Stable and Storable N(CF₃)₂ Transfer Reagents

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In memory of Siegfried Hünig.

Abstract: Fluorinated groups are essential for drug design, agrochemicals, and materials science. The bis(trifluoromethyl) amino group is an example of a stable group that has a high potential. While the number of molecules containing perfluoroalkyl, perfluoroalkoxy, and other fluorinated groups is steadily increasing, examples with the N(CF₃)₂ group are rare. One reason is that transfer reagents are scarce and metal-based storable reagents are unknown. Herein, a set of Cu and Ag bis(trifluoromethyl)amido complexes stabilized by N- and P-donor ligands with unprecedented stability are presented. The complexes are stable solids that can even be manipulated in air for a short time. They are bis(trifluoromethyl) amination reagents as shown by nucleophilic substitution and Sandmeyer reactions. In addition to a series of benzylbis(trifluoromethyl)amines, 2-bis(trifluoromethyl)amino acetate was obtained, which, upon hydrolysis, gives the fluorinated amino acid N,N-bis(trifluoromethyl)glycine.

Transition metal perfluoroalkyl complexes are highly valuable reagents for the synthesis of fluorinated biologically active molecules that are employed as pharmaceuticals or agrochemicals and in materials applications.[1–6] Especially, copper(I) complexes are important as they enable the introduction of a broad variety of perfluoroalkyl groups into organic molecules that range from the simplest congener, trifluoromethyl, to complexes are used either in situ or immediately after generation, some complexes have been isolated and characterized, in detail. These complexes are often stabilized by co-ligands that typically are pyridines or phosphines, for example [(bpy)CuC≡CF₃] (Figure 1)[11] and [(Ph₃P)₂Cu(CF₃)₂] [(Ph₃P)₂Cu(hfip)].[12] Silver(I) complexes have been employed as perfluoroalkylation reagents as well,[11–14] although to a lesser extent than the related copper(I) derivatives. Because of their easy accessibility using silver(I) fluoride and the respective perfluoroalkane, for example, heptafluoropropene and tetrafluoroethylene,[15] they

![Diagram of N(CF₃)₂ transfer reagents](image-url)
Nitrogen derivatives have been developed in recent years. The chemistry of related perfluoroalkyl nitrogen substituents has been studied to a much lesser extent. Some synthetic strategies towards \(N\)-trifluoromethylamines and related \(N\)-perfluoroalkylnitrogen derivatives have been developed in recent years. Efficient strategies towards \(N,N\)-bis(perfluoroalkyl)nitrogen compounds remain scarce, presumably, because of the lack of suitable starting materials. Especially the \(N,N\)-bis(trifluoromethyl)amino group is of interest as its organic derivatives are known to exhibit high stability, for example against acids and bases, and because its potential as a substituent in pharmaceuticals was demonstrated, earlier. \(N,N\)-Bis(trifluoromethyl)amino derivatives have been obtained from perfluoroazapropene \(\text{CF}_3\text{N} = \text{CF}_2\) as initial starting compound or through tedious reaction sequences. Perfluoroazapropene is only accessible through laborious multistep syntheses, it is a reactive gas that requires special equipment for handling, and its transformation into the synthetically useful bis(trifluoromethyl)amide ion \(\text{N} = \text{CF}_2\text{SO}_2\text{M}^+\) is usually accompanied by dimerization giving \(\text{CF}_3\text{N} = \text{CF}_2\text{N} = \text{CF}_2\) (Figure 1). \(N,N\)-Bis(trifluoromethyl)trifluoromethanesulfonimide \(\text{CF}_3\text{SO}_2\text{N} = \text{CF}_2\text{SO}_2\text{M}^+\) is accessible through electrochemical fluorination (ECF) of \(\text{CF}_3\text{SO}_2\text{N}(\text{CH}_2)_2\) in anhydrous hydrogen fluoride (aHF) according to the Simons process on a large scale. Some \(N,N\)-bis(trifluoromethyl)amides with organic cations are stable whereas metal salts can only be handled in solution to prevent decomposition. Few of these organic salts have been used in metatheses or for the synthesis of organic molecules with the \(\text{N} = \text{CF}_2\text{SO}_2\text{M}^+\) group. So far, mercury complexes, for example \([\text{Hg} \text{N} = \text{CF}_2\text{SO}_2\text{M}^+]\), are the sole stable metal complexes with the \(\text{N} = \text{CF}_2\text{SO}_2\text{M}^+\) ligand, known. The salts \([\text{M} \text{N} = \text{CF}_2\text{SO}_2\text{M}^+]\) have been described as white solids. However, these salts cannot be stored because they immediately start to decompose, even at low temperature. So, they are not a convenient, storable \(\text{N} = \text{CF}_2\text{SO}_2\text{M}^+\) transfer reagents.

Herein, we present a set of stable and storable copper(I) and silver(I) complexes of the bis(trifluoromethyl)amido ligand. These complexes have been found to be promising compounds for the transfer of the bis(trifluoromethyl)amido group into organic molecules. Copper(I) complexes with the \(\text{N} = \text{CF}_2\text{SO}_2\text{M}^+\) ligand have been synthesized via metatheses using \(\text{CH}_2\text{CN}\) solutions of rubidium or cesium bis(trifluoromethyl)amide that were generated from \(\text{CF}_3\text{SO}_2\text{N}(\text{CH}_2)_2\) and the respective dry alkali metal fluoride (Figure 2). The dark orange complex \([\text{bpy}]\text{Cu}[\text{N} = \text{CF}_2\text{SO}_2\text{M}^+]\) (1a, bpy = 2,2'-bipyridine) was prepared from a solution of Rb

Figure 2. Synthesis and crystal structures of the copper(I) complexes 1a–1e (thermal ellipsoids set at 25% probability; H atoms are omitted for clarity; C atoms of the N- and P-donor ligands are depicted as stick models).

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The copper(I) derivative [Cu(bpy)]_2[ClCu]_2 was either isolated and redissolved or prepared in situ from copper(I) chloride and 2,2′-bipyridine giving almost equal yields for 1a of 83 and 82 %, respectively. Alternatively, Cu(NCF_3)_3 was synthesized from CuCl and Rb(NCF_3)_3 in acetonitrile, and 2,2′-bipyridine was added to give 1a in 41 % yield (Figure 2). Because of the lower yield, all further copper(I) bis(trifluoromethyl)amido complexes were synthesized from preformed copper(I) complexes and Rb(NCF_3)_3 or Cs(NCF_3)_3. In addition to 1a, the analogous dark orange 1,10-phenanthroline (phen) complex [(phen)Cu(NCF_3)_3] (1d) was isolated in 90 % yield. The colorless triphenylphosphane complex [(Ph_3P)_2Cu(NCF_3)_3] (1b) that was obtained in almost quantitative yield represents the third complex with a tricoordinate copper center. In contrast, the yellow-orange mixed complexes [(bpy)(Ph_3P)Cu(NCF_3)_3] (1c) and [(phen)(Ph_3P)Cu(NCF_3)_3] (1e) that were isolated in 77 and 79 % yield, respectively, contain four coordinate Cu centers (Figure 2).

Acetonitrile solutions of the silver(I) salt Ag(NCF_3)_2 obtained from silver(I) fluoride and CF_3SO_3NCF_3 (Figure 1) were used for the synthesis of silver(I) bis(trifluoromethyl)amido complexes (Figure 3). In analogy to the copper(I) N(CF_3)_3 derivatives, three- and four-coordinate Ag complexes were obtained. The three colorless complexes [(bpy)Ag(NCF_3)_3] (2a), [(Ph_3P)_2Ag(NCF_3)_3] (2b), and [(bpy)(Ph_3P)Ag(NCF_3)_3] (2c) were isolated in yields of 78, 89, and 90 %, respectively. The 2,2′:6′,2″-terpyridine (terpy) derivative [(terpy)Ag(NCF_3)_3] (2f) was obtained as a yellow crystalline material in 62 % yield. The silver(I) triphenylphosphane complex 2b reacts with additional triphenylphosphane under formation of the complex salt [Ag(Ph_3P)_3][NCF_3]_3 (3) that is composed of the tetrahedral [Ag(Ph_3P)_3][NCF_3]_3 cation and a non-coordinated N(CF_3)_3^− anion. Salt 3 was selectively prepared from triphenylphosphane and Ag(NCF_3)_2 in 60 % yield and characterized, in detail (Figure 3). In contrast to [(Ph_3P)_2Ag(NCF_3)_3] (2b), the respective copper(I) complex [(Ph_3P)_2Cu(NCF_3)_3] (1b) does not react with an excess of triphenylphosphane to result in a complex salt and 1b was obtained even in the presence of a twofold excess of Ph_3P in 78 % yield.

The copper(I) and silver(I) bis(trifluoromethyl)amido complexes are thermally stable with decomposition temperatures ranging from 114 to 204 °C (onset, DSC measurements). The solid complexes can be stored in a glove box in an inert atmosphere for more than one year without noticeable decomposition and they can be manipulated in air for a short period of time enabling a convenient handling.

The coordination of the bis(trifluoromethyl)amido ligand to copper in 1a–1e and to silver in 2a–2c and 2f in the solid state is evident from single-crystal X-ray diffraction (SC-XRD) analyses, which are the first examples for SC-XRD studies on N(CF_3)_3 coordination compounds (Figures 2 and 3 and Table S5 in the Supporting Information). The metal-nitrogen distances depend on the coordination number of the metal center. So, d(Cu–N(CF_3)_3) is 1.900(9)–2.004(8) Å in the tricoordinate complexes 1a, 1b, and 1d but 2.0654(16) and 2.1012 Å in four-coordinate 1c and 1e, respectively. As expected from the slightly smaller covalent radius of copper (1.32 Å for Cu vs. 1.45 Å for Ag), the metal–N(CF_3)_3 distance is longer in the silver(I) complexes with 2.138(2) and 2.255(4) Å for tricoordinate complexes 2a and 2b and 2.330(5) and 2.233(3) Å for the four-coordinate derivatives 2c and 2f. The crystal structure of 3 proves the ionic nature of the complex salt (Figure 3). The N(CF_3)_3^− ion, which was until now not characterized by SC-XRD, at all, is disordered over two positions precluding a detailed discussion of bonding parameters.

All copper(I) and silver(I) N(CF_3)_3 derivatives were characterized by multinuclear NMR, IR, and Raman spectroscopy, as well as by elemental analysis. The 19F NMR signal of the complexes is in the range from –40.7 to –43.7 ppm, which is similar to δ(19F) of Ag(NCF_3)_3 and Cu(NCF_3)_3 in CD_2CN with –42.1 and –43.4 ppm, respectively. The signal of Rb(NCF_3)_3 in CD_2CN is observed at a significantly lower chemical shift of –37.5 ppm (Figure S17). Thus, the interaction between the coinage metal and the N(CF_3)_3^− ligand in solution is evident.

![Figure 3. Synthesis and crystal structures of the silver(I) complexes 2a–2c, 2f and of the complex silver(I) salt 3 (thermal ellipsoids set at 25 % probability; H atoms are omitted for clarity; C atoms of the N- and P-donor ligands are depicted as stick models).](image)
from the $^{19}$F NMR spectroscopic data. The signal of the complex salt $[\text{Ag(PPh}_3]_2\{\text{N(CF}_3)_2\}$ (3) in CD$_2$Cl$_2$ is observed at $-39.6$ ppm, which, in turn, is indicative for the ionic nature that was proven by the SC-XRD study. Solid state $^{19}$F NMR spectra reveal an even more pronounced difference for $\delta_{iso}(^{19}$F) with $-31.6$ and $-34.6$ ppm for the salt 3 and $-40.4$ and $-41.4$ ppm for the complexes [(Ph$_3$P)$_2$Ag{N(CF$_3$)$_2$}] (2b) and [(Ph$_3$P)$_2$Cu{N(CF$_3$)$_2$}] (1b) (Figure S19). The $^{31}$P and $^{13}$C solid state NMR spectra of 3 and 2b also reveal the different bonding situations in the two related silver(i) bis(trifluoromethyl)amido complexes. Especially, the smaller $^{31}$J(Ag$^{19}$F) coupling constants observed for 3 are indicative for a four-coordinate complex whereas larger $^{31}$J(Ag$^{13}$P) hint towards a three-coordinate silver complex in case of 2b (Figure S18).[34]

The bis(triphenylphosphane) complexes 1b and 2b were studied by diffusion-ordered spectroscopy (DOSY) in CD$_3$CN and CD$_2$Cl$_2$ (Table S7). The diffusion constants derived from the $^1$H and $^{19}$F NMR measurements on samples dissolved in CD$_2$Cl$_2$ are very similar. The hydrodynamic radii of 1b ($^1$H DOSY: 6.15 Å; $^{19}$F DOSY: 5.97 Å) and 2b ($^1$H DOSY: 6.16 Å; $^{19}$F DOSY: 6.00 Å) calculated from diffusion constants using a modified Stokes-Einstein equation, are close to radii estimated from the crystal structures (1b: 5.07 Å; 2b: 5.08 Å; see Supporting Information for a detailed description). Thus, it can be concluded that 1b and 2b remain intact in CD$_2$Cl$_2$. In contrast, in CD$_3$CN the diffusion constants derived from the $^1$H NMR signal of the PPh$_3$ ligands and from the $^{19}$F NMR signal of the N(CF$_3$)$_2$- ligand are significantly different. However, the diffusion constant of the unbound N(CF$_3$)$_2^-$ ion ($D(^{19}$F) = 24.04 · 10$^{-10}$ m$^2$ s$^{-1}$) derived from a DOSY study on 3 in CD$_3$CN is much larger than $D(^{19}$F) measured for 1b (17.48 · 10$^{-10}$ m$^2$ s$^{-1}$) and 2b (14.65 · 10$^{-10}$ m$^2$ s$^{-1}$) in the same solvent. These data indicate an equilibrium between coordinated and free N(CF$_3$)$_2^-$ in solutions of 1b and 2b in CD$_3$CN as $D(^{19}$F) is an averaged value since $\text{N}^{\text{--}}\text{CF}_3$ distances in 5 (1.399(5) Å) and 7 (1.409(3) Å) are longer than in the coinage metal(I) complexes (ca. 1.35 Å).

The reaction of 2-bromoacetophenone with [(bpy)Cu(N(CF$_3$)$_2$)] (1a) was screened in acetonitrile, dichloromethane, N,N-dimethylacetamide (DMAC), toluene, pyridine, and THF. The highest yield for 7 was observed in CD$_3$CN. In dichloromethane and DMAC significantly lower yields were obtained and in toluene, pyridine, and THF almost no conversion to 7 was observed by $^{19}$F NMR spectroscopy (Table S1).

2-Bis(trifluoromethyl)amino acetate (8a) was isolated in 56% yield (Figure 5). Its conversion into ethyl N,N-bis(trifluoromethyl)glycine (8b) was described, earlier.[39] The synthesis of 8b was repeated and the fluorinated amino acid was characterized by SC-XRD for the first time. Two formula units of 8b form dimers in the solid state via a cyclic H-bond motif with $d(O\cdotsO') = 2.679(3)$ Å that are located on a center of inversion (Figure 5).

The conversion of ethyl bromoacetate into 8a using different copper(i) and silver(i) bis(trifluoromethyl)amido complexes was monitored by $^{19}$F NMR spectroscopy in CD$_3$CN using...
benzotrifluoride as internal reference (Table 1). Especially, the complexes with 2,2'-bipyridine and 1,10-phenanthroline were found to be efficient N(CF$_3$)$_2$ transfer reagents and the copper(l) complexes 1a and 1d were identified as most efficient reagents with internal yields of 74 and 75%, respectively. The related silver(l) complex 2a gave ester 8a in significantly lower yield of 54%. Triphenylphosphane complexes are less efficient N(CF$_3$)$_2$ transfer reagents and the amount of 8a formed, dropped with increasing number of PPh$_3$ ligands at copper(l) or silver(l). The lower yields were accompanied with an increasing amount of side products. A major side product was identified as Ph$_2$PF$_3$ that was confirmed by $^{19}$F and $^{31}$P NMR spectroscopy in the reaction mixtures. Most of the phosphorane formed crystallized from the CD$_3$CN solutions upon cooling to room temperature and a single crystal of Ph$_2$PF$_3$ was characterized by X-ray diffraction (Figure S16).

The lower yield of ester 8a starting from [[bpy]Ag(N(CF$_3$)$_2$)] (2a) compared to [[bpy]Cu(N(CF$_3$)$_2$)] (1a; Table 1), tempted us to perform a comparative study on nucleophilic substitution reactions using complexes 1a and 2a (Table S2). Similar to the syntheses of 8a, lower yields were observed for reactions using the silver(l) complex 2a. The reactions studied include the synthesis of benzylbis(trifluoromethyl)amine 4 starting from benzylbromide and benzylidazole as well as the formation of 7 starting from the respective bromide. Furthermore, the conversion of allylbromide into allylbis(trifluoromethyl)amine (10) showed a much lower yield for (CF$_3$)$_2$NCH$_2$CH$_2$ (10) in case of the reaction from 2a (38%) compared to 1a (75%).

The further potential of the coinsage metal(l) complexes as bis(trifluoromethyl)amination reagents was demonstrated by the conversion of 4-fluorobenzenediazonium tetrafluoroborate into 1-fluoro-4-bis(trifluoromethyl)amino benzene (9) with [[bpy]Cu(N(CF$_3$)$_2$)] (1a) in 34% yield as assessed by $^{19}$F NMR spectroscopy (Scheme 1). An analogous Sandmeyer reaction resulting in 9 was reported in the literature$^{[40]}$ starting from the corresponding 4-fluorobenzenediazonium bis(trifluoromethyl) amide and a copper(l) salt with a yield of 43%$^{[51]}$. However, the preformation of the diazonium bis(trifluoromethyl)amide salt is inconvenient compared to a reaction with a stable and storable metal complex of the N(CF$_3$)$_2$ ligand. Furthermore, the addition of elemental copper was necessary to get any product. Preliminary results indicate a higher yield of 9 for the reaction of 4-fluorobenzenediazonium tetrafluoroborate with 1a, as well.

The first copper(l) and silver(l) bis(trifluoromethyl)amido complexes using stabilizing N- and P-donor ligands have been obtained in high yield starting from CF$_3$SO$_2$N(CF$_3$)$_2$, which is easily accessible by electrochemical fluorination (ECF). The complexes have unprecedented stabilities that allow for a long-term storage and easy handling. This is a prerequisite for their application as bis(trifluoromethyl)amination reagents. The potential of these complexes, especially with pyridine-type ligands, to serve as convenient N(CF$_3$)$_2$ transfer reagents was demonstrated by nucleophilic substitution reactions and a Sandmeyer reaction.

### Table 1. Reactivity screening of copper(l) and silver(l) bis(trifluoromethyl)amido complexes with ethyl bromoacetate to give 2-bis(trifluoromethyl)amino acetate (8a).$^{[a]}$

| Complex | Yield [%] |
|---------|-----------|
| 1 [[bpy]Cu(N(CF$_3$)$_2$)] | 75 |
| 2 [[phen]Cu(N(CF$_3$)$_2$)] | 74 |
| 3 [[phen][Ph,P]Cu[N(CF$_3$)$_2$)] | 33 |
| 4 [[phen][Ph,P]Cu[N(CF$_3$)$_2$)] | 39 |
| 5 [[Ph,P]Cu[N(CF$_3$)$_2$)] | 8 |
| 6 [[bpy][Ph,P]Ag[N(CF$_3$)$_2$)] | 54 |
| 7 [[bpy][Ph,P]Ag[N(CF$_3$)$_2$)] | 28 |
| 8 [[Ph,P]Ag[N(CF$_3$)$_2$)] | 7 |

[a] The reactions were performed in Young NMR tubes and monitored by $^{19}$F NMR spectroscopy using equimolar amounts of the coinage metall(1) complex and ethyl bromoacetate. The internal yields were determined with benzotrifluoride as standard.

### Scheme 1. Sandmeyer-type reaction of 1d giving 9 (yield of 9 determined by $^{19}$F NMR spectroscopy with benzotrifluoride as internal standard).

### Experimental Section

**Single-crystal X-ray diffraction**

Single-crystal X-ray diffraction: Deposition Numbers 2051510-2051523, 2052134 and 2055702 contain the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service www.ccdc.cam.ac.uk/structures.

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### Conflict of Interest

The authors declare no conflict of interest.

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