Carbenes

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Silver(I)-Catalyzed *N*-Trifluoroethylation of Anilines and *O*-Trifluoroethylation of Amides with 2,2,2-Trifluorodiazoethane

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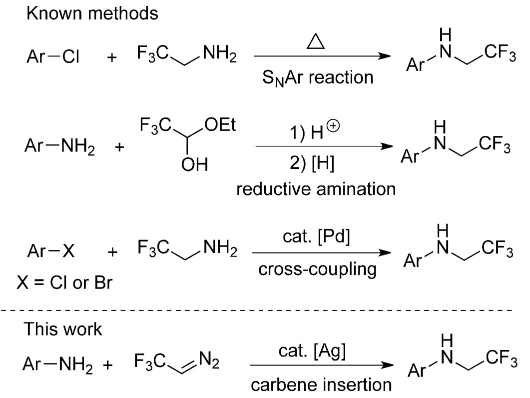
Abstract: *A straightforward N-trifluoroethylation of anilines has been developed based on silver-catalyzed N−H insertions with 2,2,2-trifluorodiazoethane (CF_3CHN_2). Mechanistically, the reaction is proposed to involve migratory insertion of a silver carbene as the key step. In contrast, when amides are employed as the substrates under similar reaction conditions, O-trifluoroethylation occurs to afford trifluoroethyl imidates.*

Because of their importance in various fields, fluorine-containing organic compounds have attracted significant attention over the decades and enormous effort has been devoted to their synthesis.[1] In this context, the methods for trifluoromethylation have been extensively investigated,[2] while the related 2,2,2-trifluoroethylation still lags behind.[3] In contrast, aniline moieties are commonly found in pharmaceuticals, agrochemicals, and pigments.[4] The introduction of a 2,2,2-trifluoroethyl group on the amino group of aniline is important because the anilines bearing electron-withdrawing substituents are expected to resist the oxidative degradation, a vital issue in medicinal chemistry as well as in agrochemistry. Consequently, *N*-trifluoroethylated aniline or amide moieties have been found in some drugs and drug candidates.[5] However, the methods for *N*-trifluoroethylation of anilines are less well developed, and significantly limits the exploration of *N*-trifluoroethylated anilines in the pharmaceutical and agrochemical industries.

The early efforts for *N*-trifluoroethylation of anilines were focused on the nucleophilic substitution of aniline with trifluoroethyl chloride at elevated temperatures (up to 250 °C).[6] In 1986, Umemoto and co-workers reported a method to achieve *N*-trifluoroethylation by using a hypervalent-iodine–CH_2CF_3 reagent.[7] The recently reported methods include S_NAr reactions[8] and reductive amination reactions using trifluoroacetaldehyde (Scheme 1 a,b).[9] Very recently, Hartwig and co-workers reported a palladium-catalyzed arylation of trifluoroethylamine with aryl bromides and aryl chlorides, thus providing an efficient approach to *N*-trifluoroethylated aniline derivatives (Scheme 1 c).[10]



Scheme 1. Strategies to access *N*-trifluoroethylated anilines.

Although progress has been made in *N*-trifluoroethylation of anilines, in view of the importance of such types of fluorine-containing molecules and the limitation of the reported methods, it is still highly desirable to develop alternative and straightforward approaches.

Recently, 2,2,2-trifluorodiazoethane (CF_3CHN_2) has emerged as an attractive CF_3-containing synthon in various reactions such as cyclopropanation,[11] cyclopropenation,[12] 1,3-dipolar cycloaddition,[13] α-trifluoromethylation of organoborons,[14,3e] and trifluoroethylation of terminal alkynes,[15] and other reactions.[16] Those transformations represent some unique and efficient methods for the synthesis of fluorine-containing molecules. Notably, N−H insertions, which are typical in metal carbene reactions,[17] have not been explored with CF_3CHN_2 as the carbene precursor. In view of the importance of *N*-trifluoroethylated anilines and also as a continuation of our interest in metal carbene chemistry, we report herein the silver(I)-catalyzed *N*-trifluoroethylation of anilines and *O*-trifluoroethylation of amides (Scheme 1 d).

At the outset, a CF_3CHN_2 solution in toluene was prepared from commercially available $CF_3CH_2NH_2{\cdot}HCl$, according to the method reported by Carreira and co-workers.[12] Subsequently, we investigated the *N*-trifluoroethylation of ethyl 4-aminobenzoate (**1a**) with the stock toluene solution of CF_3CHN_2 at 50 °C and 1,2-dichloroethane (DCE) as the solvent. A series of metal catalysts, including CuI, $FeCl_2$, $FeCl_3$, $[\{Cp^*RhCl_2\}_2]$, $[Rh_2(OAc)_4]$, $[\{Cp^*IrCl_2\}_2]$, and various silver(I) salts were examined (Table 1, entries 1–8). $FeCl_2$, $AgBF_4$, $AgPF_6$, and $AgSbF_6$ were found to be effective, thus affording the desired product **2a** in moderate to good yields. Among these salts, $AgSbF_6$ turned out to be the best catalyst for the reaction (entry 5). The effect of solvent was then investigated (entries 9–14), and toluene, CH_2Cl_2,

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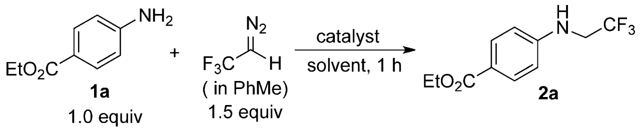
Table 1: Optimization of reaction conditions for the *N*-trifluoroethylation of **1a** with CF_3CHN_2.[a]

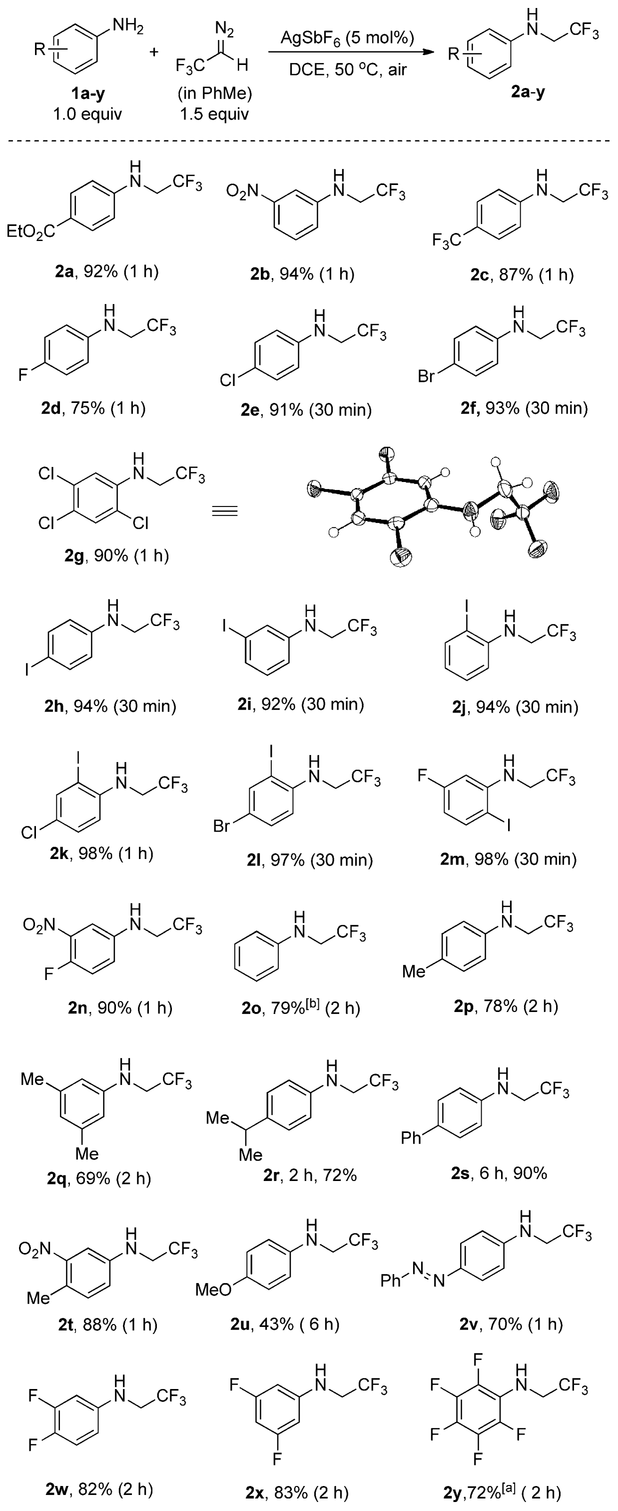


Entry	Catalyst [mol %]	Solvent	*T* [°C]	Yield [%][b]
1	cat. (*x*)[c]	DCE	50	0
2	$[Rh_2(OAc)_4]$ (2)	DCE	50	5
3	$FeCl_3$ (5)	DCE	50	trace
4	$FeCl_2$ (5)	DCE	50	46
5	$AgSbF_6$ (5)	DCE	50	93
6	$AgBF_4$ (5)	DCE	50	78
7	$AgPF_6$ (5)	DCE	50	67
8	AgOTf (5)	DCE	50	trace
9	$AgSbF_6$ (5)	toluene	50	18
10	$AgSbF_6$ (5)	CH_2Cl_2	50	46
11	$AgSbF_6$ (5)	$CHCl_3$	50	48
12	$AgSbF_6$ (5)	MeCN	50	0
13	$AgSbF_6$ (5)	acetone	50	0
14	$AgSbF_6$ (5)	MeOH	50	0
15	$AgSbF_6$ (5)	DCE	35	0
16	$AgSbF_6$ (5)	DCE	40	88
17	$AgSbF_6$ (5)	DCE	60	65

[a] Unless otherwise noted, the reaction conditions are as follows: **1a** (0.3 mmol), CF_3CHN_2 solution in toluene (0.45 mmol), DCE (3.5 mL). [b] The yield was determined by ^{19}F NMR spectroscopy by using $PhCF_3$ as the internal standard. [c] cat. (*x*) = CuI (5), $[\{Cp^*RhCl_2\}_2]$ (2), $[\{Cp^*IrCl_2\}_2]$ (2), $AgNO_3$ (5), AgOAc (5), $AgSO_3Me$ (5), AgF (5), Ag_2O (5). $Cp^* = C_5Me_5$, DCE = 1,2-dichloroethane.

and $CHCl_3$ were found to be suitable for the reaction. However, no desired product could be detected by using polar solvents, such as MeCN, acetone, and MeOH. Furthermore, the reaction temperatures (entries 15–17) were examined and the results revealed that the reaction carried out at 50 °C offered the optimal results. It was noted that no desired product could be observed when the reaction temperature was reduced to 35 °C (entry 15).

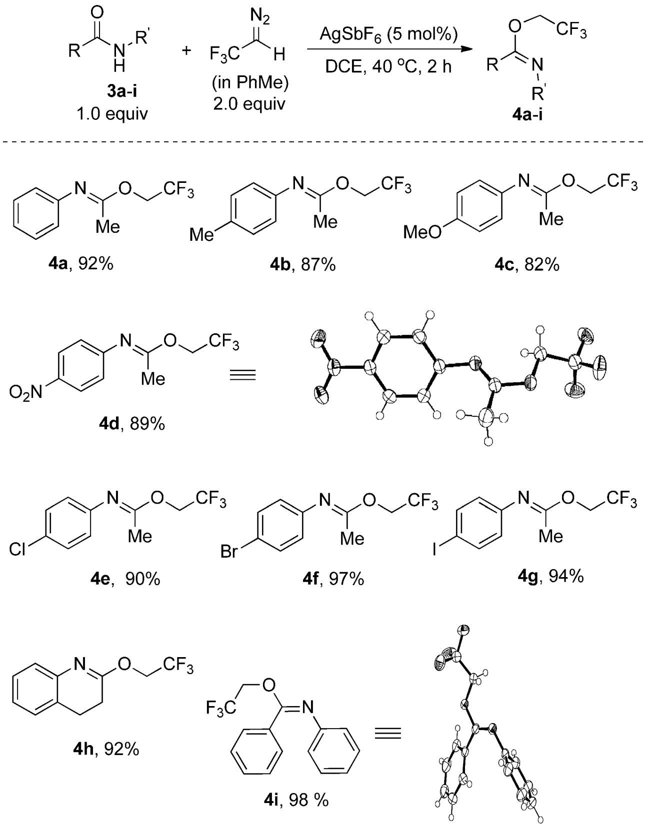
With the optimized reaction conditions in hand,[18] we then proceeded to expand the scope with respect to the substrates with a series of functionalized aniline derivatives. As summarized in Scheme 2, in general moderate to excellent yields were obtained under the optimized reaction conditions. The *N*-trifluoroethylation has shown excellent tolerance to both electron-withdrawing and electron-donating groups as aromatic substituents, including ester (**2a**), nitro (**2b**, **2n**, **2t**), trifluoromethyl (**2c**), alkane (**2p**, **2q**, **2r**, **2t**), aryl (**2r**), methoxy (**2u**), and azo (**2v**) groups. The diminished yield in the case of **2u** may be attributed to deactivation by the methoxy substituent, presumably caused by the coordination of the lone pair of the methoxy group with the silver cation. Notably, the reaction tolerates halogen substituents on the aromatic rings, including fluoro (**2d**, **2m**, **2n**, **2w–y**), chloro (**2e**, **2g**, **2k**), bromo (**2f**, **2l**), and iodo (**2h–m**) groups. Essentially no steric effect was observed as shown by the reactions with *para*-, *ortho*-, and *meta*-iodo anilines as the substrates (**2h–j**). In addition, the reaction with poly-fluoroanilines also afforded the desired product in good yields. In the case of **2y** the yield of the isolated product was diminished and attributed to the volatility of the products. The reaction showed 72 % yield as determined by ^{19}F NMR spectroscopy.



Scheme 2. Silver(I)-catalyzed *N*-trifluoroethylation of aniline derivatives with CF_3CHN_2. Unless otherwise noted, the reaction conditions are as follows **1a** (0.3 mmol), CF_3CHN_2 solution in toluene (0.45 mmol), DCE (3.0 mL). All the yields refer to those of the isolated products unless otherwise noted. [a] Yield determined by ^{19}F NMR spectroscopy. Thermal ellipsoids shown at 30% probability.

The structure of **2g** was unambiguously confirmed by the X-ray crystallographic analysis.[19]

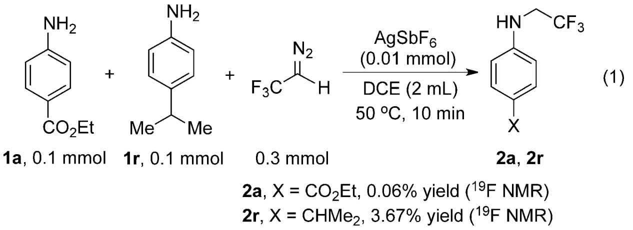
Furthermore, we applied the same protocol to the synthesis of *N*-trifluoroethylated amide derivatives. To our surprise, the expected N−H insertion products were not observed, and instead, *O*-trifluoroethylation occurred to afford trifluoroethyl imidates. As summarized in Scheme 3, in general the reactions occurred smoothly under similar reaction conditions, thus affording products bearing OCH_2CF_3 groups in good to excellent yields. The results indicate that the reaction of the substrates bearing electron-withdrawing groups on aromatic rings (**4d**–**g**) affords slightly higher yields than those bearing electron-donating groups (**4b**,**c**). The reaction with *N*-phenyl-substituted benzamide afforded the product **4i** in 98% yield. The structures of **4d** and **4i** were unambiguously confirmed by the X-ray crystallographic analysis.[19]



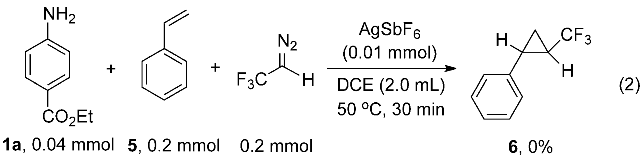
Scheme 3. Silver(I)-catalyzed *O*-trifluoroethylation of amides with CF_3CHN_2. Unless otherwise noted, the reaction conditions are as follows: **3a**–**i** (0.3 mmol), CF_3CHN_2 solution in toluene (0.60 mmol), DCE (3.5 mL). All the yields refer to the isolated products. Thermal ellipsoids shown at 30% probability.

To gain insight into the reaction mechanism, some control experiments have been carried out. First, when a clear solution of **1a** in toluene was added dropwise to a clear solution of $AgSbF_6$ in toluene at room temperature, the solution turned turbid and a white suspension quickly precipitated.[20] This observation indicates the possible formation of an Ag^I/aniline complex as shown in the proposed reaction mechanism (see below). Then CF_3CHN_2 in toluene was added and the mixture was stirred at 50 °C for 30 minutes. The color of the mixture turned from yellow to grey, and was accompanied by the extrusion of N_2 from the solution. A standard work up afforded **2a** in 90% yield upon isolation.

Next, intramolecular competition experiments were carried out between **1a** and **1r** [Eq. (1)]. The mixture was stirred under the standard reaction conditions and the reaction was terminated after 10 minutes. Inspection of the crude reaction mixture by ^{19}F NMR spectroscopy showed that the ratio of **2a** to **2r** was approximately 1:61, thus clearly indicating that the reaction with the aniline bearing an electron-donating substituent is favored over that bearing an electron-withdrawing substituent.

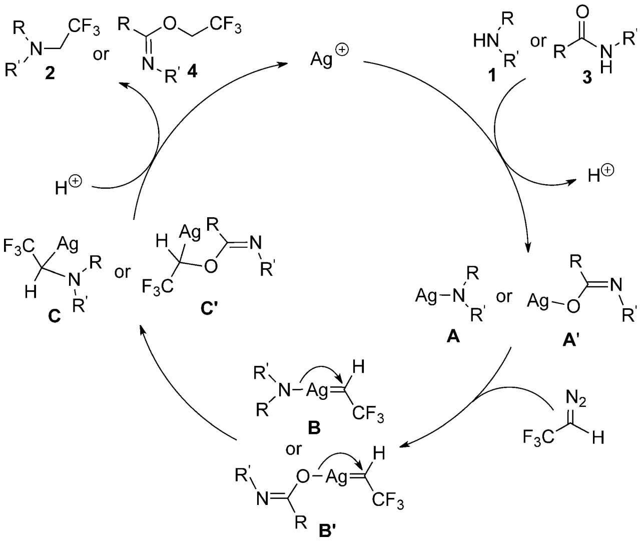


Finally, we attempted the trapping of the possible Ag/carbene intermediate through cyclopropanation. Thus, in the presence of catalytic amount of **1a** and $AgSbF_6$, styrene (**5**) was subjected to the reaction with CF_3CHN_2 under the standard reaction conditions. The anticipated cyclopropanation product **6** was not observed, but the *N*-trifluoroethylation product **2a** formed in 65% yield based on the amount of added **1a** [Eq. (2)]. In the absence of **1a**, the same trapping reaction also did not show the formation of **6**.



Based on these experimental observations, a plausible mechanism is proposed as shown in Scheme 4. The aniline derivatives **1** firstly react with Ag^+ to form the Ag^I/aniline complex **A**. Then, the reaction of CF_3CHN_2 with **A** produces the Ag^I/carbene intermediate **B**.[21,22] Migratory insertion of the amine ligand to the carbenic carbon atom gives the intermediate **C**, from which protonation affords the *N*-trifluoroethylated product **2**. For *O*-trifluoroethylation of amides, a similar mechanism is proposed. In this case, the Ag^I/imidate complex **A′** is favored because of the relatively hard basicity of the oxygen atom relative to the nitrogen atom. Imidate ligand migration from the Ag^I/carbene intermediate **B′**, followed by protonation affords the product **4**.

Notably, for the *N*-trifluoroethylation of anilines, an alternative mechanism cannot be ruled out, that is, the direct insertion of a N−H bond with Ag/carbene (or through ylide formation and 1,2-H shift), as generally accepted for



Scheme 4. Proposed reaction mechanism.

classic metal carbene N–H insertions.[17,20,22] However, such mechanism seems less likely in view of the control experiment results as well as the *O*-trifluoroethylation in the case of amide under the similar reaction conditions.

In summary, we have developed a silver-catalyzed *N*-trifluoroethylation of anilines with CF_3CHN_2, which can be generated from readily available $CF_3CH_2NH_2{\cdot}HCl$. Mechanistically, this formal N–H insertion reaction is proposed to involve Ag^I/carbene formation and subsequent amine ligand migratory insertion. With amides as the substrates, *O*-trifluoroethylation products were obtained following a similar reaction mechanism. Since the reaction conditions are mild and the reaction tolerates various functional groups, this novel tactic for trifluoroethylation may find useful applications in the drug discovery process in medicinal chemistry.[23]

Experimental Section

General procedure for *N*-trifluoroethylation of aniline derivatives. The aniline derivative (**1a–y**; 0.3 mmol) and $AgSbF_6$ (0.015 mmol, 5.2 mg) were added to a Schlenk tube. 1,2-dichloroethane (3.0 mL) and CF_3CHN_2 in toluene (about 0.85 M, 0.45 mmol) were then added. The resulting mixture was stirred at 50 °C for 0.5–5 h. Upon completion of the reaction, the solvent was removed and the resulting residue was purified by column chromatography on silica gel to afford the *N*-trifluoroethylation products **2a–y**.

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[18] We have also tried the *N*-trifluoroethylation reaction by in situ generation of CF_3CHN_2, however, no desired product could be obtained.

[19] CCDC 1414829, 1414830, and 1415161 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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[23] We have also attempted the *O*- and *S*-trifluoroethylation with phenol and thiophenol under similar conditions. The corresponding products could be identified by GC-MS. However, the reactions were not efficient. Further optimization of the reaction conditions is under way.

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