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## Direct Fluoroalkylation of Indoles with Fluoroalkyl Halides Mediated by Copper

Ru-Yi He,<sup>[a]</sup> Hui-Ting Zeng,<sup>[a]</sup> and Jing-Mei Huang\*<sup>[a]</sup>

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An efficient and mild copper-mediated reaction for the direct perfluoroalkylation and difluoromethylation of indoles with perfluoroalkyl halides and  $ICF_2COOEt$  to produce 2-substituted indoles was developed. Both free indole derivatives

Introduction

Exploitation of efficient methods to construct  $C-R_f$  ( $R_f$  = trifluoromethyl and perfluoroalkyl group) bonds has attracted much attention owing to the special biological and physical properties of fluorine-containing organic compounds.<sup>[1]</sup> Compared to methods for the incorporation of the trifluoromethyl group into organic molecules,<sup>[2,3]</sup> methods for perfluoroalkylation reactions, particularly on aryl or heteroaryl rings, are less developed,<sup>[4]</sup> despite the fact that the properties of perfluoroalkyl compounds ( $C \ge 2$ ), in certain cases, are superior to those of CF<sub>3</sub> derivatives.<sup>[5,1b]</sup>

Indoles are ubiquitous motifs present in both physiologically active natural products and important pharmaceuticals, and the synthesis of this important structure has attracted extensive attention from chemists for many years. However, methods for the perfluoroalkylation of indoles are quite rare.<sup>[6]</sup> One type of transformation relies on the indirect synthesis of the indole ring through cyclization by multistep reactions.<sup>[7]</sup> For the direct synthesis, several methods have been reported. Yoshida's group reported the perfluoroalkylation of nitrogen-containing heteroaromatic compounds by using bis(perfluoroalkyanoyl) peroxides.<sup>[8]</sup> Kamigata reported a method for the synthesis of fluoroalkyl-containing aromatic heterocyclic compounds from F(CF<sub>2</sub>)<sub>n</sub>SO<sub>2</sub>Cl catalyzed by RuCl<sub>2</sub>(PPh<sub>3</sub>)<sub>3</sub>.<sup>[9]</sup> Later, an approach relying on the employment of a reaction system of perfluoroalkyl iodides/H2O2/Fe2+ in DMSO that worked on pyrroles and some derivatives was reported.<sup>[10]</sup> Chen and Huang reported the perfluoroalkylation of aromatic and heteroaromatic compounds with perfluoroalkyl chlorides in the presence of sodium dithionite.<sup>[11]</sup> In these reports, only

and N-substituted indole derivatives could be used in this process to obtain the desired products in moderate to good yields.

a limited number of examples of a simple indole were studied.<sup>[9–11]</sup> Médebielle developed an electrochemical approach for the synthesis of perfluoroalkylated purine and indole analogues of plant-growth regulators, but only indole-3-acetic acid (ester) was studied.<sup>[12]</sup> Currently, no general method with full scope for the perfluoroalkylation of indoles has been reported. Thus, the development of straightforward and effective methods for the facile introduction of a perfluoroalkyl group to indoles is highly desirable. In connection with our interests in the construction of substituted indoles,<sup>[13]</sup> herein we report the first method for the Cu-mediated direct C–H perfluoroalkylation and difluoromethylation of indoles with perfluoroalkyl halides and ICF<sub>2</sub>COOEt under mild conditions.

#### **Results and Discussion**

Initially, we selected 3-methylindole (1a) as a model substrate and *n*-C<sub>4</sub>F<sub>9</sub>I as a perfluoroalkylation reagent to optimize the reaction conditions (Table 1). Inspired by previous work on copper-catalyzed or -mediated functionalization of arenes, we chose copper as a catalyst. Treatment of a mixture of 1a (1.0 equiv.) and  $n-C_4F_9I$  (1.4 equiv.) with CuI (0.5 equiv.) and 2,2'-bipyridine (bipy, 0.2 equiv.) in N,N-dimethyformamide (DMF) at 80 °C in air for 24 h resulted in desired product 3a in 36% yield (Table 1, entry 1). Encouraged by this result, different copper sources were further examined. Reactions performed with the use of Cu powder and Cu<sub>2</sub>O provided higher yields than those reactions promoted by CuBr, CuCl, CuCl<sub>2</sub>, and Cu(OAc)<sub>2</sub>·H<sub>2</sub>O (Table 1, entries 2-7). If 1.5 equiv. of Cu powder was used, the yield of 3a dramatically increased to 79% (Table 1, entry 8), and it was found that Cu<sub>2</sub>O was the most efficient catalyst: 3a was delivered in 80% yield if 0.5 equiv. of Cu2O was employed (Table 1, entry 9). Other solvents and ligands were also screened, but the yield of 3a was not as good as that obtained if DMF and bipy were applied (Table 1, en-

 <sup>[</sup>a] School of Chemistry and Chemical Engineering, South China University of Technology, Guangzhou, Guangdong 510640, China E-mail: chehjm@scut.edu.cn http://www.scut.edu.cn/

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tries 10–21). With regard to the effect of temperature on the reaction, we discovered that if the temperature was decreased, the yield of the desired product dropped drastically (Table 1, entries 22–24). If the reaction was conducted at a higher temperature (100 °C), the yield decreased slightly (Table 1, entry 25). No product was detected in the absence of copper (Table 1, entry 26). Notably, the product was obtained in only 4% yield if no ligand was employed (Table 1, entry 27).

Under the optimized conditions, various indole derivatives were used to react with perfluoroalkyl halides. Cu powder was chosen as a promoter for some substrates, and the results are summarized in Table 2. Both free indole derivatives (e.g., **1a**–**h**, see Table 2) and *N*-substituted indole derivatives (e.g., **1i**–**l**, see Table 2) reacted with perfluoroalkyl halides to give the desired products (e.g., **3a**–**l**, see Table 2). Moreover, a wide range of functional groups was tolerated under the reaction conditions, including hydroxy, ester, amide, carboxylic acid, and acyl groups (see products **3c–h**, **3l**, and **4p**). Perfluoroalkyl bromides also underwent this transformation to produce good yields without raising the temperature (**3b** and **3**<sub>j</sub>; see Table 2). The  $CF_2H$  unit is of special interest in isoster-based drug design and has great potential value, but methods for the introduction of a difluoromethyl group into arenes or heteroarenes are limited.<sup>[14]</sup> Under the present conditions, we were delighted to find that coupling of indoles with commercial ICF<sub>2</sub>COOEt afforded difluoromethylated products 4m-p in good yields. Thus, this reaction provides a new approach for the construction of difluoromethylated compounds. 1-Methylindole (1q) was also subjected to the standard reaction conditions (Table 2, entry 17), and the desired C2-perfluoroalkylated product was isolated in 25% yield. The C3-perfluoroalkylated product was obtained in 32% yield on the basis of <sup>1</sup>H NMR spectroscopy. The structures of **3a**, **3b**, and **3g** were confirmed by X-ray diffraction analysis (Table 2, entry 18).<sup>[15]</sup>

Notably, to test whether this method could be used to introduce a trifluoromethyl group into the indoles, the reaction of **1i** (0.25 mmol, 1.0 equiv.) with a stock solution of  $CF_3I$  (10.0 equiv.) in the presence of Cu powder (2.5 equiv.) was performed (Scheme 1). Delightedly, desired product **4i** 

Table 1. Optimization of the reaction conditions for the Cu-mediated coupling of 3-methyl-1H-indole with perfluoroalkyl iodides.<sup>[a]</sup>

[Cu]

		I N N	+ C <sub>4</sub> F <sub>9</sub> I solvent, li	gand V-C4	F <sub>9</sub>	
		Н 1а	T, 24	h Н <b>За</b>		
Entry	[Cu]	Solvent	Ligand	<i>T</i> [°C]	Conv. <sup>[b]</sup> [%]	Yield <sup>[b,c]</sup> [%]
1	CuI	DMF	bipy	80	47	36
2	CuBr	DMF	bipy	80	41	34
3	CuCl	DMF	bipy	80	35	25
4	CuCl <sub>2</sub>	DMF	bipy	80	8	0
5	Cu(OAc) <sub>2</sub> ·H <sub>2</sub> O	DMF	bipy	80	36	24
6	Cu powder	DMF	bipy	80	69	61
7 <sup>[d]</sup>	Cu <sub>2</sub> O	DMF	bipy	80	84	68
8[e]	Cu powder	DMF	bipy	80	98	79
9 <sup>[f]</sup>	Cu <sub>2</sub> O	DMF	bipy	80	>99	80 (72)
10	Cu <sub>2</sub> O	DMA	bipy	80	94	74
11	Cu <sub>2</sub> O	DMSO	bipy	80	96	76
12	Cu <sub>2</sub> O	NMP	bipy	80	94	77
13	Cu <sub>2</sub> O	CH <sub>3</sub> CN	bipy	80	92	70
14	Cu <sub>2</sub> O	CH <sub>3</sub> OH	bipy	80	81	63
15	Cu <sub>2</sub> O	dioxane	bipy	80	31	21
16	Cu <sub>2</sub> O	THF	bipy	80	61	57
17	Cu <sub>2</sub> O	toluene	bipy	80	32	14
18	Cu <sub>2</sub> O	DMF	phen <sup>[g]</sup>	80	67	53
19	Cu <sub>2</sub> O	DMF	tmeda <sup>[h]</sup>	80	90	72
20	Cu <sub>2</sub> O	DMF	eta <sup>[i]</sup>	80	50	47
21	Cu <sub>2</sub> O	DMF	$PPh_3$	80	8	0
22	Cu <sub>2</sub> O	DMF	bipy	60	61	53
23	Cu <sub>2</sub> O	DMF	bipy	40	33	19
24	Cu <sub>2</sub> O	DMF	bipy	r.t.	10	trace
25	Cu <sub>2</sub> O	DMF	bipy	100	97	70
26	_	DMF	bipy	80	6	0
27	Cu <sub>2</sub> O	DMF	-	80	14	4

[a] Reaction conditions: **1a** (0.25 mmol, 1.0 equiv.),  $n-C_4F_9I$  (0.35 mmol, 1.4 equiv.), Cu catalyst (0.125 mmol, 0.5 equiv.), ligand (0.05 mmol, 0.2 equiv.) in solvent (1.0 mL) for 24 h, unless otherwise noted. [b] Determined by analysis of the crude reaction mixture by <sup>1</sup>H NMR spectroscopy with nitrobenzene as an internal standard; yields are based on starting material **1a**. [c] In most cases, compounds from further perfluoroalkylation of the benzene ring were observed as the major byproducts. [d] Cu<sub>2</sub>O (0.25 equiv.). [e] Cu powder (1.5 equiv.). [f] Yield of isolated product is given in parentheses. [g] phen = 1,10-phenanthroline. [h] tmeda = N, N, N', N'-tetramethylethane-1,2-diamine.





Table 2. Scope of Cu-mediated coupling of indoles with fluoroalkyl halides.<sup>[a]</sup>

		$\bigcirc$	$\mathbb{R}^{1}$ + $\mathbb{N}_{\mathbb{R}^{2}}$	R <sup>f</sup> X or CF <sub>2</sub> CC	- DOEt	Cu <sub>2</sub> O or Cu bipy (20 mol-%) DMF, 80 °C, time					
		1	2 (1	1.4–2.5	equiv.)		CF <sub>2</sub> CC	DOEt			
Entry	Product	[Cu] (equiv.)	<b>2</b> [equiv.]	Time [h]	Yield <sup>[b]</sup> [%]	Entry	4 Product	[Cu] (equiv.)	<b>2</b> [equiv.]	Time [h]	Yielo [%
1	$C_4F_9$	Cu <sub>2</sub> O (0.5)	1.4	24	72	9	$C_4F_9$	Cu (2.5)	2.5	48	72
2	$C_6F_{13}$	Cu (1.5) Cu <sub>2</sub> O (0.5)	1.4	24	70 64 65	10	$\begin{array}{c} \mathbf{3i} \\ \mathbf{3i} \\ \mathbf{3i} \\ \mathbf{C}_{6} \mathbf{F}_{13} \\ \mathbf{N} \\ \mathbf{S}_{1} \\ \mathbf{C}_{6} \mathbf{F}_{13} \\ \mathbf{S}_{1} \\ \mathbf{S}_{1} \\ \mathbf{S}_{1} \\ \mathbf{S}_{2} \\ \mathbf{S}_{1} \\ \mathbf{S}_{2} \\ \mathbf{S}_{1} \\ \mathbf{S}_{2} \\ \mathbf{S}_{2} \\ \mathbf{S}_{1} \\ \mathbf{S}_{2} \\ \mathbf{S}_{2}$	Cu (2.5)	2.5	48	74 76
3	$\begin{array}{c} K A = C_{6}F_{13}BF \\ CH_2CH_2OH \\ CH_2CH_2OH \\ H \\ \mathbf{3c} \\ CH_2COOCH_3 \end{array}$	Cu <sub>2</sub> O (0.5)	2.0	24	55	11	$R'X = C_6F_{13}Br$ $R'X = C_4F_9$ $C_4F_9$ $R'X = C_4F_9$ $R'X = C_4F_9$	Cu (2.5)	2.5	60	45
4	$C_4F_9$	Cu <sub>2</sub> O (0.5)	2.0	24	50	12	C <sub>4</sub> F <sub>9</sub>	Cu (1.5)	2.5	24	50 <sup>[f</sup>
5	CH <sub>2</sub> CONH <sub>2</sub> CH <sub>2</sub> CONH <sub>2</sub> C <sub>4</sub> F <sub>9</sub> 3e	Cu <sub>2</sub> O (0.5)	2.0	24	50	13		t Cu (2.5)	2.0	24	52
6	$C_4F_9$ H 3f	Cu (2.5)	2.5	48	30 <sup>[c]</sup>	14		<sup>t</sup> Cu (2.5)	2.0	24	68
7	$CCOCH_3$ $C_4F_9$ H 3g	Cu <sub>2</sub> O (0.5)	2.0	24	54 <sup>[d]</sup>	15	4n CF <sub>2</sub> COOE Ph 40	<sup>t</sup> Cu (2.5)	2.0	36	50
8		Cu (2.5)	2.5	48	22 <sup>[e,c]</sup>	16		t Cu (2.5)	2.0	36	80
	3h ,					17	$\begin{array}{c} 4p\\ \\ \swarrow \\ V\\ 4q \end{array} C_4 F_9$	Cu <sub>2</sub> O (0.5)	1.5	48	25 <sup>[g</sup>
						18		C7 C7 C10 C10 C10 C10 C10 C10 C10 C10	F4 F6	F8 ØF7	
							;	X-ray structure c	₩ F9		

[a] Reaction conditions: 1 (0.25 mmol, 1.0 equiv.), bipy (0.2 equiv.), 80 °C. Unless otherwise noted, the conversion of 1 was >95%. [b] Yield of isolated product based on starting material 1. [c] Byproducts were not identified. [d] The starting material was recovered in 15% yield. [e] The starting material was recovered in 47% yield. [f] The starting material was recovered in 25% yield. [g] For details of other regioisomers, see the Supporting Information. [h] The ORTEP view of **3a** is drawn at the 30% probability level.

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was obtained in 83% yield based on conversion. This result provides promising precedent for the viability of the Cumediated trifluoromethylation of indoles with CF<sub>3</sub>I. The optimization of this process is currently under investigation in our laboratory. Furthermore, other aromatic heterocycles as well as (electron-rich) benzene derivatives, such as benzofuran, quinoline, and anisole, were also examined under our standard reaction conditions for perfluoroalkylation, but we failed to detect the desired products.



Scheme 1. Cu-mediated trifluoromethylation of indoles. The conversion and yield were determined by <sup>1</sup>H NMR spectroscopy.

To gain more insight into the reaction mechanism, several control experiments were conducted (Table 3). We found that if the radical inhibitor TEMPO (2,2,6,6-tetramethylpiperidine-1-oxyl) was added to the reaction mixture, the reaction was significantly inhibited and the desired product was detected in only 6% yield. If diallyl ether (1.4 equiv.) was added to the standard reaction system, desired product **3a** was obtained in 50% yield with recovery of **1a** in 37% yield. The cyclized product from diallyl ether was also observed by GC–MS and <sup>1</sup>H NMR spectroscopy. At the currently stage, the formation of a perfluoroalkyl radical through a single-electron transfer (SET) process is tentatively proposed (Scheme 2).<sup>[16,17,4a]</sup>

Table 3. Control experiments.



[a] All yields were determined by analysis of the crude reaction mixture by <sup>1</sup>H NMR spectroscopy with an internal standard; the yields are based on staring material **1a**. [b] The cyclized product 3-(iodomethyl)-4-(2,2,3,3,4,4,5,5,5-nonafluoropentyl)tetrahydrofuran from diallyl ether was observed by GC–MS and <sup>1</sup>H NMR spectroscopy.



Scheme 2. Proposed mechanism.

#### Conclusions

In summary, we described a mild, efficient, and straightforward method for the Cu-mediated C–H perfluoroalkylation and difluoromethylation of indoles with perfluoroalkyl halides and ICF<sub>2</sub>COOEt. The reaction tolerates a broad substrate scope and a wide range of functional groups. In addition, the reaction is not sensitive to air or moisture, so it may hold great potential for medicinal chemists for the synthesis of fluorinated bioactive compounds. Further investigations of the mechanistic details and applications of this reaction are currently underway in our laboratory.

#### **Experimental Section**

Procedure for the Polyfluoroalkylation of Indoles by Using Cu<sub>2</sub>O as a Catalyst: A 4.0 mL vial was charged with Cu<sub>2</sub>O (18.0 mg, 0.125 mmol, 0.5 equiv.), bipy (7.8 mg, 0.05 mmol, 0.2 equiv.), indole 1 (0.25 mmol, 1.0 equiv.), and DMF (1.0 mL). Polyfluoroalkyl iodide 2 (typically 2.0 equiv. according to the amount of 1 added) was then added. The vial was capped, and the mixture was stirred at 80 °C. Upon completion of the reaction (typically 24 h), the mixture was cooled to room temperature. Next, the mixture was poured into cool water and then 25% (w/w) aqueous ammonia (3.0 mL) and ethyl acetate (10.0 mL) were added. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (2 × 15.0 mL). The combined organic layer was washed with brine (10.0 mL), dried with anhydrous magnesium sulfate, filtered, and concentrated in vacuo. The crude product was purified by column chromatography on silica gel.

Procedure for the Polyfluoroalkylation of Indoles by Using Cu Powder as the Catalyst: A 4.0 mL vial was charged with Cu powder (1.5 or 2.5 equiv.), bipy (7.8 mg, 0.05 mmol, 0.2 equiv.), indole 1 (0.25 mmol, 1.0 equiv.), and DMF (1.0 mL). Polyfluoroalkyl iodide 2 (typically 2.0 equiv. according to the amount of 1 added) was then added. The vial was capped, and the mixture was stirred at 80 °C. Upon completion of the reaction (typically 48 h), the mixture was cooled to room temperature. Next, the mixture was poured into cool water and then 25% (w/w) aqueous ammonia (3.0 mL) and ethyl acetate (10.0 mL) were added. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (2 × 15.0 mL). The combined organic layer was washed with brine (10.0 mL), dried with anhydrous magnesium sulfate, filtered, and concentrated in vacuo. The crude product was purified by column chromatography on silica gel.

**Supporting Information** (see footnote on the first page of this article): Control experiments, characterization data, NMR spectra for all compounds, and crystallographic data for **3a**, **3b**, and **3g**.

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**Fluoroalkylation** 

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An efficient method for the synthesis of perfluoroalkylated and difluoromethylated indole derivatives is described. The reaction is mediated by copper under mild conditions. Both free indoles and N-substituted indoles react with perfluoroalkyl halides and  $ICF_2COOEt$  to afford the desired products in moderate to good yields.

RY.	He, HT	. Zeng,	
JM.	Huang*	•••••	1–7

Direct Fluoroalkylation of Indoles with Fluoroalkyl Halides Mediated by Copper

**Keywords:** Copper / Halides / Fluorine / Fluoroalkylation / Nitrogen heterocycles