Fluorocarbons are becoming increasingly important in the medicinal, materials, and agricultural fields. 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. Thus, the vast majority of organofluorine compounds are manmade.

Consequently, synthetic methodology to incorporate fluorine and fluorous synthons 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.

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.

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, 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 involved the generation of toxic or expensive sources of the CF₃ group, and competing nucleophiles. Consequently, synthetic methodology to incorporate fluorine and fluorinated fluoroalkylation reaction products 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.

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.
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 trifluoromethyllating 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 at copper, either at room temperature or at 80°C. 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 SIPr ligand (sometimes up to four times higher), but they are also consistent for a variety of aryl iodides. Catalytic conditions using 1 equiv of KOt-Bu to regenerate complex 5 were ineffective, as KOt-Bu reacts with TMS–CF₃ at a background rate which is too fast (CF₃-H 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.

References


[26] Although no DMF-CF₃ adducts were detected by ¹⁹F NMR, we cannot rule out their existence at this time. Mechanistic studies of the trifluoromethylation reactions with 6 are underway.

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