1,1-Difluoroethylation

Copper-Mediated Aromatic 1,1-Difluoroethylation with (1,1-Difluoroethyl)trimethylsilane (TMSCF$_2$CH$_3$)

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Abstract: A new method for the formation of 1,1-difluoroethyl copper species ("CuCF$_2$CH$_3$") with 1,1-difluoroethylsilane (TMSCF$_2$CH$_3$) has been developed. The "CuCF$_2$CH$_3$" species can be applied to the efficient 1,1-difluoroethylation of diaryliodonium salts under mild conditions, affording (1,1-difluoroethyl)arenes in good to excellent yields. This convenient procedure tolerates a wide range of functional groups and thus serves as a practical synthetic tool for the introduction of CF$_2$CH$_3$ group(s) into complex molecules.

Fluorinated compounds have been widely used in the fields of pharmaceuticals, agrochemicals, and functional materials, as the introduction of fluorine atom(s) into organic molecules often results in dramatic changes in the physical properties, the chemical reactivity, and especially the biological activity.[1] Among various fluorinated moieties, the difluoroethyl group (CF$_2$CH$_3$) is of high importance because it mimics the steric and electronic features of a methoxy group and improves the bioactivity and metabolic stability of important molecules.[2] For example, the replacement of a methoxy group by a difluoroethyl group of a triazolothienopyrimidine molecule as a urea transporter UT-B inhibitor shows remarkable advantages in terms of potency and metabolic stability.[2b] However, the invention of reagents and methods for the synthesis of (1,1-difluoroethyl)arenes remains largely unexplored. Traditional methods for the synthesis of such compounds convert ketones into the corresponding difluoroalkyl groups using nucleophilic fluorination reagents such as N,N-diethylaminosulfur trifluoride (DAST).[3] However, the reaction conditions usually cannot tolerate a large number of functional groups. Recently, a radical method for 1,1-difluoroethylation of heteroaromatic compounds with sodium difluoroethylsulfinate (DFES-Na) has been disclosed by the group of Baran[4] (Scheme 1a). Furthermore, different methods to activate the benzylic C—H bond are em-
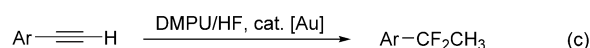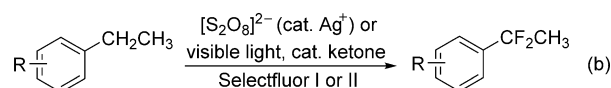
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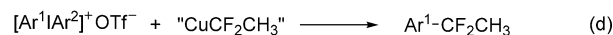
Scheme 1. Strategies for the synthesis of (1,1-difluoroethyl)arenes.

ployed to afford 1,1-difluoroethylarenes[5] (Scheme 1b). Very recently, Hammond and co-workers reported the gold-catalyzed dihydrofluorination of terminal arynes with a DMPU/HF complex for the synthesis of difluoroethylarenes[6] (Scheme 1c).

During the last few years significant progress has been made in copper-mediated or -catalyzed difluoroalkylation for the selective introduction of CF$_2$ group(s) onto aromatic rings.[7, 8] Recently, we disclosed the direct preparation of the "CuCF$_3$" reagent with phenyl trifluoromethyl sulfoxide (PhSOCF$_3$) via the treatment of CuCl and 2 equivalents of tBuOK and its application to trifluoromethylation of aryl halides.[9] We envisioned that a copper-mediated difluoroethylation via the "CuCF$_2$CH$_3$" species[10] could provide an alternative method for the synthesis of (1,1-difluoroethyl)arenes (Scheme 1d), a process that has not been reported to date. Therefore, the preparation of "CuCF$_2$CH$_3$" involved in the cross-coupling reaction was considered first.

At the onset of our investigation, we employed 1,1-difluoroethyl phenyl sulfone (PhSO$_2$CF$_2$CH$_3$, **1a**) or sulfoxide (PhSOCF$_2$CH$_3$, **1b**) as the CF$_2$CH$_3$ source. However, the conditions for the generation of "CuCF$_3$"[9] did not give the "CuCF$_2$CH$_3$" species, and only the unreacted starting material (**1a** or **1b**) and the byproduct 1,1-difluoroethene (CF$_2$=CH$_2$) were detected by ^{19}F NMR spectroscopy. The low reactivity of sulfone and sulfoxide reagents (**1a** and **1b**) could be attribut-

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ed to the difficulty in breaking the C–S bond to give $CH_3CF_2^-$ species. Thereafter, we attempted the reaction using (1,1-difluoroethyl)trimethylsilane (TMSCF$_2$CH$_3$, **1c**)[11] as the difluoroethyl precursor. To the mixture of CuCl (0.2 mmol) and *t*BuOK (2 equiv) in DMF at room temperature, reagent **1c** was added dropwise at the same temperature under an argon atmosphere (Table 1, entry 1). Indeed, the formed 1,1-difluoroethyl

Table 1. Screening of formation of "CuCF$_2$CH$_3$".[a]

$$\text{TMSCF}_2\text{CH}_3 \xrightarrow[\text{solvent, } T,\ 30\ \text{min}]{\text{CuCl, initiator}} \text{"CuCF}_2\text{CH}_3\text{"}$$
1c

| Entry	Initiator [equiv]	Solvent	T	Yield[b] [%]
1	*t*BuOK (2.0)	DMF	RT	38
2	*t*BuONa (2.0)	DMF	RT	0
3	CsF (2.0)	DMF	RT	0
4	*t*BuOK (2.5)	DMF	RT	11
5	*t*BuOK (1.5)	DMF	RT	35
6	*t*BuOK (2.0)	DMF	0 °C	67
7	*t*BuOK (2.0)	DMF	−10 °C	65
8[c]	*t*BuOK (2.0)	DMF	0 °C	53
9	*t*BuOK (2.0)	NMP	0 °C	52
10	*t*BuOK (2.0)	DMA	0 °C	60
11[d]	*t*BuOK (2.0)	DMF	0 °C	82
12[e]	*t*BuOK (2.0)	DMF	0 °C	98

[a] Reaction conditions: **1c** (0.2 mmol), CuCl (0.2 mmol), solvent (1 mL). [b] Yields were determined by ^{19}F NMR spectroscopy using PhCF$_3$ as an internal standard. [c] CuI was used. [d] **1c** (0.26 mmol) was used. "[Cu(CF$_2$CH$_3$)$_2$]$^-$" (27%, ^{19}F NMR) was produced. [e] **1c** (0.32 mmol) was used. "[Cu(CF$_2$CH$_3$)$_2$]$^-$" (32%, ^{19}F NMR) was produced.

copper species ("CuCF$_2$CH$_3$") exhibits three signals in the ^{19}F NMR spectrum: −67.0 ppm (A); −68.6 ppm (B) and −73.2 ppm (C) (q, $^3J_{F-H}$ = 28.2 Hz).[12] Similar to "CuCF$_3$" species,[13] the species A and B containing one CF$_2$CH$_3$ group, presumably complexed by DMF and chloride, denoted as "L·CuCF$_2$CH$_3$" (L = DMF, Cl$^-$), and the signal at −73.2 ppm (C) is tentatively assigned to "[Cu(CF$_2$CH$_3$)$_2$]$^-$". After screening of various initiators, we found that both *t*BuONa and CsF did not generate the "CuCF$_2$CH$_3$" species; the former mainly gave the protonated product (CH$_3$CF$_2$H) and the latter failed to activate the C-Si bond of TMSCF$_2$CH$_3$ (Table 1, entries 2–3). In addition, it was found that 2 equivalents of *t*BuOK were beneficial to produce the "CuCF$_2$CH$_3$" species (Table 1, entries 4–5). The low yield of "CuCF$_2$CH$_3$" generated from **1c** is probably due to its low thermal stability at room temperature. When the reaction was carried out at 0 °C (Table 1, entry 6), the yield of "CuCF$_2$CH$_3$" was increased to 67%. However, a lower temperature did not increase the yield (Table 1, entry 7). Furthermore, the employment of CuI failed to improve the yield of "CuCF$_2$CH$_3$" (Table 1, entry 8). After solvent screening, it was found that NMP or DMA was inferior to DMF (Table 1, entries 9–10).

In an attempt to improve the yield of "CuCF$_2$CH$_3$", we increased the loading of **1c** under the optimized conditions. When the amount of **1c** was increased to 1.3 equiv, the yield of the "CuCF$_2$CH$_3$" species was correspondingly enhanced to 82% (Table 1, entry 11). It should be noted that in this case, **1c**

was completely consumed and the amount of "[Cu(CF$_2$CH$_3$)$_2$]$^-$" increased. Consequently, when 1.6 equivalents of **1c** was used, the total yield of the "CuCF$_2$CH$_3$" species was increased to 98% (Table 1, entry 12), with 66% contribution from "L·CuCF$_2$CH$_3$" (L = DMF, Cl) and 32% from "[Cu(CF$_2$CH$_3$)$_2$]$^-$".

With an efficient method for the generation of "CuCF$_2$CH$_3$" in hand, we next investigated the 1,1-difluoroethylation reaction of aryl iodides with "CuCF$_2$CH$_3$". However, only a small amount of the difluoroethylated product was detected, even though we used both electron-deficient and electron-rich aryl iodides.[7c, h] The low efficiency of the cross-coupling reaction between aryl iodides and "CuCF$_2$CH$_3$" is probably due to the fact that the oxidative addition process usually requires high temperature and/or long reaction time. Thus, we envisioned that diaryliodonium salts, a more reactive version of aryl iodides in metal-catalyzed or -mediated reactions,[7l, 14] could react with "CuCF$_2$CH$_3$" for the synthesis of (1,1-difluoroethyl)arenes. After optimization of the reaction conditions, the reaction of diaryliodonium salts with "CuCF$_2$CH$_3$" neutralized by Et$_3$N·3HF[9, 10c, 15] (0.5 equiv) could provide the desired products in good yields at room temperature for 1 hour (Scheme 2).
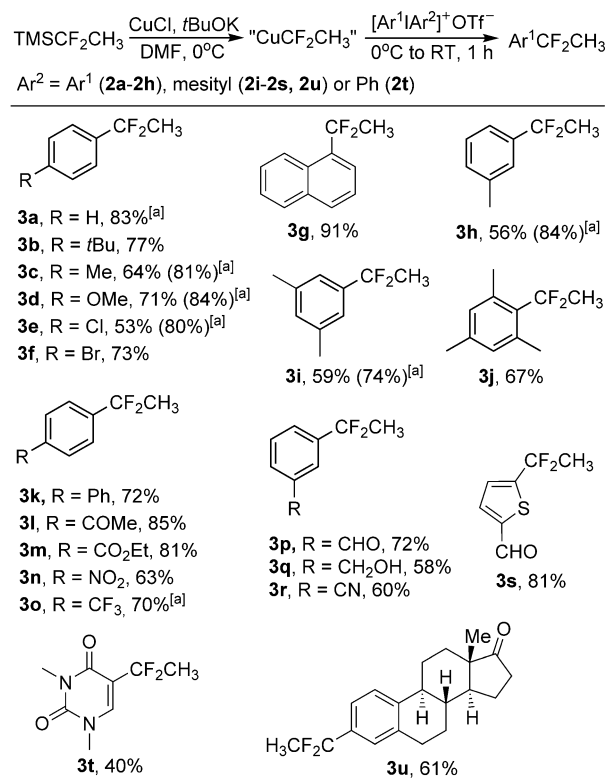
Scheme 2. Scope of 1,1-difluoroethylation of diaryliodonium salts with "CuCF$_2$CH$_3$". Reaction conditions: diaryliodonium salts (0.4 mmol), "CuCF$_2$CH$_3$" (1.5 equiv) neutralized by Et$_3$N·3HF (0.5 equiv), DMF (4 mL). Yields were of isolated products. [a] Yields were determined by ^{19}F NMR spectroscopy using PhCF$_3$ as an internal standard.

Generally, both electron-rich and -deficient aryl groups of diaryliodonium salts (**2**) were successfully transformed to give the corresponding (1,1-difluoroethyl)arenes (**3**) in 40% to 91% yields. This method tolerates various functional groups, such
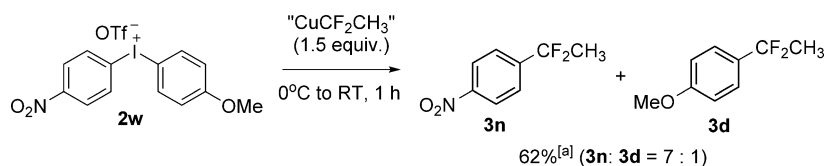
as *tert*-butyl (**3 b**), methoxyl (**3 d**), halides (**3 e** and **3 f**), acetyl (**3 l**), ester (**3 m**), nitro (**3 n**), trifluoromethyl (**3 o**), formyl (**3 p**), hydroxyl (**3 q**), nitrile (**3 r**), affording the desired products in moderate to good yields. It is noted that the (difluoroethyl)arenes bearing methyl group(s) (**3 c**, **3 h**, **3 i** and **3 j**) were obtained in good yields, which is impossible to accomplish by the activation of benzylic C−H bonds.[5] The employment of some aryl(mesityl)iodonium salts (**2 i**, **2 k**−**2 s**, **2 u**), owing to their straightforward preparation, provided the selective transfer of the smaller aryl groups,[16,17] even though a little amount of (mesityl)difluoroethyled compound was detected by GC-MS. Gratifyingly, the reaction worked well with a sterically hindered dimesityliodonium salt (**2 j**) under the optimized conditions, affording the difluoroethylated product (**3 j**) in a yield of 67 %. In addition, heteroaromatic iodonium salts (**2 s** and **2 t**) were also employed to provide the corresponding difluoroethyled heteroarenes (**3 s** and **3 t**) in moderate to good yields. Furthermore, a difluoroethylated estrone derivative (**3 u**) was also obtained by the reaction of an estrone-derived iodonium salt (**2 u**) with "CuCF$_2$CH$_3$" under the optimized conditions.

To further demonstrate the synthetic application of our 1,1-difluoroethylation protocol, we sought to apply the method to the difluoroethylation of medicinally important molecules. Naproxen, an anti-inflammatory drug, is usually modified to improve its potency by esterification of the carboxylic acid.[18] Herein, we synthesized a difluoroethyled naproxen derivative, substituting a difluoroethyl group for a methoxy group (Scheme 3). After the hydroxyl derivate of naproxen protected
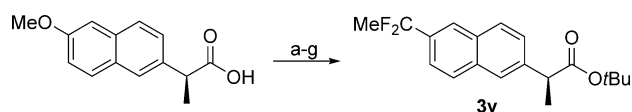
Scheme 3. Synthesis of a difluoroethyled naproxen derivative **3 v**. a) 40 % (w/w) HBr, reflux, 2 h, 86 %; b) i) (CF$_3$CO)$_2$O, THF, 0 °C, 4 h, ii) *t*BuOH, 0 °C to RT, 14 h, iii) 28 % (w/w) NH$_3$·H$_2$O, 0 °C to RT, 1 h, 72 %; c) Tf$_2$O (1.1 equiv), Et$_3$N, CH$_2$Cl$_2$, 0 °C to RT, 1.5 h, 92 %; d) [Pd(dppf)Cl$_2$] (4 mol %), (BPin)$_2$ (1.2 equiv), KOAc (3 equiv), DMSO, 80 °C, 58 %; e) NaIO$_4$ (3 equiv), 1N HCl, THF/H$_2$O (4:1, v/v), RT, 8 h, 85 %; f) i) MesI(OAc)$_2$ (1.1 equiv), BF$_3$·Et$_2$O (2 equiv), CH$_2$Cl$_2$, 0 °C to RT, 3 h, then NaBF$_4$ (aq), ii) NaOTf (aq), 52 %; g) i) TMSCF$_2$CH$_3$ (2.4 equiv), CuCl (1.5 equiv), *t*BuOK (3 equiv), DMF, ii) Et$_3$N·3HF (0.5 equiv), 82 %.

as a *tert*-butyl ester, the pinacol boronic ester group was accomplished by a palladium-catalyzed borylation of the corresponding triflate, and then hydrolyzed to the boronic acid. Finally, the naproxen-derived iodonium salt was obtained and transformed to the difluoroethyled naproxen derivative (**3 v**) in 82 % yield.
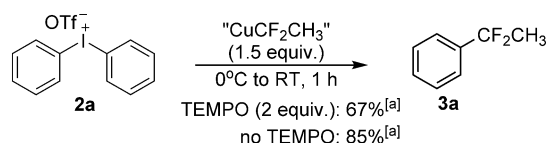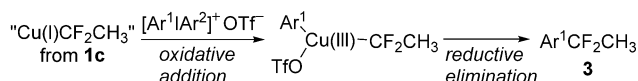
In the copper-mediated 1,1-difluoroethylation reaction, aryl groups instead of the mesityl group of aryl(mesityl)iodonium salts (Ar ≠ mesityl) are transferred to form the difluoroethylated products due to the steric effect of mesityl group, irrespective of electronic properties. Subsequently, we examined the electronic effect using an anisyl(*p*-nitrophenyl)iodonium salt, the result of which revealed preferential transfer of the more electron-deficient aryl group (Scheme 4).

We performed the reaction of diphenyliodonium salt (**2 a**) with "CuCF$_2$CH$_3$" generated from TMSCF$_2$CH$_3$ in the presence of 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) as a radical inhibitor, and found no significant decrease of the reaction efficiency (Scheme 5). The results indicate that the involvement of

Scheme 5. Radical trapping experiment and plausible reaction pathways for 1,1-difluoroethylation of diaryliodonium salts. [a] Yields were determined by ^{19}F NMR spectroscopy using PhCF$_3$ as an internal standard.

a radical pathway is unlikely. According to previous reports[7l, 13a] and our experimental results, we envisioned that the present copper-mediated 1,1-difluoroethylation reaction of diaryliodonium salts involves a Cu$^{I/III}$ process (Scheme 5). The pre-generated "Cu^{I}CF$_2$CH$_3$" species performs oxidative addition reaction with diaryliodonium salts to form the Cu^{III} species. The formed "ArCu^{III}CF$_2$CH$_3$" species undergoes reductive elimination to give the coupling products **3**.

In summary, the first copper-mediated 1,1-difluoroethylation reaction has been developed by using TMSCF$_2$CH$_3$. The pre-generated "CuCF$_2$CH$_3$" species from TMSCF$_2$CH$_3$ is found to be remarkably efficient for 1,1-difluoroethylation of diaryliodonium salts under mild conditions, affording electron-rich, electron-poor, and sterically hindered difluoroethylated arenes in good to excellent yields. The developed methodology proves to be highly functional group tolerant and is amenable to the 1,1-difluoroethylation of biologically active molecules: difluoroethyled estrone and naproxen derivatives were successfully synthesized under the optimized conditions. Furthermore, the

Scheme 4. Chemoselectivity of an anisyl(*p*-nitrophenyl)iodonium salt. [a] The yield was determined by ^{19}F NMR spectroscopy using PhCF$_3$ as an internal standard.

copper-mediated 1,1-difluoroethylation reaction probably involves a $Cu^{I/III}$ process.

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