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

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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.

Scheme 1. Strategies of introducing perfluoroalkyl groups into arenes.

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)cupper 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)cupper agents reacted with haloarenes or arylboronate esters to obtain perfluoroalkylarenes.[4d,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.

Initially, we selected 4-methylbenzenediazonium tetrafluoroborate as aryl precursor, copper powder (freshly prepared from CuSO_4·5H_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 19F 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.

Scheme 1. Strategies of introducing perfluoroalkyl groups into arenes.

\[
\text{Previous work: } \text{ArH} + \text{RF}X \xrightarrow{\text{radical initiator}} \text{ArRF} \\
\text{ArI} + \text{RFI} \xrightarrow{\text{Cu}} \text{ArRF} \\
\text{ArI} + \text{R}_2\text{H} \xrightarrow{[\text{Cu}], \text{base}} \text{ArRF} \\
\text{ArBP}_{\text{Pin}} \text{or ArI} + (\text{phen})\text{CuRF} \rightarrow \text{ArRF} \\
\text{ArBH(OH)}_2 + \text{RFI} \xrightarrow{\text{Cu}} \text{ArRF}
\]

\[
\text{This work: } \text{ArN}_2^+ + \text{RF}_2\text{Cu} / \text{or} \text{Cl} \rightarrow \text{ArRF}
\]

Equation (1)
Further screening of cupric 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 CH₃Cl (entries 6–8). In methanol, only 11% of the desired product and 46% yield of Cl(CF₂)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(CF₂)₄COOH, which may be attributed to partial quenching of Cl(CF₂)₄⁺ radical by oxygen, 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]

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>1</td>
<td>CH₃CN</td>
<td>Cu</td>
<td>31</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>2</td>
<td>CH₃CN</td>
<td>CuCl</td>
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<td>0</td>
<td>0</td>
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<tr>
<td>3</td>
<td>CH₃CN</td>
<td>CuI</td>
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<td>0</td>
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<tr>
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<td>CuZn</td>
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<td>CuZn</td>
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<td>0</td>
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<td>Cu/Zn</td>
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<td>11</td>
</tr>
<tr>
<td>10</td>
<td>acetone</td>
<td>Cu/Zn</td>
<td>19</td>
<td>0</td>
<td>.[c]</td>
</tr>
<tr>
<td>11[f]</td>
<td>CH₂CN/H₂O</td>
<td>Cu/Zn</td>
<td>47</td>
<td>3</td>
<td>9</td>
</tr>
<tr>
<td>12[g]</td>
<td>CH₂CN/H₂O</td>
<td>Cu</td>
<td>56</td>
<td>1</td>
<td>11</td>
</tr>
</tbody>
</table>

[a] Reaction conditions: 4-methylbenzenediazonium tetrafluoroborate (0.4 mmol), [Cu] (0.4 mmol), Zn (0.2 mmol, if added), Cl(CF₂)₄I (0.2 mmol), solvent, in air, r.t., 30 min. [b] Yields were determined by 19F NMR analysis using trifluorotoluene as an internal standard. [c] A = Cl(CF₂)₄H₂. [d] B = Cl(CF₂)₄COOH. [f] Cu (0.8 mmol) was used.

Further study indicated that the counterners of arenediazonium salts played an important role in the reaction (Table 2). HSO₄⁻ 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 tBuONa 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 tBuONO after the diazotization of arylamines without affecting the reaction, and the 19F 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]

<table>
<thead>
<tr>
<th>Entry</th>
<th>HX</th>
<th>tBuONO [equiv.]</th>
<th>Yield [%][b]</th>
<th>C[c]</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>HCl</td>
<td>1.2</td>
<td>47</td>
<td>.[d]</td>
</tr>
<tr>
<td>2</td>
<td>HPF₆</td>
<td>1.2</td>
<td>58</td>
<td>.[d]</td>
</tr>
<tr>
<td>3</td>
<td>H₃PO₄</td>
<td>1.2</td>
<td>61</td>
<td>.[d]</td>
</tr>
<tr>
<td>4</td>
<td>H₂SO₄</td>
<td>1.2</td>
<td>65</td>
<td>27</td>
</tr>
<tr>
<td>5</td>
<td>H₂SO₄</td>
<td>1.0</td>
<td>69</td>
<td>3</td>
</tr>
<tr>
<td>6[e]</td>
<td>H₂SO₄</td>
<td>1.2</td>
<td>78</td>
<td>0</td>
</tr>
</tbody>
</table>

[a] Reaction conditions: 1a (0.4 mmol), HX (0.48 mmol), tBuONO (0.48 mmol), F(CF₂)₄I (0.2 mmol), copper (0.8 mmol), CH₃CN/H₂O (3:2 v/v), –20 °C to room temp., 30 min, under N₂ atmosphere. [b] Yields were determined by 19F NMR analysis using trifluorotoluene as an internal standard. [c] C = F(CF₂)₄COOH. [d] Not detected. [e] Hydroquinone (20 mol-%) 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 alkyl 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 regioselectivity 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).[14f,16]
Table 3. Substrate scope.[a]

<table>
<thead>
<tr>
<th>R</th>
<th>Product</th>
<th>Yield (%)</th>
<th>Regioselectivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>MeO</td>
<td>3a</td>
<td>76% [b]</td>
<td>(57%) [c]</td>
</tr>
<tr>
<td>OMe</td>
<td>3b</td>
<td>75% [b]</td>
<td>(58%)</td>
</tr>
<tr>
<td>EtO</td>
<td>3c</td>
<td>70% [b]</td>
<td>(56%)</td>
</tr>
<tr>
<td>OEt</td>
<td>3d</td>
<td>74% [b]</td>
<td>(58%)</td>
</tr>
<tr>
<td>Br</td>
<td>3e</td>
<td>56%</td>
<td></td>
</tr>
<tr>
<td>MeO</td>
<td>3f</td>
<td>60% [b]</td>
<td>(31%)</td>
</tr>
<tr>
<td>Br</td>
<td>3j</td>
<td>30%</td>
<td></td>
</tr>
<tr>
<td>Cl</td>
<td>3i</td>
<td>45%</td>
<td></td>
</tr>
<tr>
<td>O</td>
<td>3k</td>
<td>48%</td>
<td></td>
</tr>
<tr>
<td>OMe</td>
<td>3l</td>
<td>40%</td>
<td></td>
</tr>
</tbody>
</table>

[a] Reaction conditions: 1 (0.4 mmol), H₂SO₄ (0.48 mmol), tBuONO (0.48 mmol), F(CF₂)₄I (0.2 mmol), CH₃CN/H₂O (3:2 v/v), hydroquinone (0.08 mmol), copper (0.8 mmol), under N₂ atmosphere, −20 °C to room temp., 30 min. [b] Yields were determined by 19F 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.[9] 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(CF₂)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(CF₂)₄Cu”
intermediate, which may subsequently react with arene-
diazonium salt to generate the target product in a SET pro-
cess.

\[ \text{Scheme 3. Proposed mechanism for the reactions of arenediazo-
nium salts with RF mediated by copper.} \]

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” decom-
posed 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)_4-
Cu(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.

\[ \text{We then included 2,2,6,6-tertramethylpiperidine-N-oxyl (TEMPO; 2.0 equiv.), a radical scavenger, to quench the reac-
tion under standard conditions, and observed that TEMPO-(CF_2)_4F (8) was formed in 38 % 19F NMR yield} \]

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 arenediazo-
nium salts with stable F(CF_2)_4Cu(CH_3CN) complex, we
tried to use this complex as perfluorobutylating agent di-
rectly in acetonitrile. To our delight, the reaction proceeded.
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, alkoxy, 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_F Cu(CH_3CN) were successfully prepared and used as perfluoroalkylating agents to react with a variety of arenediazonium salts to provide the corresponding perfluorouralkylarenes 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, 13C, and 19F resonances at 400, 101, and 376 MHz, respectively. Chemical shifts were reported in parts per million (ppm) relative to TMS as an internal standard (δ = 0 ppm) for 1H and 13C NMR spectra and CFCl_3 as an external standard (negative for upfield) for 19F NMR spectra. GC–MS (EI) data were determined with an Agilent 5975C. HRMS (EI) data were obtained with a Waters 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 19F 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$_3$CN/H$_2$O (3:2 v/v, 2.0 mL), H$_2$SO$_4$ (12 N, 40 μL, 0.48 mmol) and tBuONO (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$_2$)$_4$I (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 filtrate was evaporated, petroleum ether (50 mL) and degassed water (30 mL). The organic layer was dried with MgSO$_4$ for 30 min, filtered, and concentrated. The resulting residue was purified by flash chromatography (petroleum ether/ethyl acetate) to obtain the corresponding perfluoroalkylated arene.

**Procedure B**

1. **Preparation of F(CF$_2$)$_4$Cu(CH$_3$CN) Complex. Typical Procedure:**

   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$_2$)$_4$I (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). The reaction mixture was stirred at r.t. for 30 min, diluted with MgSO$_4$ for 30 min, filtered, and concentrated. The residue was purified by flash chromatography (petroleum ether/ethyl acetate) to obtain the corresponding perfluoroalkylated arene.

2. **Preparation of Arenediazonium Tetrafluoroborate. General Procedure:**

   To a solution of arylamine (1.0 mmol) in THF (2.0 mL), BF$_3$·Et$_2$O (213 mg, 1.5 mmol) was added slowly under cooling with an ice-water bath. tBuONO (137 mg, 1.2 mmol) was then added and 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 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.

3. **Reaction of R$_2$Cu(CH$_3$CN) with Arenediazonium Salts. General Procedure:**

   A Schlenk tube was charged with R$_2$Cu(CH$_3$CN) 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 perfluoroalkylated arene.

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

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