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J. Am. Chem. Soc., **Just Accepted Manuscript** • Publication Date (Web): 25 Jan 2019

Csp^3-Csp^3 Bond-Forming Reductive Elimination from Well-Defined Copper(III) Complexes

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KEYWORDS trifluoromethyl • reductive elimination • high-valent copper • DFT calculation • organometallic reactions

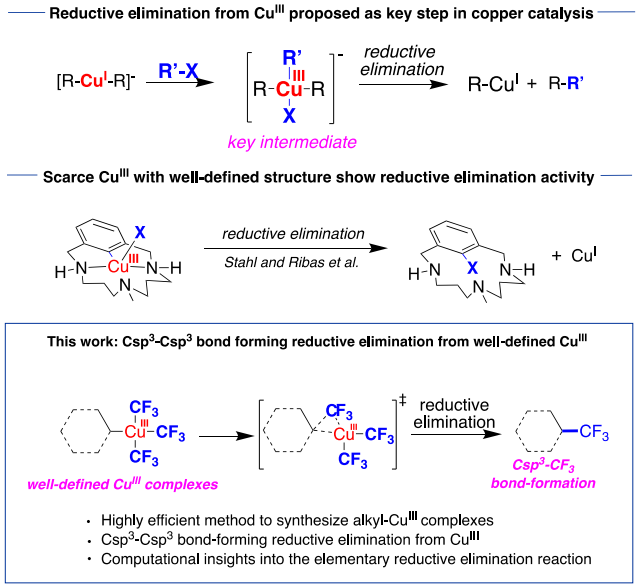
ABSTRACT: Carbon-carbon bond-forming reductive elimination from elusive organocopper(III) complexes has been considered the key step in many copper-catalyzed and organocuprate reactions. However, organocopper(III) complexes with well-defined structures that can undergo reductive elimination are extremely rare, especially for the formation of Csp^3-Csp^3 bonds. We report herein a general method for the synthesis of a series [alkyl-Cu^{III}-$(CF_3)_3$]$^-$ complexes, the structures of which have been unequivocally characterized by NMR, mass spectrometry and X-ray crystal diffraction. At elevated temperature, these complexes undergo reductive elimination following first-order kinetics, forming alky-CF_3 products with good yields (up to 91%). Both Kinetic studies and DFT calculations indicate that the reductive elimination to form Csp^3-CF_3 bonds proceeds through a concerted transition state, with a $\Delta H^{\ddagger}$=20 kcal/mol barrier.

INTRODUCTION

As an inexpensive, earth-abundant and non-toxic metal, copper has found a wide range of applications in homogenous catalysis, allowing for the construction of important pharmaceuticals, materials and commodity chemicals.[1-4] High-valent organocopper(III) compounds have long been proposed as key intermediates in many copper-catalyzed reactions, in which the carbon-carbon or carbon-heteroatom bond-forming reductive elimination from Cu^{III} species is considered the final product-releasing step.[5-12] Therefore, significant amounts of work have been conducted to synthesize organocopper(III) complexes and understand their reactivity.[13-21] However, Cu^{III} complexes with well-defined structures remain rather limited and most reported examples were stabilized by rigid macrocyclic chelating ligands or perfluorinated groups,[18, 22-26] few of which provide experimental evidence for reductive elimination of Cu^{III} species to form C-C or C-heteroatom bonds.[27-29] Seminal work by Stahl and Ribas have shown that a series of Cu^{III}-mono-aryl species stabilized by an electron-donating macrocyclic ligand can undergo C-heteroatom bond-forming reductive elimination reactions. The Xi group has recently reported a novel organocopper(III) spiro complex that can undergo intramolecular C-C bond-forming reductive elimination. However, these reported examples require special ligands and/or are limited to specific structures and, as a result, considerable controversy remains over the mechanism of the reductive elimination from Cu^{III} species.

Trifluoromethyl groups (CF_3) have been playing an important role in organocopper(III) chemistry. On one hand, CF_3 groups are known to stabilize Cu^{III} complexes, probably due to the strong Cu^{III}-CF_3 sigma bond and thus the high thermal stability.[30-32] Burton has reported the first crystallographically characterized copper(III) complex, [$Cu^{III}(CF_3)_2(SC(S)NEt_2)$], in 1989.[22] Later, $Cu^{III}(CF_3)_4^-$ anion was first synthesized by Neumann[33] and, very recently, by Grushin using an optimized method.[18] Cu^{III}-CF_3 complexes bearing nitrogen-containing ligands or a methyl group have recently been synthesized by Grushin[18], Zhang[34-36] and Li.[37] On the other hand, the unique properties of CF_3 groups in medicinal chemistry[38-39] have driven the development a large number of copper-promoted C-CF_3 bond-forming reactions.[40-49] In some of these reactions, C-CF_3 bond-forming reductive elimination from Cu^{III} is indicated as the key step.[50-51] However, this elementary reductive elimination step remains poorly understood, especially for the

Csp^3-CF_3 bond-forming reductive elimination. Although aryl-CF_3 bond-forming reductive elimination has been studied on $Pd^{II/IV}$, Ni^{III} and Au^{III} complexes,[4, 52-55] Csp^3-CF_3 bond-forming reductive elimination from any transition metal complexes with well-defined structures remains essentially unknown. Toste has recently reported a formal Csp^3-CF_3 reductive elimination from Au^{III} *via* a fluoride-rebound mechanism.[56] This work represents the first net Csp^3-CF_3 bond-forming reaction from structurally-defined complexes, although the C-C bond is formed via the alkyl-migration pathway. Li's group and our group have shown that a [$Cu^{I}CF_3$] species generated possibly *in situ* via the reductive elimination of a Cu^{III} complex promotes trifluoromethylation of alkyl radicals.[37, 49] However, the reductive elimination is only limited to a methyl-containing copper(III) complex.



Due to the importance of Cu^{III} in copper catalysis and the lack of isolable yet reactive Cu^{III} complexes, development of general methods for the synthesis of structurally-defined organocopper(III) complexes and study their ability for C-C bond-forming reductive elimination will be vital in the progression of Cu-based organometallic chemistry and catalysis. Furthermore, understanding the Csp^3-CF_3 bond-forming reductive elimination from high-valent metal complexes will also help the development of novel alkyl trifluoromethylation reactions, which are highly important in medicinal chemistry but remain less-explored compared to well-developed aryl trifluoromethylation reactions. In this article, we report the design, synthesis and reductive elimination activity of a novel class of organometallic copper (III) complexes, [alkyl-Cu^{III}-$(CF_3)_3$]$^-$, with diverse functional groups. The molecular structures of these complexes have been determined by NMR, MS and X-ray crystal structure. More importantly, these complexes undergo Csp^3-CF_3 reductive elimination, forming the corresponding alkyl-CF_3 products with excellent yields. These copper(III) complexes, for the first time, allow for the study of Csp^3-Csp^3 bond-forming reductive elimination on well-defined copper(III) complexes.

RESULTS AND DISCUSSION

Synthesis and characterizations of [(alkyl)$Cu^{III}(CF_3)_3$]$^-$ complexes. We reason that a [Cu^{III}-CF_3] complex containing a replaceable ligand could serve as the precursor for the [alkyl-Cu^{III}-CF_3] complexes. Thus, we synthesized complex **1,** [$PyCu^{III}(CF_3)_3$] (Py = pyridine), following the literature method.[36] Although the structure of compound **1** with a DMF ligand (**1-DMF**) has been reported, the crystal of compound **1** without additional ligands can be obtained by the slow diffusion of pentane to a DCM solution of **1**. In contrast to the square pyramidal structure of **1-DMF**, crystal structure of **1** adopts the square-planar geometry (**Fig. S1**), with the pyridine ring perpendicular to the plane of copper.

Treating **1** with 1 equiv. of various alkyl zinc reagents at room temperature affords the corresponding [(alky)$Cu^{III}(CF_3)_3$]$^-$ species within 5 mins in nearly quantitative yields (**Fig. 1**). Compound **1** displays two ^{19}F-NMR signals at 38 ppm and 24 ppm, while [(alky)$Cu^{III}(CF_3)_3$]$^-$ complexes show two new peaks at ~ -35 ppm and -36 ppm, with an integral of 1:2, consistent with a planar structure with two inequivalent CF_3 groups. In addition, [(alky)$Cu^{III}(CF_3)_3$]$^-$ display well-resolved ^{1}H-NMR spectrum, consistent with a low spin d^8 configuration of Cu^{III}. For example, the proton of the CH_2 groups connecting to copper in **1a** and **1d** displays chemical shifts at 3.6 and 2.4 ppm, respectively, indicating the moderate electron-deficiency nature of the Cu^{III} center. The moderate stability of these [(alky)$Cu^{III}(CF_3)_3$]$^-$ (hours at r.t. and weeks at -20°C) allowed us to confirm their composition using high-resolution electrospray ionization mass spectrometry (HR ESI-MS). Gratifyingly, these [(alky)$Cu^{III}(CF_3)_3$]$^-$ anions can be easily detected at negative mode with normal ESI parameters (See SI for details). For example, compound **1a** and **1d** show peaks at m/z = 360.9695 and 326.9854, respectively, consistent with the formation of [(benzyl)$Cu^{III}(CF_3)_3$]$^-$ and [(*n*Bu)$Cu^{III}(CF_3)_3$]$^-$ anions.

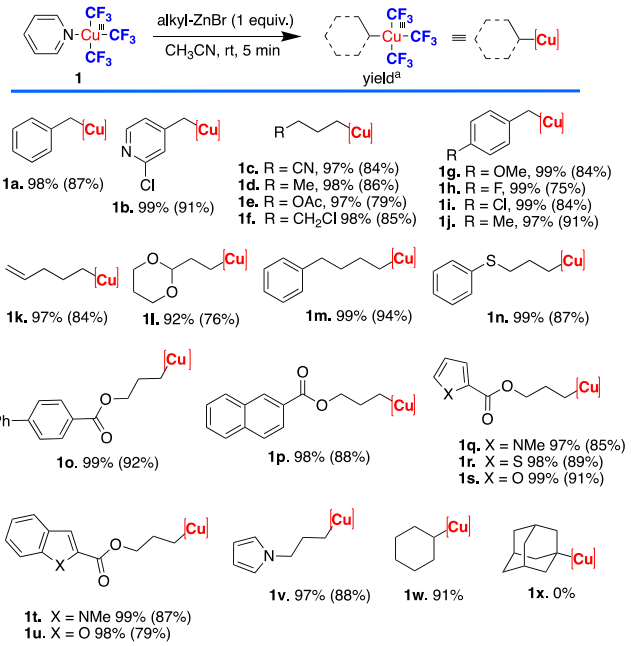


Figure 1. Synthesis of [(alkyl)$Cu^{III}(CF_3)_3$]$^-$ species. Yields determined by ^{19}F-NMR using 1-fluoro-3-nitrobenzene as the internal standard. Isolate yields as $[nBu_4N]^+$ salts are included in parenthesis.

This transmetallation protocol allows for the synthesis of a large variety of [(alkyl)$Cu^{III}(CF_3)_3$]$^-$ complexes (**Fig. 1**). Common functional groups, including alkenyl, nitrile, acetal, thiol ether *etc.* are compatible with the reaction conditions. In

addition, molecules containing different heterocycles are also tolerated under this condition. This method works well for the construction of both primary and secondary alkyl-Cu^{III} species, but our attempts to the synthesis of tertiary alkyl-Cu^{III} species (**1x**) were not successful, probably due to slow transmetallation of **1** with the bulky adamantyl zinc reagent as well as the instability of the resulting Cu^{III} species. Nevertheless, we were able to detect the transient formation of **1x** using HR ESI-MS (**Fig. S2**).

The structures of these Cu^{III} complexes were further confirmed by single crystal X-ray diffraction. One equivalent of tetrabutylammonium bromide (n-Bu_4NBr) was added to the Cu^{III} solutions to form the corresponding $[n\text{-}Bu_4N]^+$ salts, which can be purified by silica gel column chromatography at -78 °C. The crystals of **1a-1c** as $[n\text{-}Bu_4N]^+$ salts were grown by the slow diffusion of pentane into a methylene chloride solution at –20 °C over a week. **1a-1c** display square planar geometry with slight distortion (**Fig. 2**). The bond lengths of Cu^{III}-CF_3 bonds *trans* to the alkyl group are in a range of 1.979 – 1.987 Å, slightly longer than that of Cu^{III}-CF_3 bonds *cis* to the alkyl groups (Cu-C 1.944 -1.961 Å). The bond lengths of Cu-C_{alky} bonds are longer in **1a** and **1b** (1.997(3) Å and 1.988(3) Å), which contain benzyl groups, than that in **1c** (1.956(3) Å). In addition, on the contrary to the perpendicular geometry of pyridine and copper plane in compound **1**, the aryl rings in compounds **1a** and **1b** form V-shape geometry with the copper plane with a dihedral angle of ~105°**.** Well-defined organocopper(III) complexes are rare and it is noteworthy that compounds shown here represent the only isolated organocopper(III) complexes containing alkyl groups other than a simple methyl group.

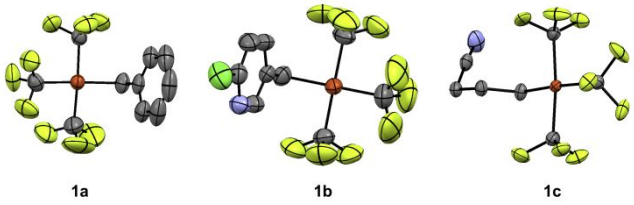


Figure 2. X-ray crystal structures of complexes **1a, 1b** and **1c** as $[n\text{Bu}_4\text{N}]^+$ salts. Oak Ridge thermal ellipsoid plot (ORTEP) drawing with atoms at 50% probability; hydrogen atoms and $[n\text{Bu}_4\text{N}]^+$ counter cations omitted for clarity.

Reductive elimination activity of $[(alkyl)Cu^{III}(CF_3)_3]^-$ complexes. With these Cu^{III} complexes in hand, we then studied their reductive elimination reactivity. At elevated temperature (55 °C), these complexes undergo reductive elimination, leading to the consumption of starting Cu^{III} and concomitant formation alkyl-CF_3 products with varying yields (**Fig. 3**). We followed the reductive elimination of **1d** in a temperature range of 45 - 65°C by ^{19}F-NMR (**Fig. 4A** and **Fig. S3**). At all temperature, reductive elimination of **1d** follows a first-order rate law (**Fig. 4B**) forming **2d** as the major products with yield ranging from 85-89%. The Cu^{I} byproducts of the reactions are $Cu(CF_3)_2^-$, which has been detected by ESI-MS (**Fig. S4**). We also observed the formation of $Cu^{III}(CF_3)_4^-$, presumably formed via aerobic oxidation of the Cu^{I} complexes. The observed first-order rates for the reductive elimination of **1d** is $k_{65} = 1.04 \times 10^{-3}$ s^{-1} at 65°C and $k_{45} = 1.45 \times 10^{-4}$ s^{-1} at 45°C, respectively. Eyring plot analysis of the reductive elimination rate at different temperature reveals that reductive elimination of **1d** proceeded with activation enthalpy of 20.3 kcal/mol and activation entropy of -12.4 e.u. (**Fig. 4C**), comparable to the reductive elimination of aryl-Pd^{II}-CF_3 complexes reported by Buchwald.[57]

Reductive elimination of Cu^{III} complexes bearing benzyl groups (**1a, 1g-1j**) affords the corresponding trifluoromethylated products in moderate yields (32-62%). Analysis of the crude reaction mixtures by GC/MS reveals that dimerized products (bibenzyl) were formed. In addition, when the reductive elimination reactions were conducted under air, benzyl alcohol and benzaldehyde were also formed, while the yields of trifluoromethylated products were not affected. These results suggest that the homolytic cleavage of the Cu^{III}-benzyl bonds to form benzylic radicals competes with the reductive elimination pathway. As expected, homolytic cleavage of Cu^{III} complexes leads to the formation of $[Cu^{II}(CF_3)_3]^-$, which has been detected by ESI-MS (**Fig. S5**) and EPR (**Fig. S6**). Moreover, studying the reductive elimination of **1a** and **1g-1j** reveals that reductive elimination generally proceeds faster with electron-donating substituents on the *para* position of the phenyl ring. A Hammet plot of $\log(k_{obs}/k_{obs(H)})$ (k_{obs} are calculated using initial rates for the formation of trifluoromethylated products) *vs* σ_{para} yields a ρ value of –0.602 and a modest correlation ($R^2 = 0.840$) (**Fig. S7**), suggesting that alkyl groups act as the nucleophilic partners in C-C bond formation. The yields of bibenzyl products derived from radical dimerization decreased with electron-donating substituents on the *para* position. Furthermore, the Cu^{III} complex bearing a secondary alkyl group, **1w**, is much more reactive toward reductive elimination than its primary analogues. More than 95% **1w** reductively eliminates within 5 minutes at 55 °C. At 25°, **1w** can also reductively eliminates, forming **2w** with a first-order rate constant $k_{obs} = 2.7 \times 10^{-3}$ s^{-1}. (**Fig. S8**)

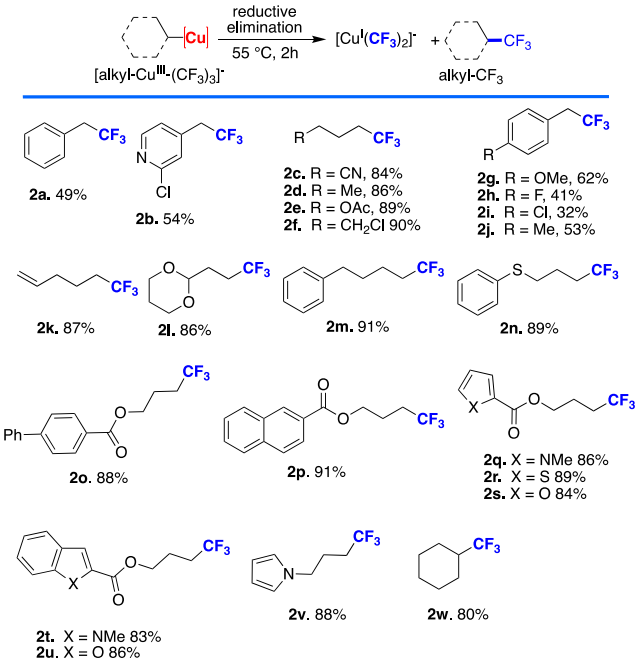


Figure 3. Reductive elimination of $[(alkyl)Cu^{III}(CF)_3]^-$ affords the corresponding alkyl-CF_3 products. Reductive elimination reactions were conducted in CD_3CN at 55°C; Yield determined by ^{19}F-NMR using 1-fluoro-3-nitrobenzene as the internal standard.

Given the mild conditions for both the transmetallation and reductive elimination steps, this procedure allows for the late-

stage trifluoromethylation of complex organozinc reagents (**Fig. 5**). We synthesized the organozinc derivatives of five bioactive molecules, including estrone, gemfibrozil, Vitamin E,

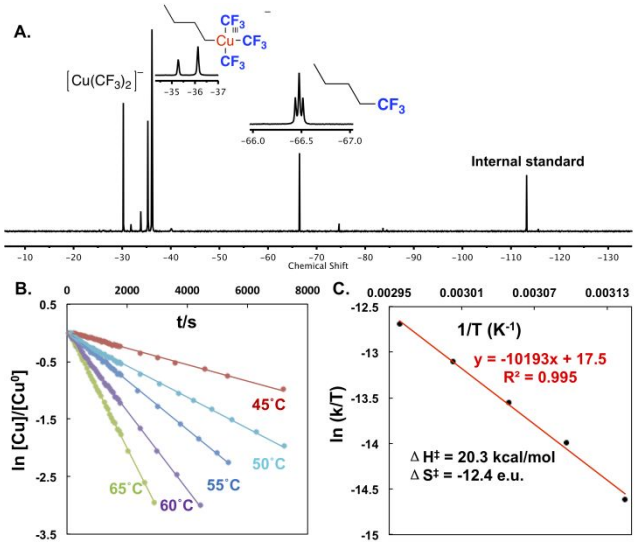


Figure 4. Kinetic studies of the reductive elimination of compound [*n*Bu$_4$N]-**1d**. **A.** Representative ^{19}F-NMR spectra of the reductive elimination of [*n*Bu$_4$N]-**1d**; **B.** First-order plot of reductive elimination of [*n*Bu$_4$N]-**1d** at different temperature; **C**. Erying Plot analysis of the reductive elimination of [*n*Bu$_4$N]-**1d**.

indomethacin and thalidomide. Upon treating **1** with these organozinc reagents at room temperature, a new set of ^{19}F-NMR peaks appeared consistent with the formation of the [(alkyl)Cu(CF$_3$)$_3$]$^-$ species. Heating the solutions of Cu^{III} at 55 °C for 2 hours afforded the corresponding trifluoromethylated products in excellent yields. Although trifluoromethylation of alkyl halides have been reported,[58-59] our procedure allows for the late-stage incorporation of CF$_3$ into complex molecules within a short amount of time and with excellent yields.

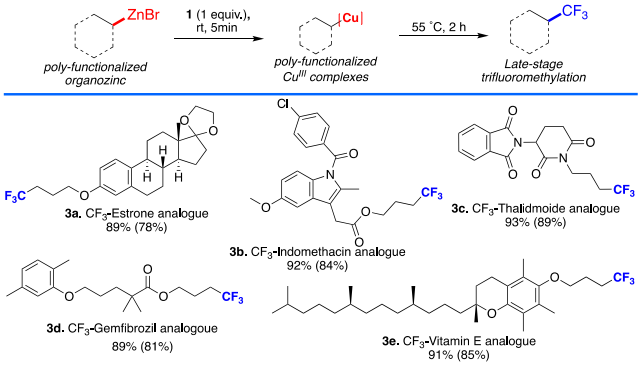


Figure 5. Late-stage trifluoromethylation of highly-functionalized organozinc reagents. Yields determined by ^{19}F-NMR using 1-fluoro-3-nitrobenzene as the internal standard. Isolated yields are listed in parenthesis.

DFT calculations of the reductive elimination reactions. To gain more insights into this Csp^3-CF$_3$ bond-forming reductive elimination, we performed DFT calculations at the B3LYP level combined with Poisson-Boltzmann continuum solvation to probe the mechanism of this elementary reaction (full details in SI). Based on literature precedents and our experimental results, four pathways were considered (**Fig. 6**). In **Path A**, reductive elimination occurs directly on the [(alkyl)Cu(CF$_3$)$_3$]$^-$ species, whereas, in **Path B**, homolytic cleavage of the Cu-alkyl bond takes place first to generate an alkyl radical which then rebounds to one of the copper-bounded CF$_3$. In **Path C**, a CF$_3$ anion dissociates and then the reductive elimination occurs on the neutral intermediate. Finally, considering the fluoride-rebound mechanism for C-CF$_3$ bond formation, recently discovered by Toste,[56] we proposed **Path D** which involves fluoride dissociation, migratory insertion and C-F reductive elimination to achieve net C-CF$_3$ bond formation.

The energetics of these four pathways for the reductive elimination of **1d** are shown in **Fig. 6**. Although **Path D** is involved in Toste's Au^{III} reductive elimination in the presence of a borane catalyst,[56] this pathway is not likely involved in our system due to the high energy of the difluorocarbene intermediate formed in the absence of a catalyst (estimated to be 39.1 kcal/mol). Likewise, the dissociation of a trifluoromethyl anion in **Path C** leads to the formation of a high energy neutral intermediate (ΔH = 31.3 kcal/mol). In **Path B**, we find that the homolytic dissociation of *n*-butyl is barrierless with ΔH = 21.6 kcal/mol, in which case there is no free *n*-butyl radical available to recombine with a copper-bounded CF$_3$ to form the target product. **We assign the concerted alkyl-CF$_3$ bond-forming pathway (Path A) as the mechanism.** This has the lowest predicted activation enthalpy (ΔH‡=21.4 kcal/mol), in excellent agreement with the experimental result (ΔH‡ =20.3 kcal/mol) from the Eyring analysis. As shown by Low and Goddard, reductive coupling of such Csp^3-Csp^3 bonds has a high barrier unless the reaction is made very exothermic.[60] The reaction in path **A**, is very exothermic (ΔH = -57.9 kcal/mol) and hence is expected to yield a low barrier for the concerted reaction as observed from both theory and experiment. Moreover, the calculated reductive elimination activation energy for **1w** is lower (ΔH‡ = 20.0 kcal/mol) than that of **1d**, consistent with its faster reductive elimination rate.

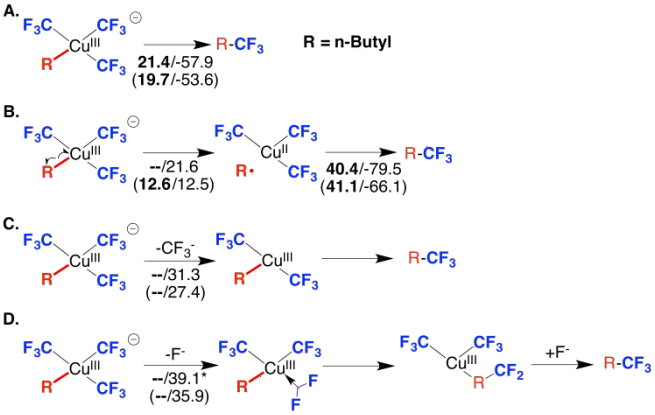


Figure 6. Reaction coordinate of reductive elimination of **1d** and **1a** (in parentheses) via four different pathways. The numbers in bold style are H‡s, whereas those in plain style are ΔHs.

Given the formation of free radicals observed in benzyl-containing Cu^{III} species, we also calculated activation energy for the reductive elimination of **1a** via **Path A** and **B**. Interestingly, the homolytic dissociation of **1a** has a lower activation energy (H‡/ΔH = 12.6/12.5 kcal/mol) than that of direct reductive elimination pathway (H‡/ΔH = 19.7/-53.6 kcal/mol), consistent with our experimental results that benzyl radicals are formed. In addition, the activation energy of the reversible reaction, in which the generated benzyl radical recombines with the Cu^{II} intermediate reforming compound **1a**,

is only 0.1 kcal/mol. This suggests that a fast equilibrium might exist between **1a** and the radical pair. The direct transfer of the CF_3 group to the benzyl radical is unlikely as indicated by the high activation energy ($H^{\ddagger}/\Delta H$ = 41.1/-66.1 kcal/mol). Moreover, our calculation results have shown that the activation energy of direct reductive elimination decreases with electron-donating groups at the *para* positions of the phenyl rings; $H^{\ddagger}$ decreases from 21.1kcal/mol for **1i** to 20.0 kcal/mol for **1h**, 19.7 kcal/mol for **1a**, and 17.7 kcal/mol for **1g**. In addition, the activation energy of radical dissociation (**Path B**) increases with electron-donating group at the *para*-position (12.6 kcal/mol for **1a** and 13.0 kcal/mol for **1g**). These calculation results are consistent with our experimental observations that the formation of benzyl radicals competes with the direct reductive elimination of benzyl-containing Cu^{III} species and that the formation radical-derived products decreases with electron-donating substituents on the phenyl rings. Finally, through natural bond orbital (NBO) analysis,[61] we have found that the NBO charge on Cu decreases from 0.84 e in the reactant, to 0.71 e in the transition state, and finally to 0.35 e in the product, demonstrating that this is indeed a reductive elimination process.

CONCLUSIONS

To conclude, we have reported a highly efficient procedure to the synthesis of novel [alkyl-$Cu^{III}(CF_3)_3]^-$ complexes, the structures of which have been well-characterized. The organocopper(III) molecules reported here represent the first class of organocopper(III) complexes containing complicated alkyl groups. These high-valent organocopper (III) species undergo reductive elimination to form the corresponding alkyl-CF_3 compounds and $[Cu^{I}(CF)_3]_2^-$ via a concerted pathway. We anticipate that this procedure could help to elucidate the structure and reactivity of other important, yet elusive Cu^{III} complexes and that the insights we learned from this reductive elimination reaction will guide the development of novel Cu-catalyzed C-C bond-forming reactions. This work on Csp^3-CF_3 bond-forming reductive elimination from Cu^{III} species indicates a possible catalytic oxidative pathway for trifluoromethylation in which an alkyl-Cu^{III}-CF_3 intermediate is generated in situ *via* chemical oxidation, which reductively eliminates to form the CF_3 products and regenerate Cu^{I} complexes. These research is currently ongoing in our laboratory.

ASSOCIATED CONTENT

Supporting Information

Supplementary figures, characterizations of new compounds, computational details and crystal structures. This material is available free of charge on the ACS Publications website.

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ACKNOWLEDGMENT

W.L. thanks Miami University for the start-up funding. L.Y.C, J.C.H, and M.J.C acknowledge financial support from the Ministry of Science and Technology of the Republic of China under grant no. MOST 107-2113-M-006-008-MY2.We also thank Dr. Theresa Ramelot for the assistance of HR-ESI and Prof. John Rakovan for the assistance of X-ray crystal diffraction. W.A.G. acknowledge financial support from NSF (NSF CBET 1512759)

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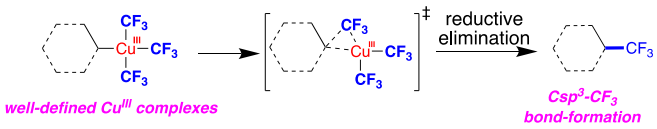
Csp^3-Csp^3 bond forming reductive elimination from well-defined Cu^{III}



- Highly efficient method to synthesize alkyl-Cu^{III} complexes
- Csp^3-Csp^3 bond-forming reductive elimination from Cu^{III}
- Computational insights into the elementary reductive elimination step