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Copper-Catalyzed Arylation of 1*H*-Perfluoroalkanes

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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 chlorides[3] 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_FI proceed by radical mechanisms and often result in isomer mixtures.[8]

In most of the above cases, R_FSiR_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.

Based on previous work on copper-catalyzed arylation of polyfluoroarenes,[9] we considered the arylation of 1*H*-perfluoroalkanes (Scheme 1). 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, stability of the perfluoroalkyl metal reagent generated in the deprotonation step needs to be considered. In contrast to pentafluoroarylmetals,[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, base type needs to be determined. Trifluoromethane possesses 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. Amide

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SUPPORTING INFORMATION AVAILABLE 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.

moiety should be hindered to prevent copper-catalyzed amination of aryl iodide.[15] These considerations led to selection of zinc bis-2,2,6,6-tetramethylpiperidide (TMP_2Zn) base.[16]

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

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, 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 <5% conversion to coupling product.

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 C_2F_5H, $CF_3CF_2CF_2H$, and 1*H*- perfluorohexane are high-yielding (entries 2–5). Substrates possessing two $–CF_2H$ 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]

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 argon atmosphere over the course of several hours, but is stable for at least 4 weeks at −35 °C under inert atmosphere. It was characterized by ^1H and ^{19}F NMR as well as X-ray crystallographic analysis.

Several ^{19}F NMR experiments were carried out to determine the identity of the species present in reaction mixture and their reactivity. Mixing CuCl and excess **1** in DMPU solvent affords negligible amounts of zinc to copper transmetallation products at 45 °C. However, the reaction at 90 °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 °C, 40 °C, 60 °C, and 90 °C. At 25 °C and 40 °C, consumption of **2** and **3** is observed and **5** is formed; however, **1** does not undergo transmetallation with copper halide. Further heating at 60 °C is required for transmetallation to occur. Heating to 90 °C leads to fast consumption of aryl iodide and **1** followed by reappearance of **2** and **3**. These experiments show that transmetallation appears to be the turnover-limiting 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 transmetallation with copper halide produces a mixture of anionic Cu species that react with aryl iodide, either directly or via a neutral perfluoroalkyl compound,[5f] to give the coupling product.

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, DMPU solvent, TMP_2Zn base, and a copper chloride/phenanthroline catalyst.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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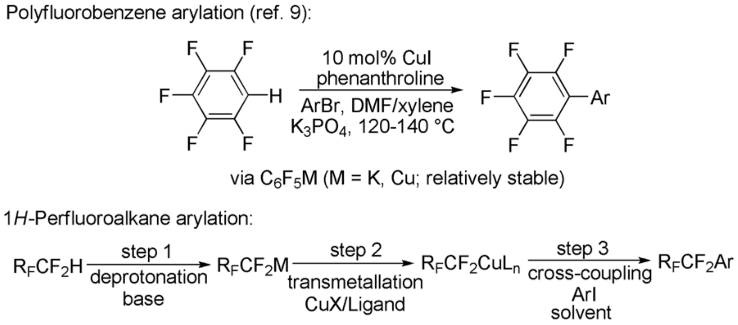
References

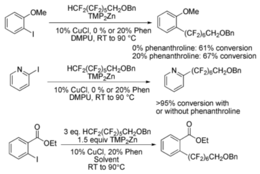
1. (a) Jeschke P. ChemBioChem. 2004; 5:570.(b) Purser S, Moore PR, Swallow S, Gouverneur V. Chem Soc Rev. 2008; 37:320. [PubMed: 18197348] (c) Schlosser M. Angew Chem, Int Ed. 2006; 45:5432.
2. (a) Dmowski W, Wielgat J. J Fluorine Chem. 1987; 37:429.(b) Bloodworth AJ, Bowyer KJ, Mitchell JC. Tetrahedron Lett. 1987; 28:5347.(c) Hudlicky M. Organic Reactions. 1988; 35:513.
3. Cho EJ, Senecal TD, Kinzel T, Zhang Y, Watson DA, Buchwald SL. Science. 2010; 328:1679. [PubMed: 20576888]
4. (a) Wang X, Truesdale L, Yu JQ. J Am Chem Soc. 2010; 132:3648. [PubMed: 20184319] (b) Ball ND, Kampf JW, Sanford MS. J Am Chem Soc. 2010; 132:2878. [PubMed: 20155920]
5. (a) Burton DJ, Lu L. Top Current Chem. 1997; 193:45.(b) Dubinina GG, Furutachi H, Vicic DA. J Am Chem Soc. 2008; 130:8600. [PubMed: 18543912] (c) Urata H, Fuchikami T. Tetrahedron Lett. 1991; 32:91.(d) Folléas B, Marek I, Normant JF, Saint-Jalmes L. Tetrahedron. 2000; 56:275.Pd: (e) Grushin VV, Marshall WJ. J Am Chem Soc. 2006; 128:4632. [PubMed: 16594700] Ni: (f) Dubinina GG, Brennessel WW, Miller JL, Vicic DA. Organometallics. 2008; 27:3933.
6. Oishi M, Kondo H, Amii H. Chem Commun. 2009:1909.
7. (a) Xiao JC, Ye C, Shreeve JM. Org Lett. 2005; 7:1963. [PubMed: 15876030] (b) Mcloughlin VCR, Thrower J. Tetrahedron. 1969; 25:5921.(c) Croxtall B, Fawcett J, Hope EG, Stuart AM. J Chem Soc, Dalton Trans. 2002:491.
8. Review: Furin GG. Russ Chem Rev. 2000; 69:491.
9. (a) Do HQ, Daugulis O. J Am Chem Soc. 2008; 130:1128. [PubMed: 18181627] (b) Do HQ, Khan RMK, Daugulis O. J Am Chem Soc. 2008; 130:15185. [PubMed: 18855471]
10. (a) Cairncross A, Sheppard WA. J Am Chem Soc. 1968; 90:2186.(b) Coe PL, Stephens R, Tatlow JC. J Chem Soc. 1962:3227.However, C_6F_5Li can be hazardous: (c) Kinsella E, Massey AG. Chem Ind (London). 1971; 36:1017B.
11. Burton DJ, Yang ZY. Tetrahedron. 1992; 48:189.

12. (a) Naumann D, Tyrra W. J Organomet Chem. 1987; 334:323.(b) Nair HK, Morrison JA. Inorg Chem. 1989; 28:2816.
13. (a) Andreades S. J Am Chem Soc. 1964; 86:2003.(b) Chabinyc ML, Brauman JI. J Am Chem Soc. 1998; 120:10863.
14. Vehkamäki M, Hatanpää T, Ritala M, Leskelä M. J Mater Chem. 2004; 14:3191.
15. Shafir A, Buchwald SL. J Am Chem Soc. 2006; 128:8742. [PubMed: 16819863]
16. (a) Rees WS Jr, Just O, Schumann H, Weimann R. Polyhedron. 1998; 17:1001.(b) Hlavinka ML, Hagadorn JR. Organometallics. 2007; 26:4105.
17. Wiemers DM, Burton DJ. J Am Chem Soc. 1986; 108:832.
18. Nair HK, Burton DJ. J Fluorine Chem. 1992; 56:341.
19. (a) Naumann D, Schorn C, Tyrra W. Z Anorg Allg Chem. 1999; 625:827.(b) Lange H, Naumann DJ. Fluorine Chem. 1984; 26:435.(c) Naumann D, Roy T, Caeners B, Hütten D, Tebbe K-F, Gilles T. Z Anorg Allg Chem. 2000; 626:999.



Scheme 1.

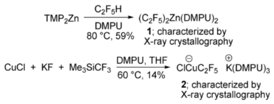
Reaction Development Considerations



Solvent	Dioxane	CH_3CN	NMP	DMF	DMSO	DMPU
Conversion by GC, %	49	34	<10	41	54	>99

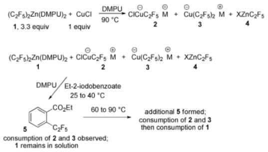
Scheme 2.

Reaction Optimization



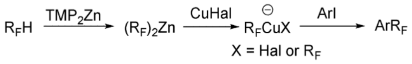
Scheme 3.

Reaction Intermediate Synthesis



Scheme 4.

NMR Experiments



$$R_FH \xrightarrow{TMP_2Zn} (R_F)_2Zn \xrightarrow{CuHal} \underset{X\,=\,Hal\text{ or }R_F}{\overset{\ominus}{R_FCuX}} \xrightarrow{ArI} ArR_F$$

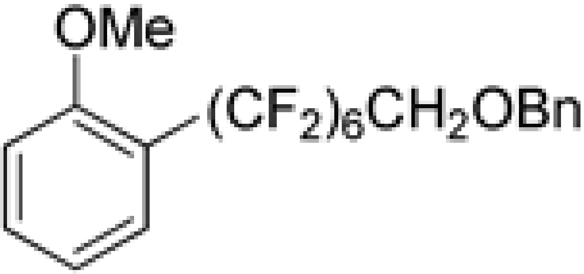
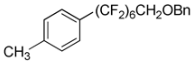
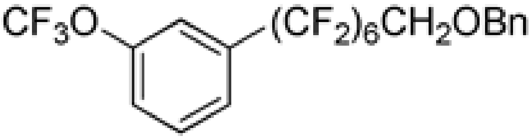
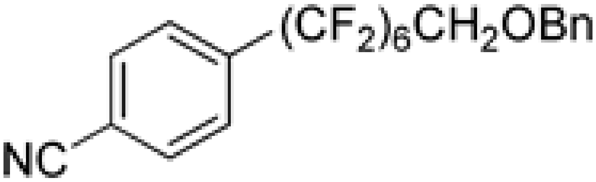
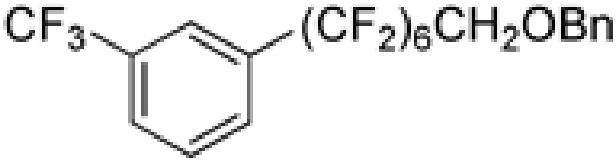
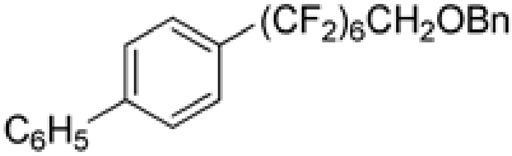
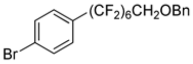
Scheme 5.

Reaction Mechanism

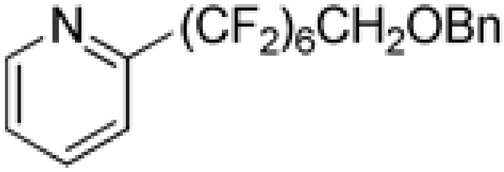
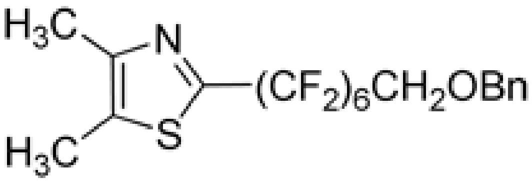
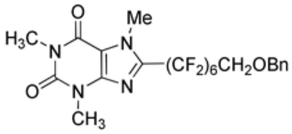
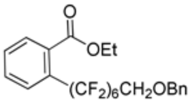
Table 1

Perfluoroalkylation Scope with Respect to ArI[a]

$$\mathrm{ArI + H(CF_2)_6CH_2OBn} \xrightarrow[\mathrm{TMP_2Zn,\ DMPU}]{\mathrm{10\,mol\%\,CuCl} \atop \mathrm{20\,mol\%\,phenanthroline}} \mathrm{Ar(CF_2)_6CH_2OBn}$$

entry	aryl iodide	product	yield, %
1	2-$MeOC_6H_4I$		51
2	4-$CH_3C_6H_4I$		51
3	3-$CF_3OC_6H_4I$		55
4[b]	4-NCC_6H_4I		83
5	3-$CF_3C_6H_4I$		61
6	4-$C_6H_5C_6H_4I$		62
7	4-BrC_6H_4I		53

$$\mathrm{ArI} + \mathrm{H(CF_2)_6CH_2OBn} \xrightarrow[\mathrm{TMP_2Zn,\ DMPU}]{\substack{10\,\mathrm{mol\%\,CuCl}\\ 20\,\mathrm{mol\%\,phenanthroline}}} \mathrm{Ar(CF_2)_6CH_2OBn}$$

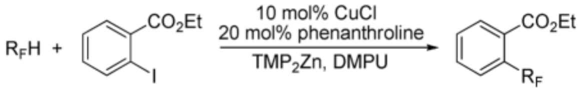
entry	aryl iodide	product	yield, %
8	2-Iodopyridine		85
9[b]	2-Iodo-4,5- dimethylthiazole		63
10[b]	8-Iodocaffeine		94
11[b]	Ethyl-2- iodobenzoate		92

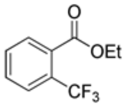
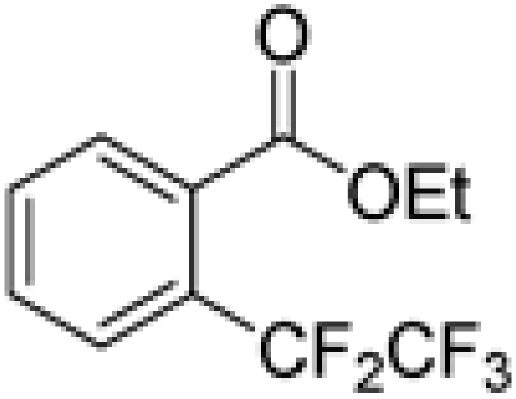
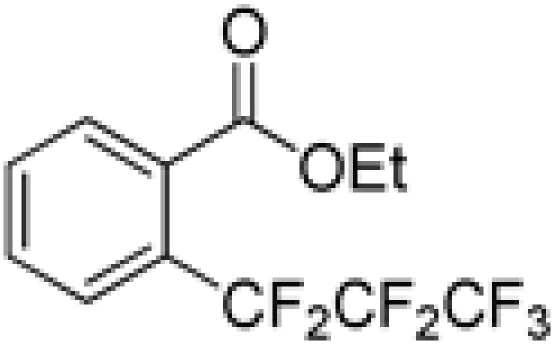
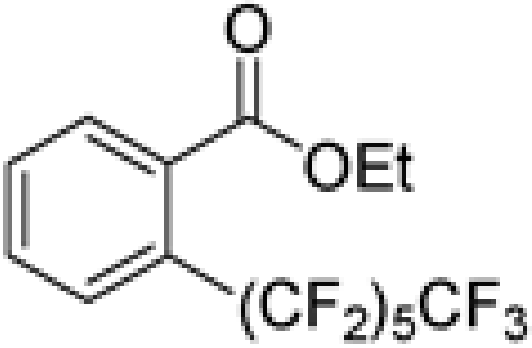
[a] $\mathrm{TMP_2Zn}$ (0.5 mmol), $\mathrm{R_FH}$ (0.5 mmol), DMPU, then ArI (1.5 mmol), phenanthroline (0.1 mmol) and CuCl (0.05 mmol), 90 °C.

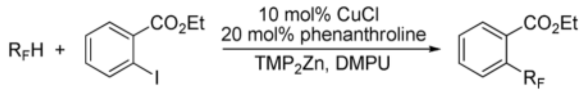
[b] $\mathrm{TMP_2Zn}$ (0.75 mmol), $\mathrm{R_FH}$ (1.5 mmol), DMPU, then ArI (0.5 mmol), phenanthroline (0.1 mmol) and CuCl (0.05 mmol).

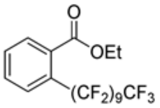
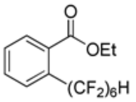
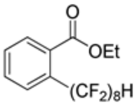
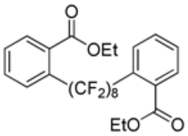
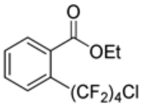
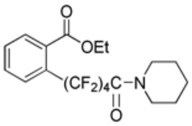
Table 2

Perfluoroalkylation Scope with Respect to R_FH[a]



entry	1*H*-polyfluoroalkane	product	yield
1[b]	CF_3H		51
2	C_2F_5H		96
3	$CF_3CF_2CF_2H$		83
4	$CF_3(CF_2)_4CF_2H$		87



entry	1*H*-polyfluoroalkane	product	yield
5	$CF_3(CF_2)_8CF_2H$		81
6	$H(CF_2)_6H$		79
7	$H(CF_2)_8H$		84
8[c]	$H(CF_2)_8H$		63
9	H(CF2)$_4$Cl		94
10[d]	$H(CF_2)_4CONC_5H_{10}$		62

[a] TMP_2Zn (0.75 mmol), R_FH (1.5–5 mmol), DMPU, ArI (0.5 mmol), phenanthroline (0.1 mmol), CuCl (0.05 mmol), 90 °C.

[b] Phenanthroline (1 mmol).

[c] TMP_2Zn (1 mmol), R_FH (0.5 mmol), DMPU, ArI (4 mmol), phenanthroline (0.1 mmol) and CuCl (0.05 mmol).

[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).