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## COMMUNICATION

# Silver-Mediated Direct Trifluoromethoxylation of $\alpha$ -Diazo Esters by –OCF<sub>3</sub> Anion

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A silver-mediated direct trifluoromethoxylation of  $\alpha$ -diazo esters and ketosteroid was disclosed. The reactions of alkyl  $\alpha$ -diazo arylacetates with AgOCF<sub>3</sub> or CF<sub>3</sub>SO<sub>2</sub>OCF<sub>3</sub> / AgF at -30 to 10 °C under a N<sub>2</sub> atmosphere provided  $\alpha$ -trifluoromethoxyl arylacetates in up to 90% yield, while alkyl  $\alpha$ -diazo vinylacetates reacting with CF<sub>3</sub>SO<sub>2</sub>OCF<sub>3</sub> / AgF or AgOCF<sub>3</sub> afforded  $\gamma$ -trifluoromethoxyl  $\alpha$ , $\beta$ unsaturated esters in up to 94% yield. The  $\alpha$ -diazo ketosteroid was also trifluoromethoxylated under the standard reaction conditions. This protocol allows for an effective and convenient access to a large number of synthetic building blocks which are promising in the development of new functional OCF<sub>3</sub>-molecules.

OCF<sub>3</sub>-containing organic frameworks have attracted great interests in the recent years.<sup>1</sup> Such compounds have been extensively exploited in medicinal chemistry, agrochemical industry, and materials science, due to the unique stereoelectronic properties and the excellent lipophilicity of the OCF<sub>3</sub> substituents.<sup>1-3</sup> The introduction of OCF<sub>3</sub> groups into biologically active molecules can improve their in vivo uptake and transport, and enhance their efficacy and minimize the side effects.<sup>1,2</sup> The incorporation of OCF<sub>3</sub> moiety into materials can widen the temperature range of liquid state of materials under ambient pressure and lower their surface tension and dielectric constants, which are the key to the development of high performance liquid crystals and semiconductors.<sup>[1a,3]</sup> In view of these wide applications, the exploration of OCF<sub>3</sub>-containing organofluorines is of great importance.

Although the huge advances have been made in transition-metalmediated formation of C-F, C-CF<sub>3</sub>, C-CF<sub>2</sub>R, C-SCF<sub>3</sub>, and C-SCF<sub>2</sub>R bonds,<sup>4</sup> methods for the direct construction of C-OCF<sub>3</sub> bonds are still lacking, with the trifluoromethoxy group being the least well understood.<sup>1-3</sup> The conventional preparation of OCF<sub>3</sub>-containing molecules mainly relied on the chlorine/fluorine exchange of trichloromethoxylated precursors.<sup>1,5</sup> Alternative approaches involved the deoxyfluorination of fluoroformates and the oxidative

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.<sup>+</sup> Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

fluorodesulfurization of carbonodithioate.<sup>6,7</sup> These protocols have limitations such as the use of highly toxic HF, SbF<sub>3</sub>, or SF<sub>4</sub>, and the narrow functional group tolerance. Later, electrophilic trifluoromethylation of alcohols and phenols by Umemoto or Togni's reagents was employed to produce R-OCF<sub>3</sub>, which was subjected to harsh reaction conditions, poor substrate scope, or low efficiency.<sup>8</sup> The silver-mediated oxidative trifluoromethylation of phenols and alcohols by TMSCF<sub>3</sub> was also applied to prepare trifluoromethyl ethers, which, nevertheless, requires a large excess of expensive additives.<sup>9</sup> Very recently, a two-step route to ArOCF<sub>3</sub> was achieved by trifluoromethylation of protected *N*-(hetero)aryl-*N*-hydroxylamines followed by intramolecular rearrangement of the *N*-OCF<sub>3</sub> intermediates; however, this reaction could only be applied to *N*-arylhydroxylamines.<sup>10</sup>

Previous direct trifluoromethoxylation with "OCF3" reagents

(a) 
$$R-X + "^{-}OCF_3" \xrightarrow{S_1/2 \text{ type}} R-OCF_3$$
  
(X = halides, OTF, OTs, etc)

(b) 
$$Ar - X + [TAS]^{\dagger}[OCF_3]^{\bullet} \xrightarrow{AQP+6} Ar - OCF_3$$
  
(X = SnBua B(OH)a)

(c) 
$$R_1 R_2$$
 NHZ + AgOCF<sub>3</sub>  $Pd(CH_3CN)_2Cl_2$   $R^2$   $F$ -TEDA-BF<sub>4</sub>

This work

$$\begin{array}{c} N_2 \\ R \xrightarrow{} CO_2 R^1 \end{array} + AgOCF_3 \text{ or } CF_3SO_3CF_3 / AgF \xrightarrow{} CH_3CN \\ \hline 30 \ C \text{ to r.t.} \end{array} \xrightarrow{} \begin{array}{c} OCF_3 \\ R \xrightarrow{} CO_2 R^1 \end{array} \xrightarrow{} OCF_3 \\ R \xrightarrow{} CO_2 R^1 \end{array}$$

The direct nucleophilic trifluoromethoxylation using OCF<sub>3</sub> as the  $\mathsf{OCF}_3$  sources has provided a straightforward access to trifluoromethyl ethers.  $^{11}$  Owing to the inherent instability of the OCF<sub>3</sub> anion,<sup>11</sup> there have been few reports on transition-metalmediated trifluoromethoxylation with "OCF3" reagents. To seek metal-OCF<sub>3</sub> complexes that are suitable out for trifluoromethoxylation,<sup>12</sup> we first synthesized N-heterocyclic carbene stabilized (NHC)CuOCF<sub>3</sub> and (NHC)AuOCF<sub>3</sub> from acetonitrile-solvated AgOCF<sub>3</sub> reagent.<sup>12a</sup> The first silver-mediated cross coupling of arylstannanes or arylboronic acids with [TAS][OCF<sub>3</sub>] and the recent palladium-catalyzed trifluoromethoxylation of prefunctionalized alkenes by AgOCF<sub>3</sub> have represented the state-of-the-art methods for transition-metalmediated nucleophilic trifluoromethoxylation to date.<sup>13</sup> Besides, no other reactions with "  ${}^{-}\mbox{OCF}_3{}^{\prime\prime}$  reagents mediated by a certain transition-metal have been reported. Hence, the transition-metal-

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mediated direct trifluoromethoxylation with thermally unstable  $\[OCF_3\]$  anion is much challenging.

On the other hand,  $\alpha$ -diazo compounds have been explosively utilized to construct cyclopropanes, heterocycles, hydrazones, tetrasubstituted olefins, and other functional molecules in the past few years.<sup>14-18</sup> The combination of  $\alpha$ -diazo compounds with fluorine chemistry has also achieved great successes, e.g., the Cu-mediated trifluoromethylation or trifluoromethylthiolation of  $\alpha$ -diazo esters by TMSCF<sub>3</sub> or AgSCF<sub>3</sub>, respectively, the Cu-mediated gem-difluoroolefination of diazo compounds by TMSCF<sub>3</sub> or Ph<sub>3</sub>P<sup>+</sup>CF<sub>2</sub>CO<sub>2</sub><sup>-</sup>, and the metal-free gem-difluoroolefination of diazo compounds by TMSCF<sub>3</sub>, TMSCF<sub>2</sub>Br, or TMSCF<sub>2</sub>Br / TBAB, which have furnished a variety of useful functionalized feedstocks.<sup>19</sup> Given the unique properties of  $^{-}$ OCF<sub>3</sub> anion and the versatility of  $\alpha$ -diazo compounds, we envisioned whether the direct trifluoromethoxylation of  $\alpha$ -diazo esters with " $^{-}$ OCF<sub>3</sub>" reagents may be a facile way to form  $\alpha$ -OCF<sub>3</sub> carbonyls.

Table 1 Trifluoromethoxylation of alkyl  $\alpha\text{-diazo}$  arylacetates with CF\_3SO\_2OCF\_3 / AgF reagents  $^a$ 



 $^a$  Reaction conditions: CF<sub>3</sub>SO<sub>2</sub>OCF<sub>3</sub> (2.5 mmol) was added into a mixture of 1 (0.5 mmol), AgF (1.0 mmol), and CH<sub>3</sub>CN (2.5 mL) at -30  $^\circ$ C in one portion via syringe under a N<sub>2</sub> atmosphere. After 5 mins, the reaction mixture was warmed to 10  $^\circ$ C overnight. Isolated yields.

To verify this, the reaction of ethyl 2-diazo-2-(naphthalen-1yl)acetate (1a) with AgOCF<sub>3</sub> was explored. It was found that addition of 2 equiv of AgOCF<sub>3</sub> (0.5 or 1.0 M in CH<sub>3</sub>CN) into a mixture of 1a and CH<sub>3</sub>CN at 10  $^{\circ}$ C under a N<sub>2</sub> atmosphere afforded 2a in 43% yield (see SI, Table 1). Using 4 equiv of AgOCF<sub>3</sub> in the same reaction, 2a was obtained in 53% yield (see SI, Table 1). Increasing the reaction temperature from 10 to 25 °C, no remarkable change in the yield of 2a was observed (58%, see SI, Table 1). Inverse addition of 1a into 2 or 4 equiv of AgOCF<sub>3</sub> provided 2a in 38% or 60% yield, respectively (see SI, Table 1). Since AgOCF<sub>3</sub> was prepared by the reaction of  $\mathsf{CF}_3\mathsf{SO}_2\mathsf{OCF}_3$  with  $\mathsf{AgF}$  in  $\mathsf{CH}_3\mathsf{CN},^{[12,13b]}$  the convenient one-pot reaction of 1a with CF<sub>3</sub>SO<sub>2</sub>OCF<sub>3</sub> and AgF was harnessed. Intriguingly, addition of 1a into a mixture of AgF (2 equiv.), CF<sub>3</sub>SO<sub>2</sub>OCF<sub>3</sub> (8 equiv.), and MeCN at -30<sup>o</sup>C and reacted at 10 °C overnight provided 2a in 58% yield (see SI, Table 2), while introducing  $CF_3SO_2OCF_3$  (8 equiv.) into the mixture of 1a, AgF (2 equiv.), and MeCN at -30  $^\circ\text{C}$  and reacted at 10  $^\circ\text{C}$  overnight produced 2a in 77% yield (see SI, Table 2). If CF<sub>3</sub>SO<sub>2</sub>OCF<sub>3</sub> was added

at 10 °C, **2a** was furnished in 89% yield (see SI, Table 2), but the reaction is severe and releases a great amount of gasses, which limits its use on large scales. Furthermore, if AgF (2 equiv.) was added into a mixture of **1a**,  $CF_3SO_2OCF_3$  (8 equiv.), and MeCN at -30 °C and reacted at 10 °C overnight, the reaction provided **2a** in 76% yield (see SI, Table 2).

In addition, the molar ratio of 1a, AgF, and CF<sub>3</sub>SO<sub>2</sub>OCF<sub>3</sub> have a significant impact on the reaction. For example, treatment of 1a and  $CF_3SO_2OCF_3$  (8 equiv) with equal equivalent of AgF gave 2a in 36% yield (see SI, Table 2), while the reaction using 3 or 5 equiv of AgF afforded 2a in 84% or 92% yield, respectively (see SI, Table 2). The reaction of 1a with 2 equiv of AgF and 5 equiv of CF<sub>3</sub>SO<sub>2</sub>OCF<sub>3</sub> provided 2a in 76% yield (see SI, Table 2). If 1a reacted with CF<sub>3</sub>SO<sub>2</sub>OCF<sub>3</sub> (8 equiv) in the absence of AgF, no 2a was produced (see SI, Table 2). When 1a was treated with CF<sub>3</sub>SO<sub>2</sub>OCF<sub>3</sub> (8 equiv) in the presence of [TAS][Me<sub>3</sub>SiF<sub>2</sub>] (2 equiv), CsF (2 equiv), KF (2 equiv), or [Me<sub>4</sub>N]F (2 equiv) in CH<sub>3</sub>CN, 2a was hardly formed (see SI, Table 3). Nevertheless, if  $Ag_2CO_3$  or  $Ag_2O$  was added into a reaction mixture of 1a, [Me<sub>4</sub>N]F (2 equiv), and CF<sub>3</sub>SO<sub>2</sub>OCF<sub>3</sub> (8 equiv), 2a was obtained in 32% or 23% yield, respectively (see SI, Table 3). All these indicated that the silver is indispensable for the trifluoromethoxylation reaction.

Next, a combination of 1a / AgF (2.0 equiv) / CF<sub>3</sub>SO<sub>2</sub>OCF<sub>3</sub> (5.0 equiv) /  $CH_3CN$  / -30 to 10  $^{\circ}C$  /  $N_2$  / overnight was chosen as the standard reaction conditions to test the scope of the reaction. To our delight, ethyl α-diazo arylacetates with various electrondonating or weakly electron-withdrawing groups such as CH<sub>3</sub>, OCH<sub>3</sub>, F, Cl, Br, t-Bu, and C<sub>6</sub>H<sub>5</sub> were all successfully transformed which furnished the corresponding  $\alpha$ -trifluoromethoxyl arylacetates (2bo) in good yields (Table 1). The position of the substituents on the phenyl rings has considerable influence on the reaction. The orthoand/or *para*-substitution on the phenyl rings of  $\alpha$ -diazo esters gave higher yields of the products (e.g. 2c, 2e, 2f, and 2i), whereas the meta-substitution moderately frustrated the trifluoromethoxylation, which provided slightly lower yields of the products (e.g. 2d, 2g, and 2h). Moreover, the highly electron-poor 2-diazo-2-(3-nitrophenyl)acetate (1p) reacting ethyl with CF<sub>3</sub>SO<sub>2</sub>OCF<sub>3</sub> and AgF under the standard reaction conditions afforded 2p in 27% yield. Treatment of ethyl 2-diazo-2-(naphthalen-2-yl)acetate (1q) and ethyl 2-(benzodioxol-5-yl)-2-diazoacetate (1r) with CF<sub>3</sub>SO<sub>2</sub>OCF<sub>3</sub> / AgF supplied 2q in 67% yield and 2r in 72% yield, respectively. Heteroaromatic  $\alpha$ -diazo esters, such as ethyl 2-diazo-2-(thiophen-3-yl)acetate (1s) and ethyl 2-diazo-2-(1-tosyl-1H-indol-3-yl)acetate (1t), reacted with CF<sub>3</sub>SO<sub>2</sub>OCF<sub>3</sub> and AgF to afford respective 2s in 55% yield and 2t in 90% yield. Other alkyl  $\alpha$ -diazo esters like methyl, propyl, isopropyl, butyl, tert-butyl, benzyl, allyl, and adamantanyl  $\alpha$ -diazo phenylacetates were also readily converted under the standard reaction conditions to form 2u-2bb in 53-90% yields. Furthermore, the reaction of (1S,2R,5S)-2-isopropyl-5-methylcyclohexyl 2-diazo-2-phenylacetate (1cc) with CF<sub>3</sub>SO<sub>2</sub>OCF<sub>3</sub> / AgF provided 2cc in 71% yield with a dr value of 1.1 : 1, which was determined by <sup>1</sup>H and <sup>19</sup>F NMR spectroscopy (see SI).

Besides,  $\alpha$ -diazo vinylacetates are suitable substrates to the reaction (**Table 2**). When (*E*)-ethyl 2-diazo hex-3-enoate (**3a**), hept-3-enoate (**3b**), and oct-3-enoate (**3c**) were treated with CF<sub>3</sub>SO<sub>2</sub>OCF<sub>3</sub> and AgF at -30 to 10 °C under a N<sub>2</sub> atmosphere overnight, **4a**, **4b**, and **4c** were obtained in 89%, 72%, and 94% yields, respectively. (*E*)-Methyl 2-diazo non-3-enoate (**3d**) reacting with CF<sub>3</sub>SO<sub>2</sub>OCF<sub>3</sub> / AgF under the standard reaction conditions gave **4d** in 91% yield. Treatment of (*E*)-ethyl 2-diazo-4-phenylbut-3-enoate (**3e**) with CF<sub>3</sub>SO<sub>2</sub>OCF<sub>3</sub> and AgF afforded **4e** in 82% yield. Moreover, the

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reaction of **3b** with AgOCF<sub>3</sub> (5 equiv) at 10  $^{\circ}$ C under a N<sub>2</sub> atmosphere overnight could also generate 4b (83% yield). Remarkably,  $\alpha$ -diazo ketosteroid **3f** reacted with CF<sub>3</sub>SO<sub>2</sub>OCF<sub>3</sub> (8 equiv) / AgF (5 equiv) in CH<sub>2</sub>Cl<sub>2</sub> or with AgOCF<sub>3</sub> (5 equiv) in CH<sub>2</sub>Cl<sub>2</sub> / CH<sub>3</sub>CN providing **4f** in 48% or 30% yield, respectively.<sup>20</sup> The silvermediated trifluoromethoxylation seems to happen at the vinylogous position of **3** to form y-substituted  $\alpha$ ,  $\beta$ -unsaturated carbonyls, which was determined by NMR analysis of the products.<sup>20</sup> The geometry of **4a-e** (*E*-isomers) can be confirmed by the values of the coupling constants between the vinyl protons of the products in <sup>1</sup>H NMR spectra (e.g.  ${}^{3}J_{trans-HH} = 15.7$  Hz, see SI) according to the literatures.<sup>21</sup>

Table 2 Trifluoromethoxylation of  $\alpha$ -diazo vinyl carbonyls with CF<sub>3</sub>SO<sub>2</sub>OCF<sub>3</sub> / AgF reagents



 $^a$  Reaction conditions: CF\_3SO\_2OCF\_3 (2.5 mmol) was introduced into a mixture of  ${\bf 3}$  (0.5 mmol), AgF (1.0 mmol), and CH<sub>3</sub>CN (2.5 mL) at -30 °C in one portion via syringe under a  $N_2$  atmosphere. After 5 mins, the reaction mixture was warmed to 10  $^\circ\text{C}$  overnight. Isolated yields.  $^{\rm b}$  3b was added into a solution of AgOCF3 (5 equiv) in CH3CN at 10  $^{\circ}C$ under a N2 atmosphere, and the mixture was reacted overnight. <sup>c</sup> CF3SO2OCF3 (0.8 mmol) / 3f (0.1 mmol) / AgF (0.5 mmol) / CH<sub>2</sub>Cl<sub>2</sub> (0.5 mL). <sup>d</sup> A solution of 3f (0.1 mmol) in CH<sub>2</sub>Cl<sub>2</sub> was added into a solution of AgOCF<sub>3</sub> (0.5 mmol) in CH<sub>3</sub>CN

To gain some insights into the reaction mechanism, several control experiments were performed (Scheme 1). Initially, the reaction of 1a, AgF (2 equiv), and CF<sub>3</sub>SO<sub>2</sub>OCF<sub>3</sub> (5 equiv) in CD<sub>3</sub>CN under the standard reaction conditions gave 2a in 80% yield with 13% of deuterated form, implying that acetonitrile is not the major "proton source" for 2a. Nevertheless, if 1.1 equiv of D<sub>2</sub>O was added into a mixture of 1a, AgF (5 equiv), CF<sub>3</sub>SO<sub>2</sub>OCF<sub>3</sub> (8 equiv), and CH<sub>3</sub>CN under the standard reaction conditions, 2a was obtained in a lower yield but with much higher percentage of deuterated form (Condition B: 33% yield, 88% D-form, Scheme 1). If a mixture of 1a, AgF (5 equiv), CF<sub>3</sub>SO<sub>2</sub>OCF<sub>3</sub> (8 equiv), and CH<sub>3</sub>CN was reacted at -30 to 10  $^{\circ}$ C overnight and quenched by D<sub>2</sub>O, 91% yield of **2a** with 74% of D-form was produced (Condition C, Scheme 1). Similar results were also observed in the case of 3c with CF<sub>3</sub>SO<sub>2</sub>OCF<sub>3</sub> / AgF under the standard reaction conditions. These suggest that the trifluoromethoxylation is sensitive to moisture, which is attributed to the *in situ* generation of <sup>-</sup>OCF<sub>3</sub> species, and, most importantly, that the  $\alpha$ -proton of **2a** (or **4c**) might dominantly originate from water or moisture during the workup. Since the addition of 2 equiv of TEMPO into the reaction mixture of 1a, AgF, CF<sub>3</sub>SO<sub>2</sub>OCF<sub>3</sub>, and CH<sub>3</sub>CN under the standard reaction conditions rarely prohibited the formation of 2a, the radical process might be excluded in the reaction. Based on these, a plausible nucleophilic reaction mechanism was suggested in Scheme 2. At the beginning, CF<sub>3</sub>SO<sub>2</sub>OCF<sub>3</sub> reacting with AgF in situ forms ionic AgOCF<sub>3</sub>. The Ag<sup>+</sup> ion first integrates with  $\alpha$ -diazo esters generating the key intermediate 5a or 5b. Trifluoromethoxylation of 5a or 5b by free <sup>-</sup>OCF<sub>3</sub> anion produces **6a** or **6b**, respectively, which is guenched by

water (or moisture) after trifluoromethoxylation to give the desired products. However, the details still remain unclear.



Condition A: AgF (2 equiv), CF<sub>3</sub>SO<sub>2</sub>OCF<sub>3</sub> (5 equiv), CD<sub>3</sub>CN; 80% isolated yield of 2a, 13% D-form. Condition B: AgF (5 equiv), CF<sub>3</sub>SO<sub>2</sub>OCF<sub>3</sub> (8 equiv), D<sub>2</sub>O / CH<sub>3</sub>CN; 33% isolated yield of 2a, 88% D-form. Condition C: AgF (c equiv), CF<sub>3</sub>SO<sub>2</sub>OCF<sub>3</sub> (8 equiv), CH<sub>3</sub>CN, quenched by D<sub>2</sub>O; 91% isolated yield of 2a, 74% D-form





Scheme 1 Trifluoromethoxylation of  $\alpha$ -diazo esters by CF<sub>3</sub>SO<sub>2</sub>OCF<sub>3</sub> / AgF in the presence of  $D_2O$  or TEMPO



Scheme 2 Proposed reaction mechanism for silver-mediated trifluoromethoxylation of  $\alpha$ -diazo esters

In conclusion, we have developed an effective and convenient method for the synthesis of trifluoromethoxylated esters and steroid under the mild reaction conditions. In this approach, numerous alkyl  $\alpha$ -diazo arylacetates were converted to give the corresponding  $\alpha$ -trifluoromethoxyl esters in good to high yields. In the cases of alkyl  $\alpha$ -diazo vinylacetates, the silver-mediated reaction exhibited good region- and stereoselectivity, which provided ytrifluoromethoxyl (E)- $\alpha$ , $\beta$ -unsaturated esters in excellent yields. For  $\alpha$ -diazo ketosteroid, the desirable trifluoromethoxylated product was also obtained in moderate yield. This promising and operationally simple protocol has supplied a number of synthetic building blocks for the development of new functional molecules, which would render the direct trifluoromethoxylation viable to a broader synthetic community. The application of this strategy to other nucleophilic trifluoromethoxylation is currently under way in our lab.

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