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Copper-Mediated Radical Cross-Coupling Reaction of 2,2-Dichloro-1,1,1-trifluoroethane (HCFC-123) with Phenols or Thiophenols

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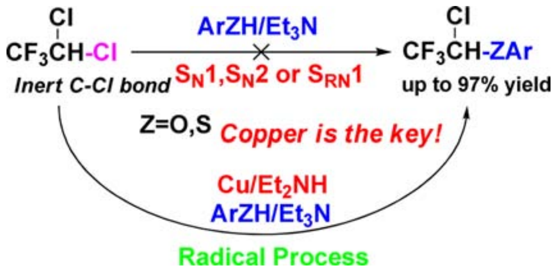
ABSTRACT



A copper-mediated cross-coupling reaction between HCFC-123 and phenols or thiophenols has been achieved. It is found that diethyl amine, which serves as both the activator and ligand of copper, plays a key role in this reaction. Two possible radical involved processes are proposed for the reaction mechanism.

According with Montreal Protocol, ozone-depleting hydrochlorofluorocarbons (HCFCs) will be completely forbidden as refrigerants, aerosol propellants, or cleaning solvents in 2030.[1] However, from a synthetic viewpoint, some HCFCs are indispensable for both syntheses of fluorinated building blocks and industrial applications. For example, a widely used refrigerant, difluorochloroethane (HCFC-22), is not only a well-known difluorocarben reagent[2] in the laboratory but also a key starting material in the manufacture of tetrafluoroethene (TFE) in the industry.[3] Because of the electronic effect and steric hindrance of fluorinated groups, compared with common alkyl chlorides, most HCFCs are reluctant to undergo S_N1 or S_N2 reactions. In this sense, converting ozone-depleting and easily available HCFCs to useful organfluorine compounds via direct cleavage of unactivated C−Cl bonds to useful fluorinated compounds will contribute to both the progress of organofluorine chemistry and environmental protection.[4] To some extent, the chemical reactivities of C−Cl bonds in the HCFCs are similar to those of carbon−halogen bonds of aryl halides, which can react with enolates,[5] thiolates,[6] or diphenylphosphide ions[7] via Single Electron Transfer (SET) processes.[8] In most cases, compared with thiolates, as a class of poor electron donors, it is

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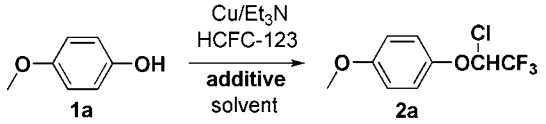
difficult for phenolates to initiate $S_{RN}1$ reactions directly,[9] so it is still a challenge to synthesize R_f–OAr from R_f–X and ArOH directly.

Among the family of HCFCs, 2,2-dichloro-1,1,1-trifluoroethane (HCFC-123) is an easily available and largely used cleaning solvent and refrigerant in the industry. Early reports showed that the C–Cl bond in HCFC-123 can be cleaved smoothly in the presence of copper.[10] Similar to the classical copper-mediated Ullmann cross-coupling reaction, a SET process was also involved in the cleavage of the C–Cl bond of HCFC-123. Inspired by the classical copper-mediated Ullmann reaction between aryl halides and aryl halides,[11] phenols, anilines, or thiophenols,[12] it can be anticipated that copper-mediated Ullmann-type cross-coupling reactions between HCFC-123 and phenols or thiophenols may be practicable. Herein, we report our results in this communication.

Optimizations of reaction conditions using *p*-MeOPhOH (**1a**) as the model substrate are listed in the Table 1. Initially, DMSO, a general solvent used for classical Ullmann reaction, was selected as the solvent. Unexpectedly, according to ^{19}F NMR spectra, no change in HCFC-123 was detected even when the amount of Et_3N was increased to 3 equiv (entries 1 and 2). To our delight, a low new ^{19}F NMR signal at −80 ppm (d, J = 4 Hz) was found when 1 equiv of diethyl amine was added as the additive (entry 3). As expected, a similar result was obtained when DMF was used in place of DMSO (entry 4). Upon consideration of a more simple operation, we turned toward using HCFC-123 itself as the solvent directly. However, the C–Cl bond of HCFC-123 was inert when no Et_2NH was added (entries 5 and 6). Surprisingly, a 61% spectrum yield of expected product **2a** was observed when Et_2NH was used as the additive (entry 7). The yield of **2a** was decreased significantly to 33% when pyrrolidine was added as the additive (entry 8).

These results indicate that a secondary amine, Et_2NH, or pyrrolidine may activate copper in this reaction. Furthermore, we observed a yellow Cu(I) coordination compound when Et_2NH served as a ligand, precipitating slowly in the reaction process. In contrast, both copper and HCFC-123 remained unchanged when *i*-Pr_2NH, a secondary amine with steric hindrance, was used as the additive in place of Et_2NH (entry 9). As foreseen, no product of **2a** was found in the absence of copper, which confirms that a simple S_N1 or S_N2 reaction could not take place between phenonates and HCFC-123 (entry 10). In order to obtain a better yield of **2a**, we decided to increase the use of copper. The spectrum yield of **2a** was updated to 89% when 1.5 equiv of copper were used (entry 11). Excitedly, the spectrum yield of **2a** was improved to 100% when 2 equiv of copper were added (entry 12). Furthermore, when DCE or DCM was used as the solvent, the product of **2a** was found with 68%, 78% ^{19}F NMR yield, respectively (entries 13 and 14). Based the on the experimental results above, entry 12 was selected as the best conditions.

Table 1. Optimizations of Copper-Mediated Cross-Coupling between HCFC-123 and **1a**



entry	Cu/**1a**/Et_3N	additive[a]	solvent[b]	*t*/°C	yield[c]
1	1.25:1:1.25	–	DMSO	80	N.R.
2	1.25:1:3	–	DMSO	80	N.R.
3	1.25:1:1.25	Et_2NH	DMSO	80	trace
4	1.25:1:1.25	Et_2NH	DMF	80	trace
5	1.25:1:1.25	–	HCFC-123	60	N.R.
6	1.25:1:3	–	HCFC-123	60	N.R.
7	1.25:1:1.25	Et_2NH	HCFC-123	60	61%
8	1.25:1:1.25	pyrrolidine	HCFC-123	60	33%
9	1.25:1:1.25	*i*-Pr_2NH	HCFC-123	60	N.R.
10	0:1:1.25	Et_2NH	HCFC-123	60	N.R.
11	1.5:1:1.25	Et_2NH	HCFC-123	60	89%
12	2:1:1.25	Et_2NH	HCFC-123	60	100%
13	2:1:1.25	Et_2NH	DCM[d]	60	68%
14	2:1:1.25	Et_2NH	DCE[d]	60	75%

[a] The ratio of Cu and the additive is 1:1. [b] [**1a**] = 0.5 mol/L; reaction time was 3 h; **1a**/HCFC-123 = 1:2 when DMSO or DMF was used as the solvent. All reactions were performed in a sealed tube. [c] The yield is determined by ^{19}FNMR using $PhCF_3$ as internal standard. [d] [**1a**] = 0.5 mol/L; **1a**/HCFC-123 = 1:2; reaction time is 5 h.

With the optimized conditions in hand, this transformation was applied to substituted phenols. The representative instances are illustrated in Scheme 1. As seen, phenols bearing electron-donating (alkyl, methoxy and phenyl), electron-withdrawing (cyano, nitro, aldhyde, and ester) substituents and halogens (chloro and bromo) all resulted in **2** with excellent yields (84–97%). A variety of potentially reactive groups such as cyano, nitro, aldhyde, and bromo are well-tolerated in this reaction. The low yield (58%) of **2b** may be due to the poor solubility of *p*-AcNH-PhOH in the HCFC-123. It is also noted that the reaction time for the substrate of pyridin-3-ol needed to be prolonged to 10 h. According to the observed experimental phenomenon, this may be attributed to the intereference by the nitrogen atom in the pyridin-3-ol in the activation of copper by Et_2NH.

Subsequently, we sought to expand this reaction to substrates of thiophenols. Selecting 4-methylbenzenethiol (**3a**) as the model substrate, optimized conditions are

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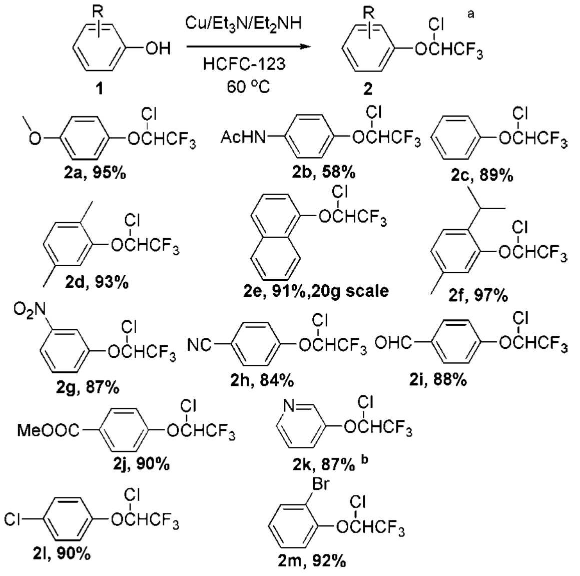
Scheme 1. Substrate Scope for Copper-Mediated Cross-Coupling between HCFC-123 and Phenols

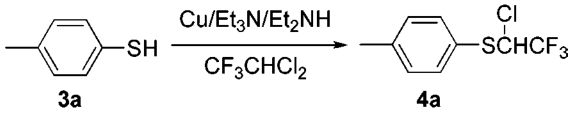


[a] $Cu/Phenol/Et_2NH/Et_3N$ = 2:1:2:1.25; HCFC-123 is used as the solvent, and reactions are stirred in 60 °C for 3 h in a sealed tube. All yields of **2** are isolated yields based on the phenol. [b] The reaction time is prolonged to 12 h.

shown Table 2. To our surprise, only a trace of product of **4a** was obtained when previous conditions were used even for 24 h at 60 °C (entry 1). As observed, most of the copper was sustained because thiolates may poison copper compared with phenolates. Realizing this result, we decided to increase the use of Et_2NH. Regretfully, a similar result was obtained when the ratio of copper and Et_2NH was changed to 2:2.5 (entry 2). To our delight, a 62% spectrum yield of **4a** was observed when the ratio of Cu/Et_2NH/**3a** = 2:2.5:1 (entry 3). When changing the ratio of Cu and Et_2NH to 2:3, a side product, *p*-tolyl(2,2,2-trifluoroethyl) sulfane[13] (^{19}F NMR: −65.8 ppm, t, J = 10 Hz), was obtained in the reaction although the yield of **4a** was increased to 78% (entry 4). Undoubtedly, *p*-tolyl(2,2,2-trifluoroethyl) sulfane was originated from the reduction of **4a** by excess copper. By changing the ratio of copper and Et_2NH to 1.7:3, the spectrum yield of **4a** was increased to 86% (entry 5). However, the yield of **4a** was reduced to 74% if the ratio of copper and Et_2NH was 1.5:3 (entry 6). As expected, the yield of **4a** was reduced to 65% when the use of Et_2NH was minimized (entry 7). Based on optimizations, the ratio of Cu/Et_2NH/**3a** = 1.7:3:1 (entry 5) is an appropriate condition for this reaction.

The scope of this reaction is exhibited by the results shown in Table 3. In general, good total yields of **4** and **4′** were obtained from thiophenols bearing different substituents. Similar to the substrate of phenols, this reaction can also tolerate functional groups such as ethers, halogens, and amides. It should be noted that the product **4′** originating from **4** cannot be avoided in this reaction when the amount of copper was decreased. This is because the SET process between **4** and copper can be assisted by the π^* MO in **4** compared with HCFC-123.[14]

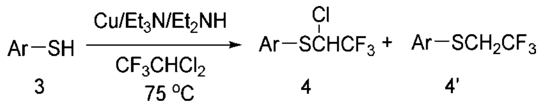
Table 2. Optimizations of Copper-Mediated Cross-Coupling between HCFC-123 and **3a**



entry	*t*/°C	Cu/Et_2NH/**3a**/Et_3N[a]	yield[b]
1	60	2:2:1:1.25	trace
2	60	2:2.5:1:1.25	trace
3	75	2:2.5:1:1.25	62%
4	75	2:3:1:1.25	78%
5	75	1.7:3:1:1.25	86%
6	75	1.5:3:1:1.25	74%
7	75	1.7:1.7:1:1.25	65%

[a] Using HCFC-123 as the solvent, [**3a**] = 0.5 mol/L; all reactions are performed in the sealed tube for 24 h. [b] The yield is determined by ^{19}F NMR using $PhCF_3$ as internal standard.

Table 3. Substrate Scope for Copper-Mediated Cross-Coupling between Thiophenols and HCFC-123



entry	Ar-SH[a]	yield **4**[b]	 **4′**[c]
1	*p*-Me-PhSH (**3a**)	**4a**, 79%	**4′a**, 13%
2	*p*-isopropyl-PhSH (**3b**)	**4b**, 71%	**4′b**, 15%
3	*p*-MeO-PhSH (**3c**)	**4c**, 81%	**4′c**, 14%
4	*p*-AcNH-PhSH (**3d**)	**4d**, 85%	**4′d**, 10%
5	*o*-Br-PhSH (**3e**)	**4e**, 55%	**4′e**, 41%
6	*p*-Cl-PhSH (**3f**)	**4f**, 75%	**4′f**, 20%
7	pyridine-2-thiol (**3g**)	**4g**, 18%	**4′g**, 46%

[a] Cu/Et_2NH/**3**/Et_3N = 1.7:3:1:1.25, [**3**] = 0.5 mol/L. All reactions are performed in a sealed tube for 24 h. [b] Isolated yield based on **3**. [c] ^{19}F NMR yield based on **3**, using $PhCF_3$ as internal standard.

As described in literature, the product **4** can be applied to trifluoroethylation of aromatic compounds.[15] For the product **2**, it may be used to synthesize some useful building blocks for the existence of the Cl atom. By treatment with Zn powder in the DMSO at 110 °C for 3 h, the product **2** can be transformed into a monomer of

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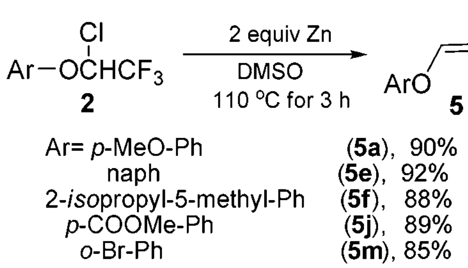
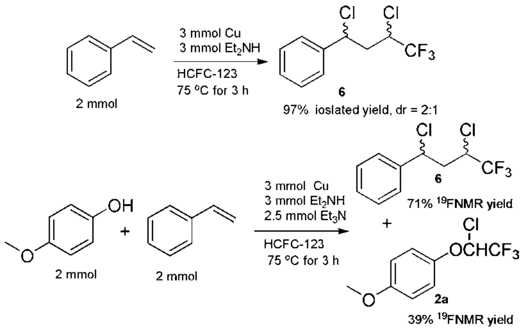
fluorinated polymers, difluoroviny aryl ether **5** with excellent yields (Scheme 2). Compared with previous method of defluorination of 2,2,2-trifluoroethyl aryl ether with a strong organic base,[16] this method has good functional tolerance and high yields.

Scheme 2. Synthesis of Difluoroviny Aryl Ether from **2**



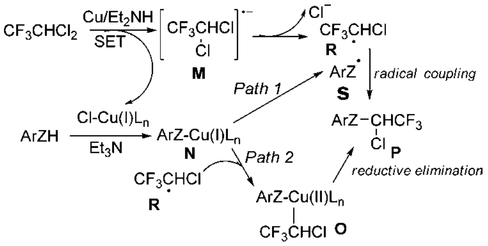
Finally, we turned toward investigating the mechanism of this cross-coupling reaction. The Atom Transfer Radical Addition[17] product of **6** was obtained with 97% isolated yield when styrene was used as the radical trapper. Furthermore, when the same amount of *p*-MeOPhOH and styrene were added, the product **6** and the cross-coupling product **2a** were obtained in 71% and 39% ^{19}F NMR yield (Scheme 3), respectively. These results indicate that a 2,2,2-trifluoro-1-chloroethyl radical intermediate is in a "free" status in this cross-coupling reaction.

Scheme 3. Trapping the Radical Intermediate with Styrene



In light of these results, our proposed mechanism is depicted as follows (Scheme 4). The Single Electron Transfer (SET) reaction between Cu and HCFC-123 gives rise to the anion radical **M** and CuCl. Quick fragmentation of the anion-radical **M** results in the 2,2,2-trifluoro-1-chloroethyl radical intermediate **R**. On the other hand, phenolates or thiolates can be converted to Cu(I)-ZAr **N** in the presence of Cu(I).[18] Starting from the intermediate Cu(I)-ZAr **N**, two possible paths may exist in the following process. For Path 1, hemolytic cleavage of the Cu−Z bond in **N** will produce Cu(0) and the radical intermediate **S**. A double radical coupling between the radical intermediate **S** and **R** leads to the product **P**. For Path 2, coupling with the radical intermediate **R** results in the the Cu(I) intermediate **N** which can be converted to another Cu(II) intermediate **O**. Reductive elimination of the Cu(II) intermediate **O** affords the product **P**.

Scheme 4. Proposed Mechanism for the Copper-Mediated Radical Cross-Coupling Reaction



In summary, we have completed an interesting copper-mediated cross-coupling reaction between HCFC-123 and phenols or thiophenols with excellent yields. The resulted products can be used as useful fluorinated building blocks. In this cross-coupling reaction, Et_2NH serves as not only the activator of copper powder but also the ligand for copper species. The radical intermediate is found to be at a free status when using styrene as the radical trapper. Differing from the existing common S_N1, S_N2, and $S_{RN}1$ reactions, this cross-coupling reaction displays a novel pathway for a substitution reaction in an unactived alkyl chloride, HCFC-123. More detailed mechanism research and further development of this cross-coupling reaction are in progress.

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Supporting Information Available. Full experimental data and characterization for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

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