

Perfluoroalkylation | Hot Paper |

## Dialkylzinc-Mediated Cross-Coupling Reactions of Perfluoroalkyl and Perfluoroaryl Halides with Aryl Halides

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**Abstract:** A highly chemoselective perfluoroalkylation reaction of aromatic halides is reported. Thermally stable perfluoroalkylzinc reagents, generated by a rapid halogen-zinc exchange reaction between diorganozinc and perfluoroalkyl halide species, couple with a wide range of aryl halides in the presence of a copper catalyst, in moderate to high yields. Good stability of the perfluoroalkylzinc species was indicated by DFT calculation and the reagents were storable for at least three months under argon without loss of activity. This method is applicable to gramscale synthesis, and its functional group tolerance compares favorably with reported protocols.

Fluorine-containing organic compounds, especially aromatic and  $\pi$ -conjugated molecules, have attracted much attention in medicinal chemical and materials sciences and tremendous efforts have been devoted to development of efficient methods for introduction of fluorine atoms or the trifluoromethyl groups into organic molecules.<sup>[1]</sup> Perfluoroalkyl (R<sub>F</sub>) groups have been less well utilized as functional building blocks,<sup>[2,3]</sup> mainly due to the lack of an efficient synthetic methodology for regiocontrolled installation of R<sub>F</sub> groups on aromatic rings.<sup>[4,5]</sup> The Swarts-type transformation<sup>[6]</sup> is not applicable to the synthesis of perfluoroalkylated aromatics from their alkyl counterparts. The main hurdle is that R<sub>F</sub>-metal species are very unstable, even at very low temperatures, and readily decompose via  $\alpha$ - or  $\beta$ -elimination of fluoride.<sup>[7]</sup> This largely accounts for the immaturity of perfluoroalkylation reactions to date. Our approach capitalizes on the soft reactivity of organozinc reagents. We have been working on development of methods for chemoselective zincation of organic molecules based on halogen-zinc exchange, utilizing monoanion- and dianion-type ate complexes,<sup>[8]</sup> as well as deprotonative zincation by zinc ate bases.<sup>[9]</sup> In 2011, Daugulis and co-workers elegantly demon-

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strated deprotonative metalation of a 1*H*-perfluoroalkane by TMP<sub>2</sub>Zn (TMP = 2,2,6,6-tetramethylpiperidido) to form R<sub>F2</sub>Zn and utilized it in copper-catalyzed cross-coupling reactions with aryl iodides.<sup>[10]</sup> However, this metalation process required laborious preparation of TMP<sub>2</sub>Zn. We became interested in R<sub>F</sub> halides as metalation precursors to obtain R<sub>F</sub>-zinc reagents for cross-coupling, because R<sub>F</sub> halides have a number of synthetic advantages as R<sub>F</sub> sources, including ready availability of a great variety of R<sub>F</sub> halides, low cost,<sup>[11]</sup> and ease in handling in both laboratory research and in industry as compared to R<sub>F</sub>–H<sup>[10,11]</sup> or R<sub>F</sub>–SiR<sub>3</sub> species.<sup>[12,13]</sup> Herein, we report operationally benign, chemo-/regioselective, copper(I)-catalyzed cross-coupling reactions between R<sub>F</sub> halides and aryl halides, via the formation of thermally and chemically stable R<sub>F</sub>–zinc species.<sup>[14]</sup>

Our investigation commenced with exploration of an appropriate metalation method to form  $R_F$ -zinc species using nonafluorobutyl iodide as the  $R_F$  source. As a model reaction, we selected the coupling reaction between the intermediate  $R_F$ -zinc species and *ortho*-iodobenzoate **1a** in the presence of 10 mol% of CuCl (Table 1). When mono-anionic [Me<sub>3</sub>Zn]Li was



used, a trace amount of the desired coupling product **2 aa** was detected by GC/MS (Table 1, entry 1). The dianion-type zincate [Me<sub>4</sub>Zn]Li<sub>2</sub> developed by our group<sup>[8b]</sup> was found to be unproductive (Table 1, entry 2). In both cases, unreacted **1 a** was not recovered, which might be attributed to the instability of the generated R<sub>F</sub>-zincate species at the reaction temperature. The use of less reactive Me<sub>2</sub>Zn led to the formation of **2 aa** in 17%



yield (Table 1, entry 3). This indicated that metalation had successfully occurred<sup>[15,16]</sup> and the resulting R<sub>F</sub>--zinc species was reasonably stable under these reaction conditions. The use of Et<sub>2</sub>Zn in lieu of Me<sub>2</sub>Zn did not improve the yield significantly (20% yield; Table 1, entry 4), but a better result was obtained by raising the reaction temperature to 90 °C (64% yield; Table 1, entry 5), although the crude reaction mixture was messy.

We next investigated the effect of solvent (Table 2, entries 1–9). With cyclopentylmethylether (CPME), **2 aa** was obtained in only 21% yield (Table 2, entry 2). Acetonitrile slightly

Table 2. Initial optimization of the reaction conditions. <sup>[a]</sup>							
C₄F	9-l +	$O = \underbrace{\bigcup_{12}}_{0} \underbrace{\bigcup_{12}}_{25} \underbrace{\operatorname{Et}_{2}\operatorname{Zr}}_{25} \\ \operatorname{CuX} (10 \text{ r})$					
		⟨⟩ 1a	solvent <b>C</b> <sub>4</sub> <b>F</b> <sub>9</sub> <b>-</b> 90°C, 16 h		aa		
Entry	Solvent	Et <sub>2</sub> Zn [equiv]	C₄F <sub>9</sub> I [equiv]	Cu salt	Yield [%] <sup>[b]</sup>		
1	THF	1.5	2.25	CuCl	64		
2	CPME	1.5	2.25	CuCl	21		
3	CH₃CN	1.5	2.25	CuCl	73		
4	DMF	1.5	2.25	CuCl	69		
5	DMSO	1.5	2.25	CuCl	66		
6	NMP	1.5	2.25	CuCl	79		
7	DMPU	1.5	2.25	CuCl	89		
8	toluene	1.5	2.25	CuCl	8		
9	DCE	1.5	2.25	CuCl	20		
10	DMPU	1.0	1.5	CuCl	74		
11	DMPU	1.5	2.25	CuBr	91		
12	DMPU	1.5	2.25	Cul	90		
13	DMPU	1.5	2.25	CuCN	82		
14	DMPU	1.5	2.25	CuOAc	77		
15	DMPU	1.5	2.25	CuCl–phen <sup>[c]</sup>	87		
16	DMPU	1.5	2.25	CuCI–IPr <sup>[d]</sup>	83		
17	DMPU	-	3.0	-	0		
18	DMPU	-	3.0	CuCl	0		
19	DMPU	1.5	3.0	-	22		

[a] Reaction conditions:  $C_4F_9I$ ,  $Et_2Zn$  (1.06  $\mbox{m}$  solution in *n*-hexane), **1a** (0.5 mmol), Cu salt (10 mol%) in solvent (0.5 mL) were stirred at 90  $^\circ$ C under an argon atmosphere for 16 h. [b] Determined by GC using dodecane as an internal standard. [c] 20 mol% of phen was used. [d] IPr=1,3-bis(2,6-diisopropylphenyl)imidazoI-2-ylidene.

improved the yield (Table 2, entry 3). Nonprotic, strongly coordinating solvents were effective for smooth conversion of **1 a**. DMF and DMSO gave **2 aa** with similar yield to that in THF (Table 2, entries 4 and 5). *N*-Methyl pyrrolidone (NMP) improved the yield of **2 aa** to 79% yield (Table 2, entry 6). To our delight, the reaction proceeded remarkably cleanly in even more strongly coordinating *N*,*N'*-dimethylpropyleneurea (DMPU), affording **2 aa** in excellent yield (89%; Table 2, entry 7). This result can be explained in terms of well-balanced stability and reactivity of the R<sub>F</sub>-zinc species, with coordination of DMPU to the vacant orbitals.<sup>[17]</sup> As expected, reactions in solvents with low polarity, such as toluene and 1,2-dichloroethane, resulted in low yields (8% and 20%, respectively; entries 8 and 9). Based on these results, further optimization was performed using DMPU as the solvent. Reducing the amount

of Et<sub>2</sub>Zn to one equivalent with respect to 1a decreased the yield to 74% (Table 2, entry 10). CuBr and Cul gave 2aa in comparable yields to that with CuCl (Table 2, entries 11 and 12 vs. entry 7), whereas CuCN and CuOAc gave slightly lower yields (82%, entry 13, and 77%, entry 14). Addition of 1,10phenanthroline (phen; 2 equiv) to the CuCl catalyst gave the product in high yield (Table 2, entry 15)<sup>[18]</sup> and the N-heterocyclic carbene-Cu complex was also an effective catalyst (entry 16).<sup>[19]</sup> Control experiments revealed that Et<sub>2</sub>Zn, C<sub>4</sub>F<sub>9</sub>I, and Cu salt were all necessary for smooth reaction (Table 2, entries 17-19). In the absence of the copper catalyst (Table 2, entry 19), a small yield of 2 aa was obtained. Nucleophilic aromatic substitution reaction was ruled out by DFT calculations<sup>[17]</sup> and 2 aa was presumably formed via a radical mechanism.<sup>[20]</sup> It is worth noting that Bu<sub>2</sub>Mg did not give any of the desired product under the optimized reaction conditions outlined in Table 2, entry 12.

After identifying the optimal reaction conditions, we examined the scope of this reaction using a range of perfluoroalkyl halides and fluorinated aryl halides (Table 3). The coupling re-



<sup>(0.75</sup> mmol; 1.06  $\mu$  in *n*-hexane), Cul (10 mol%) in DMPU (0.5 mL) were stirred at 90 °C under an argon atmosphere for 16 h. Yields given are for isolated products. [b] Bromine–zinc exchange reaction was run at 77 °C for 3 h prior to addition of **1a** and Cul, then the mixture was stirred at 90 °C for 13 h. [c] 20 mol% of phen was added. [d] lodine–zinc exchange reaction was run at 77 °C for 3 h prior to addition of **1a** and Cul, then the mixture was stirred at 120 °C for 13 h.

action between nonafluorobutyl iodide and **1a** gave the desired product **2aa** in 89% yield. It should be emphasized that this reaction can be easily scaled up; **2aa** was obtained on a gram scale in 93% yield. C3, C5, C6, and C8 homologous iodides reacted similarly to give the corresponding products in excellent yields (**2ab**: 91%; **2ac**: 91%; **2ad**: 91%; **2ae**: 86%) and the C10 derivative (**2af**) could be similarly synthesized in

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good yield (72%). Importantly, less reactive perfluoroalkyl bromide also gave the product **2 ae** in 94% yield. Perfluoroalkylation did not proceed when  $\alpha$ -branched R<sub>F</sub>–I (*i*-C<sub>3</sub>F<sub>7</sub>I), was employed, presumably due to the high stability of the corresponding zinc reagent. This protocol is applicable to perfluoroarylation of **1 a**.<sup>[21]</sup> Pentafluorophenylation gave **2 ah** in 88% yield and less fluorinated 2,6-difluoro-1-iodobenzene participated in the coupling reaction to afford **2 ai** in 74% yield.

We next examined the storability of perfluoroalkylzinc solution (Scheme 1). We performed the model perfluoroalkylation reaction with four identically prepared zinc reagent solutions. The reagent was found to be stable and to afford the desired product **2aa** without loss of activity for at least three months.



Scheme 1. Storability of perfluoroalkylzinc solution.

These results clearly show the robustness, practicality, and broad applicability of this methodology for functional mole-cule synthesis.

A wide range of aryl- and heteroaryl halides was found to provide the corresponding perfluoroalkylated products (Table 4). Benzyl 2-iodobenzoate gave the product 2ba in 88% yield. The more labile aryl ester functionality was tolerated, and 2 ca was obtained in 95% yield. The regioisomers of 1 a, 3and 4-iodobenzoates, were less reactive than the model substrate 1a and required both a higher reaction temperature (120°C) and a longer reaction time (38 h) to give the desired products in satisfactory yields (2da: 87%; 2ea: 72%). To our surprise, this reaction was compatible with the strong oxidant 3-iodobenzoquinone, affording the desired product 2ga in 60% yield. A boronate moiety was not damaged under the reaction conditions and synthetically useful perfluoroalkylated aryl boronate 2ha was obtained in 65% yield. Nucleophilic perfluoroalkylation of the ketone functionality was not observed and 2-R<sub>F</sub>-benzophenone 2ia was isolated in 95% yield. Cyano group survived under these conditions (2 ja and 2 ka). R<sub>F</sub>-phthalonitrile 2ka is an especially interesting compound with potential for the synthesis of multiply perfluoroalkylated phthalocyanines.<sup>[22]</sup> Recalcitrant substrates, for example, iodonaphthalenes and iodobiphenyl without an electron-withdraw-



[a] Reaction conditions: **1** (0.5 mmol),  $R_F$ –I (1.13 mmol),  $Et_2Zn$  (0.75 mmol; 1.06 M in *n*-hexane), Cul (10 mol%), and phen (20 mol%) in DMPU (0.5 mL) were stirred at 90 °C under an argon atmosphere for 16 h. Yields given are for isolated products, with NMR-evaluated yields, determined from the <sup>1</sup>H NMR spectra using mesitylene as an internal standard, given in parentheses. [b] Without phen. [c] T=120 °C. [d] t=38 h. [e] Cul (20 mol%) and phen (20 mol%) were used. [f] t=40 h. [g] t=42 h. [h] Run with Me<sub>2</sub>Zn.

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ing substituent, were converted to the corresponding perfluoroalkylated products in moderate to high yields at 120 °C (2 la, 2ma, 2na, 2oa, and 2pa). Protected iodophenol derivatives also gave the desired products (2 ga, 2 ra, 2 sa, and 2 ta). Notably, no desilylation of benzylic silyl ether was observed (2ua). Heteroaromatic compounds also participated in this perfluoroalkylation reaction. Thiophenes were perfluoroalkylated with high efficiency (2va: 90%; 2wa: 83%). Perfluoroalkylated indole 2xa was obtained in 50% yield. Pyridine and pyrazine reacted smoothly to afford the desired nitrogen heteroaromatics in high yields, although significantly lower yields were obtained, compared to the NMR-evaluated yields, due to high volatility of these compounds (2 ya and 2 za). Quinoline and pyrimidine gave the desired products 2 aaa and 2 baa, albeit in low yields. 2-lodobenzothiazole suffered from dimerization, probably due to competition with perfluoroalkyl iodide in the iodine-zinc exchange process owing to its high reactivity. Use of Me<sub>2</sub>Zn instead of Et<sub>2</sub>Zn solved this problem, providing 2 caa in 66% yield. R<sub>F</sub>-caffeine 2 daa was synthesized in 60% yield and R<sub>F</sub>-uracil 2eaa was also obtained in 57% yield.

Aryl bromides with a directing ester group were perfluoroalkylated at 120 °C (Table 5). Dodecyl 2-bromobenzoate gave the product 2 aa in 86% yield, whereas its 2-trifluoromethanesulfo-



nyloxy counterpart remained intact under the reaction conditions. Next, several bromothiophenes were examined, since functionalized (oligo)thiophenes are extremely useful for creating novel functional materials.<sup>[2]</sup> It would be synthetically advantageous if bromides could be used as coupling precursors. Reactions of brominated thiophenecarboxylates proceeded in good yield irrespective of the position of the bromine atom (2 va: 48%; 4 aa: 37%, 4 ba: 89%). The substrate 3 ca gave an unassignable complex mixture arising from debromination at the 5-position and other side reactions. The dodecylthioester 3 da gave the product 4 da in 36% yield, although a small amount of ethyldodecylsulfide was formed via cleavage of the thioester moiety.<sup>[18]</sup> 3-Perfluoroalkylated aldehyde 4ea was obtained in moderate yield.

Envisioning applications of this methodology in functional materials synthesis, we also examined the feasibility of multiple perfluoroalkylation reactions (Table 6). 1,4-Diiodobenzene was



[a] Detailed reaction conditions are given in the Supporting Information. Yields given are for isolated products, with NMR-evaluated yields, determined from the <sup>1</sup>H NMR spectra using mesitylene as an internal standard, given in parentheses. [b] A small amount of mono-perfluoroalkylated byproduct and mesitylene (an internal standard for the NMR yield) were not separable.

converted to the corresponding diperfluoroalkylated benzene 6 aa in 38% yield and the diperfluoroarylated product 6 ba was obtained in 90% yield. Perfluoroalkylation of 4,4'-diiodobiphenyl proceeded smoothly to give the desired product 6ca in 78% yield. The diiodinated BINOL derivative was also successfully transformed into the product 6da in 51% yield. Notably, the triperfluoroalkylated terphenyl 6ea was synthesized in 70% yield (95% yield by <sup>1</sup>H NMR) without detectable formation of mono- or diperfluoroalkylated by-products.

In conclusion, we have developed an efficient and operationally benign method for perfluoroalkylation and -arylation reactions utilizing halogen-zinc exchange as a key step. Various substrates were perfluoroalkylated with excellent functional-group tolerance in moderate to high yields, simply by mixing R<sub>F</sub>-I, Et<sub>2</sub>Zn, Cul and the corresponding aryl halides. The remarkable stability of perfluoroalkylzinc species in polar aprotic solvents, especially in DMPU, was observed experimentally and confirmed theoretically. Application of this methodology to the synthesis of perfluoroalkylated functional molecules and derivatization of biologically active compounds is under investigation in our laboratory.

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## **Experimental Section**

A heat-gun-dried 10 mL Schlenk tube equipped with a magnetic stirring bar and a rubber septum was evacuated and back-filled with argon. After two additional cycles of this operation, Et<sub>2</sub>Zn (1.06 м in *n*-hexane; 0.71 mL, 0.75 mmol, 1.5 equiv), DMPU (0.5 mL), and  $C_4F_9I$  (187.5  $\mu$ L, 1.13 mmol, 2.25 equiv) were added dropwise to the tube at room temperature. Then, 1a (208.2 mg, 0.5 mmol, 1 equiv) and Cul (9.5 mg, 10 mol%) were added, and the rubber septum was replaced with a glass stopper. The tube was sealed and immersed in an oil bath without pre-heating. The temperature was elevated to 90 °C for 16 h with stirring, while internal pressure increased. The reaction mixture was allowed to cool to room temperature and the reaction was guenched with 1 N agueous HCl. The product was extracted with  $Et_2O$  (3×30 mL), and the combined organic layer was washed with brine (30 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, and filtered. Volatiles were removed on a rotary evaporator. The crude product was purified by flash column chromatography on SiO<sub>2</sub> (eluent: hexane/CH<sub>2</sub>Cl<sub>2</sub> 7:1) to give the desired product 2 aa as a pale yellow oil (226.2 mg, 89% yield).

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## COMMUNICATION



fluoroalkylation of aromatic halides is reported. Thermally stable perfluoroalkylzinc reagents, generated by rapid halogen-zinc exchange between diorganozinc and perfluoroalkyl halide spe-

cies, couple with a wide range of aryl halides in the presence of copper catalyst, in moderate to high yields. The perfluoroalkylzinc species display good stability, as indicated by DFT calculations.



**Dialkylzinc-Mediated Cross-Coupling Reactions of Perfluoroalkyl and** Perfluoroaryl Halides with Aryl Halides