (2.4 equiv.) under argon in DMF (1.0 mL) at room temperature. [b] Isolated yield.

temperature under an Ar atmosphere. However, most of **1a** was not converted, and the desired product **2a** was not observed (Table 1, entry 1). Switching to other F-based initiators such as CsF and TBAT had no effects on the reaction (entries 2 and 3). 25% yield of the desired product **2a** was obtained when the *t*-BuOK was used as the initiator (entry 4). Further screening of *t*-BuONa and *t*-BuOLi gave no better results (entries 5 and 6). To improve the yield of **2a**, we evaluated a series of copper salts such as CuBr, CuCl, CuOAc and $Cu(OAc)_2$ (entries 7–10). CuCl was the optimal base giving **2a** in 35% yield (entry 7). Since the ligands play a key role in transition-mediated fluoroalkyl cross-coupling reactions, we next investigated the influence of the ligands. 1,10-Phenanthroline (phen) was found to be more effective than other ligands and dramatically increased the product yield to 70% (entries 11–14). A higher yield of **2a** was obtained when the reaction was conducted under the conditions of $TMSCF_2H$ (2.4 equiv.), CuCl (1.2 equiv.), phen (1.2 equiv.) and *t*-BuOK (2.4 equiv.) (entry 15). Further increasing the amount of $TMSCF_2H$, CuCl, phen and *t*-BuOK resulted in a slight lower yield (entry 16).

With the optimal conditions in hand, we next examined the substrate scope of the Cu-mediated difluoromethylation of aryl and heteroaryl iodides (Table 2). In contrast to the reaction reported by Hartwig's group that is limited to electron-rich and electron-neutral iodoarenes described,[10a] electron-deficient aryl iodides reacted in good to excellent yields under the optimal conditions. A variety of electron-withdrawing functional groups such as cyano, ester, and nitro were well-tolerated in the reaction (**2a–2f**). Sterically hindered aryl iodides



Scheme 2 Copper-mediated difluoromethylation of β-styryl iodides.

with a substituent in the *ortho* position also served as a suitable coupling partner and afforded good yields (**2b**, **2d**). However, the substrates bearing electron-donating groups gave relatively lower yields. The iodo-substituted heteroaromatic compounds were also effective in this reaction, producing the desired products in good to excellent yields (**4a–4c**).

This difluoromethylation protocol was also applied in the direct difluoromethylation of β-styryl iodides (Scheme 2). The corresponding allylic difluorinated alkenes **6a** and **6b** were obtained in moderate to good yields, with retention of configuration.

The differences between Hartwig's and our reaction systems are shown in Table 3. First, an excess amount of $TMSCF_2H$ (5.0 equiv.) was needed in their system, probably for the generation of more stable intermediate $Cu(CF_2H)_2^-$.[10a] In our system, only 2.4 equiv. of $TMSCF_2H$ was added, and the ligand phen was necessary to achieve high yields. Second, the weak base CsF was used in their system, while a strong base *t*-BuOK was needed in our system. Last but not least, the temperature was totally different (120 °C in their system *vs.* rt in our system). All these different reaction conditions, combined

Table 3 Comparing Hartwig's with our reaction systems

System	$TMSCF_2H$	Ligand	Base	Temperature
Hartwig's	5.0 equiv.	—	CsF	120 °C
Our	2.4 equiv.	Phen	*t*-BuOK	rt

together, gave totally different results, as mentioned in Scheme 1.

Conclusions

In summary, we have developed a convenient method for one-step introduction of the difluoromethyl group into different substrates by employing copper-mediated direct difluoromethylation using $TMSCF_2H$ at room temperature. The mild reaction conditions make this method attractive for the synthesis of a series of difluoromethylated compounds. Ongoing studies will focus on the mechanism and extension of the scope of this transformation.

Acknowledgements

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