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Silver-Mediated Oxidative Trifluoromethylation of Phenols: Direct Synthesis of Aryl Trifluoromethyl Ethers

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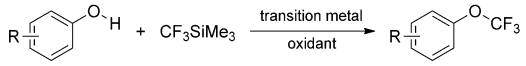
Abstract: *Aryl trifluoromethyl ethers ($ArOCF_3$) are prevalent in pharmaceuticals, agrochemicals, and materials. However, methods for the general and efficient synthesis of these compounds are extremely underdeveloped and limited. Herein, we describe a highly efficient and general procedure for the direct O-trifluoromethylation of unprotected phenols through a silver-mediated cross-coupling reaction using CF_3SiMe_3 as the CF_3 source and exogenous oxidants. This novel oxidative trifluoromethylation provides access to a wide range of aryl trifluoromethyl ethers from simple phenols. The mild process was also applied to the late-stage trifluoromethylation of a medicinally relevant compound.*

The capacity of fluorine and fluorinated moieties to enhance lipophilicity, metabolic stability, and bioavailability compared with the non-fluorinated analogues has recently driven significant research efforts towards the development of novel fluorination and fluoroalkylation methods.[1] In recent years, significant progress has been made towards the incorporation of fluorine, trifluoromethyl, and trifluoromethylthio substituents into aromatic systems.[2,3] However, methods for the construction of aryl trifluoromethyl ethers ($ArOCF_3$) are still lacking, despite the prevalence of this moiety in pharmaceuticals, agrochemicals, and materials.[4]

Aryl trifluoromethyl ethers are conventionally accessed by direct fluorination of phenol derivatives under harsh conditions that are incompatible with many functional groups.[5–8] A two-step route to $ArOCF_3$ was recently reported, but this procedure could only be applied to *N*-aryl hydroxylamines.[9] Direct aryl trifluoromethoxylation using CF_3OF or CF_3O^- as the CF_3O source provides a more direct route to these products.[10,11] However, these reactions usually suffer from the use of a hazardous reagent (e.g., CF_3OF gas) and/or are limited in scope and efficiency owing to the inherent instability of the CF_3O^- anion. Recently, a series of trifluoromethoxylated arenes were generated through the silver-mediated cross coupling of aryl stannanes and aryl boronic acids with CF_3O^- at low temperature, but this reaction utilized prefunctionalized stannanes and boronic acids as substrates, which may lessen the applicability of this method for late-stage modifications.[12]

An alternative and potentially valuable strategy for the preparation of aryl trifluoromethyl ethers is the direct O-trifluoromethylation of phenols. Although this transformation has been eagerly sought for decades, it has remained an unconquered problem. To date, only two rare examples of the trifluoromethylation of phenols with electrophilic trifluoromethylating reagents have been reported, but in these cases, harsh reaction conditions (photoirradiation at −100 °C) were required,[13] and a rather low efficiency (1 example with up to 15% yield) was observed.[14] The greatest challenge associated with achieving the selective O-trifluoromethylation of phenols with electrophilic CF_3 sources lies in the generation of the CF_3^+ cation under mild conditions.

We recently questioned whether we could achieve the selective trifluoromethylation of phenols by employing a transition-metal complex and a nucleophilic CF_3 source (Figure 1), a strategy inspired by our recent discoveries on



- Valuable moieties in pharmaceuticals and agrochemicals
- Employing abundant and inexpensive starting materials and CF_3 agent

Figure 1. Direct O-trifluoromethylation of phenols with CF_3SiMe_3.

the transition-metal-mediated oxidative trifluoromethylation of various nucleophiles with the Ruppert–Prakash reagent (CF_3SiMe_3).[15] Given the nucleophilic nature of the CF_3^- anion, we expected that the C-trifluoromethylation products would not be formed under these oxidative conditions. Furthermore, owing to the participation of a transition-metal complex, we hoped that this transformation would feature good functional-group compatibility and a broad scope, which would be valuable for the late-stage formation of $ArOCF_3$ moieties.

Herein, we report the development of a silver-mediated oxidative trifluoromethylation of unprotected phenols with CF_3SiMe_3 in the presence of exogenous oxidants at room temperature. This direct O-trifluoromethylation readily yields a wide range of aryl trifluoromethyl ethers. The late-stage O-trifluoromethylation of a widely prescribed pharmaceutical agent is also described.

On the basis of our previous works on oxidative trifluoromethylation,[15] we began our studies towards the direct

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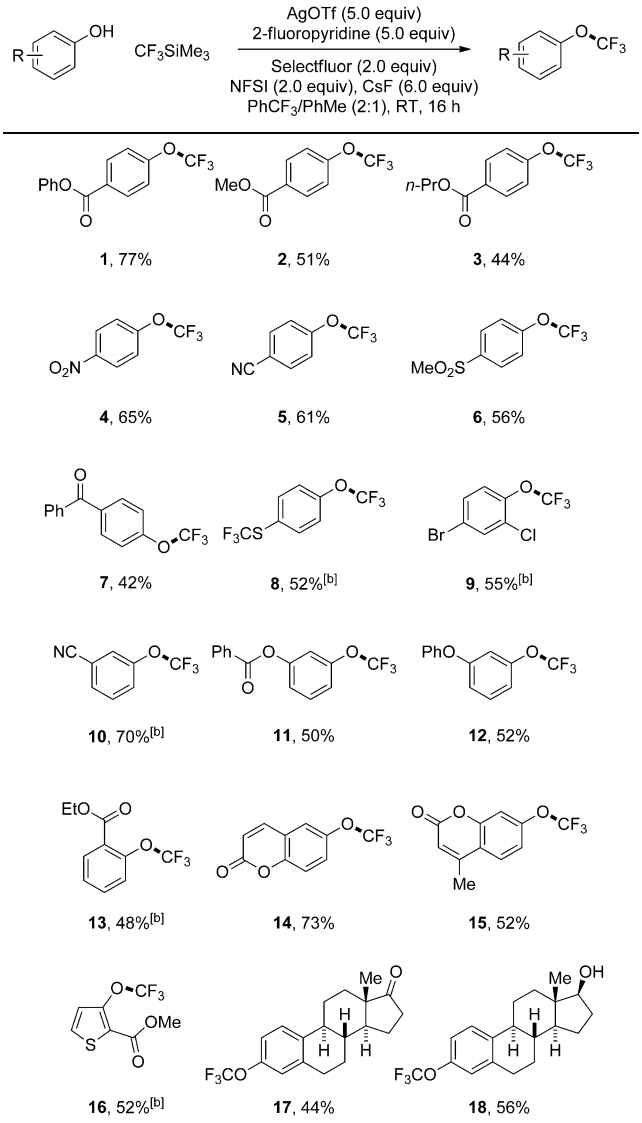
O-trifluoromethylation of phenols with an evaluation of a range of transition-metal salts, ligands, oxidants, and bases in the presence of phenyl 4-hydroxybenzoate as the representative substrate and CF_3SiMe_3 as the nucleophilic CF_3 source. We found that a combination of AgOTf (Tf = trifluoromethanesulfonyl), 2-fluoropyridine, Selectfluor, *N*-fluorobenzenesulfonimide (NFSI), and CsF in a solvent mixture of toluene and $PhCF_3$ at room temperature enabled the desired O-trifluoromethylation in 80% yield (for the optimization of the reaction conditions, see the Supporting Information, Tables S1 and S2). No products were detected in control experiments where the silver salt, ligand, or oxidant had not been added, whereas a significant decrease in yield was observed when either Selectfluor or NFSI was used as the only exogenous oxidant.

With the optimized reaction conditions in hand, we next sought to explore the substrate scope of this new AgOTf mediated oxidative trifluoromethylation reaction. As shown in Table 1, a wide range of phenols bearing electron-withdrawing groups were efficiently trifluoromethylated (**1**–**18**, 42–77% yield). A variety of important functional groups, including ester, nitrile, nitro, sulfone, amide, and ether moieties, were well tolerated under the mild reaction conditions. Moreover, ketone moieties were also tolerated, and the side products that could be formed by nucleophilic addition of the CF_3^- anion to the ketone were not observed (**7** and **17**, 42–44% yield). The direct trifluoromethylation of a bromine-substituted phenol also proceeded smoothly, leaving the bromine untouched, which could thus be used as a handle for further synthetic manipulations (**9**, 55% yield). *ortho*-Substituted phenols readily furnished the corresponding aryl trifluoromethyl ethers without any loss of efficiency in spite of the increased steric hindrance (**13** and **16**, 48 and 52% yield). Moreover, bicyclic aromatic compounds such as coumarins were suitable substrates (**14** and **15**, 73 and 52% yield). Remarkably, a thiophene derivative could also be effectively converted into its trifluoromethylated analogue with moderate efficiency (**16**, 52% yield). Perhaps most importantly, substrates with higher levels of complexity were also tolerated, as exemplified by the direct and efficient O-trifluoromethylation of estrone and estradiol (**17** and **18**, 44 and 56% yield). In the case of estradiol, excellent selectivity was observed, as phenol O-trifluoromethylation occurred preferentially over alkyl alcohol O-trifluoromethylation (**18**, 56% yield).

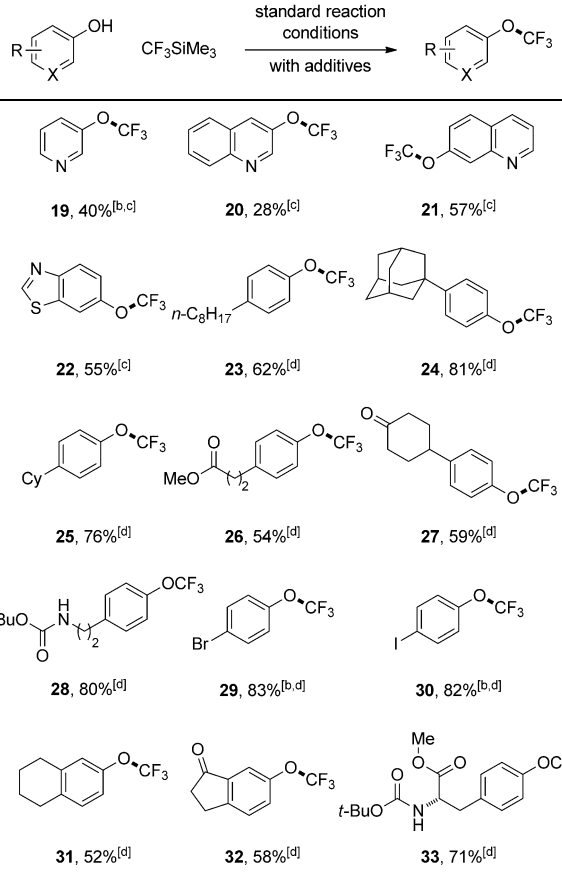
Table 1: Substrate scope of the silver-mediated direct O-trifluoromethylation: electron-poor phenol derivatives.[a]



[a] Yields of isolated products. Reactions performed on 0.5 mmol scale. See the Supporting Information for experimental details. [b] Yield determined by ^{19}F NMR spectroscopy using fluorobenzene as the internal standard.

Unfortunately, nitrogen-containing heteroaromatic substrates, such as pyridines, quinolines, and benzothiazoles, could not be trifluoromethylated under the standard conditions, presumably because of competitive coordination of the nitrogen atom to the silver center. Consistent with this assumption, the reactions of the corresponding pyridinium salts of these heteroaromatic compounds proceeded smoothly, affording the desired heteroaryl trifluoromethyl ethers in synthetically useful yields (Table 2; **19**–**22**, 28–57% yield). This two-step procedure, comprising the preparation of the pyridinium salt with trifluoromethanesulfonic acid followed by silver-mediated trifluoromethylation, can be conducted as a one-pot operation. The oxidative O-trifluoromethylation method is also applicable to phenols with electron-donating substituents. However, the reaction efficiency was diminished by the competitive formation of the corresponding sulfonates, which are generated by the reaction of the phenols with NFSI. For example, the trifluoromethylation of 4-cyclohexylphenol gave the desired product in 35% yield (**25**) along with 4-cyclohexylphenyl benzenesulfonate in 40% yield and the C-trifluoromethylated phenol side product in 8% yield under the standard reaction conditions. Interestingly, the addition of 2,4-di-*tert*-butylphenol inhibited side product formation and increased the yield of the desired trifluoromethyl ether to 76%. Under the new reaction conditions, a series of *para*-substituted, electron-rich phenols could be directly converted into the corresponding aryl trifluoromethyl ethers (Table 2; **23**–**33**, 52–83% yield). The

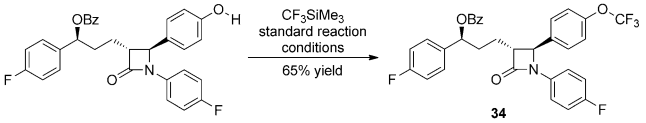
Table 2: Substrate scope of the silver-mediated direct O-trifluoromethylation: heterocycles and electron-rich phenol derivatives.[a]



[a] Yields of isolated products. Reactions performed on 0.5 mmol scale. See the Supporting Information for experimental details. [b] Yield determined by ^{19}F NMR spectroscopy using fluorobenzene as the internal standard. [c] First, the pyridinium salt was formed by the addition of trifluoromethanesulfonic acid; then it was subjected to the standard reaction conditions. [d] 2,4-Di-*tert*-butylphenol (< 2.0 equiv) was added to the reaction mixture.

reaction of a tyrosine derivative under these conditions afforded the corresponding trifluoromethyl ether with high efficiency (**33**, 71% yield). However, trifluoromethylation of 4-methoxyphenol afforded the desired 4-methoxyphenyl trifluoromethyl ether in low yield (10%) along with the formation of 4-methoxyphenyl benzenesulfonate as the major product (75%); these two compounds were characterized by ^{19}F NMR spectroscopy and GC-MS.

To further demonstrate the utility of this phenol O-trifluoromethylation method for late-stage synthetic applications, a pharmaceutically relevant molecule was subjected to the reaction conditions. The direct phenoxy trifluoromethylation of benzoyl ezetimibe, a plasma cholesterol lowering drug containing a β-lactam moiety,[16] proceeded smoothly under the optimized reaction conditions to give aryl trifluoromethyl ether **34** in 65% yield (Scheme 1). This result portrays the



Scheme 1. Direct O-trifluoromethylation of a medicinally relevant compound. Reaction performed on 0.5 mmol scale. Bz = benzoyl.

potential of this procedure for the late-stage modification of pharmaceutical agents.

A possible mechanism for this silver-mediated oxidative trifluoromethylation of phenols is shown in Figure 2. The transformation is postulated to be initiated by the in situ generation of Ag^ICF_3 species **A** from the reaction of Ag^IOTf with CF_3SiMe_3 and CsF.[17,18] Given the σ-donating nature of the CF_3 group in the Ag^ICF_3 species, it is feasible that species **A** would undergo oxidative addition with Selectfluor and/or NFSI to form $[Ag^{III}(CF_3)(F)]$ complex **B** (pathway I). Subsequent fluoride to phenoxide exchange in **B** would afford the key intermediate $[Ag^{III}(CF_3)(OPh)]$ (**C**). Finally, reductive elimination of intermediate **C** would forge the requisite O–CF_3 bond and furnish the desired aryl trifluoromethyl ether. Consistent with previous results,[15d,18–21] we observed the formation of the trifluoromethylated arenes with phenols that bear electron-donating groups, which proceeds via the CF_3 radical generated from the homolytic cleavage of the Ag–CF_3 bond (pathway II). However, the high efficiency of these reactions suggests that pathway II is inhibited under the optimized reaction conditions. To gain more insights into the oxidative trifluoromethylation reaction, we carried out a number of preliminary mechanistic studies. ^{19}F NMR spectroscopy showed that Ag^ICF_3 was formed in the presence of AgOTf (1.0 equiv), CF_3SiMe_3 (2.0 equiv), CsF (2.0 equiv), and 2-fluoropyridine (1.0 equiv) in toluene at room temperature (See Figure S1). Such a $[Ag^ICF_3]$ toluene solution, in which CF_3SiMe_3 had been fully consumed, was also prepared at a different molar ratio from a mixture of AgOTf (1.0 equiv), CF_3SiMe_3 (1.0 equiv), CsF (1.0 equiv), and 2-fluoropyridine (1.0 equiv; see Figure S2). The addition of phenyl 4-hydroxybenzonate, Selectfluor, and NFSI to the preformed Ag^ICF_3 toluene solution without CF_3SiMe_3 furnished the desired $ArOCF_3$ product without formation of the C-trifluoromethylation side product as determined by ^{19}F NMR spectroscopy (see Figure S3). These experimental results indicate that Ag^ICF_3 species **A** is an intermediate of this O-trifluoromethylation reaction of phenols.

In conclusion, we have developed a silver-mediated transformation of simple phenols into the corresponding

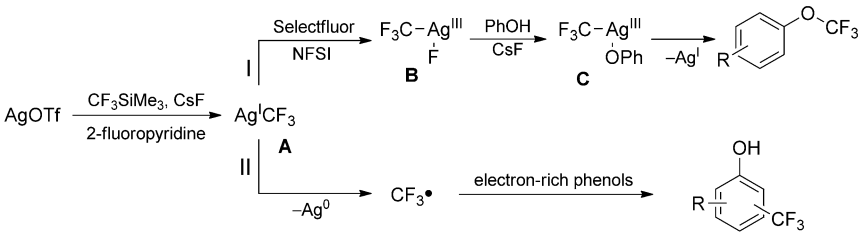


Figure 2. Proposed mechanism for the silver-mediated oxidative trifluoromethylation of phenols.

aryl trifluoromethyl ethers using commercially available and stable CF_3SiMe_3 as a nucleophilic CF_3 reagent. Phenol O-trifluoromethylation proceeds with high selectivity, provides straightforward access to a wide range of aryl trifluoromethyl ethers, and tolerates a variety of important functional groups. More importantly, a highly complex medicinally relevant compound was shown to successfully undergo late-stage trifluoromethylation under the mild reaction conditions that we have developed.

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