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Copper-Catalyzed C−H Difluoroalkylations and Perfluoroalkylations of Alkenes and (Hetero)arenes

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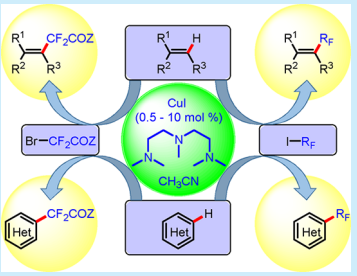
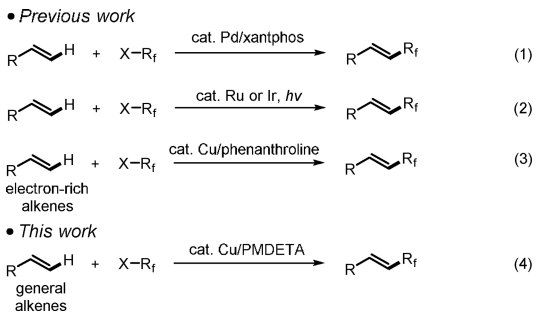
Supporting Information

ABSTRACT: A general and facile synthetic method for C(sp^2)−H difluoroalkylations and perfluoroalkylations of alkenes and (hetero)arenes with commercially available fluoroalkyl halides has been developed with a copper-amine catalyst system. This method is characterized by high yields, mild reaction conditions, low-cost catalyst, broad substrate scope, and excellent functional group compatibility, therefore providing a convenient synthetic strategy toward various difluoroalkyl- and perfluoroalkyl-substituted alkenes and (hetero)arenes.



Incorporation of fluorine atoms into organic motifs has a significant influence on the lipophilicity, metabolic stability, and bioavailability of organic molecules.[1] During the past several years, transition metal catalysis has emerged as a powerful tool for fluoroalkylation reactions. The direct C−H fluoroalkylation of alkenes and (hetero)arenes has been developed as an attractive approach to generate C−R_f bonds for the synthesis of corresponding fluoroalkylated compounds.[2,3] However, highly active trifluoromethyl reagents such as Togni's reagent and Umemoto's reagent are generally required as the fluorine sources. Recently, fluoroalkylation using relatively mild fluoroalkyl halides as a fluorine source has also been exploited by several research groups. For example, Zhang et al.[4] reported a Heck-type reaction for the synthesis of difluoromethylated alkenes using Pd as a catalyst and xantphos as a ligand (Scheme 1, eq 1). In addition, the Ru- or Ir-catalyzed fluoroalkylation of alkenes through a visible-light-induced reaction[5] was also developed (Scheme 1, eq 2). Despite all these achievements, the wide application of these strategies is limited by the high cost of the Pd or Ru catalyst systems, especially for application in large-scale synthesis of fluorinated molecules. More mild and practical catalytic systems need to be developed to provide a convenient strategy for the construction of fluorinated compounds.

Scheme 1. C−H Fluoroalkylation of Alkenes and (Hetero)arenes Using Fluoroalkyl Halides



Ethyl bromodifluoroacetate ($BrCF_2CO_2Et$, **2a**) is an inexpensive and commercially available reagent, which can serve not only as a *gem*-difluoromethylene (CF_2) group precursor but also as useful CF_2CO_2Et-containing synthons for the preparation of various difluoroalkylated compounds.[6] Cuprous iodide (CuI), which is a very cheap, bench stable, and easily handled catalyst, has been proven to be versatile for various types of reactions such as Goldberg reaction, Ullman coupling, Sonogashira coupling, and click reaction. Recently, CuI has also been proven effective in the direct transfer of the CF_2CO_2Et group from ethyl bromodifluoroacetate onto various alkenes.[7] However, these alkenes are limited to electron-rich alkenes such as enol ethers, enamides, dihydropyrans, and so on (Scheme 1, eq 3). Among these reports, phenanthroline is required as a ligand of copper and at least 1 equiv of inorganic base should be added. To study the difluoroalkylation of general alkenes, various reaction parameters especially ligands have been screened in our group. Herein we report an efficient and cost-effective strategy for the difluoroalkylation of a wide range of alkenes and (hetero)arenes using a cheap and easily accessible copper−amine catalyst system (Scheme 1, eq 4).

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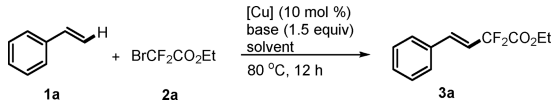
Our initial studies were focused on the difluoroalkylation of styrene (**1a**) with ethyl bromodifluoroacetate (**2a**) in the presence of CuI (10 mol %) and ligand in CH_3CN under an Ar atmosphere at 80 °C. In order to simplify the reaction system, 1.5 equiv of basic ligands were added, serving dual roles as ligand and base. As shown in Table 1, the choice of ligand is crucial in

Table 1. Optimization of Reaction Conditions[a]



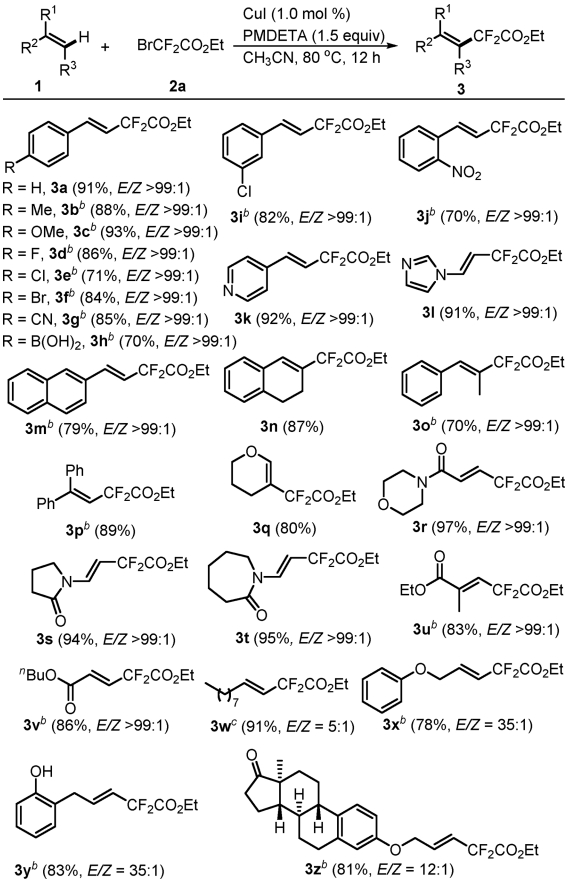
entry	[Cu]	base	solvent	yield[b](%)
1	CuI	none	CH_3CN	n.d.
2	CuI	K_2CO_3	CH_3CN	n.d.
3	CuI	DBU	CH_3CN	<5
4	CuI	Et_3N	CH_3CN	<5
5	CuI	phen	CH_3CN	<5
6	CuI	TMEDA	CH_3CN	73
7	CuI	TMPDA	CH_3CN	51
8	CuI	PMDETA	CH_3CN	97(92)
9[c]	CuI	PMDETA	CH_3CN	94(91)
10	CuCl	PMDETA	CH_3CN	75
11	CuBr	PMDETA	CH_3CN	80
12	$CuBr_2$	PMDETA	CH_3CN	65
13	$Cu(OTf)_2$	PMDETA	CH_3CN	67
14	CuI	PMDETA	toluene	26
15	CuI	PMDETA	DMSO	77
16	CuI	PMDETA	DMF	86

[a]Reaction conditions: Unless otherwise noted, all reactions were performed with **1a** (1.0 mmol), **2a** (1.5 mmol), base (1.5 mmol), and [Cu] (10 mol %), in CH_3CN (2 mL) at 80 °C under Ar for 12 h. [b]Determined by GC with dodecane as an internal standard. The values in parentheses are the isolated yields. n.d. = not detected. phen = phenanthroline. [c]1.0 mol % of CuI was used.

obtaining the desired product **3a**. No reaction occurred in the absence of ligand (entry 1). General bases such as K_2CO_3, Et_3N, DBU (1,8-diazabicyclo[5.4.0]undec-7-ene), and 1,10-phenanthroline led to no desired compounds (entries 2–5). However, when a multidentate amine such as TMEDA (*N,N,N′,N′*-tetramethyl-ethylenediamine), TMPDA (*N,N,N′,N′*-tetramethyl-1,3-propane-diamine), and PMDETA (pentamethyl-diethylenetriamine) were applied, the desired product **3a** can be afforded in good to excellent yields (entries 6–9). The key role of the multidentate amine might be its ability to stabilize the alkyl copper intermediates generated from corresponding alkyl halides and a copper catalyst.[8] Other copper salts, including CuBr, CuCl, $CuBr_2$, and $Cu(OTf)_2$, have also been screened (entries 10–13). Although good yields can be obtained, they are not higher than the yield of CuI as a catalyst. Therefore, CuI was chosen as the optimized catalyst for further reaction screening. Furthermore, when the catalyst loading was reduced to 1 mol %, the corresponding product **3a** can be achieved with a similar yield (entry 8). Various solvents, such as toluene, DMSO, and DMF (entries 14–16), were also examined, and DMF led to a similar yield as CH_3CN. Due to its easier workup procedure than in the case of DMF, CH_3CN was chosen as the most suitable solvent. Eventually, the reaction conditions in entry 8 were chosen as the optimized conditions.

With the optimized reaction conditions in hand, the substrate scope of the alkenes was investigated, and the results are summarized in Scheme 2. A variety of styrenes bearing different

Scheme 2. Copper-Catalyzed C–H Difluoromethylation of Alkenes[a]



[a]Reaction conditions: **1** (1.0 mmol, 1.0 equiv), **2a** (1.5 mmol, 1.5 equiv), PMDETA (1.5 mmol, 1.5 equiv), CuI (1.0 mol %), CH_3CN (2.0 mL), under Ar at 80 °C for 12 h. [b]5.0 mol % of CuI was used. [c]The reaction temperature was set at 100 °C.

substituents on the aromatic ring were initially examined (**3a–3p**). Various functional groups, such as halogen, ester, nitro, nitrile, ketone, and hydroxyl, were well tolerated to give desired products in moderate to excellent yields. It is noteworthy that the $B(OH)_2$ group can also be tolerated, and the product (**3h**) can be utilized for the synthesis of complex organofluoro compounds via Suzuki cross-coupling. Internal alkenes can also provide the corresponding products in high yield (**3o**) with high regioselectivity, which is difficult to realize through known methods. 1,1-Disubstituted alkenes also gave the corresponding products in high yields (**3p** and **3u**). Besides electron-rich alkenes, electron-poor alkenes can also be used as substrates to give the fluorinated alkenes (**3r**, **3u**, and **3v**) which could undergo Diels–Alder reaction to afford more complicated fluorine-containing organic molecules. Moreover, nonactivated aliphatic alkenes provided the corresponding products in high yields with high regio- and stereoselectivities under the standard conditions (**3w–3z**).

Encouraged by the above results, other functionalized difluoroalkylated bromides and perfluoroalkyl iodides were studied (Scheme 3). Gratifyingly, good yields (**4a–4c**) were obtained when bromodifluoroacetamides were used as fluorinating reagents. The *α*-bromo-*α*,*α*-difluoro-acetophenone was also a suitable substrate, providing its corresponding difluoroalkylated styrene (**4d**). It is noteworthy that bromodifluoromethyl-

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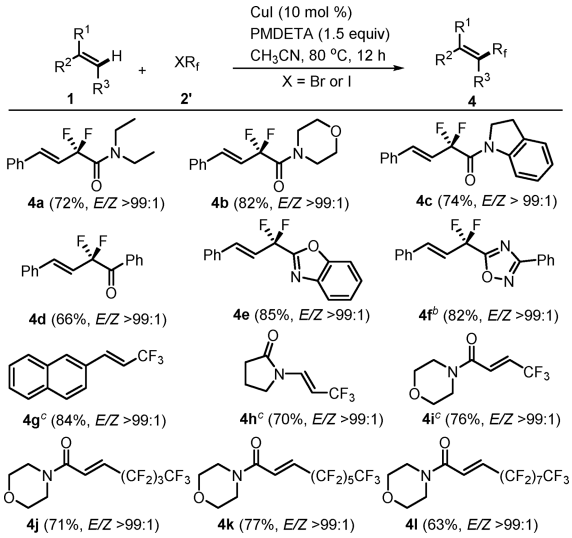
Scheme 3. Copper-Catalyzed C−H Fluoroalkylation of Alkenes[a]



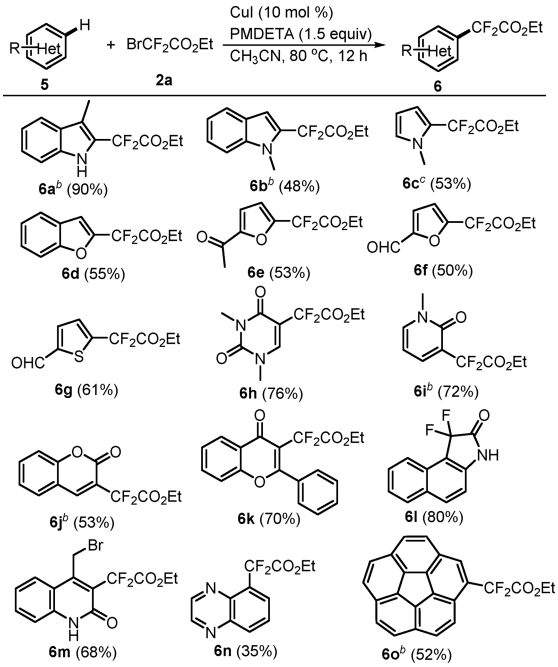
[a]Reaction conditions: **1a** (1.0 mmol, 1.0 equiv), **2′** (1.5 mmol, 1.5 equiv), PMDETA (1.5 mmol, 1.5 equiv), CuI (10 mol %), CH_3CN (2.0 mL), under Ar at 80 °C for 12 h. [b]The reaction temperature was set at 50 °C. [c]CF_3I (4.0 equiv), 90 °C.

benzoxazole and its derivatives can also be subjected to the above conditions, affording more diverse difluoromethyl benzoxazole compounds (**4e** and **4f**) which are potential pharmaceuticals and agrochemicals.[9] The reaction can also be applied to trifluoromethyl iodides, and a series of trifluoromethylated alkenes (**4g**−**4i**) were obtained through this method. Similarly, perfluoroalkyl iodides also underwent a similar transformation in good yields (**4j**−**4l**), thus providing a facile and general access to a wide range of perfluoroalkylated alkenes.

We next turned our attention to heterocycles since difluoroalkylated heterocycles are known as valuable pharmacophores. As shown in Scheme 4, a wide range of heterocycles is compatible with this new difluoroalkylation approach. The difluoroalkylation of indoles, pyrroles, furans, and thiophenes generally occurred with moderate yields and excellent regioselectivities, except that **6c** was accompanied by a bisdifluoroalkylated product (**6cc**). The major benefit of this facile difluoroalkylation method is that the late-stage incorporation of difluoroalkyl group into biologically active molecules could be realized in a regioselective manner. For instance, a uracil analog (**6h**), coumarin (**6j**), and flavones (**6k**) were selectively difluoroalkylated at specific positions, respectively. Furthermore, it was found that a 3,3-difluoro-oxindole derivative can be obtained with high efficiency when the heterocycle was replaced by *β*-naphthylamine (**6l**). The difluoroalkylation of corannulene (**6o**) can also occur in moderate yield. The trifluoromethylation and perfluoroalkylation of 3-methylindole can also be realized with good yields by improving the temperature in the standard conditions (Scheme 5).

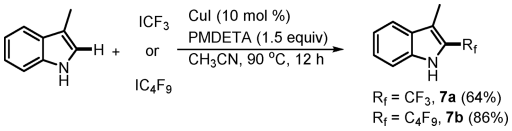
Importantly, a multigram-scale experiment has been demonstrated using styrene (**1a**) as a model substrate. Remarkably, gram-scale synthesis of **3a** in the presence of 0.5 mol % copper catalyst proceeded smoothly with high yield and stereoselectivity (Scheme 6). Thus, this general, facile, mild, and cost-effective method may offer a practical access to highly functionalized fluoroalkylated molecules.

Scheme 4. Copper-Catalyzed C−H Difluoromethylation of (Hetero)arenes[a]

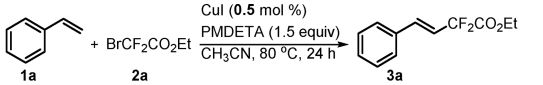


[a]Reaction conditions: **5** (1.0 mmol, 1.0 equiv), **2a** (3.0 mmol, 3.0 equiv), PMDETA (1.5 mmol, 1.5 equiv), CuI (10 mol %), CH_3CN (2.0 mL), under Ar at 80 °C for 12 h. [b]**2a** (1.5 mmol, 1.5 equiv) was used. [c]Bisdifluoroalkylation product (**6cc**) was also obtained in 21% yield.

Scheme 5. Synthesis of Perfluorinated 3-Methyl-indole



Scheme 6. Multigram-Scale Experiment



To gain some mechanistic insight into the reaction, the radical scavenger 2,2,6,6-tetramethyl-1-piperidinoxyl (TEMPO, 1.5 equiv) was added to the standard reaction mixture of **2a** and **1a**. Instead of forming **3a**, the TEMPO−CF_2CO_2Et was obtained as the only product (49% yield as estimated by ^{19}F NMR spectroscopy). *β*-Pinene, a known radical clock, was also used and gave the desired ring-opened diene in 81% yield (see the Supporting Information). In light of this result, a plausible radical pathway was proposed (Scheme 7).

In conclusion, direct C−H fluoroalkylation of alkenes and (hetero)arenes has been achieved with the bench stable cuprous iodide as a catalyst and commercially available fluoroalkyl halides (R_fX) as fluorinated reagents. Through this strategy, various types of alkenes, arenes, and heteroarenes can be regioselectively fluoroalkylated, demonstrating its broad applicability and general compatibility. The resulting fluoroalkylated alkenes and (hetero)arenes can serve as potential intermediates for further synthesis of biologically active compounds. Therefore, this

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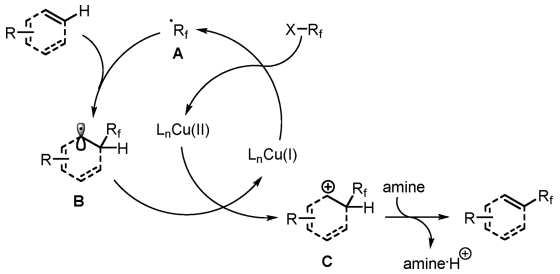
Scheme 7. Proposed Mechanism



method will not only provide a cost-effective and facile synthesis toward novel fluoroalkyl containing pharmaceutical molecules but also prompt research in low-cost transition-metal-catalyzed C(sp^2)−H fluoroalkylation reactions. Further study to elucidate the mechanism and apply this method to the synthesis of complicated bioactive molecules is underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b01712.

Experimental procedures, spectral and analytical data, copies of ^{1}H and ^{13}C NMR spectra for new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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