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Copper-Mediated Aerobic Fluoroalkylation of Arylboronic Acids with Fluoroalkyl Iodides at Room Temperature

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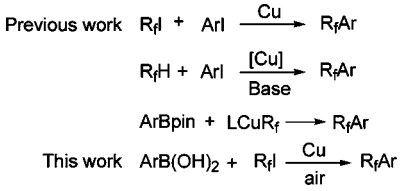
Supporting Information

ABSTRACT: A Cu-mediated ligandless aerobic fluoroalkylation of arylboronic acids under mild conditions is described for the first time. The reaction tolerates a wide range of functional groups, allowing for further transformation. Mechanistic studies suggest that [R_fCu] is the active Cu species that forms the desired perfluoroalkylarenes and that [R_fCu] is generated from [PhCu] by either an oxidative addition/reductive elimination mechanism or nucleophilic substitution via a halogen "ate" intermediate.

In the past two decades, we have witnessed the widespread use of fluoroalkylated arenes in materials science, argochemistry, and the pharmaceutical industry.[1] The "magic effect" of fluorine on the chemical, physical, and biological properties of organic compounds has made the incorporation of fluorine a routine strategy. Thu, the development of new methodologies for preparing fluoroalkylated arenes has become a subject of great interest.[2,3] Recently, significant advances in trifluoromethylation of arenes have been achieved through a radical pathway or transition-metal-catalyzed coupling.[4−8] For example, radical trifluoromethylation of simple arenes and heterocycles was performed using visible light[8] or ^{t}BuOOH[7] as the radical initiator, albeit with poor regioselectivity. More precise installation of the trifluoromethyl group was accomplished by metal-mediated coupling. A halide or boron on an aromatic ring can be replaced with a trifluoromethyl group under mild reaction conditions.[4−7] On the other hand, few general methods for perfluoroalkylation or difluoromethylation of arenes have been reported. Preparation of perfluoroalkylated or difluoromethylated arenes typically relies on Cu-mediated coupling of R_fI or R′CF_2I with ArI, discovered by McLoughlin and Thrower in the mid-1960s.[3,9,10] Only recently, Daugulis reported a Cu-catalyzed reaction of aryl iodide and 1*H*-perfluoroalkane reagents in the presence of zinc bis-2,2,6,6-tetramethylpiperidide,[11] and Hartwig reported a 1,10-phenanthroline (Phen)-ligated perfluoroalkylcopper reagent that reacts with aryl iodides or arylboronic acids to give perfluoroalkyl arenes in good yields.[6] Shreeve[12] and Qing[13] independently reported Pd-catalyzed α-arylation of difluoromethyl ester enolates. Amii reported a Cu-catalyzed coupling of aryl iodides with α-silyldifluoroacetate to give aryldifluoroacetates in moderate to good yields.[14] Baran et al. developed a new difluoromethyl reagent for radical difluoromethylation of arenes and heteroarylenes.[15] However, direct coupling of arylboronic acids with perfluoroalkyl iodides has not been reported to date.

Herein, we report a ligandless Cu-mediated fluoroalkylation of arylboronic acids with fluoroalkyl iodides under aerobic conditions (Scheme 1). Preliminary mechanistic studies revealed that the reaction proceeds via a [R_fCu] species generated by reaction of [ArCu] with R_fI.

Scheme 1. Preparation of Perfluoroalkyl Arenes



Perfluoroalkyl iodides are known to undergo oxidative addition to Pd(0),[16] and reductive eliminations from the Pd complexes [(Xantphos)Pd(Ar)(CF_3)] and [(BrettPhos)Pd(Ar)(CF_3)] to give $ArCF_3$ in high yields were reported by Grushin[17] and Buchwald,[5] respectively. In addition, pioneering work by Fu et al. demonstrated that alkyl iodides can be coupled with arylboronic acids in the presence of Pd or Ni catalysts.[18] In light of these advances, we envisioned that if R_fI could be directly coupled with arylboronic acids in the presence of a Pd or Ni catalyst with a suitable ligand, it might offer a new and efficient entry to perfluoroalkyl or difluoromethyl arenes.

We initially focused on the Pd- or Ni-catalyzed coupling reaction of phenylboronic acid with *n*-C_4F_9I in the presence of a variety of phosphine and nitrogen ligands such as Xantphos, Brettphos, Ruphos, 2,2′-bipyridine (bipy), and PyBox. However, no trace of the desired product was observed even at 90 °C in several solvents such as diglyme, DMF, or dioxane. Surprisingly, when 0.5 equiv of CuI was used in DMF, the desired product was detected in 7% yield by ^{19}F NMR spectroscopy and GC/MS (Table 1, entry 1). With careful control of the conditions, it was discovered that the presence of air is very important for the reaction, as no desired product was observed when the reaction was conducted in an argon atmosphere. Interestingly, when the reaction was conducted in an oxygen atmosphere, only the homocoupling side product 1,1′-biphenyl, was observed. The yield of C_4F_9Ph increased to 65% when DMSO was used as the solvent (entry 2). Further screening of different Cu sources disclosed that Cu powder was the most efficient catalyst, producing ArR_f in 76% yield when

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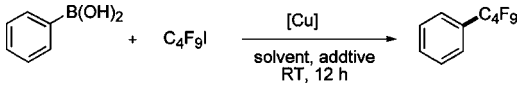
Table 1. Optimization of Conditions for Cu-Mediated Coupling of Arylboronic Acids with Perfluoroalkyl Iodides[a]



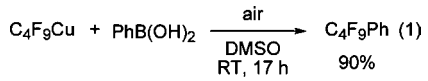
Entry	[Cu]	Solvent	Additive	Yield (%)[b]		
				C_4F_9Ph	C_4F_9I	C_4F_9H
1	CuI	DMF		7	72	-
2	CuI	DMSO		65	8	4
3	CuI	DMSO/DMF		35	53	-
4	CuBr	DMSO		63	9	3
5	CuOAc	DMSO		56	14	4
6	$Cu(OTf)_2$	DMSO		0	100	0
7	$Cu(OAc)_2$	DMSO		7	27	0
8	Cu	DMSO/DMF		76[c] (68[d])	0	2
9	Cu	MeOH		<2	90	0
10	Cu	DME		0	100	0
11	Cu	$ClCH_2CH_2Cl$		0	100	0
12	Cu	Dioxane		0	100	0
13	Cu	CH_3CN		0	100	0
14	Cu	DMSO/DMF	BINAP[e]	54	0	10
15	Cu	DMSO/DMF	PPh_3	0	100	0
16	Cu	DMSO/DMF	DPPF	0	100	0
17	Cu	DMSO/DMF	DPPE	0	100	0
18	Cu	DMSO/DMF	DPPB	0	100	0
19	Cu	DMSO/DMF	Phen	22	0	20
20	Cu	DMSO/DMF	bipy	38	3	3
21	Cu	DMSO/DMF	2,6-lutidine	25	0	5
22	Cu	DMSO/DMF	Li_2CO_3	57	<2	19
23	Cu	DMSO/DMF	K_3PO_4	28	0	12
24	Cu	DMSO/DMF	KOAc	21	0	23
25	Cu	DMSO/DMF	$NaHCO_3$	22	27	10
26	Cu	DMSO/DMF	K_2CO_3	0	100	0
27	Cu	DMSO/DMF	KF	0	77	11
28	Cu	DMSO/DMF	Cs_2CO_3	0	100	0
29	Cu	DMSO/DMF	NaO*t*Bu	0	100	0
30	Cu	DMSO/DMF	LiOH	0	100	0
31	Cu	DMSO/DMF	DBU	0	-	-

[a]Reaction conditions for eor entries 1−8: phenylboronic acid (1.6 mmol), C_4F_9I (0.82 mmol), Cu catalyst (0.5 equiv; for entry 8, 1 equiv was used) in solvent (3.0 mL) at rt for 12 h. For entries 9−31: phenylboronic acid (0.82 mmol), C_4F_9I (0.41 mmol), Cu catalyst (1.5 equiv), additive (1.0 equiv) in DMSO/DMF (3.0/0.6 mL) at rt for 12 h. [b]Yields determined by ^{19}F NMR analysis of the crude reaction mixture with an internal standard. [c]1.2 mol of phenylboronic acid was used. [d]Unpurified mixed solvents. [e]40 mol %.

5:1 DMSO/DMF was used as the solvent (entries 5−8). Interestingly, Cu foil was equally effective, giving the desired product in 59% yield, while Cu wire gave a low yield of 27%. The use of other metals (e.g., Zn, Fe, Cd, Al) resulted in no detectable formation of the desired product. The choice of solvent was very important for the reaction. No trace of product was observed when the reaction was conducted in MeOH, dimethoxyethane, 1,2-dichloroethane, dioxane, or acetonitrile (entries 9−13). Addition of phosphine ligands such as PPh_3, DPPF, DPPE, or DPPB completely shut down the reaction, while addition of BINAP gave the coupled product in a slightly lower yield (54%; entries 14−18). Notably, the yield of the reaction decreased significantly when Phen, bipy, or 2,6-lutidine was added (entries 19−21). In contrast to most Suzuki−Miyaura cross-coupling reactions, where bases such as K_3PO_4 or K_2CO_3 are indispensable, reactions in the presence of bases such as Li_2CO_3, K_3PO_4, KOAc, and $NaHCO_3$ gave lower yields (entries 22−25), while other bases such as K_2CO_3, KF, Cs_2CO_3, NaO*t*Bu, LiOH, or DBU proved to be completely ineffective, giving essentially no desired product (entries 26−31).

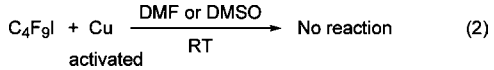
With the optimized conditions, we next examined the substrate scope of the cross-coupling reactions between R_fI and arylboronic acids (Table 2). Various boronic acids were treated with R_fI to give the corresponding perfluoroalkyl arenes in moderate to good yields. The reaction can be scaled up easily. For example, the reactions of phenylboronic acid with C_4F_9I (82 mmol) and ClC_4F_8I (30 mmol) afforded yields of 58 and 60%, respectively. The difluoromethyl group has been utilized as a thiol or hydroxyl isostere in drug design and has great potential in medicinal chemistry. It was found that the current methodology can be easily extended to the coupling of ICF_2CO_2Et and ICF_2CONEt_2 with arylboronic acids to give the difluoromethylated compounds in good yields. Interestingly, CuI could also mediate the same reactions but generally gave lower yields. In addition, the Cu-mediated coupling of arylboronic acids with R_fI is tolerant of a variety of functional groups attached to the arylboronic acid, such as ester, enolizable ketone, aldehyde, nitro, and halides, including chloride, bromide, and iodide. It is worth noting that bromide and iodide were not compatible with McLoughlin and Thrower's conditions.[9] In addition, this method takes place on unprotected systems in air at room temperature (rt) without any need for solvent purification; thus, it has great potential applications for medicinal chemists in parallel syntheses of fluorinated bioactive compounds.

To gain some insight about the mechanism and to identify the Cu species that mediates the formation of perfluoroalkylated arenes, we monitored by ^{19}F NMR spectroscopy the reaction of phenylboronic acid with C_4F_9I under the standard conditions. $[C_4F_9Cu]$ was clearly observed in 10−20% yield in the reaction solution (Figure 1 in the Supporting Information). The stoichiometric reaction of independently prepared $[C_4F_9Cu]$ with 3.0 equiv of phenylboronic acid in DMSO in air at rt formed the perfluoroalkylated benzene in 90% yield as determined by ^{19}F NMR spectroscopy (eq 1).[19] These experiments suggest that $[C_4F_9Cu]$ is the active Cu species formed in the catalytic reaction.



We speculated that the active Cu species $[C_4F_9Cu]$ could be generated via two different pathways (Scheme 2). In pathway A, C_4F_9I could oxidatively add to $[Cu^0]$ through a well-known radical mechanism to form $[C_4F_9Cu]$ and CuI.[20] Alternatively, in pathway B, [ArCu], formed by transmetalation of $ArB(OH)_2$ to CuI or reaction of $ArB(OH)_2$ with Cu in the presence of air, could react with R_fI by either an oxidative addition/reductive elimination mechanism or a nucleophilic substitution via a halogen "ate" intermediate to form $[C_4F_9Cu]$ and CuI.

To probe whether $[R_fCu]$ is formed via a free $R_f^{\bullet}$ radical, we conducted two different sets of experiments. In the first set, freshly prepared Cu powder from either reduction of $CuSO_4$ with Zn or an acid activation process was reacted with C_4F_9I in DMF or DMSO under argon or air at rt. No formation of $[C_4F_9Cu]$ was observed by ^{19}F NMR spectroscopy under these conditions (eq 2), in agreement with previous reports that



reactions of Cu with perfluoroalkyl iodides typically require temperatures higher than 60 °C.[2e] In the second set, three separate reactions were conducted by addition of a radical inhibitor (hydroquinone), an electron-transfer scavenger (1,4-

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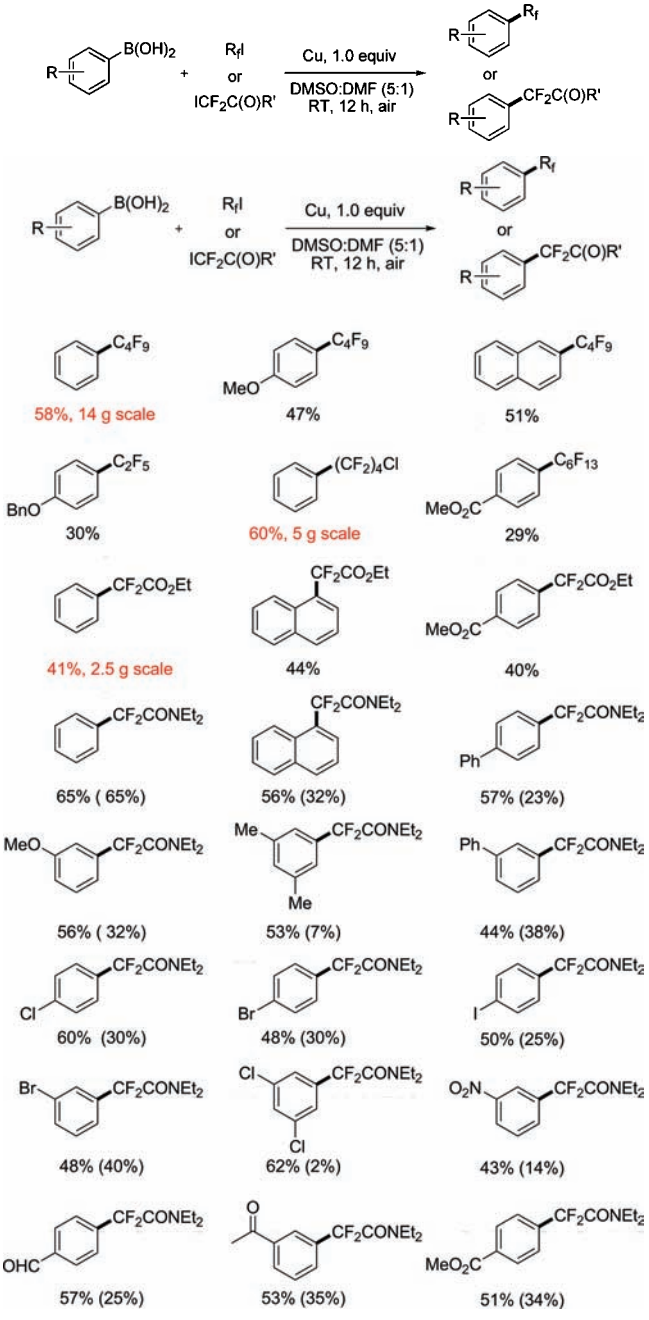
Table 2. Scope of Cu-Mediated Coupling of Arylboronic Acids with Perfluoroalkyl Iodides[a]



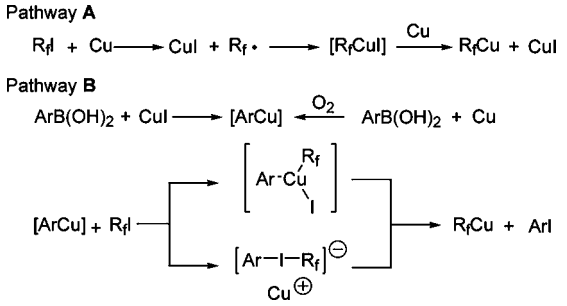
[a]Reaction conditions: arylboronic acid (1.2 mmol), C_4F_9I (0.82 mmol), Cu powder (0.82 mmol) in 5:1 DMSO/DMF (3.6 mL) at rt for 12 h. Isolated yields are shown. Yields in parentheses were determined by ^{19}F NMR analysis for reactions that used CuI (0.5 equiv) as catalyst in DMSO (3.0 mL).

dinitrobenzene), or a radical clock (diallyl ether) to the Cu-mediated coupling of phenylboronic acid with C_4F_9I (eq 3).

$$C_4F_9I + PhB(OH)_2 \xrightarrow{\text{Standard Conditions}} C_4F_9Ph \quad (3)$$

	yield
no additive	76%
20 mol% hydroquinone	43%
20 mol% 1,4-dinitrobenzene	58%
1.0 equivalent of diallyl ether	70%

Scheme 2. Possible Pathways for the Formation of R_fCu



Addition of hydroquinone or 1,4-dinitrobenzene had negligible impact on the yield of this reaction. However, even with 1.0 equiv of the additive, the reaction still proceeded smoothly after 14 h to afford the desired product in 27 or 30% yield, respectively. In addition, when 1.0 equiv of diallyl ether was added to the reaction of phenylboronic acid with C_4F_9I under the standard conditions, no radical-initiated cyclization product was observed. These experiments clearly rule out the formation of $[C_4F_9Cu]$ via a radical pathway.

To probe whether [ArCu] is involved in the formation of $[R_fCu]$, we studied the stoichiometric reaction of [ArCu] with C_4F_9I at rt (eq 4). [PhCu] was prepared as an ether solution at

$$PhLi + CuBr \xrightarrow[2)\ \text{Evaporation}]{1)\ Et_2O,\ -10\ ^\circ C} [PhCu] \xrightarrow[\text{DMSO}]{C_4F_9I} C_4F_9Cu + PhI \quad (4)$$
$$-10\ ^\circ C\ \text{-RT}$$

−10 to 0 °C according to a procedure reported by Costa.[21] We noticed that [PhCu] is not so stable at rt in ether solution but relatively much more stable in DMSO. The reaction of [PhCu] with C_4F_9I was conducted by first evaporating the diethyl ether at −5 °C, adding C_4F_9I in DMSO at −10 °C, and finally warming to rt under argon for 4 h or air for 1 h. The reaction of [PhCu] afforded $[C_4F_9Cu]$ in yields of 33% under argon and 14% under air, as determined by ^{19}F NMR spectroscopy.[22] The formation of PhI was also confirmed by GC−MS. These results provide evidence that $[R_fCu]$ is generated from [PhCu], although at this stage it is unclear whether it is formed through an oxidative addition/reductive elimination mechanism[23] or a nucleophilic substitution via a halogen "ate" intermediate.

To figure out whether [ArCu] is formed under the catalytic reaction conditions, we studied the stoichiometric reaction of $PhB(OH)_2$ with Cu in the presence or absence of air. Reaction of $PhB(OH)_2$ with Cu powder formed biphenyl in 63% yield in the presence of air.[24] However, only an 8% yield of biphenyl was isolated under an argon atmosphere. These experiments suggest that the formation of [PhCu] is likely under the current reaction conditions.

On the basis of these preliminary results, we propose the reaction mechanism outlined in Scheme 3. Arylboronic acid is first converted to [ArCu] in the presence of Cu powder and air. This cuprate then reacts with R_fI by either an oxidative addition/reductive elimination mechanism or nucleophilic substitution via a halogen "ate" intermediate to form $[C_4F_9Cu]$, which undergoes oxidative arylation with arylboronic acid in the presence of air to form the perfluoroalkylated arene product.

In summary, we have developed the first Cu-mediated ligandless aerobic fluoroalkylation of arylboronic acids under mild conditions. No bases are required, and the reaction can be easily scaled up. In addition, the reaction tolerates a wide range

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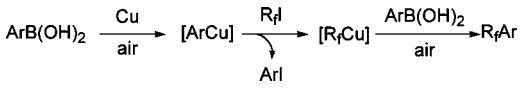
Scheme 3. Proposed Mechanism



of functional groups, allowing for further transformation. Mechanistic studies suggest that [R_fCu] is the active Cu species that forms the desired perfluoroalkylarenes and that [R_fCu] is generated from [PhCu] by either an oxidative addition/reductive elimination mechanism or nucleophilic substitution via a halogen "ate" intermediate. Future work will focus on a detailed mechanistic study of the formation of [R_fCu] from [ArCu] and applications of this method in the preparation of bioactive compounds.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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