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Copper-Catalyzed Arylation of 1H-Perfluoroalkanes

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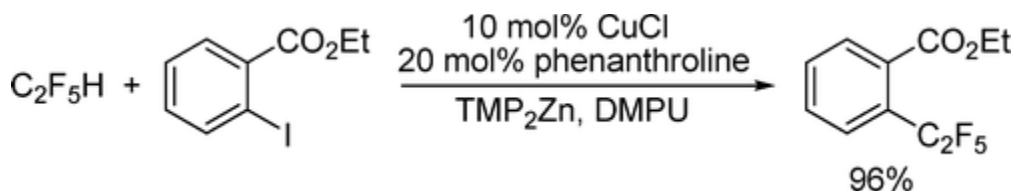
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Abstract

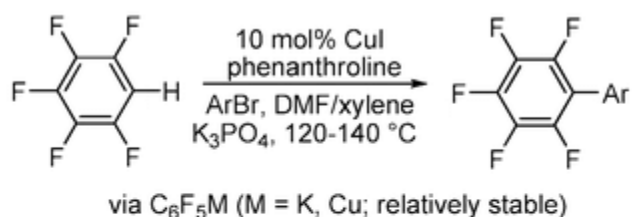


A general method has been developed for arylation of readily available 1*H*-perfluoroalkanes. The method employs aryl iodide and 1*H*-perfluoroalkane reagents, DMPU solvent, TMP_2Zn base, and a copper chloride/phenanthroline catalyst. Preliminary mechanistic studies are reported.

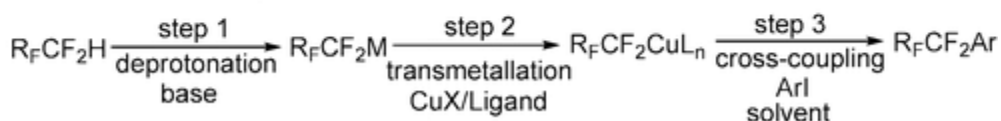
Many pharmaceuticals and agrochemicals contain aryl-trifluoromethyl or aryl-polyfluoroalkyl linkages.¹ Consequently, introduction of fluoroalkyl substituents into aromatic systems has attracted intense interest. Trichloromethyl groups and other functionalities can be converted to trifluoromethyl moieties by treatment with a fluorinating reagent.² A halide or, rarely, a hydrogen on an aromatic ring can be replaced with a trifluoromethyl group under transition metal catalysis. Examples of such reactions include palladium-catalyzed trifluoromethylation of aryl chlorides³ and *ortho*-trifluoromethylation of 2-phenylpyridines.⁴ More commonly, however, copper is employed for polyfluoroalkylation of aryl iodides. Typically, trifluoromethyltrialkylsilane reagents are used in combination with a stoichiometric copper source.⁵ A recent pioneering report describes reactions catalytic in copper. However, only electron-deficient aryl iodides react in high yields.⁶ Cross-coupling of aryl iodides and perfluoroalkyl iodides by employing 1–3 equiv copper metal has also been reported.⁷ Arene reactions with $R_F I$ proceed by radical mechanisms and often result in isomer mixtures.⁸

In most of the above cases, $R_F SiR_3$ reagents have been employed. However, only trifluoromethyl-, pentafluoroethyl-, and heptafluoropropyltrialkylsilanes are commercially available. Thus, a widely available perfluoroalkyl source should be sought to develop a generally useful synthetic methodology. We report here a method for copper-catalyzed 1*H*-perfluoroalkane arylation by aryl iodides.

Polyfluorobenzene arylation (ref. 9):



1*H*-Perfluoroalkane arylation:



Many R_FCF_2H commercially available; nontoxic and inexpensive

Scheme 1. Reaction Development Considerations

Based on previous work on copper-catalyzed arylation of polyfluoroarenes,⁹ we considered the arylation of 1*H*-perfluoroalkanes (Scheme 1). The lowest homologues of 1*H*-perfluoroalkanes are among the cheapest sources of R_F groups. Several issues had to be addressed to develop a viable method (Scheme 1). First, the stability of the perfluoroalkyl metal reagent generated in the deprotonation step needs to be considered. In contrast to pentafluoroaryl metals,¹⁰ most perfluoroalkyl metals are unstable.¹¹ Only mercury, cadmium, bismuth, thallium, and zinc perfluoroalkyls are relatively stable.^{11,12} A viable methodology will not use highly toxic Cd, Hg, or Tl reagents; thus, Bi or Zn bases must be employed. Second, the base type needs to be determined. Trifluoromethane possesses a p*K*_a of about 31 requiring an amide base for deprotonation.¹³ Bismuth amides are photolytically and thermally unstable.¹⁴ Consequently, a zinc amide base should be employed. The amide moiety should be hindered to prevent copper-catalyzed amination of aryl iodide.¹⁵ These considerations led to the selection of the zinc bis-2,2,6,6-tetramethylpiperide (TMP₂Zn) base.¹⁶

Table 1. Perfluoroalkylation Scope with Respect to ArI^a

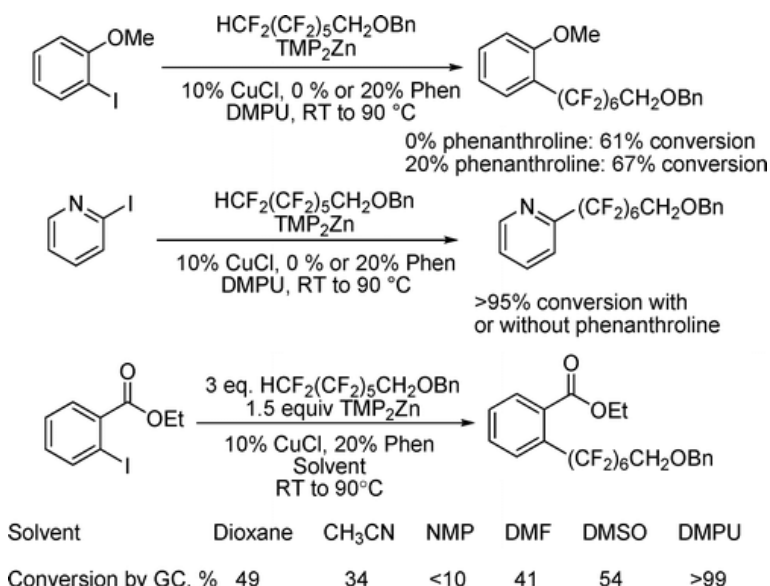
$$\text{Arl} + \text{H}(\text{CF}_2)_6\text{CH}_2\text{OBn} \xrightarrow[\text{TMP}_2\text{Zn, DMPU}]{\substack{10 \text{ mol}\% \text{ CuCl} \\ 20 \text{ mol}\% \text{ phenanthroline}}} \text{Ar}(\text{CF}_2)_6\text{CH}_2\text{OBn}$$

entry	aryl iodide	product	yield, %
1	2-MeOC ₆ H ₄ I		51
2	4-CH ₃ C ₆ H ₄ I		51
3	3-CF ₃ OC ₆ H ₄ I		55
4 ^b	4-NC ₆ H ₄ I		83
5	3-CF ₃ C ₆ H ₄ I		61
6	4-C ₆ H ₄ C ₆ H ₄ I		62
7	4-BrC ₆ H ₄ I		53
8	2-iodopyridine		85
9 ^b	2-iodo-4,5-dimethylthiazole		63
10 ^b	8-iodocaffeine		94
11 ^b	Ethyl-2-iodobenzoate		92

Table a TMP₂Zn (0.5 mmol), R_FH (0.5 mmol), DMPU, then ArI (1.5 mmol), phenanthroline (0.1 mmol), and CuCl (0.05 mmol), 90 °C.

Table b TMP₂Zn (0.75 mmol), R_FH (1.5 mmol), DMPU, then ArI (0.5 mmol), phenanthroline (0.1 mmol), and CuCl (0.05 mmol).

The reaction was optimized with respect to ligand and solvent (Scheme 2). For perfluoroalkylation of electron-rich 2-methoxyiodobenzene, a phenanthroline ligand additive afforded an increased conversion. However, high conversion to the product was observed for 2-iodopyridine perfluoroalkylation in both the presence and absence of phenanthroline. Presumably, the phenanthroline ligand stabilizes perfluoroalkyl copper species.⁶ Consequently, for functionalization of more reactive aryl iodides, phenanthroline may be omitted. Solvent optimization showed that the best results are obtained in DMPU which was used in all further reactions.



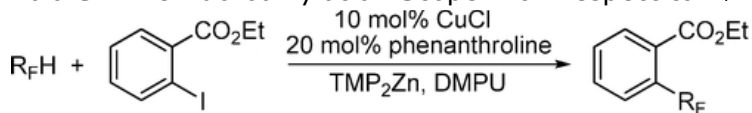
Scheme 2. Reaction Optimization

The perfluoroalkylation scope with respect to aryl iodides is presented in Table 1. We were pleased to discover that benzylated α,α,ω -trihydroperfluoroheptanol was arylated by a number of aryl iodides under the optimized reaction conditions. Electron-rich 2-iodoanisole and 4-iodotoluene are reactive affording coupling products in moderate yields (entries 1 and 2). Reactions with electron-poor ArI are higher yielding (entries 3–5, 7, 11). Functional groups such as trifluoromethoxy (entry 3), nitrile (entry 4), bromide (entry 7), and ester (entry 11) are tolerated. Iodinated heterocycles such as 2-iodopyridine, 2-iodo-4,5-dimethylthiazole, and 8-iodocaffeine react to give products in good to excellent yields (entries 8–10). 2,6-Disubstituted electron-rich aryl iodides do not afford the coupling products. Instead, the iodide moiety is reduced. Unactivated aryl

bromides are unreactive. Thus, reaction of 4-bromobiphenyl with benzylated α,α,ω -trihydroperfluoroheptanol under standard reaction conditions afforded the coupling product in <5% conversion.

The reaction scope with respect to 1*H*-perfluoroalkanes is presented in Table 2. The most difficult coupling partner is trifluoromethane (entry 1). Trifluoromethyl copper decomposes generating pentafluoroethylcopper unless it is stabilized by HMPA.¹⁷ About 10% of pentafluoroethylated substrate was observed in the crude reaction mixture, and purification by HPLC was required to obtain pure ethyl 2-(trifluoromethyl)benzoate. Reactions with other 1*H*-perfluoroalkanes, such as C₂F₅H, CF₃CF₂CF₂H, and 1*H*-perfluorohexane, are high-yielding (entries 2–5). Substrates possessing two –CF₂H moieties can be either monoarylated (entries 6 and 7) or diarylated (entry 8) depending on the reaction stoichiometry. Some functionality such as chloro and amide (entries 9 and 10) is tolerated. 2*H*-Heptafluoropropane is unreactive.¹⁸

Table 2. Perfluoroalkylation Scope with Respect to R_FH^a



entry	1 <i>H</i> -polyfluoroalkane	product	yield
1 ^b	CF ₃ H		51
2	C ₂ F ₅ H		96
3	CF ₃ CF ₂ CF ₂ H		83
4	CF ₃ (CF ₂) ₂ CF ₂ H		87
5	CF ₃ (CF ₂) ₃ CF ₂ H		81
6	H(CF ₂) ₂ H		79
7	H(CF ₂) ₃ H		84
8 ^c	H(CF ₂) ₂ H		63
9	H(CF ₂) ₂ Cl		94
10 ^d	H(CF ₂) ₂ CONC ₆ H ₁₀		62

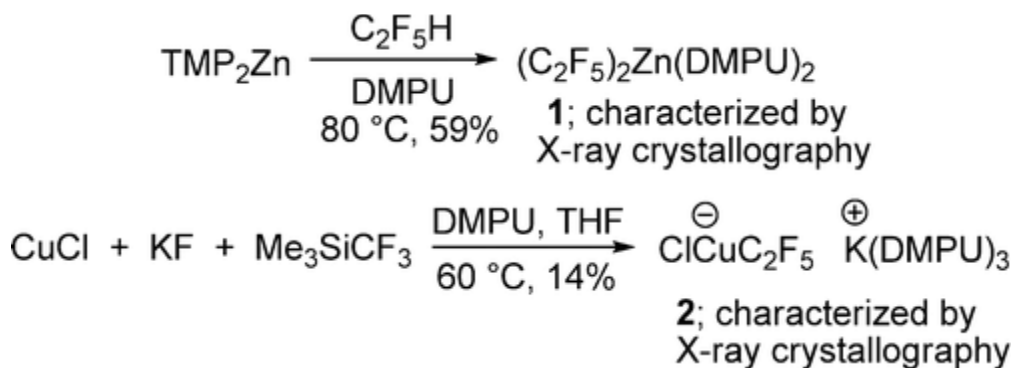
Table a TMP₂Zn (0.75 mmol), R_FH (1.5–5 mmol), DMPU, ArI (0.5 mmol), phenanthroline (0.1 mmol), CuCl (0.05 mmol), 90 °C.

Table b Phenanthroline (1 mmol).

Table c TMP₂Zn (1 mmol), R_FH (0.5 mmol), DMPU, ArI (4 mmol), phenanthroline (0.1 mmol), and CuCl (0.05 mmol).

Table d TMP_2Zn (0.5 mmol), R_fH (0.5 mmol), DMPU, ArI (1.5 mmol), phenanthroline (0.1 mmol), and CuCl (0.05 mmol).

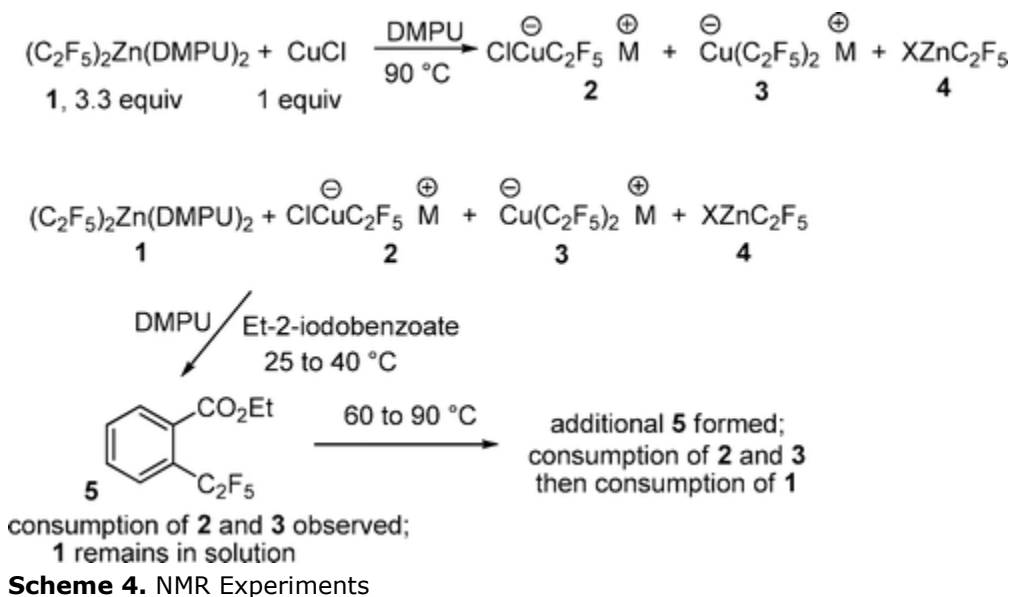
Preliminary mechanistic studies have been performed. The intermediate bis(perfluoroethyl)zinc species **1** was prepared by the reaction of TMP_2Zn with pentafluoroethane (Scheme 3). The complex was characterized by ^1H and ^{19}F NMR, X-ray crystallography, and elemental analysis. Additionally, anionic copper complex **2** was prepared in low yield by reaction of CuCl , KF , and TMSCF_3 (Scheme 3). Complex **2** exists as a temperature and moisture sensitive colorless solid that slowly decomposes at RT under an argon atmosphere over the course of several hours, but is stable for at least 4 weeks at $-35\text{ }^\circ\text{C}$ under an inert atmosphere. It was characterized by ^1H and ^{19}F NMR as well as X-ray crystallographic analysis.



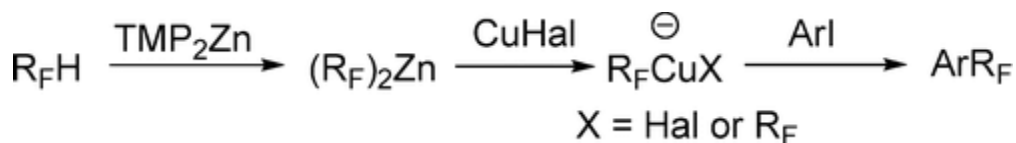
Scheme 3. Reaction Intermediate Synthesis

Several ^{19}F NMR experiments were carried out to determine the identity of the species present in the reaction mixture and their reactivity. Mixing CuCl and excess **1** in DMPU solvent affords negligible amounts of zinc to copper transmetalation products at $45\text{ }^\circ\text{C}$. However, the reaction at $90\text{ }^\circ\text{C}$ affords several species that were tentatively identified by comparison with NMR of authentic **2** and reported spectral data for **3** (Scheme 4).¹⁹ Furthermore, a preformed mixture of **2** and **3** in the presence of excess **1** was subjected to the reaction with ethyl-2-iodobenzoate at 25, 40, 60, and $90\text{ }^\circ\text{C}$. At 25 and $40\text{ }^\circ\text{C}$, consumption of **2** and **3** is observed and **5** is formed; however, **1** does not undergo transmetalation with copper halide. Further heating at $60\text{ }^\circ\text{C}$ is required for transmetalation to occur. Heating to $90\text{ }^\circ\text{C}$ leads to the fast consumption of aryl iodide and **1** followed by the reappearance of **2** and **3**. These experiments show that

transmetalation appears to be the turnover-limiting step for pentafluoroethylation of ethyl 2-iodobenzoate.



The general reaction mechanism is presented in Scheme 5. Deprotonation of 1*H*-perfluoroalkanes with TMP_2Zn affords bis(perfluoroalkyl)zinc species. Subsequent transmetalation with copper halide produces a mixture of anionic Cu species that reacts with aryl iodide, either directly or via a neutral perfluoroalkyl compound,^{5f} to give the coupling product.



Scheme 5. Reaction Mechanism

In conclusion, we have developed a general method for arylation of readily available 1*H*-perfluoroalkanes. The method employs aryl iodide and 1*H*-perfluoroalkane reagents, a DMPU solvent, a TMP_2Zn base, and a copper chloride/phenanthroline catalyst.

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Supporting Information

Experimental procedures, characterization data for new compounds, and X-ray crystallography data for **1** and **2**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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