

Active Trifluoromethylating Agents from Well-Defined Copper(I)–CF₃ Complexes

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Fluorocarbons are becoming increasingly important in the medicinal, materials, and agricultural fields.^{1–4} The ability of fluorinated molecules to modulate biological functions may not be surprising at first glance, as fluorine ranks 13th on the most naturally abundant elements list. However, only a handful of naturally occurring fluoroorganic molecules have ever been reported.⁵ Thus, the vast majority of organofluorine compounds are manmade. Consequently, synthetic methodology to incorporate fluorine and fluorosynthons must be improved in order to prepare sophisticated fluoroorganic molecules on a practical scale. There is an incredible commercial driving force for improving fluorination reactions, as three of the top eight selling drugs in 2007 contained fluorine, including two out of the top three.⁶

Cross-coupling procedures would greatly facilitate the construction of fluoroorganic molecules; however they have been slow to develop. Fluoro-alkyl cross-coupling methods, in particular, are severely lacking. This gap in synthetic methodology parallels the fact that only recently have chemists been able to effect cross-coupling reactions using simple alkyl electrophiles and alkyl nucleophiles.^{7,8}

Copper, by far, has shown the most promise in trifluoromethylation reactions. However, the copper reactions have been plagued by unreliability, the need to use extremely high temperatures,^{9–12} toxic or expensive sources of the CF₃ group,^{13–17} and competing Ullmann coupling and reduction of aryl halides that generally provide lower yields of fluorinated product. Most of the copper couplings reported to date also involved the generation of “Cu–CF₃” in situ, making it more difficult to understand and control what was happening at the copper center. We therefore sought to prepare a well-defined Cu^I–CF₃ complex in order to systematically study its reactivity with organic halides.

We found the procedure outlined in eq 1 to be the most successful synthetic approach to a stable Cu^I–CF₃ complex. Surprisingly when CF₃–SiMe₃ was added to the known NHC copper complex **1**,¹⁸ not only was the desired CF₃ group attached to copper (¹⁹F NMR, C₆D₆, δ –33.7) but the ¹H NMR data also suggested incorporation of the trimethylsilyl group into the major product. (A ~80:20 ratio of **2** to the unsilylated (IPr)Cu–CF₃ was observed by NMR spectroscopy). The crystal structure of **2** is shown in Figure 1, and the X-ray data confirms that the NHC ring was indeed silylated at the 4-position of the imidazole ring (eq 1). This remarkable silylation reaction is akin to that observed by Arnold and co-workers, who found that treatment of the neodymium complex **3** with I–SiMe₃ led to the neodymium iodide dimer **4** (eq 2).¹⁹

Complex **2**, to our knowledge, is the first example of an isolable copper(I)–trifluoromethyl complex. Burton reported NMR evidence

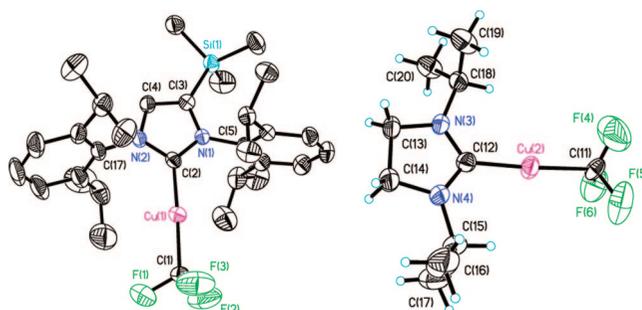
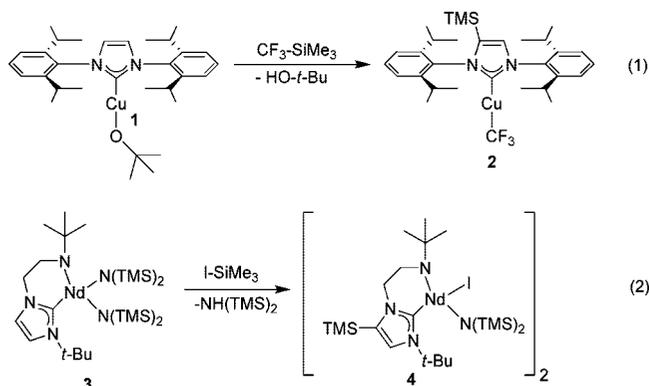


Figure 1. ORTEP diagrams of **2** (left) and **6** (right). Ellipsoids are shown at the 50% level. Selected bond lengths for **2** (Å): Cu(1)–C(2), 1.902(6); Cu(1)–C(1), 1.967(6); C(3)–C(4), 1.356(7); Si(1)–C(3), 1.888(7). Selected bond angles for **2** (deg): C(2)–N(2)–C(17), 125.5(2); C(2)–N(1)–C(5), 124.2(3); C(2)–Cu(1)–C(1), 176.71(11); C(3)–N(1)–C(5), 122.9(3); C(4)–N(2)–C(17), 123.3(3). Selected bond lengths for **6** (Å): Cu(2)–C(12), 1.906(4); Cu(2)–C(11), 2.022(4). Selected bond angles for **6** (deg): C(12)–Cu(2)–C(11), 176.72(17); N(3)–C(12)–Cu(2), 127.0(3); C(12)–Cu(2), 124.2(3); C(12)–N(4)–C(15), 124.5(3).

for solvated Cu^I–CF₃ at –50 °C;²⁰ however, decomposition was observed at higher temperatures. Importantly, Burton also noted that the thermal instability and nature of the decomposition products demonstrated that solvated Cu^I–CF₃ is more complex (in terms of aggregation) than previously appreciated, and that control of nuclearity can have significant consequences in the ability to control fluoroalkylations.²⁰ Here we report that the steric bulk of the carbene ligand in **2** rigorously controls the nuclearity, even in solution, as no evidence of dimers or higher aggregates are observed by NMR spectroscopy. The Cu–CF₃ bond length of 1.967 (6) Å in **2** is slightly longer than the Cu–CH₃ bond length of 1.913 (6) Å in the previously reported (IPr)Cu–CH₃ complex.²¹ Moreover, the Cu–C_{carbene} bond length in **2** (1.902(6) Å) is also longer than that for (IPr)Cu–CH₃ (1.887(5) Å).



As a promising lead, reaction of **2** with Ph-I (neat) at room temperature for 44 h led to Ph–CF₃ in 33% yield based on copper.

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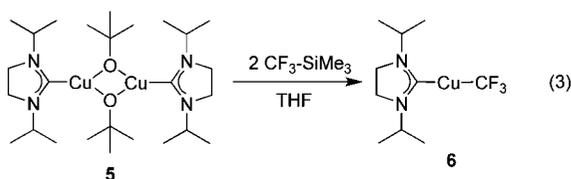
Table 1. Trifluoromethylations Mediated by **5** in DMF Solvent²⁵ Compared to Yields Using Cu–I and KF in Place of **5**^b

Entry	Starting Material	Product	Yields (%)	Yields using the Cu–I, KF protocol
1			94	25
2			91	62
3			99	41
4			99	70
5			94	3 ^a
6			58	29

^a: a white precipitate was observed ^b Yields were recorded after 112 h and measured by ¹⁹F NMR relative to 1,3-dimethyl-2-fluorobenzene as an internal standard. Yields are based on copper as the limiting reagent.

Upon heating, product formation is competitive with decomposition to a brown solid and the formation of an LCu–CF₂CF₃ species and Me₃Si–F as detected by ¹⁹F NMR spectroscopy. Similar fluorocarbon chain elongation had been observed by Burton upon warming solvated Cu^I–CF₃ solutions.²⁰

The presence of Me₃Si–F as a decomposition product in the reaction of **2** with aryl halides suggests that the silylated carbene ring is undesirable in trifluoromethylation reactions. With that in mind, we targeted the use of carbene ligands containing a saturated backbone, like SI*i*Pr shown in complex **5** (eq 3). The SI*i*Pr ligand also has the feature of being less sterically demanding than SIPr,²² which is desired to facilitate interactions with organic halides. Evidence of greater accessibility to the copper center with the SI*i*Pr ligand is seen by the fact that **5** exists as a dimer in the solid state (see Supporting Information), whereas **1** is monomeric.¹⁸ Complex **5** can be converted to the extremely air-sensitive **6** (¹⁹F NMR (C₆D₆) δ –33.1) upon treatment with CF₃–SiMe₃ with no evidence of TMS incorporation into the carbene ring. X-ray crystallographic analysis verifies the structure, and an ORTEP is shown in Figure 1.



The reactivity of both **5** and **6** with a variety of organic halides under similar reaction conditions was established. In THF solvent, both **5** (plus 2 equiv TMS–CF₃) and **6** were effective trifluoromethylating agents, and both afforded R–CF₃ products with similar yields (see Supporting Information). The efficiency of the trifluoromethylation reactions can be greatly enhanced by the use of DMF solvent, and Table 1 shows that the yields of trifluoromethylated products under these conditions are consistently in the 90% range. The state-of-the-art methods prior to these reports have used TMS–CF₃/Cu–I/KF with the absence of ligands on copper, either

at room temperature²³ or at 80 °C.²⁴ For comparison, runs employing the TMS–CF₃/Cu–I/KF system were performed under the same conditions as our runs using complex **5** as a catalyst precursor, and the results are provided in Table 1. Not only are the yields higher with the well-defined SI*i*Pr ligand (sometimes up to four times higher), but they are also consistent for a variety of aryl iodides. Catalytic conditions using 1 equiv of KO*t*-Bu to regenerate complex **5** were ineffective, as KO*t*-Bu reacts with TMS–CF₃ at a background rate which is too fast (CF₃H was determined to be the main product under catalytic conditions). If a nucleophile can be developed to preferentially transmetalate copper into a species that reacts with TMS–CF₃, then catalysis may be possible at copper. We have shown that ligand supported Cu–CF₃ complexes are stable enough that decomposition can be avoided over long reaction times.

In conclusion, we have shown that the first thermally stable and well-defined LCu(I)–CF₃ complexes can efficiently trifluoromethylate organic halides under mild conditions. Ligand choice is important, since it was shown that an unsaturated NHC may undergo silylation in the presence of TMS–CF₃. The ligand effects also demonstrate that copper can be rationally tuned with supporting ligands to afford trifluoromethylating reagents that are more reliable than any method reported to date. Further explorations in ligand and reagent design may render catalytic reactions at copper possible.

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Supporting Information Available: General experimental procedures and crystallographic data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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