## Synthetic Methods

# Stable but Reactive Perfluoroalkylzinc Reagents: Application in Ligand-Free Copper-Catalyzed Perfluoroalkylation of Aryl Iodides

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**Abstract:** The aromatic perfluoroalkylation catalyzed by a copper(I) salt with bis(perfluoroalkyl)zinc reagents  $Zn(R_F)_2(DMPU)_2$ , which were prepared and then isolated as a stable white powder from perfluoroalkyl iodide and diethylzinc, was accomplished to provide the perfluoroalkylated products in good-to-excellent yields. The advantages of this reliable and practical catalytic reaction are 1) airstable and easy-to-handle bis(perfluoroalkyl)zinc reagents can be utilized, 2) the reagent is reactive and hence the operation without activators and ligands is simple, and 3) not only trifluoromethylation but also perfluoroalkylation can be attained.

In synthetic organic chemistry, the introduction of fluoroalkylated functional groups into organic molecules continues to be a long-standing challenge due to unique property of fluorine.<sup>[1]</sup> Generally, fluoroalkylated compounds can be synthesized by using fluoroalkyl-containing building blocks<sup>[2]</sup> or fluoroalkylating reagents.<sup>[3]</sup> The former utilizes available fluoroalkyl-containing building blocks on early stage, thus playing an important role in catalytic asymmetric synthesis of optically active fluoroalkylated compounds.<sup>[2]</sup> The latter employs nucleophilic, electrophilic, and radical fluoroalkylations reactions by available fluoroalkylating reagents to directly introduce fluoroalkyl groups into target molecules not only on early stage but also late stage. Particularly, a considerable progress has been achieved on the transition-metal-mediated or -catalyzed trifluoromethylation of aromatic compounds by treatment of trifluoromethylating reagents.<sup>[3]</sup> The trifluoromethylation of aryl chloride<sup>[4]</sup> and aromatic C–H bond by directing group<sup>[5]</sup> could be catalyzed by unique palladium catalysts. On the other hand, Amii and co-workers reported that the trifluoromethylation of aryl iodides could be catalyzed by copper(I) salt through the addition of 1,10-phenanthroline as a ligand.<sup>[6]</sup> This finding triggered the development of the various stoichiometric and catalytic trifluoromethylation of aromatic system by copper(I) salt.<sup>[7,8]</sup> Especially, Hartwig<sup>[9]</sup> and Grushin<sup>[10]</sup> groups have independently reported the preparation and isolation of trifluoro-

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Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201405677. methyl-copper reagents and its application to trifluoromethylation reactions. In sharp contrast, the copper-catalyzed perfluoroalkylation of aryl halides is still undeveloped.<sup>[3]</sup> Recently, the copper-catalyzed perfluoroalkylation of aryl iodides has been disclosed for the first time, by using perfluoroalkylzinc reagents in situ pre-generated from TMP<sub>2</sub>Zn and 1*H*-perfluoroalkanes.<sup>[11]</sup> The fundamental drawback of this method is that TMP<sub>2</sub>Zn is extremely water- and air-sensitive. Therefore, the development of more reliable and practical method for catalytic perfluoroalkylation reactions on aromatic system is strongly desirable.<sup>[3]</sup> Herein, we report the ligand-free copper-catalyzed direct incorporation of not only trifluoromethyl but also perfluoroalkyl groups into aromatic moieties (Scheme 1). The ad-



Scheme 1. This work: copper-catalyzed perfluoroalkylation reactions.

vantages of our catalytic reaction are: 1) utilization of air-stable and easy-to-handle bis(perfluoroalkyl)zinc reagents; 2) a simple operation without the addition of ligands and fluoride activators, in sharp contrast to that of perfluoroalkylsilanes ( $R_FSIMe_3$ ), such as Ruppert–Prakash reagent; and 3) application to not only trifluoromethylation but also perfluoroalkylation under the relatively mild conditions.

Recently, we have reported the trifluoromethylation of aryl iodides catalyzed by copper(I) salt with trifluoromethylzinc in situ pre-generated from trifluoromethyl iodide (CF<sub>3</sub>I) and Zn dust in 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU).<sup>[12]</sup> The catalytic reaction gave moderate-to-high yields of the trifluoromethylated products under the mild reaction conditions. We envisaged the development of reliable and practical catalytic method not only for trifluoromethylation but also perfluoroalkylation by using bis(perfluoroalkyl)zinc reagents without halide, which can be isolated as air-stable and easy-to-handle solid due to the intrinsic drawback that gaseous  $CF_3I$  (boiling point -22.5 °C) is hard to handle due to the development of reactions in regular laboratories: thus, general synthetic applications are restricted. Naumann and co-workers have already reported  $Zn(CF_3)_2L_n$  (L: glyme n = 1, diglyme n = 1, pyridine n=2) complexes prepared by treatment of CF<sub>3</sub>I with dialkylzinc in the presence of Lewis base (L) in CCl<sub>3</sub>F as a solvent.<sup>[13,14]</sup> However, these reagents have never been utilized

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Scheme 2. Preparation of bis(perfluoroalkyl)zinc reagents.

successfully in catalytic reactions to the best of our knowledge. On the other hand,  $Zn(C_2F_5)_2(DMPU)_2$  but not  $Zn(CF_3)_2(DMPU)_2$ reagent prepared by a combination of C<sub>2</sub>F<sub>5</sub>H and TMP<sub>2</sub>Zn in DMPU as a solvent is also a known compound, which structure was confirmed by X-ray crystallography, was isolated by Daugulis and co-workers.<sup>[11,15]</sup> Referring to these previous reports, we investigated the synthetic methods improved for preparation and isolation of air-stable and easy-to-handle various bis-(perfluoroalkyl)zinc reagents. After a survey on the various zinc reagents, Lewis bases, and reaction conditions, it was found that the reaction with perfluoroalkyl iodides (2.5-5.0 equiv), diethyl zinc, and DMPU (2 equiv) in hexane below 0°C gave effi- $Zn(R_F)_2(DMPU)_2$  reagents **1** on gram scale ciently (Scheme 2a).<sup>[16]</sup> Reagents 1 existed as air-stable white solids, except for 1 a, which was slightly moisture sensitive and slowly decomposed in air at room temperature, but was stable for at least one month under argon atmosphere.<sup>[17]</sup> Additionally, the combination of 1 a and tetramethylethylenediamine (TMEDA; 1 equiv) in DMF underwent the ligand exchange to give the air-stable Zn(CF<sub>3</sub>)<sub>2</sub>(TMEDA) (2; Scheme 2b). The structure of complex 2, which is characterized by tetrahedral geometry of the Zn center, was undoubtedly determined by X-ray analysis of the single crystal.

The transmetallation reaction of CF<sub>3</sub> group to copper from zinc in DMPU using the zinc reagent **1a** was investigated by <sup>19</sup>F NMR spectroscopy (Scheme 3). Even at room temperature, the transmetallation proceeded to give two singlets of the cuprate species,  $[Cu(CF_3)I]^-$  (**A**:  $\delta_F = -29.1 \text{ ppm})^{[18]}$  and  $[Cu(CF_3)_2]^-$  (**B**:  $\delta_F = -31.9 \text{ ppm})^{[18]}$  in 19 and 9% yields, respectively (Eq. [1] in Scheme 3). Upon replacement with CuTC, the

Cul	Zn(CF <sub>3</sub> ) <sub>2</sub> (DMPU) <sub>2</sub> (1.0 equiv)		[Cu(CF <sub>3</sub> ) <sub>2</sub> ] <sup>¯</sup> <b>Β</b> , 9% δ <sub>F</sub> -31.9 ppm	(1)
	DMPU, rt, 1 h	<b>A</b> , 19% δ <sub>F</sub> -29.1 ppm		
CuTC	Zn(CF <sub>3</sub> ) <sub>2</sub> (DMPU) <sub>2</sub> (1.0 equiv) DMPU, rt, 5 min	CuCF <sub>3</sub> + <b>C</b> , 15% δ <sub>F</sub> -27.3 ppm	$[Cu(CF_3)_2]^{-}$ <b>B</b> , 28% $\delta_{F}$ -31.9 ppm	(2)

**Scheme 3.** Transmetallation to copper of  $CF_3$  group on zinc. Yields based on Cul or CuTC were determined by <sup>19</sup>F NMR analysis by using benzotrifluoride (BTF) as an internal standard (CuTC = copper(l)-thiophene-2-carboxylate).



Scheme 4. Copper-catalyzed trifluoromethylation of aryl iodides. Conditions: 3 (0.1 mmol), 1a (0.2 mmol), and Cul (0.01 mmol) in DMPU (0.2 mL) at 50 °C for 24 h. Yields were determined by <sup>19</sup>F NMR analysis by using BTF as an internal standard. [a] By using Cul (2 mol%). [b] Isolated yield. [c] By using 1a (1.6 equiv). [d] By using 1a (4 equiv). [e] By using CuTC (1.0 equiv) instead of Cul.

transmetallation was found to be much faster than that with Cul (Eq. [2] in Scheme 3). Interesting is that not the formation of cuprate **A** with iodide but neutral CuCF<sub>3</sub> (**C**:  $\delta_F = -27.3 \text{ ppm}$ ),<sup>[7, 10]</sup> which was clarified to be reactive species in various trifluoromethylation reactions, was confirmed to be obtained in 15% yield after five minutes, along with cuprate **B** in 28% yield.

Having established a method for the preparation of perfluoroalkylzinc reagents 1 as an air-stable solid, we explored the reliable and practical method for the copper-catalyzed trifluoromethylation and perfluoroalkylation to various aromatic rings. Initially, bis(trifluoromethyl)zinc 1 a was applied to the trifluoromethylation of aryl iodides 3 in catalytic amount of Cul (10 mol%; Scheme 4). After surveying a wide range of ligands and solvents, it was found that the reaction without ligand in DMPU at 50 °C was the most suitable. Under the optimized reaction conditions, aryl iodides with the electron-withdrawing substituents, such as ester, ketone, nitro, and nitrile, showed good-to-excellent yields (4a-d). Heteroaromatic compounds, pyridine 4e-f, pyrazine 4g, pyrimidine 4h, quinoline 4i, isoquinoline 4j, 1,3,5-triazine 4k, and purine riboside 4l were also formed by the catalytic reaction in good-to-excellent yields. Even when the amount of Cul was decreased to 2 mol%, 4h could be obtained in quantitative yield. The reaction could be performed on a gram scale without a decrease in yield. However, aryl iodide bearing the electron-donating methoxy substituents extremely decreased the reactivity to give almost virtually no product 4m even in the presence of each 1.0 equiv of Cul and 1,10-phenanthroline. In sharp contrast, the use of 1.0 equivalent of CuTC, which could generate neutral CuCF<sub>3</sub>, resulted in 74% yield of 4m, whereas the pentafluoroethylated by-product was provided in 15% yield.

The monitoring by <sup>19</sup>F NMR spectroscopy was performed to observe the formation of cuprate (**A** and **B**) prepared with Cul

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Table 1. Transmetallation to copper of perfluoroalkyl groups.								
	Z	$Zn(R_F)_2(DMPU)_2$ (1.0 equiv)						
	Cui —	DMPU, T	min)	$\frac{-}{A} \begin{bmatrix} Cu(R_F)_2 \end{bmatrix}$				
$R_{F} = C_{2}F_{5}$ (1 b)		$R_{F} = nC_{3}F_{7}$ (1 c)		R <sub>F</sub> =nC <sub>6</sub> F <sub>13</sub> ( <b>1 d</b> )				
Т	t	A/B	Т	t	A/B	Т	t	A/B
[°C]	[min]	[%] <sup>[a]</sup>	[°C]	[min]	[%] <sup>[a]</sup>	[°C]	[min]	[%] <sup>[a]</sup>
50	60	16/5	50	60	13/5	50	60	< 1/ < 1
70	5	40/19	70	5	14/7	70	5	< 1/ < 1
	30	49/31		60	29/24		60	13/5
90	5	39/19	90	5	33/18	90	5	23/10
	30	51/31		30	46/38		30	37/30
[a] Yields based on Cul were determined by <sup>19</sup> F NMR analysis by using BTF as an internal standard.								



Scheme 5. Copper-catalyzed pentafluoroethylation of aryl iodides. Conditions: 3 (0.2 mmol), 1 b (0.14 mmol), and Cul (0.02 mmol) in DMPU (0.4 mL) at 70 °C for 12–48 h. Yields were determined by <sup>19</sup>F NMR analysis by using BTF as an internal standard. [a] By using 1 b (0.5 equiv). [b] By using 1 b (1.0 equiv). [c] *p*-Nitrophenyl bromide was used instead of *p*-nitrophenyl iodide; reaction temperature was 90 °C.

and **1b-d** as a perfluoroalkyl source in DMPU (Table 1). At  $50^{\circ}$ C, the generation of cuprate **A** and **B** was observed. After the reaction mixture was gradually warmed up, the best yields were achieved at 90°C after 30 minutes, respectively. Consequently, it was elucidated that longer chain perfluoroalkyl groups showed slower transmetallation to copper from zinc.

Next, the pentafluoroethylation reaction of aryl iodides 3 was scrutinized as a coupling reaction on the aromatic system (Scheme 5). The reaction of *p*-nitrophenyl iodide even by treatment with 0.7 equivalent of zinc reagent 1b proceeded smoothly at 70 °C to give the pentafluoroethylated product 5 a in 93% yield, indicating that the second pentafluoroethyl group can transfer to copper. Although the use of 1.0 equivalent of 1b led to quantitative yield, 0.5 equivalent of 1b decreased yield (78%). Additionally, p-nitrophenyl bromide was also applicable to the present reaction in spite of moderate yield (48%). Under the optimized reaction conditions by using 0.7 equivalent of 1b, aryl iodides with the electron-withdrawing substituents and 2-iodopyridine gave excellent yields (91->99%) of the products **5b-e**. Interestingly, the electron-rich substrates could also lead to the corresponding products 5 f-h in high-to-excellent yields despite the prolonged reaction time



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**Scheme 6.** Copper-catalyzed perfluoroalkylation reactions of aryl halides. Conditions: **3** (0.2 mmol), **1 c-e** (0.2 mmol), and Cul (0.02 mmol) in DMPU (0.4 mL) at 90 °C for 72 h. Yields were determined by <sup>19</sup>F NMR analysis by using BTF as an internal standard. [a] Conditions: 90 °C for 24 h. [b] Conditions: 100 °C for 60 h. [c] Aryl bromides instead of aryl iodides were used. [d] By using **1 c-d** (0.7 equiv). [e] Isolated yield.

(48 h). This is in sharp contrast to the trifluoromethylation by using 1a, in which the decomposition of 1a occurred even at 50 °C to give extremely low yield on the electron-rich substrates (Scheme 4).

Perfluoroalkylation reactions with zinc reagent 1 c-e were also examined as the coupling reactions by using other kind of aryl halide (Scheme 6). In a similar manner to the pentafluoroethylation, aryl iodides with both the electron-withdrawing and -donating substituents gave good-to-excellent yields (**6a**– **d**, **7a**–**d**). Aryl bromides, such as *o*-ester, caffeine, and azulene, also underwent the reaction to give the corresponding products (**6**e, g, h, **7**e, g, h, and **8**g). Uracil derivative was also compatible with the reaction (**6–8**f).

The vinylic substrates were also applicable to the coppercatalyzed perfluoroalkylation reactions (Scheme 7). The use of



**Scheme 7.** Copper-catalyzed perfluoroalkylation reactions of vinyl iodides. Conditions: **9** (0.1 mmol, **9a**: R=Ph, *E/Z* 20:1; **9b**: R= $nC_6H_{13}$ , *E/Z* > 20:1), **1b** or **d** (0.1 mmol), and Cul (0.01 mmol) in DMPU (0.2 mL) at 90 or 120 °C for 24 or 48 h. Yields were determined by <sup>19</sup>F NMR analysis by using BTF as an internal standard. [a] The corresponding vinyl bromide (*E/Z* 11:1) instead of vinyl iodide **9a** was used.

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vinyl iodide **9a** (*E*/*Z* 20:1) promoted the reaction to produce the corresponding (*E*)-**10a** and **11a** in high yields and regioselectivities (93–97%, *E*/*Z* > 20:1) (Scheme 7a). Furthermore, the corresponding vinyl bromide (*E*/*Z* 11:1) could also lead to the perfluoroalkylated products **10a** and **11a** in moderate yields (67–73%, *E*/*Z* 13–14:1). Aliphatic vinyl iodide **9b** could be utilized as an available substrate. In the case of vinyl iodide **9c** (*E*/*Z* 1:17), the retention of geometry was observed (*E*/*Z* 1:17) to give good yields (Scheme 7b).

The mechanism of the present copper-catalyzed perfluoroalkylation reactions by using zinc reagents can be visualized by the following catalytic cycle (Scheme 8). During the first step,



Scheme 8. Proposed reaction mechanism.

the rate of transmetallation of perfluoroalkyl group to Cul from  $Zn(R_F)_2(DMPU)_2$  critically depends on the length of  $R_F$  to give the cuprate  $[Cu(R_F)I]^-$  and  $Zn(R_F)I(DMPU)_2$ , which readily causes Schlenk equilibrium to  $Zn(R_F)_2(DMPU)_2$  and  $ZnI_2$ .<sup>[14]</sup> Subsequently, the oxidative addition of aryl iodide to copper species ( $[Cu(R_F)I]^-$  or neutral CuR<sub>F</sub> generated by the dissociation of iodide from the cuprate), and finally the reductive elimination provides the desired perfluoroalkylated products.

In summary, we have succeeded in the aromatic perfluoroalkylation reactions catalyzed by copper(I) salt with bis(perfluoroalkyl)zinc reagents **1** prepared and then isolated from perfluoroalkyl iodide and ZnEt<sub>2</sub>. The advantages of this catalytic system are that air-stable and easy-to-handle bis(perfluoroalkyl)zinc reagents can be isolated and then utilized, the ligand/ activator-free operation without the addition of ligands (e.g., 1,10-phenanthroline) and activators (e.g., KF) is simple, and not only trifluoromethylation but also perfluoroalkylation are applicable. Further studies on new and practical perfluoroalkylation reactions with bis(perfluoroalkyl)zinc reagents are under way in our laboratory.

### **Experimental Section**

**Preparation of bis(trifluoromethyl)zinc reagent Zn(CF\_3)\_2(DMPU)\_2** (1 a; Scheme 2 a): To an oven-dried 50 mL two-neck round-bottomed flask equipped with a magnetic stir bar were added *n*hexane (15 mL) and DMPU (2.41 mL, 20 mmol) under argon atmosphere. Trifluoromethyl iodide (ca. 9.8 g, 50 mmol) was bubbled into the solution at -60 °C. Diethylzinc (1.0 m in hexanes, 10 mL, 10 mmol) was then added dropwise at -60 °C. After stirring at -20 °C for 48 h, unreacted trifluoromethyl iodide and hexanes were removed in vacuo. The solid obtained was washed with Et<sub>2</sub>O (15 mL) three times and dried under vacuum to give Zn(CF<sub>3</sub>)<sub>2</sub>(DMPU)<sub>2</sub> (**1a**) as a white powder (4.15 g, 90% yield). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  = 3.27 (t, *J* = 6.0 Hz, 8H), 2.98 (s, 12 H), 1.97 ppm (quint, *J* = 6.0 Hz, 4H); <sup>13</sup>C NMR (75 MHz, [D<sub>7</sub>]DMF):  $\delta$  = 157.3, 146.2 (qq, *J*<sub>CF</sub> = 4.8, 359.2 Hz, CF<sub>3</sub>), 48.0, 35.4, 22.2 ppm; <sup>19</sup>F NMR (282 MHz, CDCl<sub>3</sub>):  $\delta$  = -43.5 (s, 6F); HRMS (ESI-TOF) calcd for C<sub>13</sub>H<sub>24</sub>F<sub>3</sub>N<sub>4</sub>O<sub>2</sub>Zn [*M*-CF<sub>3</sub>]<sup>+</sup>: 389.1143; found: 389.1126; elemental analysis calcd for C<sub>14</sub>H<sub>24</sub>F<sub>6</sub>N<sub>4</sub>O<sub>2</sub>Zn: C 36.58, H 5.26, N, 12.19; found: C 35.99, H 4.97, N 12.01.

General procedure for trifluoromethylation of aryl iodide by using  $Zn(CF_3)_2(DMPU)_2$  (1 a; Scheme 4): To a test tube equipped with a magnetic stir bar was added  $Zn(CF_3)_2(DMPU)_2$  (1 a; 92 mg, 0.2 mmol), Cul (1.9 mg, 0.01 mmol, 10 mol%), DMPU (0.2 mL), and aryl iodide 3 (0.1 mmol) at RT under argon atmosphere. After stirring at 50 °C for 24 h, the reaction mixture was quenched with HCl (5 mL), and then Et<sub>2</sub>O (5 mL) was added. The organic layer was separated, and the aqueous layer was extracted with Et<sub>2</sub>O (5 mL×3). The combined organic layer was washed with brine (10 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, and evaporated under reduced pressure. The resulting crude product **4** was purified by silica-gel column chromatography.

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**Keywords:** copper · perfluoroalkylation · perfluoroalkylzinc · transmetallation · synthetic methods

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# COMMUNICATION

#### Synthetic Methods

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Stable but Reactive Perfluoroalkylzinc Reagents: Application in Ligand-Free Copper-Catalyzed Perfluoroalkylation of Aryl Iodides



Homogeneous catalysis: The aromatic

perfluoroalkylation catalyzed by copper

with  $Zn(R_F)_2(DMPU)_2$  reagents (DMPU =

pyrimidinone) was accomplished to pro-

1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-

 air-stable and easy-to-handle perfluoroalkylzinc reagent
 simple operation without ligand and activator
 not only trifluoromethylation but also perfluoroalkylation

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vide the products in good-to-excellent yields. The advantages of this reliable and practical catalytic reaction are given in the scheme.

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