

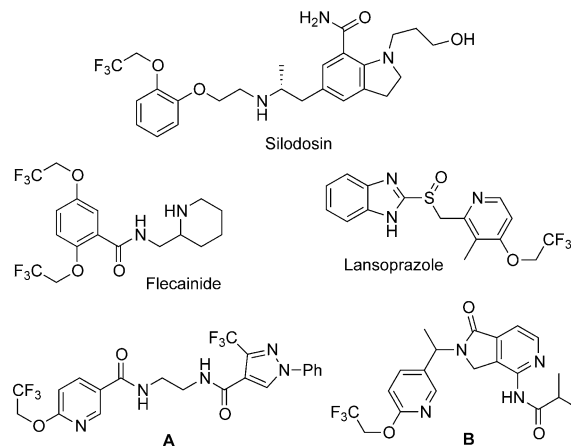
Well-Defined Copper(I) Fluoroalkoxide Complexes for Trifluoroethoxylation of Aryl and Heteroaryl Bromides**

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Abstract: Copper(I) fluoroalkoxide complexes bearing dinitrogen ligands were synthesized and the structure and reactivity of the complexes toward trifluoroethoxylation, pentafluoropropoxylation, and tetrafluoropropoxylation of aryl and heteroaryl bromides were investigated.

The development of an efficient and convenient method for the synthesis of fluoroorganic compounds is of paramount significance because of their importance in the fields of medicinal chemistry^[1–3] and material sciences.^[4] Over the last few years, numerous synthetic examples of the selective incorporation of fluorine-containing groups into organic molecules have been developed.^[5–9] Among them, trifluoroethyl aryl ethers have attracted much attention because of the high metabolic stability and significant lipophilicity of the CF₃CH₂O group.^[10,11] As a consequence of their various beneficial pharmacological activities, trifluoroethyl aryl ethers are widely used by the pharmaceutical industry in many drugs and drug candidates.^[10,12] Well-known examples include Silodosin for the symptomatic treatment of benign prostatic hyperplasia, Flecainide used to prevent and treat tachyarrhythmias, as well as proton-pump inhibitor Lansoprazole (Scheme 1).^[13]

The prevalence of this structural motif in pharmaceutical agents has resulted in methods to prepare trifluoroethyl aryl ethers having been an important theme in organic chemistry and drug discovery. Many interesting synthetic methods have been developed for their synthesis,^[14–16] including the nucleophilic addition of a phenol to trifluoroethyl iodide^[17] or trifluoroethyl mesylate^[18] in solvents such as DMSO or hexamethyl phosphoramide (HMPA) at elevated temperatures (up to 140 °C). An important alternative has also been reported, where aryl halides are used to react with trifluoroethanol. However, these methods all depend on harsh reaction conditions, such as the use of excess copper salts,



Scheme 1. Trifluoroethyl aryl ether based drugs and bioactive compounds.

high reaction temperatures, and long reaction times.^[19] Recently, Legros, Crousse, and co-workers developed a copper-catalyzed synthesis of fluorinated aryl and vinyl ether using neat fluoro alcohols as both the reactant and solvent at reflux for 17 h.^[20] Fluorinated aryl and vinyl ethers were synthesized in good to excellent yields and several aromatic substituents were tolerated. However, this procedure requires a large excess of expensive fluorinated alcohols (3–7 equiv) for effective coupling reactions. Singh and co-workers also reported a palladium-catalyzed fluoroalkoxylation by the cross-coupling of primary fluoroalkyl alcohols with activated aryl halides.^[21] However, these reported experiments required the use of the precious metal Pd and phosphine ligands, and were limited to aryl substrates containing electron-withdrawing groups.

Heteroaryl halides are a desirable class of substrates for fluoroalkoxylation reactions because of the importance of heterocyclic compounds in medicinal chemistry, agrochemistry, and materials science.^[22] Therefore, there still remains a large demand for the development of a general, practical, and selective procedure for the fluoroalkoxylation of heteroaryl halides to provide trifluoroethyl heteroaryl ethers.

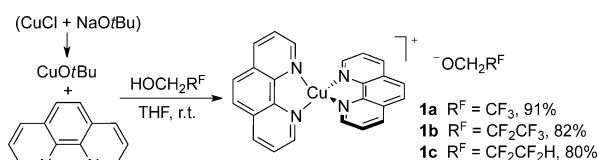
Our group has recently developed a novel and concise route to synthesize copper(I) trifluoromethylthiolate/selenolate reagents [(bpy)Cu(SCF₃)] and [(bpy)Cu(SeCF₃)]₂ for the nucleophilic trifluoromethylthiolation/selenolation of organic halides.^[23] As a continuation of our work, we herein disclose the synthesis and use of a copper(I)-OCH₂R^F complex for the fluoroalkoxylation of aryl and heteroaryl bromides.

The synthesis of copper trifluoroethoxide complexes and their higher fluorinated homologue complexes is outlined in Scheme 2. The reaction of CuO*t*Bu with phenanthroline

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Scheme 2. Synthesis of copper(I) fluoroalkoxide complexes **1a–c**. r.t. = room temperature.

(phen; 2 equiv) in THF, with subsequent addition of trifluoroethanol, led to the formation of the Cu^I complexes **1a–c** in 91 %, 82 %, and 80 % yields, respectively. These new fluoroalkoxide complexes are amenable to large-scale synthesis (≥ 2 g) and may be stored indefinitely at -30°C .

Few examples of structurally characterized fluorinated copper(I) alkoxide complexes are reported in the literature,^[24,25] and this prompted us to conduct single-crystal X-ray crystallographic studies on our complexes (Figure 1).^[26] The

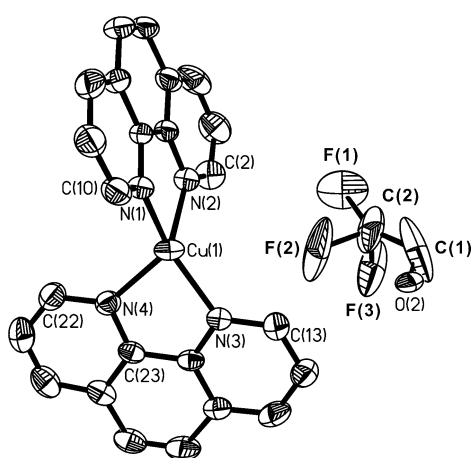


Figure 1. ORTEP diagram of **1a** with thermal ellipsoids at the 40 % probability level. Cu(1)–N(1) 2.013(4), Cu(1)–N(2) 2.063(4), Cu(1)–N(3) 2.008(4), Cu(1)–N(4) 2.071(4) Å.

solid-state structure shows that **1a** contains one cationic tetrahedral copper center ligated by two of the dative phen ligands and one free, unligated anionic $[\text{CF}_3\text{CH}_2\text{O}]^-$ moiety.

Having established the structures of the alkoxide complexes, we sought to evaluate the reactivity of these complexes toward fluoroalkoxylation. Our investigations began by examining the reaction of complex **1a** with 1-bromo-4-methoxybenzene (**2e**). After conducting a thorough screen of additives, solvents, temperature, and reaction time, we observed that NaOtBu as an additive and DMF as the solvent at 80°C for 12 h afforded a good yield of the desired product **3e** in 86 % yield (Table 1, entry 1). The addition of NaOtBu significantly enhanced the reaction efficiency, probably by facilitating the formation of the active intermediate. Notably, the reaction of **2e** with HOCH_2CF_3 and NaOtBu did not take place (entry 2). Likewise, the palladium-catalyzed method did not generate the product **3e** (entry 4).^[21] Although the copper-catalyzed trifluoroethoxylation gave a comparable yield of **3e** (85 %), a large excess (7 equiv) of $\text{CF}_3\text{CH}_2\text{OH}$ was used (entry 3).^[20]

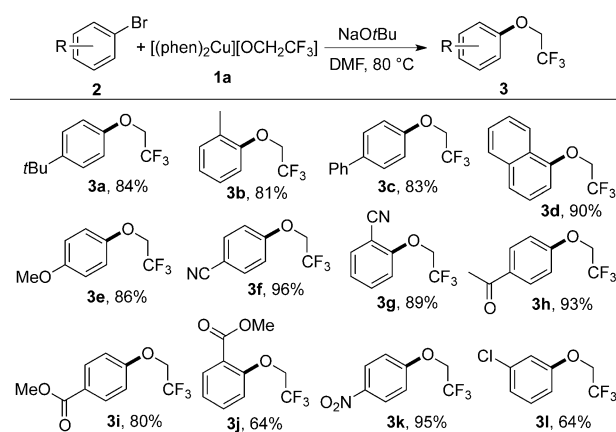
Table 1: Copper-mediated trifluoroethoxylation of 1-bromo-4-nitrobenzene.

Entry	Conditions	Yield [%]
1	$[(\text{phen})_2\text{Cu}][\text{OCH}_2\text{CF}_3]$ (1a) (1.2 equiv), NaOtBu, DMF, 80°C	86 ^[a]
2	HOCH_2CF_3 (1.2 equiv), NaOtBu (1.2 equiv), DMF, 80°C	NR ^[b]
3	$\text{CF}_3\text{CH}_2\text{OH}$ (7 equiv), CuI (10 mol %), ethyl 2-oxocyclohexanecarboxylate (20 mol %), Cs_2CO_3 (1.4 equiv), 78°C	85 ^[c]
4	$\text{CF}_3\text{CH}_2\text{OH}$ (1.5 equiv), $[\text{Pd}_2(\text{dba})_3]$ (1.0 mol %), Brett-Phos (2.5 mol %), Cs_2CO_3 (1.5 equiv), toluene, 85°C	NR ^[b,d]

[a] Yield of isolated product. [b] NR = no reaction. [c] Ref. [20].

[d] Ref. [21]. dba = *trans,trans*-dibenzylideneacetone.

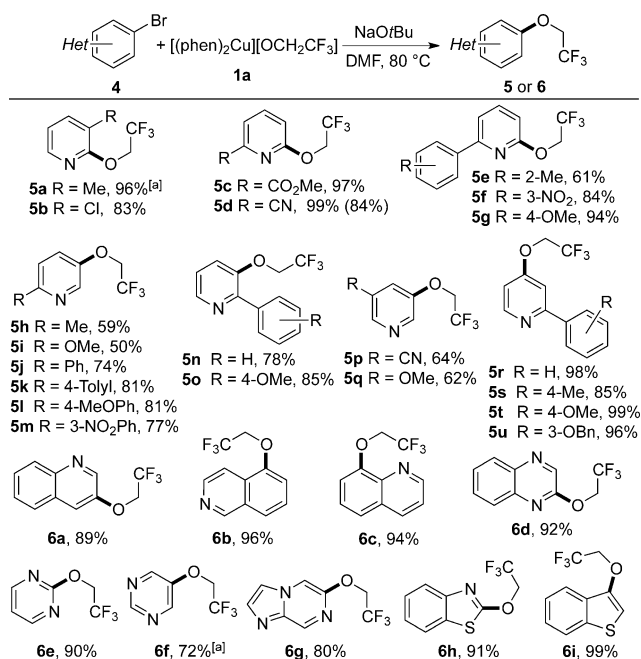
Having found an effective procedure for the trifluoroethoxylation, we next investigated the reaction scope with various bromoarenes, and the results are summarized in Scheme 3. The *para*-*tert*-butyl- and phenyl-substituted bro-



Scheme 3. Trifluoroethoxylation of aryl bromides with **1a**. Reaction conditions: **1a** (0.48 mmol), **2** (0.40 mmol), NaOtBu (0.40 mmol), DMF (2.0 mL), 12 h, N_2 , 80°C . Yields of isolated products are shown.

mobenzene reacted with 1-bromonaphthalene to give the corresponding trifluoroethoxylated products **3a**, **3c**, and **3d** in 84 %, 83 %, and 90 % yields, respectively. The sterically hindered aryl bromide 2-bromotoluene furnished the product **3b** in 81 % yield. An aryl bromide having an electron-donating 4-methoxy group exhibited good reactivity to afford **3e** in 86 % yield. Aryl bromides possessing electron-withdrawing groups, such as nitrile, ketone, ester, and nitro, were also good coupling partners, providing products **3f–k** in yields of 64–96 %. *Meta*-chloro-substituted bromobenzene was also a good substrate under our conditions to give product **3l** in 64 % yield. Moreover, the reaction is not limited to aryl bromides, it can also be performed with aryl iodides under the same reaction conditions (see the Supporting Information).

After having established that the reaction occurred with a wide range of substrates, the method was applied to

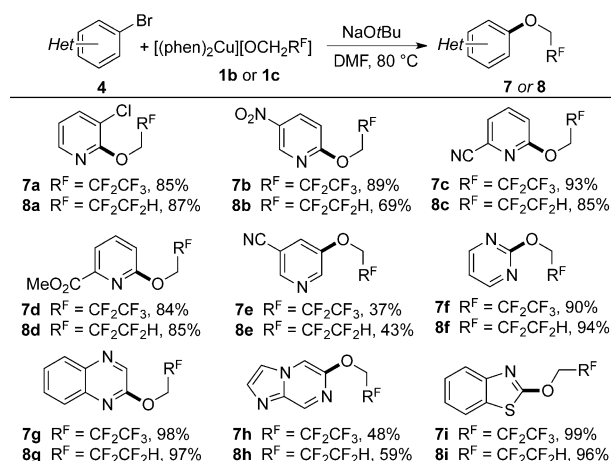


Scheme 4. Trifluoroethoxylation of heteroaryl bromides with **1a**. Reaction conditions: **1a** (0.36 mmol), **4** (0.30 mmol), NaOtBu (0.30 mmol), DMF (2.0 mL), 12 h, N₂, 80 °C. Yields of isolated products are shown. [a] Yield by ^{19}F NMR spectroscopy.

a variety of diverse heteroaryl bromides under the same set of conditions (Scheme 4). The reactions of 2-bromopyridines with either electron-withdrawing or electron-donating substituents were efficient and afforded the desired products **5a–g** in high yields. Notably, various base-labile groups such as ester, nitrile, and chloro were tolerated. 3-Bromopyridines proved to be less reactive than 2- and 4-bromopyridines because of the greater electron density at the 3-position of pyridines than at the 2- and 4-positions.^[27] Nevertheless, 3-bromopyridines were also found to react with complex **1a** under these conditions and the yields of products **5h–q** were found to be comparable to those obtained with 2-bromopyridines. Furthermore, the reaction of 4-bromopyridines gave the desired product **5r–u** in high yields.

We next explored the use of fused heterocycles, such as 3-, 5-, and 8-bromoquinoline, which furnished the corresponding products **6a–c** in yields of 89%, 96%, and 94%, respectively. Heterocycles with more than one nitrogen atom are also excellent substrates. 2-Bromoquinoxaline underwent trifluoroethoxylation to furnish **6d** in 92% yield. Likewise, the reactions of 2- and 5-bromopyrimidine afforded the expected products **6e** and **6f** in yields of 90% and 72%, respectively. Moreover, 6-bromimidazo[1,2-*a*]pyrazine underwent reaction to give **6g** in 80% yield. In the case of five-membered heterocycles, 2-bromobenzo[*d*]thiazole and 3-bromobenzo[*b*]thiophene provided the coupling products **6h** and **6i** in yields of 91% and 99%, respectively.

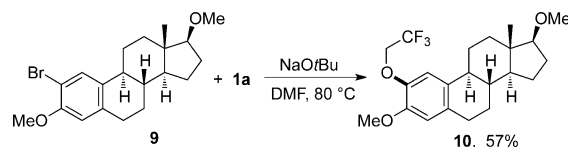
This method can be further extended to the synthesis of pentafluoropropyl and tetrafluoropropyl heteroaryl ethers. As shown in Scheme 5, the reaction is also applicable to a wide range of heterocyclic aryl bromides such as 2-pyridyl and 3-pyridyl bromides. This transformation also demon-



Scheme 5. Fluoroalkoxylation of heteroaryl bromides with **1b** and **1c**. Reaction conditions: **1b** or **1c** (0.36 mmol), **4** (0.30 mmol), NaOtBu (0.30 mmol), DMF (2.0 mL), 12 h, N₂, 80 °C. Yields of isolated products are shown.

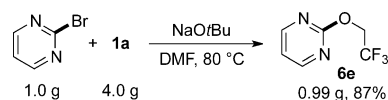
strated excellent compatibility with a wide range of functional groups, such as chloro, nitro, nitrile, and ester. The reaction with 2-pyrimidinyl, 6-imidazo[1,2-*a*]pyrazinyl, and 3-benzo[*b*]thiophenyl bromides also afforded the desired products in good to high yields.

Subsequently, the method was investigated in the late-stage synthesis of an estradiol derivative (Scheme 6). The trifluoroethoxylation of **9** with **1a** provided **10** in 57% yield. This result demonstrates that the developed method is extendable to other pharmaceutically relevant molecules.



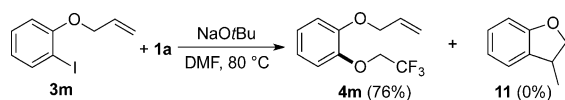
Scheme 6. Late-stage trifluoroethoxylation of an estradiol derivative.

To demonstrate the scalability of the reaction, we conducted the trifluoroethoxylation of 2-bromopyrimidine with **1a** on a 6.3 mmol scale. As shown in Scheme 7, the desired trifluoroethoxylated product **6e** was isolated in 87% yield (0.99 g).



Scheme 7. Scalability of the trifluoroethoxylation of 2-bromopyrimidine.

A preliminary investigation of the reaction of complex **1a** with a radical probe, such as 1-(allyloxy)-2-iodobenzene (**3m**),^[28] indicated that only the trifluoroethoxylated product **4m** was obtained (in 76% yield; ^{19}F NMR; Scheme 8). No cyclization product, 3-methyl-2,3-dihydrobenzofuran (**11**),



Scheme 8. Test for an aryl radical intermediate.

was observed. These results imply that the trifluoroethoxylation does not involve aryl radical intermediates.^[29]

In summary, a series of copper(I) fluoroalkoxide complexes supported by the phenanthroline ligand have been synthesized and structurally characterized. These complexes show good reactivity toward the trifluoroethoxylation, pentafluoropropoxylation, and tetrafluoropropoxylation of aryl and heteroaryl bromides. A variety of trifluoroethyl, pentafluoropropyl, and tetrafluoropropyl (hetero)aryl ethers have been synthesized in good to excellent yields.

Experimental Section

Preparation of [(phen)₂Cu][OCH₂CF₃] (1a): A solution of NaOtBu (0.48 g, 5.0 mmol) in THF (10 mL) was added to a suspension of CuCl (0.49 g, 5 mmol) in THF (20 mL), and the resulting mixture was stirred at room temperature for 30 min. The resulting light yellow mixture was filtered through a layer of celite. To this filtrate was added a solution of 1,10-phenanthroline (1.8 g, 10 mmol) in THF (10 mL). The resulting solution turned reddish brown immediately and was stirred at room temperature for an additional 5 min. CF₃CH₂OH (0.60 g, 6.0 mmol) was added dropwise and the mixture was further stirred at room temperature for 20 min. The solution was filtered and the filtrate was dried under vacuum to yield a dark red solid. The resulting solid were washed with hexanes (2 × 2 mL) and dried under vacuum to obtain 2.39 g (91%) of **1a**. ¹H NMR (400 MHz, [D₆]DMSO): δ = 9.10 (s, 4H), 8.64 (d, *J* = 7.9 Hz, 4H), 8.12 (s, 4H), 7.89 (s, 4H), 3.86 ppm (s, 2H). ¹³C NMR (101 MHz, [D₆]DMSO): δ = 150.2 (s), 144.9 (s), 137.1 (s), 129.2 (s), 127.3 (s), 124.8 (s), 67.4 ppm (s). ¹⁹F NMR (376 MHz, [D₆]DMSO): δ = -75.4 (s, 3F). Elemental analysis (%) calcd for C₂₆H₁₈CuF₃N₄O·CF₃CH₂OH: C 53.98, H 3.40, N 8.99; found: C 53.95, H 3.40, N 8.97.

Keywords: C–O bonds · copper · cross-coupling · trifluoroethoxylation

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