Structure of Bis(trifluoromethyl)cuprate and Its Role in Trifluoromethylation Reactions

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An equilibrium between [(SIMes)Cu-CF_3] (**1**, SIMes = 1,3-dimesitylimidazolin-2-ylidene) and the cuprate salt [$(SIMes)_2Cu$][$(CF_3)_2Cu$] (**2**) was observed. Synthetic methods to prepare and isolate **2** are reported. Trifluoromethylations using equilibrium mixtures of **1** and **2** occur readily for aryl iodides and even occur for aryl bromides at 90 °C. Kinetic data suggest the cuprate form does not play a significant role in trifluoromethylations using *N*-heterocyclic carbene complexes of copper.

Introduction

Traditional medicinal chemistry was very much based on the use of natural products or closely related derivatives thereof.[1] Because only a handful of naturally occurring organofluorines were (and still are) known to exist, the use of fluorinated compounds was extremely rare in early medicinal chemistry.[1] This situation has changed quite dramatically over the last 20 years. Today, as many as 30−40% of agrichemicals and 20% of pharmaceuticals on the market are estimated to contain fluorine, including three of the top eight drugs sold in 2007.[2,3] As developmental pipelines for new drugs are predicted to contain an even higher percentage of fluorinated molecules,[3] developing better methods to prepare organofluorines are expected to be paramount to the health industry.

Organofluorines containing fluoroalkyl groups represent an important subset of industrially important molecules,[4] and the trifluoromethyl group represent the simplest of these fluoroalkane moieties. The development of mild catalytic methods for the trifluoromethylation of aryl halides has been remarkably challenging, and no catalytic processes that are wide in scope are currently available.

We have recently communicated that *N*-heterocyclic carbene (NHC) ligands can stabilize trifluoromethyl complexes of copper, and that these new complexes are efficient and reliable reagents for trifluoromethylation of organic iodides.[5] The recent observation that copper complexes of the IPr and SI*i*Pr (IPr = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene; SI*i*Pr = 1,3-di-*i*-propylimidazolin-2-ylidene) ligands showed dramatic differences in their ability to trifluoromethylate organic halides[5] prompted us to explore the reactivity of an NHC ligand that was intermediate in steric bulk,[6] such as SIMes. The use of this ligand provides clean access to a surprising new cuprate species, and the details of its dynamics and reactivity are reported herein.

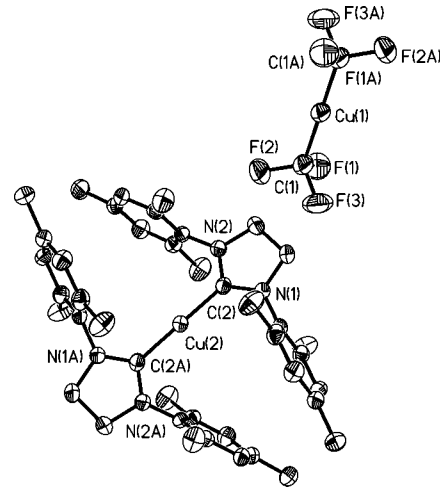

Figure 1. ORTEP diagram of **2**. Ellipsoids shown at the 40% level. Hydrogens are omitted for clarity. Selected bond lengths (Å): Cu(1)− C(1) 1.970 (6), Cu(2)−C(2) 1.959 (5). Selected bond angles (°): C(1A)−Cu(1)−C(1) 180.0(3), C(2)−Cu(2)−C(2A) 179.3(3).

Results and Discussion

Upon treatment of (SIMes)Cu−O*t*Bu with Me_3SiCF_3, a new resonance appeared in the ^{19}F NMR spectrum at δ −33 (25 °C, THF-d_8), which we attribute to the desired (SIMes)Cu-CF_3 (**1**) based on the identical chemical shift values observed for the IPr- and SI*i*Pr-derived complexes. However, unique to the SIMes derivative, an equilibrium in THF solvent is established (∼100 h to reach equilibrium at 25 °C) with another species that has a chemical shift of δ −31.5. The new species was insoluble in toluene, which permitted its separation from (SIMes)Cu−CF_3. Analysis of crystals of this new species by X-ray crystallography revealed its structure to be the cuprate salt [$(SIMes)_2Cu$][$(CF_3)_2Cu$] (**2**) (Figure 1). The X-ray structure reveals that a quite unusual ligand redistribution occurred affording a linear biscarbene cationic complex of copper paired together with the linear bis(trifluoromethyl)cuprate. The Cu−CF_3 bond length of 1.970(6) in **2** is quite longer than the Cu−CH_3 bond length found in a dimethyl cuprate (1.935(8) Å).[7]

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Scheme 1. Room Temperature Equilibrium between 1 and 2

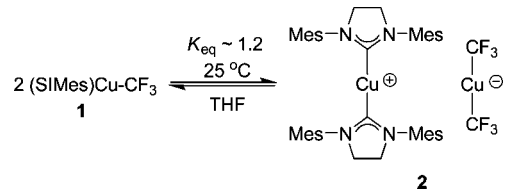
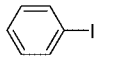
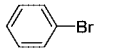
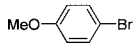


Table 1. Trifluoromethylations with 2 and 3 in Neat Aryl Halide Solution

Starting Material	*Temp (°C)*	*Time (h)*	*% Yields using 2 (0.029M)*	*% Yields using 3 (0.058 M)*
	25	4.5	99	48
	90	15	72	71
	85	2	72	37

Interestingly, a homoleptic $[Cu^{III}(CF_3)_4]$ ionic species is known[8] and the average $Cu-CF_3$ bond lengths (1.967(6) Å) are quite similar to those in **2**.

We found only two reports that mention the generation of bis(trifluoromethyl)cuprate *in situ*,[9,10] and no one has been able to separate out its properties or reactivity from other copper species present. As the solubility properties of **2** in the current system facilitated its isolation from **1**, a preliminary description of its solution chemistry can be established. Indeed, dissolution of X-ray quality crystals of **2** in THF solvent verified the equilibrium with **1** (Scheme 1). ^{19}F NMR analyses of the equilibrium provides an estimate a K_{eq} of ~1.2 at 25 °C, only slightly favoring the cuprate form.[11]

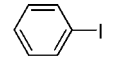
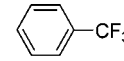
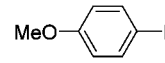
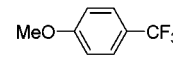
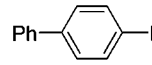
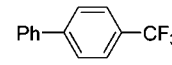
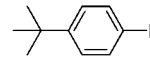
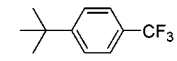
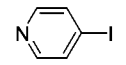
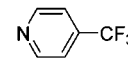
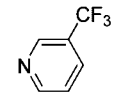
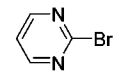
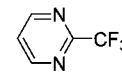
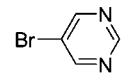
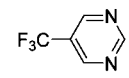
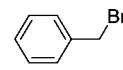
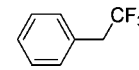
Complex **2**, in the solid state, was found to be quite stable, especially relative to the thermally sensitive [(SI*i*Pr)Cu-CF_3] (**3**) complex reported in previous studies,[5] and no decomposition over extended time periods was observed. Screens performed in neat aryl halide demonstrated that the cuprate is also an active precatalyst for trifluoromethylation reactions (Table 1). Use of aryl halide substrate as solvent even permitted the trifluoromethylation of electron rich aryl bromides (Table 1). Under these conditions, it appears that the SIMes ligand promotes better reactivity than SI*i*Pr.

Optimal conditions to suppress the formation of $Cu-CF_2CF_3$ species[5] in reactions performed under dilution of organic halide (Table 2) involved the use of benzene/DMI solvent (DMI = 1,3-dimethyl-2-imidazolidinone). Under these conditions, a variety of organic iodides and select organic bromides could be reliably trifluoromethylated.

Because of the equilibrium described in Scheme 1, it is difficult to ascertain if the active species in the trifluoromethylations is the neutral (NHC)$Cu-CF_3$ complex or the cuprate salt. However, we have determined that the *rates of trifluoromethylations using both (SIiPr)Cu−CF_3 and [(SIMes)$_2$Cu][(CF$_3$)$_2$Cu] in neat phenyl iodide at 25 °C increase upon decreasing concentration of initial copper complex* in the concentration range of 0.007−0.029 M (Figure 2). Assuming concentration dependent equilibria, *these data suggest that the cuprate form is not the active species in trifluoromethylation reactions with (NHC)Cu−CF_3 complexes at room temperature.* The SIMes derivative shows the greater rate enhancement upon decreasing concentration due to the larger K_{eq} with the cuprate, and the observed enhancements support an equilibrium for the neutral species **3** in PhI solvent. Since solvent effects are known to dramatically alter the dynamics and reactivity of organocuprates,[12,13] it was important to establish that unusual solvent effects from neat phenyl iodide were alone not responsible for the rate changes. Monitoring the trifluoromethylations in neat phenyl iodide by ^{19}F NMR spectroscopy indeed determined that similar equilibria with the cuprate form were still evident (see Supporting Information). For example, with complex **2** the [cuprate]/[neutral species] was determined to be 1.3 favoring the cuprate form (after one hour in Ph−I solvent using an initial cuprate concentration of 0.029 M).

The redistribution of ligands to form cuprate salts may be a common feature of organometallic copper carbene complexes. For example, Gunnoe found that thermolysis of [(IMes)Cu-Me]

Table 2. Trifluoromethylations of Aryl Halides Using Solid [(SIMes)$_2$Cu][(CF$_3$)$_2$Cu] (2)[a] as the Starting Material

Entry	*Starting Material*	*Product*	*Yield %*
1			86
2			89
3			93
4			70
5			57
6			88
7			77
8			0
9			36

[a] Benzene/DMI solvent (7.5/1.5), 50 °C, 28 h, **2** (0.025 M). Yields were determined by ^{19}F NMR spectroscopy relative to 1,3-dimethyl-2-fluorobenzene as an internal standard. Yields are based on copper complex as the limiting reagent.

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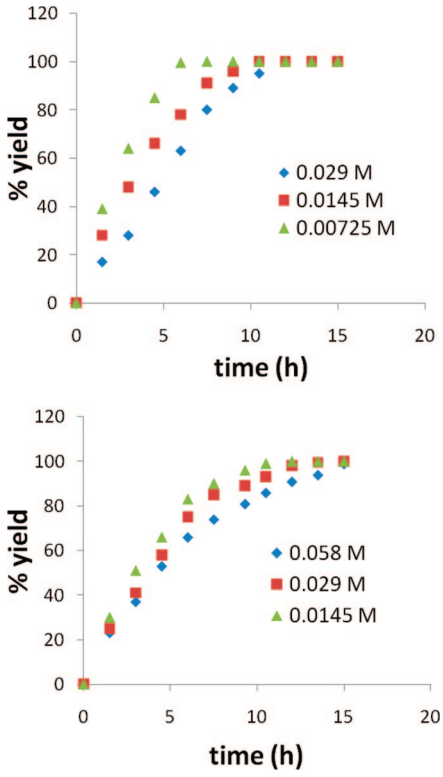

Figure 2. Plot of yields of Ph-CF_3 vs time for reactions of **2** (top) and **3** (bottom) in neat Ph−I solvent.

indeed leads to ethane formation via a nonradical bimolecular pathway that was undetermined.[14] Thus, the formation and stability of the bis(trifluoromethyl)cuprate presented here may shed light into related intermediates that may otherwise be fleeting.

Experimental Section

General Considerations. All manipulations were performed using standard Schlenk and high-vacuum techniques[15] or in a nitrogen-filled dry box, unless otherwise noted. Solvents were distilled from Na/benzophenone or CaH_2. All reagents were used as received from commercial vendors unless otherwise noted. Celite was dried at 200 °C under vacuum for two days prior to use. ^{1}H NMR spectra were recorded at ambient temperature (unless otherwise noted) on a Varian Oxford 300 MHz spectrometer and referenced to residual proton solvent peaks. ^{19}F spectra were recorded on the Varian Oxford spectrometer operating at 282 MHz and were referenced to $CFCl_3$ set to zero. A Rigaku SCXMini diffractometer was used for X-ray structure determinations.

Preparation of (SIMes)Cu-OtBu. A suspension of [(SIMes)-CuCl][16,17] (811 mg, 2 mmol) and *t*-BuOK (224 mg, 2 mmol) in 20 mL THF was stirred for 2 h at room temperature and then filtered through a pad of Celite. The Celite was washed two times with 5 mL of THF. The filtrate was evaporated on a high vacuum line and the resulting white residue was washed with pentane and filtered. Yield 89%. ^{1}H NMR (25 °C, C_6D_6): δ 1.31 (s, 9H), 2.10 (s, 6H), 2.12 (s, 12H), 2.96 (s, 4H), 6.71 (s, 4H).

Preparation of $[(SIMes)_2Cu][Cu(CF_3)_2]$ (2). A solution of (SIMes)Cu−O *t*Bu (390 mg, 0.882 mmol) and $CF_3Si(CH_3)_3$ (0.260 mL, 1.76 mmol) in 15 mL THF was stirred at room temperature. The conversion was monitored by ^{19}F NMR spectroscopy, and after 21 h the volatiles were evaporated using a high vacuum line. The white residue was filtered and washed four times with 5 mL toluene and pentane. Yield of $[(SIMes)_2Cu][Cu(CF_3)_2]$ was 67%. ^{1}H NMR (25 °C, CD_2Cl_2): δ 1.83 (s, 12H), 2.38 (s, 6H), 3.80 (s, 4H), 6.89 (s, 4H). ^{19}F NMR (25 °C, CD_2Cl_2):δ −31.33 (s, 3F). ^{1}H NMR (THF-d_8): δ 1.88 (s, 12H), 2.38 (s, 6H), 3.88 (s, 4H), 6.93 (s, 4H). ^{19}F NMR (25 °C, CD_2Cl_2): δ −31.54 (s, 3F).

NMR Spectra of $[(SIMes)CuCF_3]$ Present in Solutions of 2. ^{1}H NMR (THF-d_8): δ 2.29 (s, 6H), 2.35 (s, 12H), 4.01 (s, 4H), 6.99 (s, 4H). ^{19}F NMR (THF-d_8): δ −32.97 (s, 3F).

Experimental Procedure for Reactions in Table 1. An NMR tube was sealed with (SI*i*Pr)$CuCF_3$ (16.7 mg, 0.058 mmol) or $[(SIMes)_2Cu][Cu(CF_3)_2]$ (26 mg, 0.029 mmol), internal standard (10 ul, 0.07957 mmol) in 1 mL of corresponding aryl halide and kept at the appropriate temperature. Yields were determined by ^{19}F NMR spectroscopy relative to 1,3-dimethyl-2-fluorobenzene as an internal standard. Yields are based on copper as the limiting reagent.

Experimental Procedures for Reactions in Table 2. $[(SIMes)_2Cu][Cu(CF_3)_2]$ (99 mg, 0.1125 mmol) was dissolved in a mixture of 7.5 mL benzene, 1.5 mL DMI and internal standard (50 ul, 0.3979 mmol). Then 1 mL aliquots (0.0125 mmol) were taken for each reaction and 0.125 mmol, 5 equiv (for each trifluoromethyl group) of corresponding aryl halide was added. Reaction mixtures were placed in sealed NMR tubes and kept at 50 °C in an oil bath. Yields were determined by ^{19}F NMR spectroscopy relative to 1,3-dimethyl-2-fluorobenzene as an internal standard. Yields are based on copper as the limiting reagent.

Acknowledgment. D.A.V. thanks the Office of Basic Energy Sciences of the U.S. Department of Energy (DE-FG02-07ER15885) for support of this work.

Supporting Information Available: NMR spectra of all new compounds and crystallographic data for **2**. This material is available free of charge via the Internet at http://pubs.acs.org.

OM800794M

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