Copper–Carbon Homolysis Competes with Reductive Elimination in Well-Defined Copper(III) Complexes

Wenhao Yan,[a] Samantha Carter,[b] Chi-Tien Hsieh,[c] Jeanette A. Krause,[a] Mu-Jeng Cheng,[c] Shiyu Zhang,[b]* Wei Liu[a]*

[a]*Department of Chemistry, University of Cincinnati, Cincinnati, Ohio, 45221, United States*

[b]*Department of Chemistry & Biochemistry, The Ohio State University, Columbus, Ohio, 43210, United States*

[c]*Department of Chemistry, National Cheng Kung University, Tainan 701, Taiwan*

ABSTRACT: Despite the recent advancements of Cu catalysis for the cross-coupling of alkyl electrophiles and the frequently proposed involvement of alkyl-Cu(III) complexes in such reactions, little is known about the reactivity of these high valent complexes. Specifically, although the reversible interconversion between an alkyl-Cu^{III} complex and an alkyl radical/Cu^{II} pair has been frequently proposed in Cu catalysis, direct observation of such steps in well-defined Cu^{III} complexes remains elusive. In this study, we report the synthesis and investigation of alkyl-Cu^{III} complexes, which exclusively undergo a Cu–C homolysis pathway to generate alkyl radicals and Cu^{II} species. Kinetic studies suggest a bond dissociation energy of 28.6 kcal/mol for the Cu^{III}–C bonds. Moreover, these four-coordinate complexes could be converted to a solvated alkyl–Cu^{III}–(CF$_3$)$_2$, which undergoes highly efficient C–CF$_3$ bond-forming reductive elimination even at low temperatures (–4 °C). These results provide strong support for the reversible alkyl radicals recombination with Cu^{II} to form alkyl–Cu^{III} species, an elusive step that has been proposed in Cu-catalyzed mechanisms. Furthermore, our work has demonstrated that the reactivity of Cu^{III} complexes could be significantly influenced by subtle changes in the coordination environment. Lastly, the observation of the highly reactive neutral alkyl–Cu^{III}–(CF$_3$)$_2$ species (or with weakly bound solvent molecules) suggests they might be the true intermediates in many Cu-catalyzed trifluoromethylation reactions.

Introduction

Over the past decade, significant advancements have been made in Cu-catalyzed cross-coupling reactions, enabling the involvement of traditionally challenging alkyl electrophiles in carbon-carbon and carbon-heteroatom bond formation.[1] In many of these catalytic transformations, formal alkyl–Cu^{III} complexes, generated via the oxidative addition from Cu^{I} catalysts, have been proposed as the key intermediates.[2] The ensuing reductive elimination from these high-valent complexes furnishes the desired coupling products and regenerates the Cu^{I} catalysts. While Cu^{III} intermediates have been proposed frequently, it is only recently that isolated Cu^{III} complexes displaying catalytically relevant reactivity have been identified, with most studies primarily focusing on their reductive elimination reactivity. Noteworthy contributions by Ribas and Stahl demonstrated that aryl-Cu^{III} complexes stabilized by macrocyclic ligands can reductively eliminate to form C–N, C–O, and C–halogen bonds.[3] Xi has reported the discovery of a spiro Cu^{III} complex that undergoes C(sp^2)–C(sp^3) bond-forming reductive elimination reactions.[4] Our group and the Shen group have successfully synthesized alkyl- and aryl-Cu^{III}–CF$_3$ complexes capable of participating in C–CF$_3$ bond-forming reactions.[5] Additionally, Tilley recently published a study on Cu^{III} metallacyclopentadiene dimer complexes, which can undergo reductive elimination to generate phenanthrocyclobutadiene in quantitative yield.[6] More recently, Sanford has reported the characterization of Cu^{III}-aryl intermediates in aminoquinoline-directed C–H functionalization.[7]

Despite significant progress in understanding the reductive elimination step in Cu catalysis, the involvement of Cu^{III} species in Cu catalysis remains speculative. Particularly in Cu-catalyzed C(sp^3) cross-coupling reactions with alkyl radicals, an ongoing debate persists regarding the formation of Cu^{III} species in these transformations. Two distinct pathways have been proposed to elucidate the interaction between alkyl radicals and Cu catalysts: an inner sphere and an outer sphere pathway (**Figure 1a**). In the former pathway, a carbon-centered radical engages with a Cu^{II} species to generate the reactive organo-Cu^{III} intermediate.[8] This step is considered to be reversible since the Cu^{III}–C is expected to be relatively weak. Homolysis of an alkyl–Cu^{III} complex could regenerate an alkyl radical and a Cu^{II} complex. Alternatively, in the outer sphere pathway, the alkyl radical directly reacts with the Cu^{II} intermediate via group transfer, resulting in the formation of the coupling product.[9] Experimental evidence has indeed supported the occurrence of the outer sphere pathway in certain Cu-catalyzed transformations. For example, Peters and Fu recently demonstrated that in a photoinduced, Cu-catalyzed enantioselective N-alkylation reaction, the chiral amine product was generated through the direct transfer of an amide group from a Cu^{II}-amide species to an alkyl radical, without the formation of a Cu^{III} intermediate.[10] On the other hand, while a reversible combination of alkyl radicals with Cu^{II} is postulated to form the Cu^{III} intermediate in the inner sphere pathway, there is limited experimental evidence supporting either the homolysis reactivity of Cu^{III} complexes or the formation of Cu^{III} through a radical combination process. Consequently, the inner sphere pathway, despite being routinely proposed for Cu catalysis, remains largely elusive.[11]

Our groups have a long-term goal to understand the role of elusive metal intermediates, especially high-valent metal complexes, in catalytic reactions.[12] In our previous studies, we have reported the synthesis of anionic [alkyl–Cu^{III}–(CF$_3$)$_3$]$^-$ complexes, which could undergo predominantly C(sp^3)–CF_3 bond-forming reductive elimination reactions.[5] These complexes, along with a five-coordinate neutral complex reported by Shen,[13] represent the rare examples of isolated alkyl–Cu^{III} complexes that can undergo reductive elimination reactions (**Figure 1b**). Motivated by these findings, we recently questioned whether analogous complexes with well-defined structures could exhibit the putative Cu^{III}–C bond homolysis reactivity, thus shedding light on the inner sphere pathway of Cu catalysis. In this work, we present the synthesis and exploration of alkyl–Cu^{III} complexes that can exclusively undergo Cu^{III}–C homolytic cleavage reactions to form alkyl radicals and Cu^{II} species (**Figure 1c**). Through kinetic studies of the homolysis reactions, we have, for the first time, determined the bond dissociation energy of Cu^{III}–alkyl bonds. Furthermore, these complexes could be transformed to solvated alkyl–Cu^{III}–$(CF_3)_2$ species, which undergo exclusive C–CF_3 reductive elimination reactions occurring orders of magnitude faster than previously reported alkyl-Cu^{III} complexes.

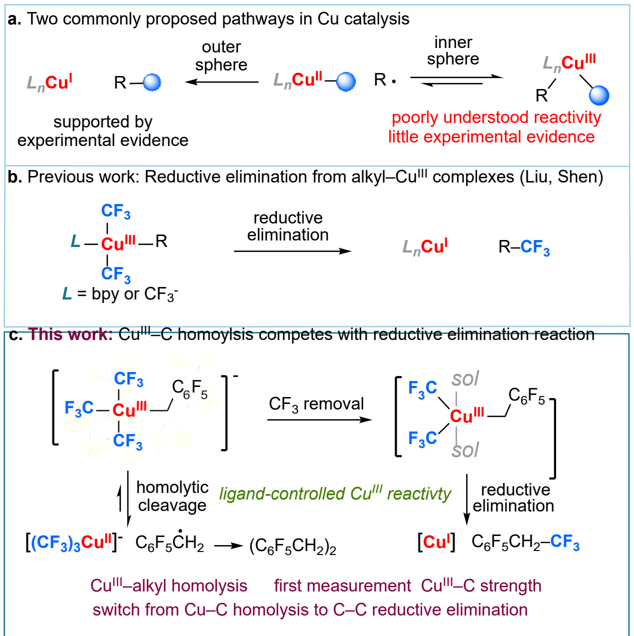


Figure 1. Understanding the Cu^{III}–C homolysis reactivity in well-defined Cu^{III} complexes should shed light on the hypothetical inner sphere pathway for Cu catalysis.

Results and Discussion

Design and synthesis of alkyl–Cu^{III} complexes with homolysis reactivity

We anticipated that two crucial requirements would be necessary to prepare isolable alkyl-Cu^{III} complexes that can undergo predominantly Cu–C homolysis. First, we opted for CF_3 groups as the ancillary ligand, taking into account our and others' previous studies indicating that such strong donor ligands are capable of stabilizing organo–Cu^{III} complexes.[13-14] Secondly, we have selected electron-deficient alkyl groups as the participating groups to minimize the competing reductive elimination pathway. This decision draws inspiration from prior investigations in Pd catalysis, where it was observed that complexes incorporating less electron-rich reactive groups exhibit slower rates of reductive elimination compared to those with more electron-rich counterparts.[15]

Based on these two criteria, we prepared complexes **1a** and **1b,** featuring electron-deficient benzyl groups. The synthesis involved the treatment of the neutral (Py)$Cu^{III}(CF_3)_3$ complex with the corresponding benzyl zinc reagent at room temperature. Subsequently, the resulting anionic complexes were isolated as their tetraphenyl phosphonium salts. Remarkably, both complexes exhibit excellent stability under aerobic conditions and at ambient temperatures, allowing for their characterization using various spectroscopic techniques. The structures of these two complexes were confirmed by X-ray crystallography, and an ORTEP structure of each is shown in **Figure 2**. Both complexes exhibit a slightly distorted square planar geometry. The average distance between Cu^{III} center and the CF_3 group in **1a** is 1.957 Å, while bond length between the benzyl carbon and Cu is 1.984 Å, closely resembling the bond length observed in the previously reported non-fluorinated analog (1.997 Å).[5]

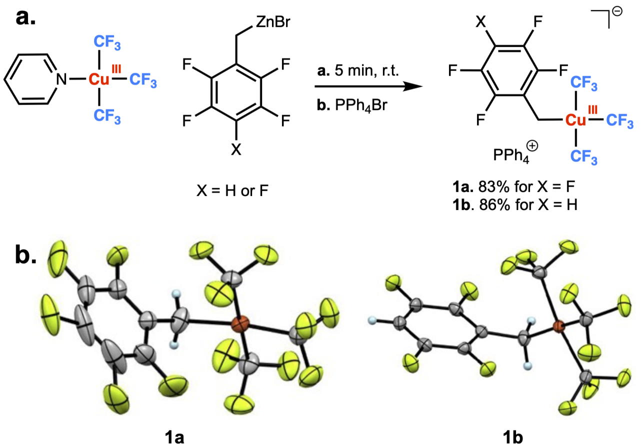


Figure 2. **a.** Synthesis and characterization of [alky-Cu^{III}–$(CF_3)_3$]$^-$ complexes. **b.** X-ray crystal structures of complexes **1a** and **1b** as $[PPh_4]^+$ salts. Oak Ridge thermal ellipsoid plot (ORTEP) drawings with atoms at 50% probability; $[PPh_4]^+$ counter cations omitted for clarity.

Reactivity of isolated Cu^{III} complexes

Next, we sought to probe the reactivity of these complexes toward Cu^{III}–C homolysis. Heating a solution of **1a** in CH_3CN at 55°C for two hours under anaerobic conditions resulted in the substantial consumption (90%) of the initial Cu^{III} complexes, along with the formation of bibenzyl as the major organic products in 72% yield (**Figure 3a** and **Figure S1**). Similar results were obtained for the thermal decomposition of **1b**. Notably, no formation of benzyl trifluorides was detected in either case. These findings starkly contrast with the behavior exhibited by previously reported [alkyl–Cu^{III}–$(CF_3)_3$]$^-$ complexes or five-coordinate (bpy)Cu^{III}(Me)$(CF_3)_2$, which primarily undergo C–CF_3 bond-forming reductive elimination reactions.

We then investigated the fate of the Cu center during the homolysis reactions. It is anticipated that the release of a benzylic radical from **1a** would result in the formation of a [Cu^{II}–CF_3] complex, which can be detected using electron paramagnetic resonance (EPR) spectroscopy. X-band EPR analysis of a MeCN solution (100 K) of compound **1a** after heated at 50 °C, revealed the presence of two distinct S=1/2 Cu^{II} signals. Simulation of the EPR spectra with two S=1/2 components provides $g_1 = g_2 = 2.044$, $g_3 = 2.25$, $A_3 = 310$ MHz for component **A** and $g_1 = 2.00$, $g_2 = 2.10$, $g_3 = 2.16$, $A_3 = 630$ MHz for component **B** (**Figure 3a** and **3b**). Although the definitive structure determination of these two components remains challenging, DFT calculations on a range of potential [Cu^{II}–CF_3] species suggest that **A** is likely an anionic [$Cu^{II}(CF_3)_3$]$^-$ complex, while **B** corresponds to a neutral $Cu^{II}(CF_3)_2(CH_3CN)_2$ complex (see Supporting Information). The assignment of component **A** as anionic

$[Cu^{II}(CF_3)_3]^-$ (m/z = 269.9) was further supported by ESI-MS analysis (see Supporting Information for details, **Figure S2**).

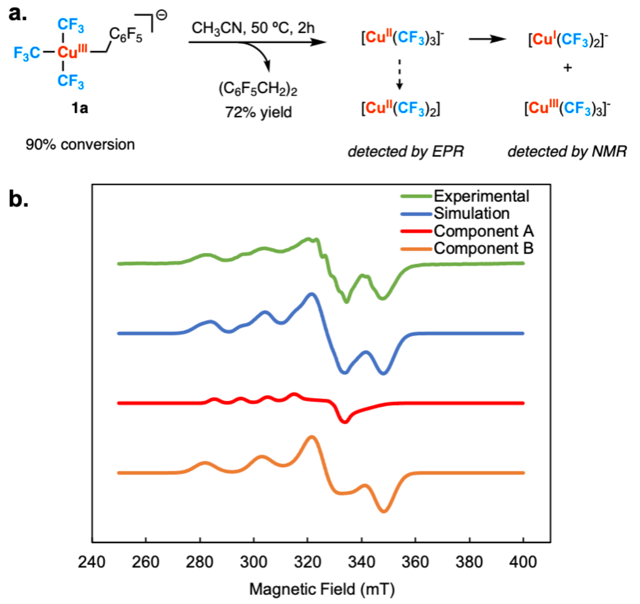


Figure 3. Cu-C homolysis reactivity of compound **1a**. **a**. At elevated temperatures, complex **1a** undergoes Cu–C homolysis to form the dimerization product and Cu^{II} species. **b.** EPR spectra of the homolysis reaction.

Quantification of EPR spin signals revealed that only 20% of Cu^{II} species were formed after the release of the benzyl radical (**Figure S3**). This low yield of Cu^{II} could be attributed to the subsequent disproportionation of copper(II) CF_3 species, leading to the formation of copper(I) and copper(III) CF_3 species (**Figure 3a**). We reason that the disproportionation is initiated by the homolysis of $[Cu^{II}(CF_3)_3]^-$, leading to the formation of a CF_3 radical and $[Cu^{I}(CF_3)_2]^-$.[16] The CF_3 radical can then react with another equivalent of $[Cu^{II}(CF_3)_3]^-$ to form $[Cu^{III}(CF_3)_3]^-$. Indeed, both $[Cu^{I}(CF_3)_2]^-$ and $[Cu^{III}(CF_3)_3]^-$ were detected by ESI-MS (m/z = 200.9 and 338.9, respectively, **Figure S2**). Quantification of $[Cu^{I}(CF_3)_2]^-$ and $[Cu^{III}(CF_3)_3]^-$ from the same reaction mixture using ^{19}F NMR revealed 42 yield for $[Cu^{I}(CF_3)_2]^-$, and 32 % yield for $[Cu^{III}(CF_3)_3]^-$ (**Figure S4**). Accounting for all the observed copper species, including the NMR active ones $[Cu^{I}(CF_3)_2]^-$ (42%) and $[Cu^{III}(CF_3)_3]^-$ (32%), along with the EPR active ones $Cu^{II}(CF_3)_2(CH_3CN)_2$ and $[Cu^{II}(CF_3)_3]^-$ (20%), the overall yield for detected Cu products is ca. 94%. This suggests that most Cu products have been accounted for.

Kinetics of the homolysis step

We next sought to investigate the kinetics of the homolysis reactions. The thermal decomposition of **1a** at 55 °C displayed a pseudo-first-order kinetic behavior with a rate constant of $(2.77 \pm 0.07) \times 10^{-4}$ s^{-1} (**Figure S1**). However, this observed decay rate should correspond to the combined rate of the forward homolytic dissociation and reverse radical oxidative recombination steps. On the other hand, the rate for the homolysis step alone can be separately measured if the oxidative radical recombination step is removed from the kinetic scheme. This can be achieved by employing a radical trap that rapidly and irreversibly reacts with the generated radicals. This trapping strategy has previously been used to study the activation barrier for other metal-carbon homolysis reactions, including the homolytic splitting Co–C cleavage in vitamin B_{12} and related model complexes.[17] TEMPO was found to be a suitable radical trap for the purpose of our study. In the presence of 2 equiv. of TEMPO, the thermal decomposition of **1a** followed a first-order rate law in a temperature range of 40 – 60 ˚C ($k = 3.9 \times 10^{-4}$ s^{-1} at 40 ˚C and $k = 6.8 \times 10^{-3}$ s^{-1} at 60 ˚C.), affording TEMPO–$CH_2C_6F_5$ and TEMPO–CF_3 as the only observable organic products (**Figure 4a** and **4b**). Notably, the formation of the bibenzyl compound, which arises from the dimerization of the benzyl radical, was not detected. This observation is consistent with the efficient trapping of the benzylic radical by TEMPO, preventing its dimerization. When the thermolysis was conducted with more than 2 equiv. of TEMPO, the decay rate for **1a** remains the same (**Figure S5**). This saturation behavior is consistent with our hypothesis that the reverse radical oxidative recombination step was suppressed with an excess amount of radical trapping agent while the Cu–C homolysis step remains undisturbed.

^{19}F NMR analysis of the Cu complex following thermolysis revealed that the predominant species was $[Cu^{I}(CF_3)_2]^-$ (72%), while only a small amount of $[Cu^{III}(CF_3)_4]^-$ (~5%) was detected by ^{19}F NMR spectroscopy. This finding supports the notion that the CF_3 radical is captured by TEMPO, thereby suppressing the disproportionation pathway of $[Cu^{II}(CF_3)_3]^-$.

Eyring analysis of the rate constant at different temperatures reveals that Cu^{III}–C homolysis from **1a** proceeded with $\Delta H^\ddagger = 28.6 \pm 1.6$ kcal/mol, $\Delta S^\ddagger = 16.8 \pm 4.9$ e.u., and $\Delta G^\ddagger_{298} = 23.6$ kcal/mol (**Figure 4c**). Given the low barrier for the radical recombination step, we reason that the measured value of activation enthalpy, 28.6 ± 1.6 kcal/mol in CH_3CN, can be used as an estimate of the bond dissociation energy of Cu^{III}–alkyl bonds in compound **1a**.

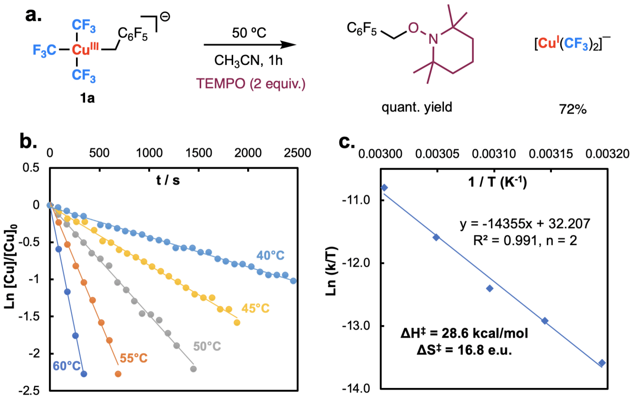


Figure 4. Kinetic studies of the Cu–C homolysis of **1a** in the presence of a radical trap. **a.** Homolysis of **1a** with 2 equiv. of TEMPO affords the radical trapping product. **b.** First-order plot of the homolysis at various temperatures in the presence of two equiv. of TEMPO. **c.** Eyring analysis of the homolysis reaction.

From Cu^{III}–C homolysis to C–CF_3 reductive elimination

In the context of Cu-catalyzed trifluoromethylation reactions, it is commonly proposed that organo–Cu^{III}–CF_3 complexes undergo C–CF_3 bond-forming reductive elimination, leading to the formation of trifluoromethylated products.[8a, 8b, 14a, 18] However, the results shown here suggest the possibility of an alternative homolytic cleavage pathway for such complexes. This intriguing new reactivity prompts us to explore whether there exists a means to control the reactivity of organo-Cu^{III} complexes, directing them either towards Cu-C homolysis or reductive elimination.

Previous studies on well-defined Pd^{II} compounds have revealed that complexes with three-coordinate metal centers tend to undergo faster reductive elimination than those with four-coordinate centers.[15] Building upon this knowledge, we thus speculate whether complex **1a** could be converted to its neutral three-coordinate alkyl–Cu^{III}–$(CF_3)_2$ analog, which might favor reductive elimination reactions. To accomplish this transformation, the selective removal of a CF_3 ligand from the Cu^{III} center is required. Previous work has shown that Brønsted or Lewis acids can promote the activation of the C–F bonds in metal-trifluoromethyl complexes, leading to the formation of metal-difluorocarbene species that can undergo diverse transformations.[19] For example, Reger has shown that the reaction of $CpMo(CO)_3CF_3$ with SbF_5 leads to the formation of $[CpMo(CO)_3CF_2]SbF_6$, which transforms to $[CpMo(CO)_4]$ SbF_6 during the attempts to isolate the difluorocarbene species.[20] Baker has reported that a Co^{III} difluorocarbene species could undergo hydrolysis to form a Co^{III} carbonyl species.[21] Toste and coworkers have shown that treating an Au^{III}–CF_3 complex with tris(pentafluorophenyl)borane, $B(C_6F_5)_3$, leads to the formation of a difluorcarbenoid complex capable of undergoing an unusual fluoride rebound process.[22] Similar reactivity has been observed on copper(III) species. Grushin reported the reaction of a four-coordinate $[Cu^{III}(CF_3)_4]^-$ complex with acetic acid, resulting in the loss of a CF_3 group and the formation of a five-coordinate $(bpy)Cu^{III}(CF_3)_3$ compound when the bipyridine ligand is present.[14c] This strategy has been used by Shen to synthesize neutral five-coordinate $(bpy)Cu^{III}(CF_3)_2(Me)$ and $(bpy)Cu^{III}(aryl)(CF_3)_2$ complexes.[13, 23]

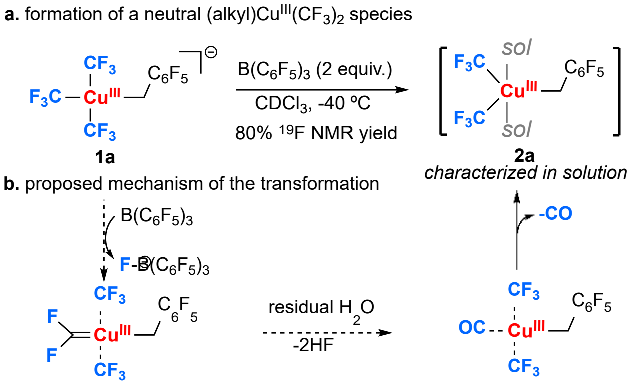


Figure 5. Formation of solvated alkyl–Cu^{III} species. **a.** The addition of $B(C_6F_5)_3$ to a solution of **1a** leads to the formation of new Cu^{III} species. **b.** Mechanism for the formation of species **2a**.

Motivated by these precedents, we studied the reaction of **1a** with various acids. While most acids either caused the intractable decomposition of **1a** or showed no reactivity towards it, the addition of $B(C_6F_5)_3$ to a $CDCl_3$ solution of **1a** resulted in immediate effervescence. Monitoring this reaction by ^{19}F NMR spectroscopy (**Figure S6**) at –25 °C revealed the rapid disappearance of original CF_3 groups (–35.5 ppm and –36.7 ppm) and the appearance of a new singlet at –43.5 ppm. Quantitative analysis of the new peak, using an internal standard, indicated that two CF_3 groups were bound to the Cu center, consistent with the formation of a new $[Cu^{III}$–$(CF_3)_2]$ species featuring two equivalent CF_3 groups (**Figure 5a**). Given the effervescence observed during the reaction, we further analyzed the headspace using gas chromatography (**Figure S7**), which demonstrated the formation of CO. Based on these results, together with the precedents on fluoride abstraction from metal–CF_3 compounds by $B(C_6F_5)_3$, we propose that the borane abstracts a fluorine atom from **1a**, leading to the formation of an unstable Cu^{III}–difluorocarbene species **(Figure 5b)**. Subsequent hydrolysis, facilitated by trace amounts of water in the solvent, gave rise to the formation of a Cu^{III}–carbonyl complex. This complex readily released one equiv. of carbon monoxide to form a ligandless [benzyl–$Cu^{III}(CF_3)_2$] species **2a** (or with weakly bound solvents). The structure of compound **2a** is supported by 2D NMR (see Supporting Information for details). A similar compound **2b** could be formed via the reaction of compound **1b** with $B(C_6F_5)_3$ (**Figure S9**).

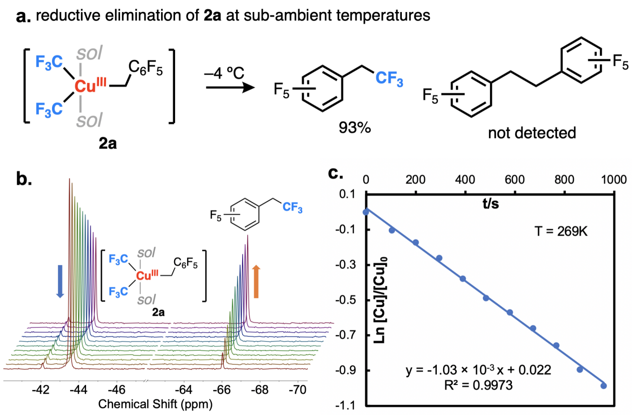


Figure 6. Reactivity of compound **2a**. **a.** Compound **2a** exhibits exclusive reductive elimination reactivity. **b.** Monitoring the reductive elimination of **2a** by ^{19}F NMR at –4 °C in $CDCl_3$. **c.** First-order plot of reductive elimination of **2a** at –4 °C.

The reactivity of this newly formed species **2a** was investigated. Unlike **1a**, which undergoes a homolysis reaction, complex **2a** undergoes reductive elimination within seconds at ambient temperature, yielding the benzyl trifluoride product as the only organic compound (**Figure 6a**). At sub-ambient temperatures (–4 °C), the reductive elimination of **2a** followed the first-order kinetics, with a rate constant of 1.03×10^{-3} s^{-1} (**Figure 6b** and **Figure 6c**). Similar reactivity has been observed with the three-coordinate compound derived from **1b**, which reductively eliminates with faster kinetic rates ($k > 10^{-2}$ s^{-1} at –4 °C and $k = 1.37 \times 10^{-3}$ s^{-1} at –15 °C) (**Figure S9**). Notably, these rates of reductive elimination are at least three orders of magnitude faster than that of the previously reported anionic $[^{n}Bu$–Cu^{III}–$(CF_3)_3]^-$ and five-coordinate $(bpy)Cu^{III}(CF_3)_2CH_3$ species (*calc.* rate constant for reductive elimination at –4 °C based on Erying plot: $\sim 0.4 \times 10^{-6}$ s^{-1} and $\sim 0.9 \times 10^{-6}$ s^{-1}, respectively).

DFT calculations

To gain further insights into the significant difference in the reactivity between the four-coordinate complex **1a** and apparent three-coordinate complex **2a**, we conducted DFT calculations on these two compounds (see Supporting Information for details). In agreement with the experimental findings, DFT calculations show that the reductive elimination of complex **2a** proceeds with much lower activation enthalpy ($\Delta H^{\ddagger} = 11.9$ kcal/mol) than the four-coordinate and anionic analog **1a** ($\Delta H^{\ddagger} = 30.8$ kcal/mol). In addition, the enthalpy change of the homolysis reaction of **1a** has been calculated as $\Delta H = 23.1$ kcal/mol. This is in good agreement with the experimental activation enthalpy $\Delta H^{\ddagger} = 28.6 \pm 1.6$ kcal/mol, when taking into account the small barrier for the recombination of the benzylic radical with the Cu^{II} species.

To illustrate the variation of bonding orbitals during reductive elimination, we used the intrinsic bond orbital (IBO) scheme to localize the canonical molecular orbitals for each point along the intrinsic reaction coordinate (IRC) for both compounds **1a** and **2a**.[24] Our analysis showed that two Cu–C σ-bonds involved in reductive elimination change more significantly than the others (**Figure 7**). One evolves into a C–C σ-bond, whereas the other becomes a Cu d-orbital. At the transition states, the newly generated Cu d-orbital suffers from repulsive interaction with the CF_3 ligands that do not participate in reductive elimination. Compound **1a** has two such ligands to affect the transition state, whereas compound **2a** has only one. As a result, the transition state of **2a** is less destabilized as compared to that of **1a**, leading to its lower barrier. A similar explanation is documented to explain the influence of the coordination number on the rate of reductive elimination of other d^8-organotransition metal complexes.[25]

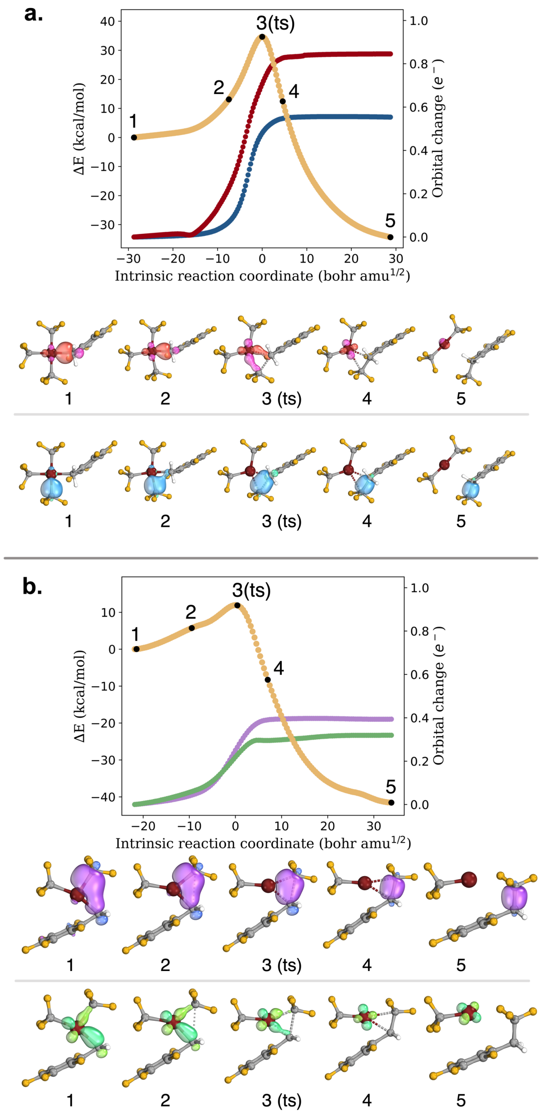


Figure 7. IBO analysis of reductive elimination. **a.** Evolution of IBOs of two Cu-C σ-orbitals during reductive elimination of compound **1a**. **b.** Evolution of IBOs of two Cu-C σ-orbitals during reductive elimination of compound **2a.**

The discovery of a highly reactive [alkyl–Cu^{III}–(CF$_3$)$_2$] complex opens up an intriguing possibility for understanding the mechanistic aspect of Cu-catalyzed trifluoromethylation reactions. While previously reported anionic [alkyl–Cu^{III}–(CF$_3$)$_3$]$^-$[5] and neutral (bpy)Cu^{III}(Me)(CF$_3$)$_2$[13] complexes exhibit catalytically relevant reductive elimination reactivity, their sluggish reactivity at ambient temperatures raises questions on their involvement in catalytic trifluoromethylation reactions. Moreover, certain Cu-catalyzed trifluoromethylation reactions occur under ambient temperatures and/or in the absence of exogenous ligands,[8b, 26] suggesting the possible participation of more reactive solvated organo-Cu^{III}–CF$_3$ species in catalysis. Therefore, we propose that the neutral organo-Cu^{III}–(CF$_3$)$_2$ species, with or without weakly bound solvent molecules, could serve as the true intermediates in some Cu-catalyzed trifluoromethylation reactions. Detailed investigations of these three-coordinate [Cu^{III}–CF$_3$] complexes in Cu-catalyzed trifluoromethylation and other Cu-catalyzed reactions are currently being conducted in our laboratory, and we will report our findings in due course.

Conclusions

In summary, these complexes represent the first examples of well-defined Cu^{III} complexes that exhibit the putative Cu^{III}–alkyl homolysis reactivity, a commonly proposed step in Cu catalysis. Through kinetic studies, the bond dissociation energy of Cu^{III}-alkyl bonds has been estimated experimentally for the first time, which is supported by DFT calculations. Additionally, the conversion of the four-coordinate alkyl-Cu species to its apparent three-coordinate analog has been achieved by removing a CF$_3$ ligand. Notably, the resulting neutral complex displays exclusive reactivity towards C–CF$_3$ bond-forming reductive elimination under sub-ambient temperatures, with a rate constant significantly faster than previously reported for alkyl-Cu^{III}-CF$_3$ species. These findings provide valuable insights into the reactivity and potential catalytic applications of Cu^{III} complexes in Cu-catalyzed reactions.

ASSOCIATED CONTENT

Supporting Information.

The Supporting Information is available free of charge

Detailed experimental section, characterization methods, NMR spectra, and DFT calculation details.

CCDC-2286828 and CCDC-2286829 contain crystallographic information of compounds **1a** and **1b** and are provided free of charge from the Cambridge Crystallographic Database Centre www.ccdc.cam.ac.uk/.

AUTHOR INFORMATION

Corresponding Author

Shiyu Zhang, *Department of Chemistry & Biochemistry, The Ohio State University, Columbus, Ohio, 43210, United States*
Email: zhang.8941@osu.edu

Wei Liu, *Department of Chemistry, University of Cincinnati, Cincinnati, Ohio, 45221, United States,*
Email: liu2w2@uc.edu

Authors

Wenhao Yan, *Department of Chemistry, University of Cincinnati, Cincinnati, Ohio, 45221, United States*

Samantha Carter, *Department of Chemistry, The Ohio State University, Columbus, Ohio, 43210, United States*

Chi-Tien Hsieh, *Department of Chemistry, National Cheng Kung University, Tainan 701*

Jeanette A. Krause, *Department of Chemistry, University of Cincinnati, Cincinnati, Ohio, 45221, United States*

Mu-Jeng Cheng, *Department of Chemistry, National Cheng Kung University, Tainan 701*

ACKNOWLEDGMENT

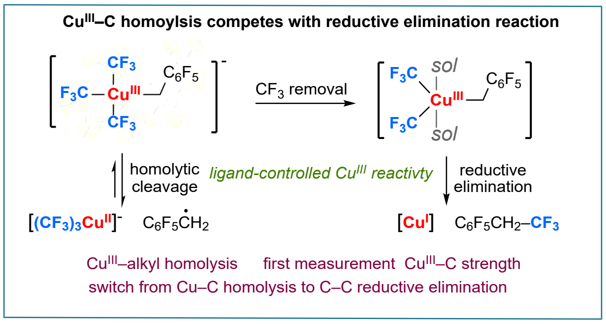
This work was supported by the National Science Foundation under Grant No. CHE-2237757 (W.L.) and CHE-2246440 (S.Z.). W.L. thanks the ACS Herman Frasch Foundation (926-HF22) and University of Cincinnati for financial support. We also thank Jiang's lab for the help with CO detection. NMR experiments were performed using a Bruker AVANCE NEO 400 MHz NMR spectrometer, funded by NSF-MRI grant CHE-1726092. Funding for the D8 Venture diffractometer was through NSF-MRI grant CHE-1625737.

REFERENCES

1. (a) Hossain, A.; Bhattacharyya, A.; Reiser, O., Copper's rapid ascent in visible-light photoredox catalysis. *Science* **2019,** *364* (6439), eaav9713; (b) Bertz, S. H.; Hardin, R. A.; Murphy, M. D.; Ogle, C. A.; Richter, J. D.; Thomas, A. A., Rapid Injection NMR Reveals η3 'π-Allyl' CuIII Intermediates in Addition Reactions of Organocuprate Reagents. *J. Am. Chem. Soc.* **2012,** *134* (23), 9557-9560; (c) Gu, Q.-S.; Li, Z.-L.; Liu, X.-Y., Copper(I)-Catalyzed Asymmetric Reactions Involving Radicals. *Acc. Chem. Res.* **2020,** *53* (1), 170-181.
2. (a) Li, S.-J.; Lan, Y., Is Cu(iii) a necessary intermediate in Cu-mediated coupling reactions? A mechanistic point of view. *Chem Commun.* **2020,** *56* (49), 6609-6619; (b) DiMucci, I. M.; Lukens, J. T.; Chatterjee, S.; Carsch, K. M.; Titus, C. J.; Lee, S. J.; Nordlund, D.; Betley, T. A.; MacMillan, S. N.; Lancaster, K. M., The Myth of d8 Copper(III). *J. Am. Chem. Soc.* **2019,** *141* (46), 18508-18520; (c) Casitas, A.; Ribas, X., The Role of Organometallic Copper(III) Complexes in Homogeneous Catalysis. *Chem. Sci.* **2013,** *4* (6), 2301-2318; (d) Hickman, A. J.; Sanford, M. S., High-valent organometallic copper and palladium in catalysis. *Nature* **2012,** *484*, 177; (e) Liu, H.; Shen, Q., Well-defined organometallic Copper(III) complexes: Preparation, characterization and reactivity. *Coord. Chem. Rev.* **2021,** *442*, 213923; (f) Liu, L.; Xi, Z., Organocopper (III) Compounds with Well-defined Structures Undergo Reductive Elimination to Form C—C or C–Heteroatom Bonds. *Chinese J. Chem.* **2018,** *36* (12), 1213-1221; (g) Bertz, S. H.; Cope, S.; Murphy, M.; Ogle, C. A.; Taylor, B. J., Rapid Injection NMR in Mechanistic Organocopper Chemistry. Preparation of the Elusive Copper(III) Intermediate. *J. Am. Chem. Soc.* **2007,** *129* (23), 7208-7209.
3. (a) Casitas, A.; Canta, M.; Solà, M.; Costas, M.; Ribas, X., Nucleophilic Aryl Fluorination and Aryl Halide Exchange Mediated by a CuI/CuIII Catalytic Cycle. *J. Am. Chem. Soc.* **2011,** *133* (48), 19386-19392; (b) King, A. E.; Huffman, L. M.; Casitas, A.; Costas, M.; Ribas, X.; Stahl, S. S., Copper-Catalyzed Aerobic Oxidative Functionalization of an Arene C−H Bond: Evidence for an Aryl-Copper(III) Intermediate. *J. Am. Chem. Soc.* **2010,** *132* (34), 12068-12073; (c) Casitas, A.; King, A. E.; Parella, T.; Costas, M.; Stahl, S. S.; Ribas, X., Direct observation of CuI/CuIII redox steps relevant to Ullmann-type coupling reactions. *Chem. Sci.* **2010,** *1* (3), 326-330.
4. Liu, L.; Zhu, M.; Yu, H.-T.; Zhang, W.-X.; Xi, Z., Organocopper(III) Spiro Complexes: Synthesis, Structural Characterization, and Redox Transformation. *J. Am. Chem. Soc.* **2017,** *139* (39), 13688-13691.
5. Paeth, M.; Tyndall, S. B.; Chen, L.-Y.; Hong, J.-C.; Carson, W. P.; Liu, X.; Sun, X.; Liu, J.; Yang, K.; Hale, E. M.; Tierney, D. L.; Liu, B.; Cao, Z.; Cheng, M.-J.; Goddard, W. A.; Liu, W., Csp3–Csp3 Bond-Forming Reductive Elimination from Well-Defined Copper(III) Complexes. *J. Am. Chem. Soc.* **2019,** *141* (7), 3153-3159.
6. Bergman, H. M.; Beattie, D. D.; Handford, R. C.; Rossomme, E.; Suslick, B. A.; Head-Gordon, M.; Cundari, T. R.; Liu, Y.; Tilley, T. D., Copper(III) Metallacyclopentadienes via Zirconocene Transfer and Reductive Elimination to an Isolable Phenanthrocyclobutadiene. *J. Am. Chem. Soc.* **2022,** *144* (22), 9853-9858.
7. Blythe, I. M.; Xu, J.; Fernandez Odell, J. S.; Kampf, J. W.; Bowring, M. A.; Sanford, M. S., Characterization and Reactivity of Copper(II) and Copper(III) σ-Aryl Intermediates in Aminoquinoline-Directed C–H Functionalization. *J. Am. Chem. Soc.* **2023,** *145* (33), 18253-18259.
8. (a) Kautzky, J. A.; Wang, T.; Evans, R. W.; MacMillan, D. W. C., Decarboxylative Trifluoromethylation of Aliphatic Carboxylic Acids. *J. Am. Chem. Soc.* **2018,** *140* (21), 6522-6526; (b) Kornfilt, D. J. P.; MacMillan, D. W. C., Copper-Catalyzed Trifluoromethylation of Alkyl Bromides. *J. Am. Chem. Soc.* **2019,** *141* (17), 6853-6858; (c) Zhang, X.; Smith, R. T.; Le, C.; McCarver, S. J.; Shireman, B. T.; Carruthers, N. I.; MacMillan, D. W. C., Copper-mediated synthesis of drug-like bicyclopentanes. *Nature* **2020,** *580* (7802), 220-226; (d) Górski, B.; Barthelemy, A.-L.; Douglas, J. J.; Juliá, F.; Leonori, D., Copper-catalysed amination of alkyl iodides enabled by halogen-atom transfer. *Nat. Cat.* **2021,** *4* (7), 623-630; (e) Cai, A.; Yan, W.; Liu, W., Aryl Radical Activation of C–O Bonds: Copper-Catalyzed Deoxygenative Difluoromethylation of Alcohols. *J. Am. Chem. Soc.* **2021,** *143* (26), 9952-9960; (f) Zeng, X.; Yan, W.; Zacate, S. B.; Cai, A.; Wang, Y.; Yang, D.; Yang, K.; Liu, W., Copper-Catalyzed Deaminative Difluoromethylation. *Angew. Chem. Int. Ed.* **2020,** *59* (38), 16398-16403; (g) Cai, A.; Yan, W.; Wang, C.; Liu, W., Copper-Catalyzed Difluoromethylation of Alkyl Iodides Enabled by Aryl Radical Activation of Carbon–Iodine Bonds. *Angew. Chem. Int. Ed.* **2021,** *n/a* (n/a); (h) Zeng, X.; Yan, W.; Zacate, S. B.; Chao, T.-H.; Sun, X.; Cao, Z.; Bradford, K. G. E.; Paeth, M.; Tyndall, S. B.; Yang, K.; Kuo, T.-C.; Cheng, M.-J.; Liu, W., Copper-Catalyzed Decarboxylative Difluoromethylation. *J. Am. Chem. Soc.* **2019,** *141* (29), 11398-11403.
9. (a) Liu, Z.; Chen, H.; Lv, Y.; Tan, X.; Shen, H.; Yu, H.-Z.; Li, C., Radical Carbofluorination of Unactivated Alkenes with Fluoride Ions. *J. Am. Chem. Soc.* **2018,** *140* (19), 6169-6175; (b) Xiao, H.; Shen, H.; Zhu, L.; Li, C., Copper-Catalyzed Radical Aminotrifluoromethylation of Alkenes. *J. Am. Chem. Soc.* **2019,** *141* (29), 11440-11445; (c) Shen, H.; Liu, Z.; Zhang, P.; Tan, X.; Zhang, Z.; Li, C., Trifluoromethylation of Alkyl Radicals in Aqueous Solution. *J. Am. Chem. Soc.* **2017,** *139* (29), 9843-9846; (d) Wang, J.; Shang, M.; Lundberg, H.; Feu, K. S.; Hecker, S. J.; Qin, T.; Blackmond, D. G.; Baran, P. S., Cu-Catalyzed Decarboxylative Borylation. *ACS Catal.* **2018,** *8* (10), 9537-9542; (e) Ahn, J. M.; Ratani, T. S.; Hannoun, K. I.; Fu, G. C.; Peters, J. C., Photoinduced, Copper-Catalyzed Alkylation of Amines: A Mechanistic Study of the Cross-Coupling of Carbazole with Alkyl Bromides. *J. Am. Chem. Soc.* **2017,** *139* (36), 12716-12723.
10. Lee, H.; Ahn, J. M.; Oyala, P. H.; Citek, C.; Yin, H.; Fu, G. C.; Peters, J. C., Investigation of the C–N Bond-Forming Step in a Photoinduced, Copper-Catalyzed Enantioconvergent N–Alkylation: Characterization and Application of a Stabilized Organic Radical as a Mechanistic Probe. *J. Am. Chem. Soc.* **2022,** *144* (9), 4114-4123.
11. While this work is under review, Shen and Hartwig have reported a pioneering work on the oxidative addition of Cu^{I} species with alkyl halides: Luo, Y.; Li, Y.; Wu, J.; Xue, X.-S.; Hartwig, J. F.; Shen, Q., Oxidative addition of an alkyl halide to form a stable Cu(III) product. *Science* **2023,** *381* (6662), 1072-1079.
12. (a) Bower, J. K.; Cypcar, A. D.; Henriquez, B.; Stieber, S. C. E.; Zhang, S., C(sp3)–H Fluorination with a Copper(II)/(III) Redox Couple. *J. Am. Chem. Soc.* **2020,** *142* (18), 8514-8521; (b) Bower, J. K.; Reese, M. S.; Mazin, I. M.; Zarnitsa, L. M.; Cypcar, A. D.; Moore, C. E.; Sokolov, A. Y.; Zhang,

S., C(sp3)–H cyanation by a formal copper(iii) cyanide complex. *Chem. Sci.* **2023,** *14* (5), 1301-1307.

13. Liu, S.; Liu, H.; Liu, S.; Lu, Z.; Lu, C.; Leng, X.; Lan, Y.; Shen, Q., C(sp3)-CF3 Reductive Elimination from a Five-Coordinate Neutral Copper(III) Complex. *J. Am. Chem. Soc.* **2020,** *142* (21), 9785-9791.
14. (a) Lu, Z.; Liu, H.; Liu, S.; Leng, X.; Lan, Y.; Shen, Q., A Key Intermediate in Copper-Mediated Arene Trifluoromethylation, [nBu4N][Cu(Ar)(CF3)3]: Synthesis, Characterization, and C(sp2)−CF3 Reductive Elimination. *Angew. Chem. Int. Ed.* **2019,** *58* (25), 8510-8514; (b) Willert-Porada, M. A.; Burton, D. J.; Baenziger, N. C., Synthesis and X-ray structure of bis(trifluoromethyl)(N,N-diethyldithiocarbamato)-copper; a remarkably stable perfluoroalkylcopper(III) complex. *Chem. Comm.* **1989,** (21), 1633-1634; (c) Romine, A. M.; Nebra, N.; Konovalov, A. I.; Martin, E.; Benet-Buchholz, J.; Grushin, V. V., Easy Access to the Copper(III) Anion [Cu(CF3)4]−. *Angew. Chem. Int. Ed.* **2015,** *54* (9), 2745-2749; (d) Zhang, S.-L.; Bie, W.-F., Isolation and characterization of copper(iii) trifluoromethyl complexes and reactivity studies of aerobic trifluoromethylation of arylboronic acids. *RSC Adv.* **2016,** *6* (75), 70902-70906; (e) Zhang, S.-L.; Bie, W.-F., Ligand-dependent formation of ion-pair CuI/CuIII trifluoromethyl complexes containing bisphosphines. *Dal. Trans.* **2016,** *45* (44), 17588-17592; (f) Zhang, S.-L.; Xiao, C.; Wan, H.-X., Diverse copper(iii) trifluoromethyl complexes with mono-, bi- and tridentate ligands and their versatile reactivity. *Dal. Trans.* **2018,** *47* (14), 4779-4784; (g) Tan, X. Q.; Liu, Z. L.; Shen, H. G.; Zhang, P.; Zhang, Z. Z.; Li, C. Z., Silver-Catalyzed Decarboxylative Trifluoromethylation of Aliphatic Carboxylic Acids. *J. Am. Chem. Soc.* **2017,** *139* (36), 12430-12433; (h) Zhang, H.-R.; Feng, C.-C.; Chen, N.; Zhang, S.-L., Direct Arene Trifluoromethylation Enabled by a High-Valent CuIII−CF3 Compound. *Angew. Chem. Int. Ed.* **2022,** *61* (40), e202209029.
15. Hartwig, J. F.; Collman, J. P., *Organotransition metal chemistry: from bonding to catalysis*. University Science Books Sausalito, CA: 2010; Vol. 1.
16. (a) Jacquet, J.; Salanouve, E.; Orio, M.; Vezin, H.; Blanchard, S.; Derat, E.; Desage-El Murr, M.; Fensterbank, L., Iminosemiquinone radical ligands enable access to a well-defined redox-active CuII–CF3 complex. *Chem Commun.* **2014,** *50* (72), 10394-10397; (b) Jacquet, J.; Blanchard, S.; Derat, E.; Desage-El Murr, M.; Fensterbank, L., Redox-ligand sustains controlled generation of CF3 radicals by well-defined copper complex. *Chem. Sci.* **2016,** *7* (3), 2030-2036.
17. (a) Daikh, B. E.; Finke, R. G., The persistent radical effect: a prototype example of extreme, 105 to 1, product selectivity in a free-radical reaction involving persistent .cntdot.CoII[macrocycle] and alkyl free radicals. *Journal of the American Chemical Society* **1992,** *114* (8), 2938-2943; (b) Collman, J.; McElwee-White, L.; Brothers, P.; Rose, E., Radical mechanism for the decomposition of RuOEP (CH2CH3) 2. Determination of the metal-carbon bond dissociation energy. *J. Am. Chem. Soc.* **1986,** *108* (6), 1332-1333; (c) Finke, R. G.; Smith, B. L.; Mayer, B. J.; Molinero, A. A., Cobalt-carbon bond homolysis and bond dissociation energy studies for the coenzyme B12 analog RCo [C2 (DO)(DOH) pn] I (R= PhCH2-,(CH3) 3CCH2-). *Inorg. Chem.* **1983,** *22* (25), 3677-3679; (d) Finke, R. G.; Hay, B. P., Thermolysis of adenosylcobalamin: a product, kinetic, and cobalt-carbon (C5') bond dissociation energy study. *Inorg. Chem.* **1984,** *23* (20), 3041-3043; (e) Hay, B. P.; Finke, R. G., Thermolysis of the cobalt-carbon bond of adenosylcobalamin. 2. Products, kinetics, and cobalt-carbon bond dissociation energy in aqueous solution. *J. Am. Chem. Soc.* **1986,** *108* (16), 4820-4829.
18. Le, C.; Chen, T. Q.; Liang, T.; Zhang, P.; MacMillan, D. W. C., A radical approach to the copper oxidative addition problem: Trifluoromethylation of bromoarenes. *Science* **2018,** *360* (6392), 1010.
19. (a) Morrison, J. A., Trifluoromethyl-Containing Transition Metal Complexes. In *Advances in Organometallic Chemistry*, Stone, F. G. A.; West, R., Eds. Academic Press: 1993; Vol. 35, pp 211-239; (b) Brothers, P. J.; Roper, W. R., Transition-metal dihalocarbene complexes. *Chem. Rev.* **1988,** *88* (7), 1293-1326; (c) Zhou, W.; Pan, W.-J.; Chen, J.; Zhang, M.; Lin, J.-H.; Cao, W.; Xiao, J.-C., Transition-metal difluorocarbene complexes. *Chem Commun.* **2021,** *57* (74), 9316-9329.
20. Reger, D. L.; Dukes, M. D., Molybdenum perfluorocarbene complexes. *J. Organometallic. Chem.* **1978,** *153* (1), 67-72.
21. Leclerc, M. C.; Bayne, J. M.; Lee, G. M.; Gorelsky, S. I.; Vasiliu, M.; Korobkov, I.; Harrison, D. J.; Dixon, D. A.; Baker, R. T., Perfluoroalkyl Cobalt(III) Fluoride and Bis(perfluoroalkyl) Complexes: Catalytic Fluorination and Selective Difluorocarbene Formation. *J. Am. Chem. Soc.* **2015,** *137* (51), 16064-16073.
22. Levin, M. D.; Chen, T. Q.; Neubig, M. E.; Hong, C. M.; Theulier, C. A.; Kobylianskii, I. J.; Janabi, M.; O'Neil, J. P.; Toste, F. D., A catalytic fluoride-rebound mechanism for C(sp(3))-CF3 bond formation. *Science* **2017,** *356* (6344), 1272-1275.
23. Wang, G.; Li, M.; Leng, X.; Xue, X.; Shen, Q., Neutral Five-Coordinate Arylated Copper(III) Complex: Key Intermediate in Copper-Mediated Arene Trifluoromethylation. *Chinese J. Chem.* **2022,** *40* (16), 1924-1930.
24. (a) Knizia, G., Intrinsic Atomic Orbitals: An Unbiased Bridge between Quantum Theory and Chemical Concepts. *Journal of Chemical Theory and Computation* **2013,** *9* (11), 4834-4843; (b) Klein, J. E. M. N.; Knizia, G., cPCET versus HAT: A Direct Theoretical Method for Distinguishing X–H Bond-Activation Mechanisms. *Angew. Chem. Int. Ed.* **2018,** *57* (37), 11913-11917.
25. Tatsumi, K.; Hoffmann, R.; Yamamoto, A.; Stille, J. K., Reductive Elimination of d8-Organotransition Metal Complexes. *Bull. Chem. Soc. Jpn.* **1981,** *54* (6), 1857-1867.
26. Xiao, H.; Liu, Z.; Shen, H.; Zhang, B.; Zhu, L.; Li, C., Copper-Catalyzed Late-Stage Benzylic C(sp3)–H Trifluoromethylation. *Chem* **2019,** *5* (4), 940-949.


CuIII–C homoylsis competes with reductive elimination reaction
CF3
F3C
CuIII
CF3
C6F5
CF3 removal
F3C
sol
CuIII
C6F5
F3C
sol
homolytic cleavage
ligand-controlled CuIII reactivty
reductive elimination
[(CF3)3CuII]-
C6F5CH2
[CuI]
C6F5CH2–CF3
CuIII–alkyl homolysis
first measurement CuIII–C strength
switch from Cu–C homolysis to C–C reductive elimination