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Facile Access to $AgOCF_3$ and Novel Applications as Reservoir for OCF_2 for the direct Synthesis of *N*-CF_3, Aryl or Alkyl Carbamoyl Fluorides

*Abdur Turksoy, Thomas Scattolin, Sam Bouayad-Gervais and Franziska Schoenebeck**

***Abstract**: The development of innovative fluorination strategies is greatly dependent also on the availability, safety and practicability of available fluorinating reagents. We herein present a straightforward and quantitative strategy for the preparation of valuable $AgOCF_3$ at room temperature and showcase its performance in trifluoromethoxylations or as reservoir for $O{=}CF_2$. This enabled the direct, practical and safe synthesis of valuable N-alkyl/aryl and N-CF_3 carbamoyl fluorides from secondary amines and isothiocyanides respectively. Our mechanistic data indicate that $AgOCF_3$ does not liberate $O{=}CF_2$ until it is activated by a nucleophilic nitrogen, reinforcing the stability of the salt under our new preparation strategy.*

Owing to the beneficial effects of fluorination on the physical properties of organic molecules, such as increasing their lipophilicity or metabolic stability features paired with inverted charge or conformational distributions,[1] there is a significant demand for the development of novel fluorination strategies.[1e, 1f, 2] In this context, the wider applicability of any developed methodology will ultimately also depend on the accessibility of the fluorination agents as well as their overall sustainability. For example, the installation of the trifluoromethoxy group ("OCF_3") – also known as a "super-halogen"[3] that induces advantageous properties in bioactive molecules (high lipophilicity, biostability)[4] and materials (lowering surface tension or dielectric constants),[3, 5] frequently relies on $AgOCF_3$ as trifluoromethoxylation reagent.[6] $AgOCF_3$ in turn is generally prepared as a stock solution from reaction of AgF with the highly volatile liquid $CF_3SO_2OCF_3$ (TFMT; BP: 19 °C).[6c, 7] As such, rather low temperature (*i.e.* -40°C) needs to be maintained throughout the reaction to avoid the loss of the reagent. Moreover, the by-product (CF_3SO_2F) subsequently needs to be removed by purging of the stock solution with argon[6c] (Figure 1, B). Recently, researchers attempted to devise less tedious strategies to generate the required $AgOCF_3$ *in situ* from suitable organic precursors. In this context, trifluoromethyl aryl sulfonates (TFMSs) have been widely utilized, which in combination with AgF release $AgOCF_3$.[6g, 6h, 6j] However, this approach leads to the generation of stoichiometric organic by-products, which eventually either need to be removed or if remaining *in situ*, these side-species could potentially perturb the transformation of interest, especially more sensitive metal-catalysed approaches[8].

As part of our ongoing program in developing efficient methods for the installation of (heteroatom-containing) fluorinated motifs,[9] we set out to develop a practical and quantitative approach to access $AgOCF_3$ and used the reagent in novel applications to access highly valuable fluorinated amine motifs.

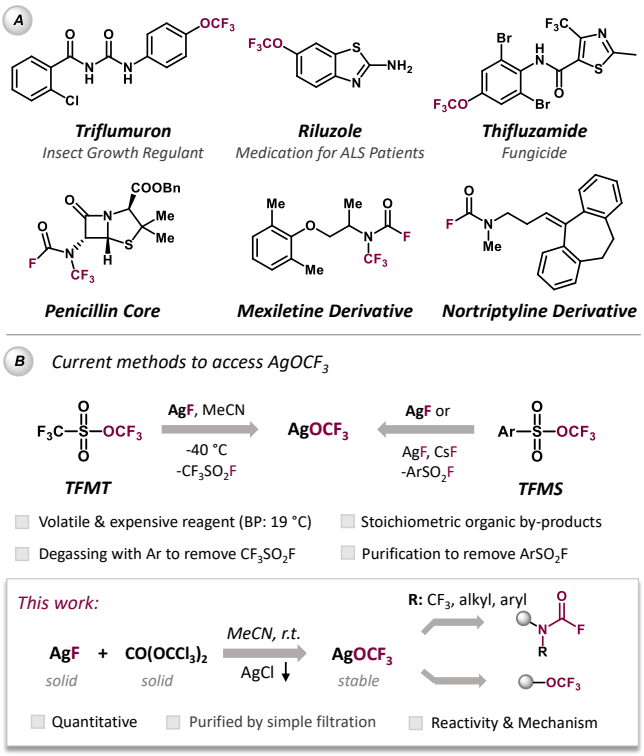

Figure 1. A) Biologically active and relevant fluorinated compounds; B) Current approaches to access $AgOCF_3$; the stock solution reparation on the left, *in-situ* preparation on the right, and this work.

We envisioned that the minimalistic approach to $AgOCF_3$ would essentially be the direct addition of AgF to fluorophosgene ($F_2C{=}O$). While this transformation would formally be waste-free, the fact that fluorophosgene is a toxic and corrosive gas, would make the overall process less practical. However, we recently showed that the subjection of AgF to the solid reagent bis(trichloromethyl) carbonate (BTC) leads to *in-situ* liberation of $O{=}CF_2$ along with AgCl formation.[9a] As such, and in view of practicability, safety and minimal production of waste, we chose to study the reaction between the solid reagent BTC (0.33 equiv.) with AgF (3 equiv.) in MeCN. To this end, we added MeCN in single portion to a vial containing both solids at room temperature and stirred the mixture overnight (18 h) at room temperature. We subsequently filtered the insoluble material, (*i.e.* AgCl) under an inert atmosphere (Figure 2), and its facile recovery offers the opportunity for recycling.[10] To our delight, the remainder in solution proved to be $AgOCF_3$, which formed quantitatively and exclusively as judged by ^{19}F-NMR spectroscopic analysis. Importantly, we repeated the experiment also at larger scale (up to 1.5 g scale) and the reaction proceeded equally efficiently. There was also no need for cooling or careful reaction control.

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Moreover, the $AgOCF_3$ solution appears to be storable for extended times. In our tests, we found it to be unchanged and equally reactive after storage for three months (at -30°C under inert conditions).

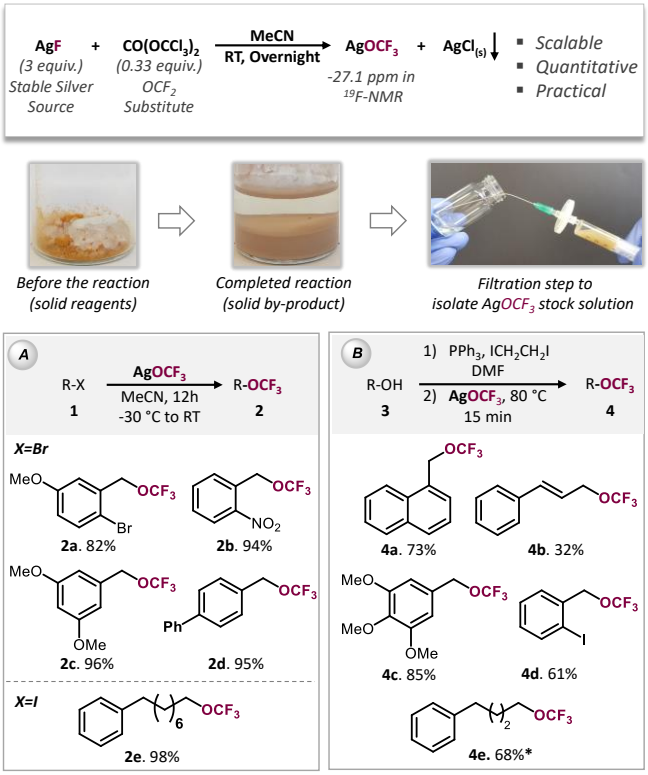

Figure 2. The synthesis of $AgOCF_3$ stock solution (top). Reactants before (left), after (middle) the reaction and filtration over a syringe filter to isolate the stock solution of $AgOCF_3$ (right). A) Substitution scope with benzyl bromides and alkyl iodide; B) the dehydrotrifluoromethoxylation of alcohols. *Alkyl alcohols require allyl diphenyl phosphine & 100 °C.

We subsequently set out to test whether the $AgOCF_3$ prepared *via* our new approach would give similar reactivity to differently synthesized $AgOCF_3$ reagents. To this end, we subjected our $AgOCF_3$ stock solution to benzyl bromides and an alkyl iodide at room temperature for 12 h. The corresponding substitution reactions proved to be highly efficient independently of the substitution pattern of the reactant (*ortho*, *meta or para*), see Figure 2A (2a-2e). Unlike to previously reported by-products in substitution reactions with trifluoromethoxy anions,[6d, 7] we did not observe any considerable amount of fluorinated by-products. This suggests that our practical preparation of $AgOCF_3$ at room temperature has no adverse impact on reactivity or stability; in fact, the $AgOCF_3$ appears to be stable in the reaction medium even for extended periods of time. Similarly, our $AgOCF_3$ stock solution also performed well in reactions with alcohols to produce R-OCF_3 at up to 100°C reaction temperature (see Figure 2B); this otherwise known[6e] transformation relies on the generation of an iodophosphonium salt ($R_3IP^+I^-$) and Vilsmeier-Haack-type intermediate which can activate alcohols to form the trifluoromethoxylated product through dehydration. Another popular reaction is the silver mediated transformation of α-diazo esters into α-OCF_3 esters.[6f] The reported precedence for the synthesis of α-OCF_3 esters utilized both $AgOCF_3$ stock solution and *in situ* release of the trifluoromethoxide anion from trifluoromethyl triflate (TFMT) with AgF. Subjection of our stable stock solution of $AgOCF_3$ to ethyl 2-diazo-2-phenylacetate at room temperature yielded the corresponding OCF_3 ester (42% based on ^{19}F-NMR) in comparable yield as previous reports.[6f]

Having established that our newly developed approach to $AgOCF_3$ can readily be applied in a variety of known $AgOCF_3$ reactions, without any compromise on yield or efficiency, we subsequently set out to investigate novel applications of the $AgOCF_3$ reagent in synthesis. We recently reported the first straightforward and general access to *N*-CF_3 carbonyl containing molecules, (*i.e.* *N*-CF_3 amides, ureas, carbamates and thiocarbamates).[9a] The transformation relied on the initial conversion of isothiocyanates to *N*-trifluoromethylcarbamoyl fluorides, which in turn were readily diversified. The latter forms through initial desulfurization of the isothiocyanate with AgF, resulting in RN=CF_2, which reacts further with AgF and is trapped with O=CF_2. Given that $AgOCF_3$ could in principle reversibly release O=CF_2 and AgF, we were intrigued to examine whether subjection of our prepared $AgOCF_3$ to a number of isothiocyanates (R-N=C=S) results in direct formation of the vital *N*-CF_3 carbamoyl motif. To our delight, we observed efficient transformation of isothiocyanate **5a** with the $AgOCF_3$ stock solution under air at 50 ºC within 18 hours. We successfully prepared a number of *N*-trifluoromethylcarbamoyl fluorides in good to excellent yields (Figure 3A). Importantly, the only by-product in this transformation is Ag_2S, which we collected through filtration of the reaction mixture (see Figure 3B (top part)), leaving the carbamoyl fluoride essentially pure after solvent removal. Our previous method[9a] used 5 equiv. of silver salt, while the current only formally needs two equivalents (excluding those used to make $AgOCF_3$). As such, we also set out to test the reactivity of *in situ* generated $AgOCF_3$ from trifluoromethyl benzene sulfonate with AgF. This also gave the efficient formation of the *N*-CF_3 carbamoyl motif of **5c** with 65% yield based on ^{19}F-NMR, and therefore allows to apply this methodology readily to applications where the use of silver is desired to be minimized. Electron-rich and deficient aromatic, heterocyclic as well as alkyl isothiocyanates underwent smooth transformation, see Figure 3A.

To unambiguously confirm our hypothesis that $AgOCF_3$ would release O=CF_2 and AgF *in situ*, we undertook a series of ReactIR investigations. We initially monitored whether $AgOCF_3$ spontaneously releases O=CF_2 upon heating; however, there was no sign of any change and $AgOCF_3$ appears to be stable for several hours at 50 ºC in solution by itself (see SI for React IR profile). We subsequently conducted the analogous monitoring for the actual transformation, *i.e.* in the presence of isothiocyanate **6c** at 50°C. The resulting profile is shown in Figure 3B (bottom part). There is an initial consumption of $AgOCF_3$ (974 cm^{-1}) as well as an instantly proportional formation of O=CF_2 (characteristic signal at 1245 cm^{-1}). This is likely the result of destabilization of the $AgOCF_3$ salt by isothiocyanate coordination, which appears to trigger the fluorophosgene liberation. The reaction profiles monitored at both, 25ºC and 50ºC, showed clear formation of a compound with a characteristic signal at 1641 cm^{-1}, which we previously assigned to be the desulfurization product, *i.e.* R-N-C=F_2.[9a] Upon addition of $AgOCF_3$ the *N*-CF_3 carbamoyl fluoride **6c** (characteristic band at 1848 cm^{-1}) appeared. As such, $AgOCF_3$ displays rather high thermal stability and only liberates O=CF_2 through coordination with the isothiocyanate, which subsequently desulfurizes upon reaction with the silver in solution and ultimately generates the R-NCF_3COF upon trapping with O=CF_2 (see Figure 3B, bottom).

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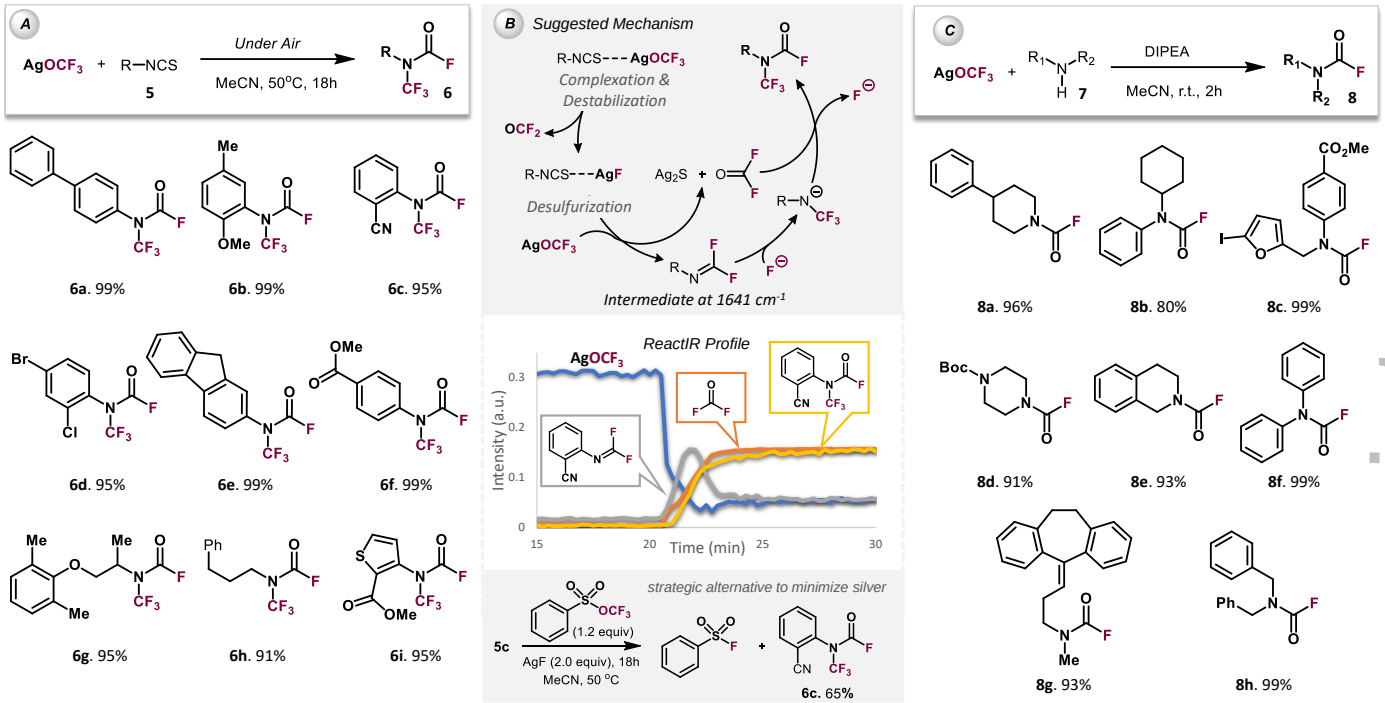

Figure 3. A) Scope of formation of *N*-trifluoromethylcarbamoyl fluoride derivatives from isothiocyanates under air at 50 °C for 18 hours; B) suggested mechanism for the formation of *N*-trifluoromethylcarbamoyl fluorides from isothiocyanates (top part), the graphical representation of ReactIR profile of the reaction at 50 °C (middle part), the synthesis of 6c via *in situ* generation of $AgOCF_3$ (bottom part); C) scope of formation of carbamoyl fluorides from secondary amines at room temperature.

These data indicate that $AgOCF_3$ is a rather stable reservoir of $O{=}CF_2$ which only gets "activated" upon coordination of a nucleophilic reaction partner. To this end, we envisioned that subjection of secondary amines might allow the direct generation of *N*-disubstituted carbamoyl fluorides. Such compounds in turn have shown activities and applications as insecticides or esterase inhibitors,[11] and serve as valuable intermediates in the synthesis of unsymmetrical, disubstituted carbonyl compounds. While traditional synthetic approaches involve highly toxic and gaseous reagents,[12] there have recently been elegant advances involving the direct conversion of amines with CO_2 and a deoxyfluorination reagent,[13] or using difluorocarbenes.[14] Pleasingly, the subjection of secondary amine **8a** to $AgOCF_3$ along with the base (DIPEA) at room temperature gave the corresponding carbamoyl fluorides within 2h reaction time. We explored a number of examples; electron-rich, deficient and heterocyclic (**8c**) amines as well as drug derivative **8g** and the Boc-protected amine (**8f**) all generated the corresponding carbamoyl fluorides in high yields (see Figure 3C) without any formation of double addition products.[15] As such, this method presents a convenient, safe and highly practical route into carbamoyl fluorides.

In conclusion, we have developed a simple, environmentally benign and quantitative approach to synthesize $AgOCF_3$ and demonstrated its robust performance in direct trifluoromethoxylations and as $O{=}CF_2$ precursor. Our mechanistic data suggest that $AgOCF_3$ is stable in solution and requires activation by a nucleophile to liberate $O{=}CF_2$. This highly controlled *in-situ* release in turn allowed the direct synthesis of *N*-alkyl/aryl as well as *N*-CF_3 carbamoyl fluorides, which in turn are valuable bioactive compounds themselves or powerful intermediates to *N*-alkyl/aryl or *N*-CF_3 amides, ureas or (thio)carbamates.

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Conflict of interest

The authors declare no conflict of interests.

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