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A General, Regiospecific Synthetic Route to Perfluoroalkylated Arenes via Arenediazonium Salts with $R_FCu(CH_3CN)$ Complexes

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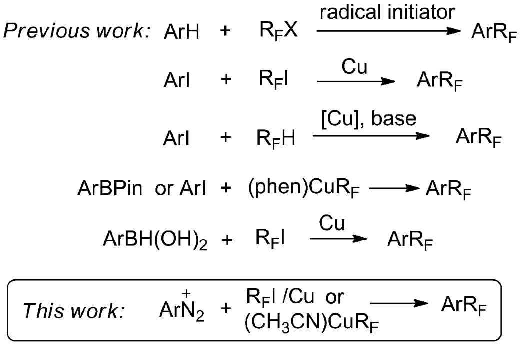
Keywords: Alkylation / Fluorine / Copper / Solvent effects / Regioselectivity / Radical reactions

A mild method of converting arylamines into perfluoroalkylated arenes is described. Relatively stable $R_FCu(CH_3CN)$ complexes are used as perfluoroalkylating agents, which react smoothly with arenediazonium salts to produce various perfluoroalkylarenes in good yields. Based on the results of clock trapping experiments with diallyl ether, a radical process might be involved in the reaction.

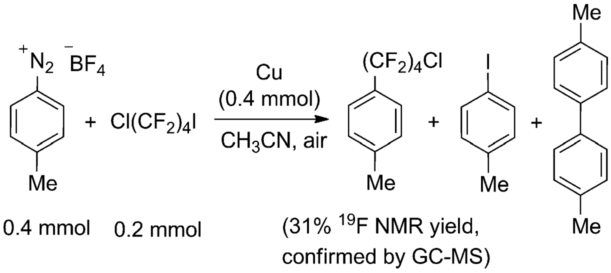
Perfluoroalkylarenes have become increasingly indispensable for material, pharmaceutical and agrochemical industries.[1] McLoughlin and Thrower accomplished their creative work of Ullmann perfluoroalkylation of aryl iodides.[2] Later, (perfluoroalkyl)copper species, especially trifluoromethylcopper species, and their properties were extensively studied.[3] Remarkable process has been achieved in the area of radical perfluoroalkylation of arenes (Scheme 1).[4] However, all these methods may result in regioselectivity problems in many cases. A general and regiospecific perfluoroalkylation of arenes under mild conditions has long been desired, and some progress has been achieved (Scheme 1). Daugulis et al. reported cross-coupling reactions of iodoarenes and R_FH under alkaline conditions in the presence of a catalytic amount of cuprous chloride.[5] Shen and Lu et al. achieved copper-mediated coupling of arylboronic acids and perfluoroalkyl iodides to give perfluoroalkylarenes in good yields.[6] Hartwig and co-workers reported that 1,10-phenanthroline-ligated (perfluoroalkyl)copper agents reacted with haloarenes or arylboronate esters to obtain perfluoroalkylarenes.[3d,7] Grushin and co-workers realized the highly efficient perfluoroethylation of aryl halides with C_2F_5H in the presence of CuCl and *t*BuOK.[8]

Arenediazonium salts, due to their higher reactivity and availability from economical arylamines, are very useful and important alternatives to aryl halides and can be converted into numerous valuable compounds under mild conditions.[9] Recently, such compounds have been utilized by Fu,[10] Wang,[11] and Gooßen,[12] to realize aryl trifluoromethylation or trifluoromethylthiolation. In light of these advances, we envisaged that perfluoroalkylated arenes may be accessed via their respective arenediazonium salts by using R_FI and suitable copper salts. Herein, we present the results.



Scheme 1. Strategies of introducing perfluoroalkyl groups into arenes.

Initially, we selected 4-methylbenzenediazonium tetrafluoroborate as aryl precursor, copper powder (freshly prepared from $CuSO_4{\cdot}5H_2O$ and Zn powder) as reductant, $Cl(CF_2)_4I$ as fluoroalkylating agent, and acetonitrile as solvent. To our delight, the target product was detected in 31% yield by ^{19}F NMR spectroscopic analysis, and its identity was confirmed by GC–MS analysis. 1-Iodo-4-methylbenzene was identified as the main by-product and a trace amount of 4,4′-dimethyl-1,1′-biphenyl was also detected [Equation (1)]. It should be mentioned that no reaction occurred with the C–Cl bond of $Cl(CF_2)_4I$.



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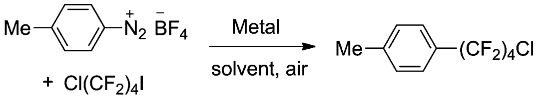
Further screening of cuprous salts such as CuCl, CuI, and copper(I) thiophene-2-carboxylate (CuTC) achieved no better results than achieved with copper powder under air conditions (Table 1, entries 1–4). Interestingly, the yield of the desired product slightly increased when zinc powder was added in the reaction (entry 5), but zinc was not necessary when copper powder was used immediately after preparation. Solvents played an important role in the reaction. Acetonitrile was the optimal medium among solvents screened. No desired reaction took place in toluene, tetrahydrofuran (THF), or CH_2Cl_2 (entries 6–8). In methanol, only 11% of the desired product and 46% yield of $Cl(CF_2)_4H$ by-product were observed (entry 9), whereas the use of acetone as solvent provided the desired product in 19% yield (entry 10). It was found that about 30–40% water by volume in acetonitrile promoted the reaction and improved the yield to 47% at 0 °C (entry 11). The use of 2.0 equiv. of copper improved the yield further to 56% (entry 12). In most of the above cases, $Cl(CF_2)_3COOH$,[13] which may be attributed to partial quenching of $Cl(CF_2)_4^{\cdot}$ radical by oxygen,[14] was observed as a by-product; this process could be suppressed if the system was carefully degassed, although the yield of the product remained unchanged. In addition, a number of additives were checked, but no better results were obtained (see the Supporting Information).

Table 1. Exploring the reaction conditions.[a]

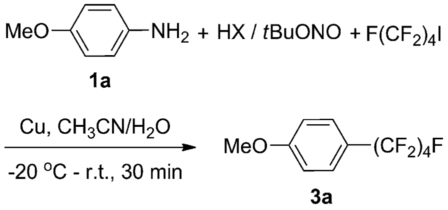


Entry	Solvent	Metal	Yield [%][b] p-$MeC_6H_4(CF_2)_4Cl$	A[c]	B[d]
1	CH_3CN	Cu	31	2	6
2	CH_3CN	CuCl	0	0	0
3	CH_3CN	CuI	0	0	0
4	CH_3CN	CuTC	9	0	0
5	CH_3CN	Cu/Zn	38	3	8
6	toluene	Cu/Zn	0	0	0
7	CH_2Cl_2	Cu/Zn	0	0	0
8	THF	Cu/Zn	0	79	0
9	CH_3OH	Cu/Zn	11[c]	46	11
10	acetone	Cu/Zn	19	0	–[e]
11[f]	CH_3CN/H_2O	Cu/Zn	47	3	9
12[g]	CH_3CN/H_2O	Cu	56	1	11

[a] Reaction conditions: 4-methylbenzenediazonium tetrafluoroborate (0.4 mmol), [Cu] (0.4 mmol), Zn (0.2 mmol, if added), $Cl(CF_2)_4I$ (0.2 mmol), solvent, in air, r.t., 30 min. [b] Yields were determined by ^{19}F NMR spectroscopic analysis with trifluorotoluene as internal standard. [c] A = $Cl(CF_2)_4H$. [d] B = $Cl(CF_2)_3COOH$. [e] Complex mixture. [f] Reaction performed at 0 °C. [g] Cu (0.8 mmol) was used.

Further study indicated that the counterions of arenediazonium salts played an important role in the reaction (Table 2). HSO_4^- provided a better result than other anions (entries 1–5). However, it was noted that the yield of the desired product was not steady and by-product perfluorobutyric acid always appeared even though the reaction system was carefully degassed. By checking the amounts of reagents used, we found that extra *t*BuONO had a negative effect on the reaction and led to more by-product and lower yield of the desired product (entries 4 and 5). However, hydroquinone could be employed as a reductant to remove the extra *t*BuONO after the diazotization of arylamines without affecting the reaction, and the ^{19}F NMR yield of the desired product was improved to 78% on average at a stable level (entry 6). Finally, addition of nitrogen-containing ligands did not improve the yield (see the Supporting Information).

Table 2. Exploring the effect of counterions of arenediazonium salts with the one-pot method.[a]

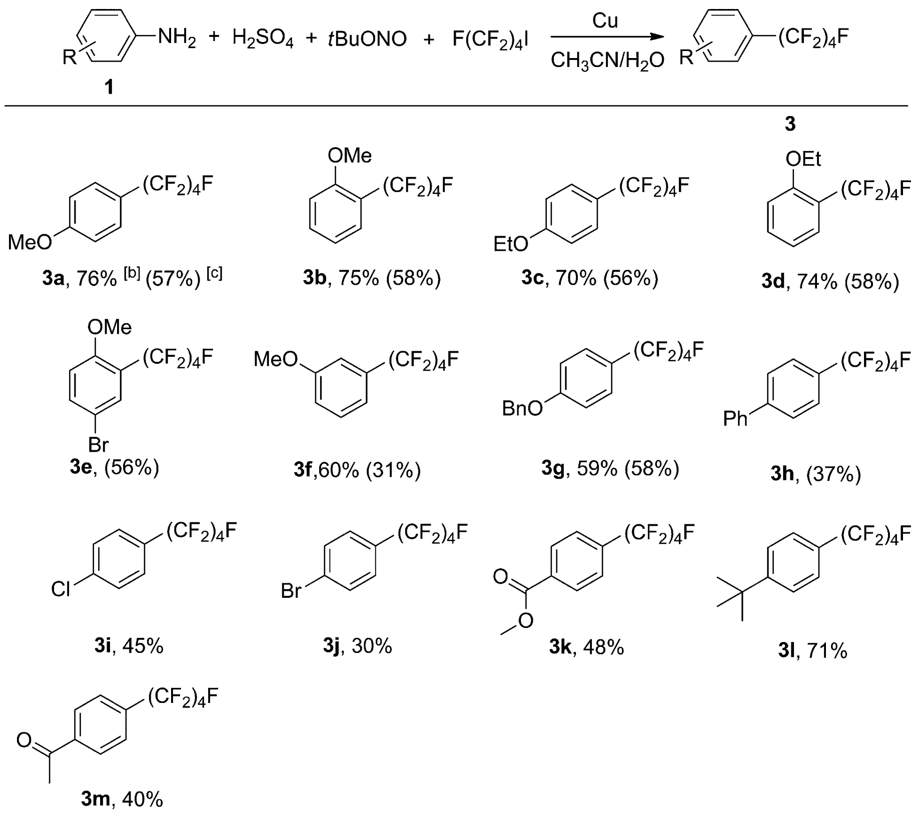


Entry	HX	*t*BuONO [equiv.]	Yield [%][b] p-$CH_3OC_6H_4(CF_2)_4F$	C[c]
1	HCl	1.2	47	–[d]
2	HPF_6	1.2	58	–[d]
3	H_3PO_4	1.2	61	–[d]
4	H_2SO_4	1.2	65	27
5	H_2SO_4	1.0	69	3
6[e]	H_2SO_4	1.2	78	0

[a] Reaction conditions: **1a** (0.4 mmol), HX (0.48 mmol), *t*BuONO (0.48 mmol), $F(CF_2)_4I$ (0.2 mmol), copper (0.8 mmol), CH_3CN/H_2O (3:2 v/v), –20 °C to room temp., 30 min, under N_2 atmosphere. [b] Yields were determined by ^{19}F NMR analysis using trifluorotoluene as internal standard. [c] C = $F(CF_2)_3COOH$. [d] Not detected. [e] Hydroquinone (20 mmol-%) was added after diazotization.

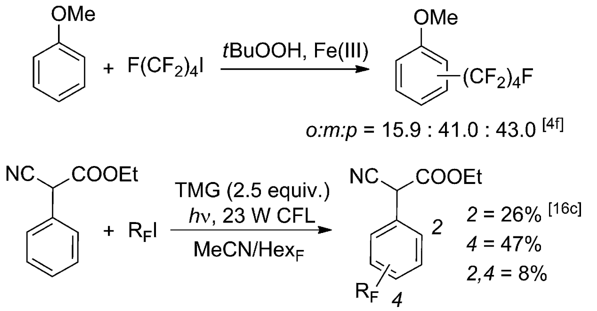
With the optimized conditions in hand (Table 2, entry 6), we investigated the substrate scope of the reaction. As shown in Table 3, a range of arylamines with either electron-donating or -withdrawing groups were subjected to the reaction conditions, to provide the desired perfluorobutylarenes in acceptable yields. It should be mentioned that the main by-products of the reactions were the corresponding aryl iodides, which complicated the purification. However, the substrates with alkyloxy or phenyl groups could be successfully purified by exhausting silica gel column chromatography. Importantly, most substrates, if not exclusive, afforded the desired products without detectable regioisomers. For example, the structure and purity of products **3a**, **3b**, and **3f** were confirmed by GC–MS and ^1H NMR analyses, and no regioisomers were observed. The regiospecific reactivity of diazonium salts[12a,15] is in contrast to the reported direct perfluoroalkyl radical addition to arenes, for which a lack of regioselectivity was a common issue (Scheme 2).[4f,16]

Table 3. Substrate scope.[a]



3a, 76% [b] (57%) [c]
3b, 75% (58%)
3c, 70% (56%)
3d, 74% (58%)
3e, (56%)
3f,60% (31%)
3g, 59% (58%)
3h, (37%)
3i, 45%
3j, 30%
3k, 48%
3l, 71%
3m, 40%

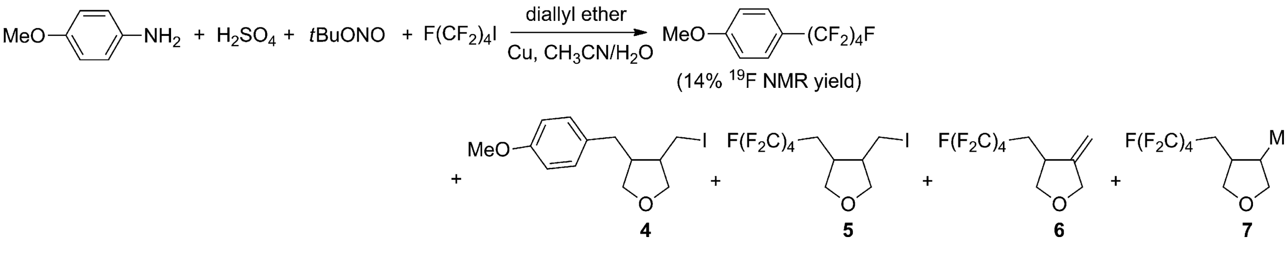
[a] Reaction conditions: **1** (0.4 mmol), H_2SO_4 (0.48 mmol), *t*BuONO (0.48 mmol), $F(CF_2)_4I$ (0.2 mmol), CH_3CN/H_2O (3:2 v/v), hydroquinone (0.08 mmol), copper (0.8 mmol), under N_2 atmosphere, –20 °C to room temp., 30 min. [b] Yields were determined by ^{19}F NMR spectroscopic analysis with trifluorotoluene as internal standard. [c] Isolated yield in parentheses.



Scheme 2. Examples of regioselectivity of direct radical perfluoroalkylation of arenes.

A preliminary mechanistic investigation was carried out on this reaction and, as a result, the new findings made it possible to improve the reaction further. It was reported that arenediazonium salts in general tend to react through an aryl radical process.[9a] Initially, a radical clock (diallyl ether) was added to the reaction, to identify possible radical species [Equation (2)]. Addition of diallyl ether (1.0 equiv.) led to a clear reduction in the yield, and traces of various radical-initiated cyclization products **4**–**7** were detected.

Based on these preliminary results, we assumed that perfluorobutylcopper "$F(CF_2)_4Cu$" species might be the key intermediate in the reaction, and that the reaction might proceed through a radical process. As shown in Scheme 3, an aryl radical produced by a SET process of the arenediazonium salt may abstract the iodine atom from a perfluorobutyl iodide to release the perfluorobutyl radical. The latter may be captured by Cu to form the "$F(CF_2)_4Cu$"



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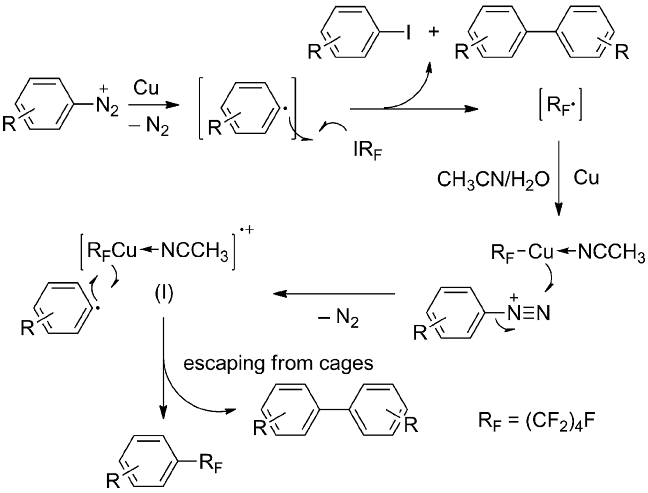
intermediate, which may subsequently react with arenediazonium salt to generate the target product in a SET process.

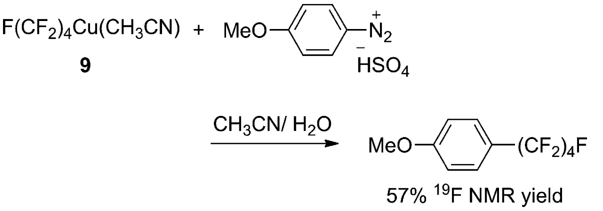


Scheme 3. Proposed mechanism for the reactions of arenediazonium salts with R_FI mediated by copper.

To test our hypothesis, we attempted to synthesize the "$F(CF_2)_4Cu$" complex according to a reported procedure.[2] However, we found that ligandless "$F(CF_2)_4Cu$" decomposed instantly once the solvent was evaporated. Fortunately, we noted that acetonitrile could stabilize "$F(CF_2)_4Cu$" species by forming a relative stable $F(CF_2)_4Cu(CH_3CN)$ complex, which was separated and characterized by elemental and ^1H NMR spectroscopic analyses. Interestingly, acetonitrile protons in $F(CF_2)_4Cu(CH_3CN)$ complex are shifted downfield by 0.3 ppm compared with that of free acetonitrile in ^1H NMR spectra [Equation (3)]. 4-Methoxybenzenediazonium and $F(CF_2)_4Cu(CH_3CN)$ complex were then mixed together in CH_3CN/H_2O and 57% of the desired product was achieved [Equation (4)]. This result may also explain why acetonitrile acts as such an effective solvent.

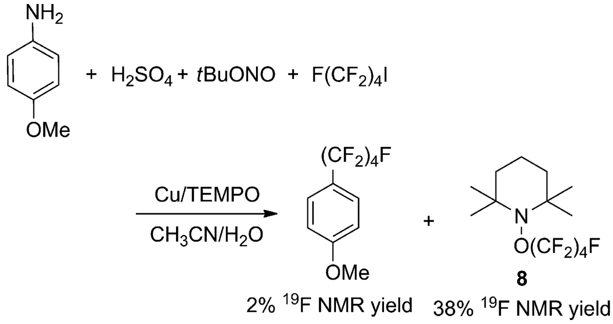
$$\begin{array}{c}\mathrm{F(CF_2)_4I}\\+\\\mathrm{Cu}\end{array}\xrightarrow[110\ ^{\circ}\mathrm{C}]{\mathrm{DMSO}}\text{"}\mathrm{F(CF_2)_4Cu}\text{"}\xrightarrow{\mathrm{CH_3CN}}\underset{\mathbf{9}}{\mathrm{F(CF_2)_4Cu(CH_3CN)}}$$

(^1H NMR: $\delta = 2.28$ ppm
vs δ (CH_3CN) = 1.98 ppm) (3)



(4)

We then included 2,2,6,6-tertramethylpiperidine-*N*-oxyl (TEMPO; 2.0 equiv.), a radical scavenger, to quench the reaction under standard conditions, and observed that TEMPO-$(CF_2)_4F$ (**8**) was formed in 38% ^{19}F NMR yield [Equation (5)]. When TEMPO (2.0 equiv.) was introduced to a mixture of **9** and 4-methoxybenzenediazonium in CH_3CN/H_2O, the yield decreased about 40%, giving 12% **8** and a trace amount of **10** [Equation (6)]. The direct reaction of $F(CF_2)_4Cu(CH_3CN)$ complex with TEMPO resulted in the formation of **8** [Equation (7)], which was similar to the reported result.[11] We also found that Cu^I salts could induce the reactions (see the Supporting Information). These results supported the conclusion that intermediate **I** (Scheme 3) had a longer lifetime than the perfluorobutyl radical. It was reported that arenediazonium salts have a stronger oxidizing ability than TEMPO,[17] so we proposed that $F(CF_2)_4Cu(CH_3CN)$ reacted with arenediazonium salt in a SET process to form aryl radical and intermediate **I**, the cross-coupling of which finally produced the desired product (Scheme 3).[18]



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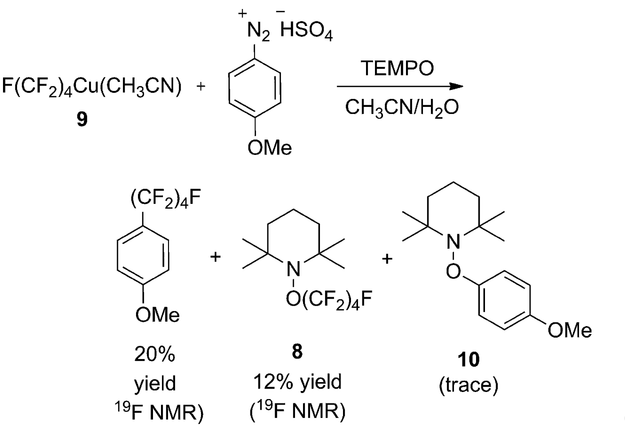

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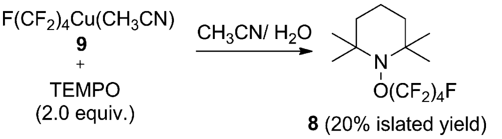

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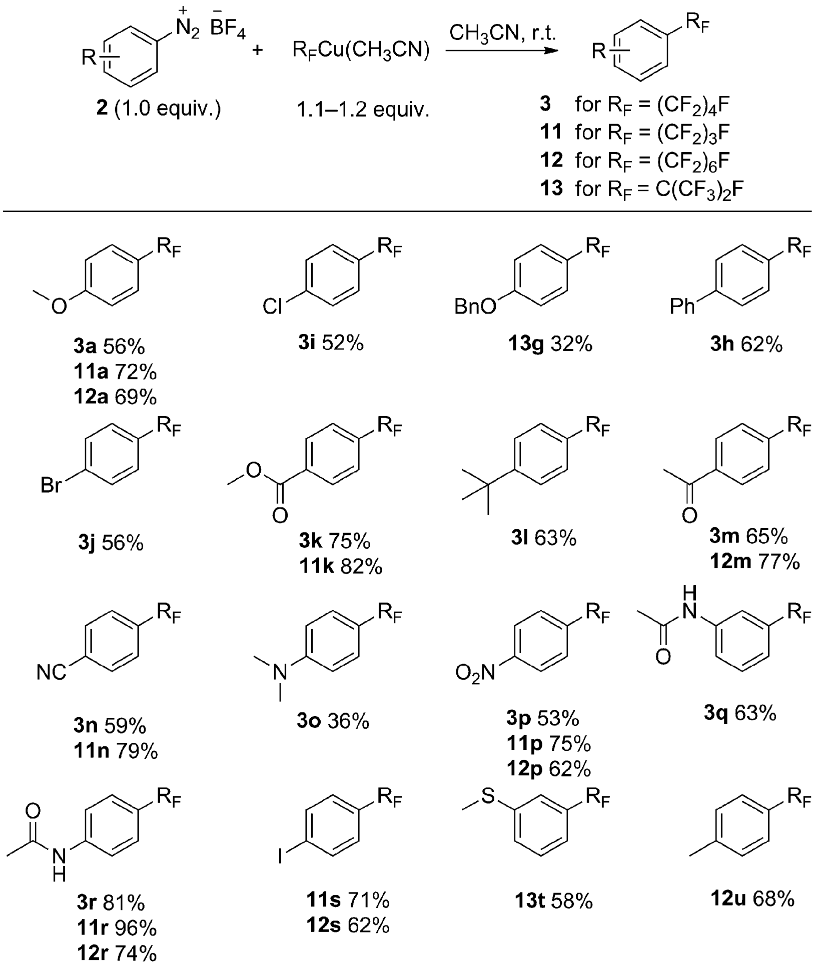
Considering the problems associated with purification of the product in the presence of aryl iodides and to avoid the use of an excess of arylamine in the reaction of arenediazonium salts with stable $F(CF_2)_4Cu(CH_3CN)$ complex, we tried to use this complex as perfluorobutylating agent directly in acetonitrile. To our delight, the reaction proceeded

Table 4. Scope of the perfluoroalkylation of arenes by the reaction of arenediazonium tetrafluoroborates with $R^FCu(CH_3CN)$ complexes.[a,b]



[a] Reaction conditions: **2** (0.4 mmol), $R^FCu(CH_3CN)$ (0.44–0.48 mmol), CH_3CN (4.0 mL), 30 min, under N_2. [b] Isolated yield.

smoothly and arenediazonium tetrafluoroborates with various functional groups were effectively converted into the corresponding perfluoroalkylated arenes in good yields under mild conditions. Substrates with either electron-donating or electron-withdrawing groups gave similar high yields (Table 4). Many functionalities such as alkyl, alkyloxy, ester, acyl, acylamino, cyano, nitro, and halo (Cl, Br, I) were tolerated in the reaction. In addition, the reaction could also be extended to include perfluoropropyl, perfluorohexyl, and perfluoroisopropyl groups.

Conclusions

We have developed a convenient and efficient method of converting various arylamines into perfluoroalkylarenes under mild conditions. In view of the preliminary mechanism study, relatively stable $R_FCu(CH_3CN)$ were successfully prepared and used as perfluoroalkylating agents to react with a variety of arenediazonium salts to provide the corresponding perfluoroalkylarenes in high yields without formation of aryl iodide by-products. The method thus provides a convenient way of introducing perfluoroalkyl groups to various arenes in late-stage procedures.

Experimental Section

General: NMR spectra were obtained with an Agilent 400M NMR system using $CDCl_3$ or $[D_6]$acetone as deuterated solvents, with ^1H, ^{13}C, and ^{19}F resonances at 400, 101, and 376 MHz, respectively. Chemical shifts were reported in parts per million (ppm) relative to TMS as an internal standard ($\delta = 0$ ppm) for ^1H and ^{13}C NMR spectra and $CFCl_3$ as an external standard (negative for upfield) for ^{19}F NMR spectra. GC–MS (EI) data were determined with an Agilent 5975C. HRMS (EI) data were obtained with a Water Micromass GCT Premier. Element analysis data were determined with an Elementar VARIO EL apparatus. Acetonitrile was distilled from CaH_2. All the other solvents or reagents were used as commercial sources without purification. All reactions were performed in standard Schlenk tubes and monitored by TLC or ^{19}F NMR spectroscopy. Flash column chromatography was carried out by using 300–400 mesh silica gel.

Typical Procedures for Perfluoroalkylation of Arenediazonium Salts

Procedure A: To a solution of arylamine (0.4 mmol) in CH_3CN/H_2O (3:2 v/v, 2.0 mL), H_2SO_4 (12 N, 40 µL, 0.48 mmol) and *t*BuONO (54.9 mg, 0.48 mmol) were added sequentially under cooling with an ice-water bath. The reaction mixture was kept for 15 min, then hydroquinone (8.8 mg, 0.08 mmol), $F(CF_2)_4I$ (69.3 mg, 0.2 mmol), and freshly prepared copper (50.8 mg, 0.8 mmol) were sequentially added under a nitrogen atmosphere. The reaction mixture was stirred at r.t. for 30 min, diluted with ethyl acetate (20 mL) and filtered through a pad of Celite. The organic layer was collected and washed with water (20 mL) and the aqueous layer was further extracted with ethyl acetate (2 × 20 mL). The combined organic layer was dried with $MgSO_4$ for 30 min, filtered, and concentrated. The residue was purified by flash chromatography (petroleum ether/ethyl acetate) to obtain the corresponding perfluoralkylated arene.

Procedure B

(1) Preparation of $F(CF_2)_4Cu(CH_3CN)$ Complex. Typical Procedure:[2] All the operations were performed under a nitrogen atmosphere. A 200 mL Schlenk tube was charged with copper (1.6 g, 25 mmol), $F(CF_2)_4I$ (3.75 g, 11 mmol) and anhydrous DMSO (15 mL). The reaction mixture was kept at 110 °C for 1.5 h. After cooling to room temperature, the mixture was poured into diethyl ether (50 mL) and degassed water (30 mL). The organic layer was collected and washed with degassed water (5 × 30 mL), dried with $MgSO_4$, and filtered to give colorless solution. Acetonitrile (5.0 mL) was added and the resulting solution was evaporated in vacuo for 2 h to give the desired complex as a clear pale-amber oil, which could be stored under an N_2 atmosphere at 4 °C for several months.

(2) Preparation of Arenediazonium Tetrafluoroborates. General Procedure:[19] To a solution of arylamine (1.0 mmol) in THF (2.0 mL), $BF_3·Et_2O$ (213 mg, 1.5 mmol) was added slowly under cooing with an ice-water bath. *t*BuONO (137 mg, 1.2 mmol) was then added dropwise. The reaction mixture was stirred for 15 min, then diethyl ether (10 mL) was added. The precipitate formed was filtered, washed with diethyl ether, and dried in vacuo for 30 min to afford the desired arenediazonium salt.

(3) Reaction of $R_FCu(CH_3CN)$ with Arenediazonium Salts. General Procedure: A Schlenk tube was charged with $R_FCu(CH_3CN)$ complex (0.44–0.48 mmol) and acetonitrile (2.0 mL) under a nitrogen atmosphere. Freshly prepared arenediazonium tetrafluoroborate (0.4 mmol) was dissolved in acetonitrile (2.0 mL) and the resulting solution was injected into the above reaction mixture dropwise under cooling with an ice-water bath. After stirring for 30 min at room temperature, the reaction mixture was diluted with ethyl acetate (20 mL) and filtered through a pad of Celite. The filtrate was collected and concentrated. The resulting residue was purified by flash chromatography (petroleum ether/ethyl acetate) to obtain the corresponding perfluoralkylated arene.

Supporting Information (see footnote on the first page of this article): Reaction optimization, mechanism experiments, characterization data, and copies of the ^1H, ^{19}F, and ^{13}C NMR spectra.

Acknowledgments

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