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RESEARCH ARTICLE

The Role of Electron Transfer in Copper-Mediated C(sp^2)-H Trifluoromethylation

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Abstract: We report copper(II) and copper(III) trifluoromethyl complexes supported by pyridinedicarboxamide ligand (**L**) as a platform for investigating the role of electron transfer in C(sp^2)-H trifluoromethylation. While the copper(II) trifluoromethyl complex is unreactive towards (hetero)arenes, the formal copper(III) trifluoromethyl complex performs C(sp^2)-H trifluoromethylation of a wide range of (hetero)arenes. Mechanistic studies using the copper(III) trifluoromethyl complex suggest that the mechanism of arene trifluoromethylation is substrate-dependent. When the thermodynamic driving force for electron transfer is high, the reaction proceeds through a previously unidentified single electron transfer (SET) mechanism, where an initial electron transfer occurs between the substrate and oxidant prior to CF_3 group transfer. Otherwise, a CF_3 radical release/electrophilic aromatic substitution (S_EAr) mechanism is followed. These studies provide valuable insights into the role of strong oxidants and potential mechanistic dichotomy in Cu-mediated C(sp^2)-H trifluoromethylation.

Introduction

The incorporation of the trifluoromethyl group (CF_3) into organic compounds plays a key role in the development of new materials, pharmaceuticals, and agrochemicals.[1–4] Copper-based catalysts have been widely employed for the catalytic formation of C-CF_3 bonds.[5–7] For example, McLoughlin et al. reported the Cu-catalyzed cross-coupling of iodofluoroalkanes and iodoarenes in 1969.[8] Since this pioneering discovery, the Ar-CF_3 cross-coupling reaction has been developed into a reliable synthetic method.[9–12] In recent decades, considerable attention has been directed towards the trifluoromethylation of C-H bonds. This has led to the development of copper-catalyzed C(sp^2)-H and C(sp^3)-H trifluoromethylation methods utilizing various nucleophilic or electrophilic CF_3 sources, e.g., $TMSCF_3$, Togni's reagents, and Umemoto's regents.[10,13–21]

High-valent Cu^{III}-CF_3 species have been widely proposed as intermediates in copper-catalyzed C-H trifluoromethylation, which are typically thought to facilitate C-CF_3 bond formation via reductive elimination (Figure 1A)[14,15,20,22–25] or CF_3 radical release/electrophilic aromatic substitution (S_EAr) (Figure 1B).[11,26,27] Studies by Shen[24,28] and Liu[20] have provided compelling evidence for the reductive elimination mechanism, demonstrating C(sp^2)-CF_3 or C(sp^3)-CF_3 formation from discrete Cu^{III}-CF_3 aryl/alkyl complexes (Figure 1A). Menjon,[27] Zhang,[29] and others[11] proposed an alternative radical pathway, where photolysis or thermolysis of Cu^{III}-CF_3 complexes liberates CF_3 radical, which can undergo S_EAr reaction to furnish the desired trifluoromethylated (hetero)arenes (Figure 1B).[29] This mechanism bears resemblance to those followed by other CF_3 radical precursors, e.g., CF_3SO_2Cl, CF_3SO_2Na, and $AgCF_3$.[30–34]

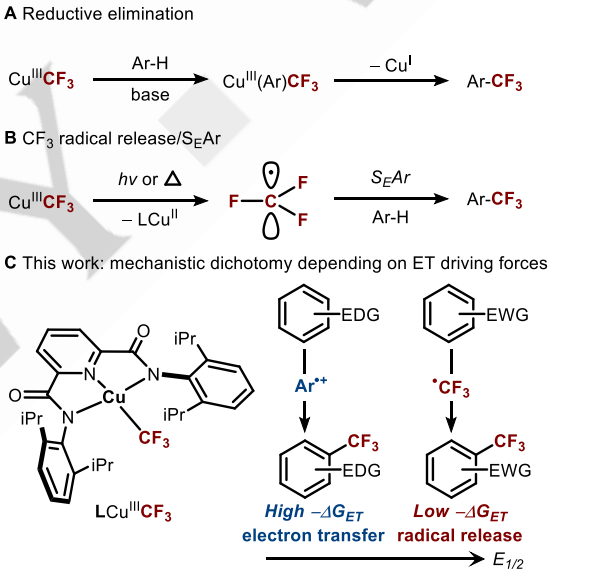


Figure 1. (A-B) Two previously reported mechanisms for C(sp^2)-H trifluoromethylation via copper(III) trifluoromethyl complexes. (C) Substrate-dependent mechanism crossover as a function of redox potential from CF_3 radical release/S_EAr to SET.

Interestingly, regardless of the proposed mechanism, strong chemical oxidants ($K_2S_2O_8$, Ag_2CO_3, Cu/O_2) or photochemical oxidants, including Ir and Ru photocatalysts, are often employed to facilitate C-CF_3 bond formation.[34–36] Even in the case of discrete Cu^{III}-CF_3 complexes, which are capable of performing trifluoromethylation alone, the inclusion of a co-oxidant markedly enhances the efficiency of the trifluoromethylation.[29] These observations suggest that single electron transfer (SET) may play a role in trifluoromethylation. However, this possibility remains unexplored.

Herein, we investigated the role of SET in CF_3 transfer from formal Cu^{III}-CF_3 complex to (hetero)arenes. We employed the versatile pyridinedicarboxamide (**L**) ligand system, a platform that can

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effectively model organometallic reactions involving copper(II/III) intermediates.[37–45] Both the copper(II) trifluoromethyl complex [TBA]**L**Cu^{II}CF$_3$ and formally copper(III) trifluoromethyl complex **L**Cu^{III}CF$_3$ were synthesized. While [TBA]**L**Cu^{II}CF$_3$ displays minimal C-H trifluoromethylation reactivity, **L**Cu^{III}CF$_3$ can transfer its CF$_3$ group to a wide range of (hetero)arenes in the presence of oxidant in 42-76% yields. Mechanistic investigations, including a Marcus study and a radical trap experiment, provide compelling evidence for a substrate-based mechanism crossover from CF$_3$ radical release/S_EAr to a previously unidentified SET mechanism.

Results and Discussion

Synthesis of [TBA]LCu^{II}CF$_3$ and LCu^{III}CF$_3$

Treatment of previously reported [TBA]**L**Cu^{II}F complex[43] with 1.5 equivalents of trimethyl(trifluoromethyl)silane (TMSCF$_3$) in tetrahydrofuran at room temperature for 30 minutes resulted in the formation of a red copper (II) trifluoromethyl complex [TBA]**L**Cu^{II}CF$_3$ complex in 90% yield (λ = 515 nm, ε = 615 M^{-1}cm^{-1} in acetonitrile, Scheme 1). X-ray diffraction (XRD) analysis of [TBA]**L**Cu^{II}CF$_3$ single crystals grown from a pentane/dichloromethane mixture shows a square planar Cu center with an average Cu-N bond length of 2.01(4) Å and a Cu-CF$_3$ bond length of 1.971(3) Å (Figure 2A). Electron paramagnetic resonance (EPR) analysis of [TBA]**L**Cu^{II}CF$_3$ in 3:1 toluene:acetone mixture at 30 K shows a rhombic S = 1/2 signal with g_x = 2.024, g_y = 2.034, g_z = 2.153, and a coupling constant A_z = 480 Hz (Figure S57). The cyclic voltammogram of [TBA]**L**Cu^{II}CF$_3$ in acetonitrile with 0.1 M TBAClO$_4$ electrolyte exhibits a quasi-reversible redox couple at $E_{1/2}$ = −0.15 V vs. Fc/Fc$^+$ in 1,2-dichloroethane (DCE) (Figure S2).

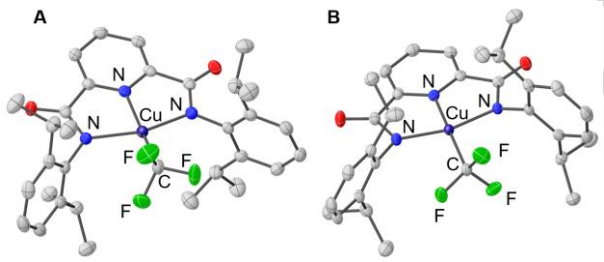
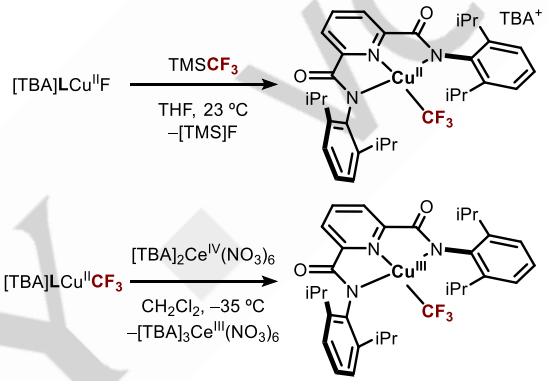


Figure 2. Single crystal XRD structures of (A) [TBA]**L**Cu^{II}CF$_3$ and (B) **L**Cu^{III}CF$_3$ with thermal ellipsoids shown at a 30% level of probability. All hydrogen atoms, solvent molecules, and countercations are omitted for clarity. Average C-N bond distances (Å): [TBA]**L**Cu^{II}CF$_3$ 2.01(4), **L**Cu^{III}CF$_3$: 1.90(4). C-CF$_3$ bond distances (Å): [TBA]**L**Cu^{II}CF$_3$: 1.971(3), **L**Cu^{III}CF$_3$: 1.9524(17).[46]

Treatment of [TBA]**L**Cu^{II}CF$_3$ with oxidant [TBA]$_2$Ce^{IV}(NO$_3$)$_6$ ($E_{1/2}$ = 0.472 V vs. Fc/Fc$^+$ in DCE) in dichloromethane affords a dark purple copper(III) trifluoromethyl complex **L**Cu^{III}CF$_3$ in quantitative yield (λ = 540 nm, ε = 10900 M^{-1}cm^{-1} in acetonitrile, Scheme 1). The isolated **L**Cu^{III}CF$_3$ is stable at room temperature in a wide range of solvents, e.g., benzene, pentane, acetonitrile, DCE, and dichloromethane. XRD analysis of the single crystals of **L**Cu^{III}CF$_3$ grown from pentane shows a square planar Cu environment with an average Cu-N bond length of 1.90(4) Å and a Cu-CF$_3$ bond length of 1.9524(17) Å (Figure 2B). Upon oxidation, the Cu-N bonds contract significantly from 2.01(4) to 1.90(4) Å, while the Cu-CF$_3$ bond length remains roughly the same (Cu^{II}: 1.971(3) to Cu^{III}: 1.9524(17) Å). ^{1}H NMR in CD$_2$Cl$_2$ shows six sharp resonances within the 0-9 ppm range, accounting for ligand protons and suggesting a diamagnetic ground state for **L**Cu^{III}CF$_3$ (Figure S35A). ^{19}F NMR analysis in CD$_2$Cl$_2$ shows a single resonance at −41.42 ppm (Figure S35B). Previous studies on formal Cu(III)-CF$_3$ complexes suggest that the Cu-CF$_3$ bond might be quite weak.[27] Therefore, we evaluated the Cu-CF$_3$ bond strength in **L**Cu^{III}CF$_3$ and compared it to (Phen)Cu^{III}(CF$_3$)$_3$ reported by Zhang et al..[29] Both complexes exhibit Cu-CF$_3$ bond strength around 33.7 kcal/mol (see Supporting Information). The relatively weak Cu-CF$_3$ bond suggests **L**Cu^{III}CF$_3$ could be utilized for CF$_3$ group transfer.

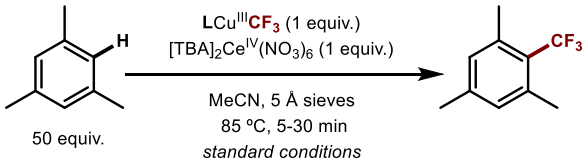


Scheme 1. Synthesis of copper(II) and copper(III)-CF$_3$ complexes.

C(sp^2)-H Trifluoromethylation Reactivity of LCu^{III}CF$_3$

The trifluoromethylation reactivity of complexes [TBA]**L**Cu^{II}CF$_3$ and **L**Cu^{III}CF$_3$ was then explored. While [TBA]**L**Cu^{II}CF$_3$ is unreactive toward (hetero)arenes, treatment of **L**Cu^{III}CF$_3$ with 50 equivalents of mesitylene and one equivalent of oxidant ([TBA]$_2$Ce^{IV}(NO$_3$)$_6$) in acetonitrile affords the trifluoromethylated product in 72% yield after 5 minutes at 85 °C (Table 1, entry 1). Without molecular sieves, the yield of the reaction drops to 62% (Table 1, entry 2), perhaps due to the residual water introduced by [TBA]$_2$Ce^{IV}(NO$_3$)$_6$.

Table 1. Optimization of C(sp^2)-H trifluoromethylation by **L**Cu^{III}CF$_3$. All yields are determined by ^{19}F NMR with a hexafluorobenzene internal standard.

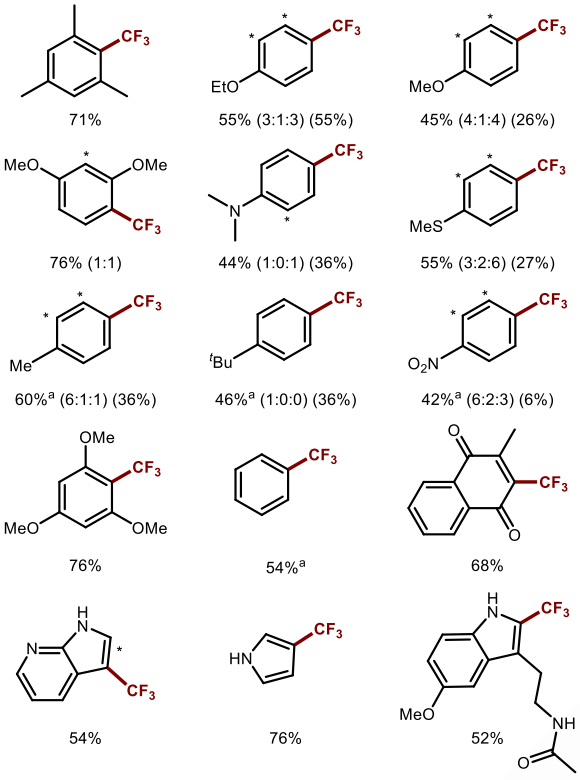


entry	deviation from standard conditions	yield (%)
1	none	72
2	no 5 Å sieves	62
3	no [TBA]$_2$Ce^{IV}(NO$_3$)$_6$ or 5 Å sieves	52
4	DCE, no sieves, 60 °C, 150 equiv. substrate	71

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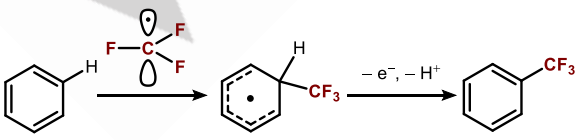
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Table 2. Scope of C(sp^2)-H trifluoromethylation by LCu^{III}CF$_3$.



Major products are shown, and the minor product(s) are indicated by asterisks. The ratio of para:meta:ortho selectivity is given in parentheses. Yields without oxidant are given in parentheses. [a] 250 equiv. substrate was used.

It has been shown previously that the inclusion of a co-oxidant in copper-catalyzed C-H trifluoromethylation can improve the reaction yield significantly.[9–15] Zhang et al. attributed these improvements to the S$_E$Ar mechanism of the reaction,[29] noting that the rearomatization of the arene CF$_3$ radical intermediate requires one equivalent of oxidant (Scheme 2). Similarly, we found that the inclusion of one equivalent of oxidant increases the yield from 52% (without oxidant, Table 1, entry 3) to 72% (with oxidant). Interestingly, while the reaction with mesitylene requires 30 minutes to complete without oxidant, it reaches completion in only 5 minutes when oxidant is included, as indicated by the disappearance of the dark purple color of **L**Cu^{III}CF$_3$. This observation implicates the involvement of the oxidant in the rate-determining step.

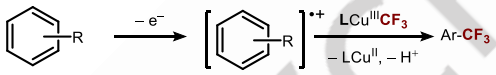


Scheme 2. Proposed S$_E$Ar mechanism for C(sp^2)-H trifluoromethylation.

Having established the optimized conditions, the scope of C(sp^2)-H trifluoromethylation was evaluated (Table 2). Overall, electron-rich (hetero)arenes show higher yields than more electron-poor substrates. The selectivity of C(sp^2)-H trifluoromethylation is consistent with the literature report.[47] For *tert*-butylbenzene, the functionalization of ortho and meta sites is reduced due to steric hindrance. Drug-like molecules, such as melatonin, can also be successfully trifluoromethylated.

The Role of Single Electron Transfer in CF$_3$ Transfer

The transfer of CF$_3$ from **L**Cu^{III}CF$_3$ suggests that the rate-limiting step may involve the cleavage of the Cu^{III}-CF$_3$ bond. However, this proposal does not align with the notably accelerated rate upon the addition of oxidant. Additionally, under standard reaction conditions, electron-rich substrates exhibit significantly faster reactions (typically 5-10 minutes), while electron-poor substrates require up to 30 minutes of reaction time.



Scheme 3. SET mechanism for C(sp^2)-H trifluoromethylation.

This correlation between the electronic character of the substrates and the reaction kinetics prompted our exploration into the possibility of a SET mechanism. We hypothesize that the reaction can be initiated by the oxidation of (hetero)arene substrate by [TBA]$_2$Ce^{IV}(NO$_3$)$_6$ to generate an aryl radical cation intermediate, which can then be functionalized by **L**Cu^{III}CF$_3$ to afford Ar-CF$_3$ (Scheme 3). If this proposed mechanism is followed, the rate-limiting step should be the electron transfer between the oxidant [TBA]$_2$Ce^{IV}(NO$_3$)$_6$ and the arene substrate. Accordingly, kinetic analysis of the reaction between **L**Cu^{III}CF$_3$ and thioanisole indicates a first-order dependence on the concentration of the oxidant and substrate (Figure 3).

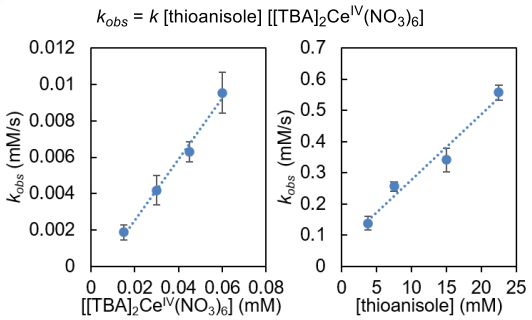


Figure 3. Determination of the reaction rate order dependence for [TBA]$_2$Ce^{IV}(NO$_3$)$_6$ oxidant and thioanisole substrate.

To further evaluate the possibility of a SET mechanism, we conducted a Marcus study,[44,48–50] in which the driving force of electron transfer ($-\Delta G_{ET}$) and the kinetics of trifluoromethylation (k_1) for a series of substituted arenes with varying electronic properties (R = H, NO$_2$, ^{t}Bu, CH$_3$, OEt, OCH$_3$, SCH$_3$, N(CH$_3$)$_2$) are assessed. We first determined the oxidation potential (E_{ox}) of each arene using cyclic voltammetry (CV, Figures S4-S11). Subsequently, we calculated the driving force for electron transfer

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with $[TBA]_2Ce^{IV}(NO_3)_6$ (expressed as $-\Delta G_{ET}$) for each substrate using the equation $-\Delta G_{ET} = -(E_{ox,substrate} - E_{1/2,oxidant})$.[51,52]

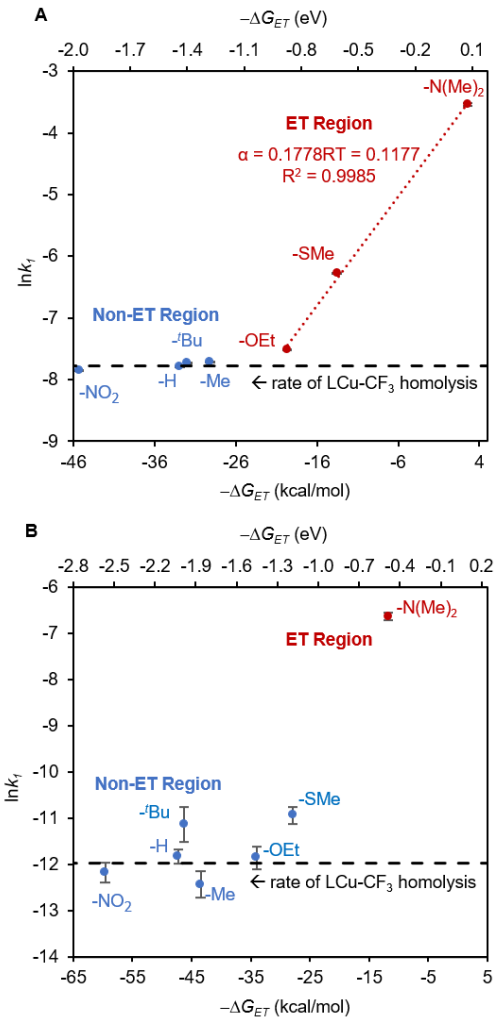


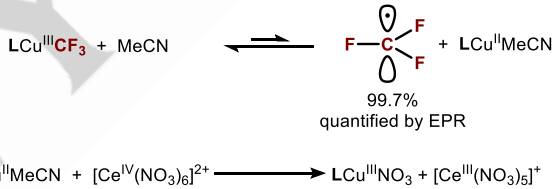
Figure 4. (A) Marcus plot in the presence of $[TBA]_2Ce^{IV}(NO_3)_6$ oxidant. (B) Marcus plot in the absence of oxidant. The electron transfer driving force ($-\Delta G_{ET}$) is determined by cyclic voltammetry. $\ln k_1$ is determined by monitoring decay of $\mathbf{L}Cu^{III}CF_3$ by UV-vis (λ_{max} = 570 nm in DCE). All studies were performed in DCE.

The rate of trifluoromethylation was determined for each substrate by monitoring the UV-vis profile of $\mathbf{L}Cu^{III}CF_3$ (λ_{max} = 570 nm) at 60 °C in DCE with 150 equivalents of substrate and one equivalent of $[TBA]_2Ce^{IV}(NO_3)_6$. A lower temperature was chosen to ensure reliable rates were properly measured. We also determined that this set of reaction conditions is suitable for our C-H trifluoromethylation reaction (Table 1, entry 4).

The resulting first-order rate constants (k_1) were used to construct a Marcus plot ($\ln k_1$ vs. $-\Delta G_{ET}$, Figure 4). If the reaction proceeds through a rate-limiting electron transfer step, we anticipate a linear correlation with slope represented by α/RT, where α is the Brønsted α value.[51,52] Interestingly, we observed two distinct regions: (1) an electron-transfer (ET) region with a linear correlation between $-\Delta G_{ET}$ and $\ln k_1$ (R^2 = 0.998k5, Figure 4, red) and (2) a non-electron-transfer region (non-ET, Figure 4, blue) where the reaction rate remains similar to that of $\mathbf{L}Cu^{III}CF_3$ self-decay (Figure 4, black line). The *α* value of ET region is modest at 0.1177 compared to the ideal value of 0.5, suggesting transition state asynchronicity caused by a delay in the product stabilization factors behind the transition state. The synchronicity of the reaction could be influenced by the aromaticity or steric effects of the arene during ET, or other molecular processes after the ET, such as the release of CF_3 radical from $\mathbf{L}Cu^{III}CF_3$.[52,53]

The two distinct regions in the Marcus plot suggest a mechanism crossover. For electron-rich substrates, the reaction proceeds through rate-limiting electron transfer between the oxidant and arene substrate (Scheme 3). The first-order dependence on the concentration of oxidant and substrate shown in Figure 3 is also consistent with this hypothesis.

Conversely, within the non-ET region, the mechanism is likely dominated by the rate of Cu^{III}-CF_3 bond homolysis. In this case, the reaction rate is not substrate-dependent and closely resembles the self-decay rate of $\mathbf{L}Cu^{III}CF_3$ (Figure 4, black line), which directly corresponds to the rate of CF_3 radical release from $\mathbf{L}Cu^{III}CF_3$ when the CF_3 radical release/S_EAr mechanism is followed (Scheme 4). Consistent with this hypothesis, EPR analysis of the products of $\mathbf{L}Cu^{III}CF_3$ self-decay in MeCN at 85 °C shows the formation of $\mathbf{L}Cu^{II}MeCN$ in >99% yield (Scheme 4, Figures S58 and S59), suggesting that the decay of $\mathbf{L}Cu^{III}CF_3$ quantitatively releases CF_3 radical.



Scheme 4. Release of CF_3 radical from $\mathbf{L}Cu^{III}CF_3$.

Since the redox potential of $\mathbf{L}Cu^{III}CF_3$ is quite high (−0.15 V vs. Fc/Fc^+), the $\mathbf{L}Cu^{III}CF_3$ complex itself could potentially engage in ET with electron-rich arenes. To examine this hypothesis, we performed an analogous Marcus study in the absence of oxidant. In this case, the driving force of ET is calculated using the redox potential of $\mathbf{L}Cu^{III}CF_3$ (−0.15 V vs. Fc/Fc^+). Indeed, the resulting Marcus plot also suggests a mechanism crossover when the ET driving force approaches −1.0 eV (Figure 4B). While the majority of arenes exhibit a rate similar to the self-decay of $\mathbf{L}Cu^{III}CF_3$, the rates of the -SMe and -NMe_2 derivatives are markedly faster, suggesting electron transfer. Notably, the rate of release of CF_3 radical from the $\mathbf{L}Cu^{III}CF_3$ is slower in the absence of an oxidant. This is due to the further reaction of $\mathbf{L}Cu^{II}$ with $[TBA]_2Ce^{IV}(NO_3)_6$ to generate $\mathbf{L}Cu^{III}NO_3$, which drives the equilibrium of CF_3 radical release to the completion (Scheme 4).

To further investigate the mechanism dichotomy, we designed a substrate, 1,2,3-trimethyl-5-(allyloxy)-benzene (Figure 5A, **1**), which has a redox potential between the ET region and the non-ET region (E_{ox} = 0.927 V vs. Fc/Fc^+ in DCE, $-\Delta G_{ET}$ = –0.455 eV). In the case of CF_3 radical release, the S_EAr reaction of arene and CF_3 radical is expected to produce **2**, and the CF_3 radical addition to the alkene is expected to produce the cyclized product **3**.[54,55] However, if the SET pathway is followed, only the cyclized product

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3 is expected.[56] This selectivity of the SET pathway to **3** is because the oxidation of **1** takes place at the arene group rather than the allyl ether, as the oxidation potential of **3** (E_{ox}, 0.927 V vs. Fc/Fc^+) closely matches that of **4** (0.928 V vs. Fc/Fc^+) and is much lower than **5** (1.210 V vs. Fc/Fc^+, Figure 5B, see Supporting Information). Since the SET pathway exclusively yields compound **3**, a higher selectivity for **3** is anticipated when the reaction is carried out in the presence of a strong oxidant. Indeed, when the trifluoromethylation reaction of **1** is conducted in the presence of one equivalent of $[TBA]_2Ce^{IV}(NO_3)_6$ oxidant, the ratio of **2** to **3** shifts from 1.2:1 (without oxidant) to 1:1.3 (with oxidant). The flipped product distribution is consistent with the proposed mechanism dichotomy – the SET driving force is higher in the presence of $[TBA]_2Ce^{IV}(NO_3)_6$, therefore increasing the contribution of SET pathway to trifluoromethylation.

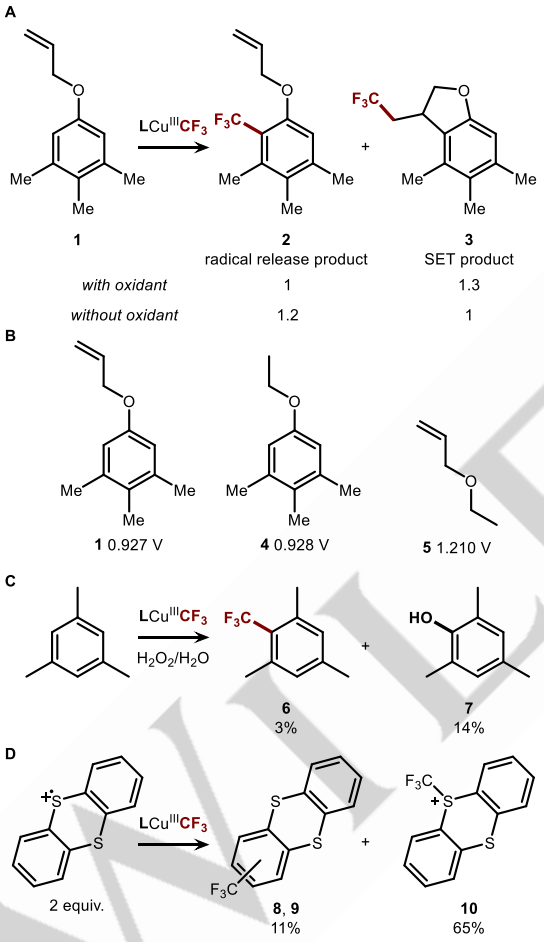


Figure 5. (A) Aryl radical trap experiment via intramolecular cyclization. (B) Oxidation potentials (V vs. Fc/Fc^+) of aryl radical trap substrate in comparison to other model compounds. (C) The aryl radical cation intermediate can be trapped with H_2O_2/H_2O to produce phenol. (D) Thianthrene radical cation reacts with **L**$CuCF_3$ to produce trifluoromethylated products.

The SET mechanism was further tested by trapping the aryl radical cation intermediate. Trifluoromethylation of mesitylene was performed in the presence of excess amount of H_2O_2 (24 equiv. in 56 equiv. H_2O). Under these conditions, the yield of the trifluoromethylated product **6** drops from 72% to 3%, while phenol product **7** is observed at a 14% yield, suggesting the aryl radical cation intermediate is trapped with H_2O_2 or H_2O prior to functionalization by **L**$Cu^{III}CF_3$ (Figure 5C). Finally, to evaluate whether **L**$Cu^{III}CF_3$ can capture aryl radical cations, we investigated its reaction with thioanthrene radical cation PF_6 salt.[57,58] The stable radical cation serves as a model for the aryl radical cation intermediate generated via the electron transfer mechanism. Treatment of **L**$Cu^{III}CF_3$ with two equivalents of thioanthrene radical cation afforded Ar-CF_3 coupled products **8** and **9** in a total 11% yield (Figure 5D). The modest yield is attributed to competitive S-CF_3 coupling, which produced 5-(trifluoromethyl)-5H-thianthren-5-ium (**10**) in 65% yield. Despite the low efficiency, the successful Ar-CF_3 bond formation supports the proposed coupling between radical cations and **L**$Cu^{III}CF_3$ complex.

Conclusions

In summary, we have synthesized and characterized formal Cu^{II} and Cu^{III} monotrifluoromethyl complexes as a platform to investigate the mechanism of copper-mediated C(sp^2) trifluoromethylation. The **L**$Cu^{III}CF_3$ complex can perform trifluoromethylation of a wide range of (hetero)arenes. Marcus studies suggest a mechanism crossover as a function of the electron transfer driving forces. For electron-rich substrates, a SET mechanism is followed, and the oxidation of the arenes occurs as the first step. In contrast, electron-poor substrates undergo a S_EAr mechanism involving CF_3 radical release. Our finding explains why excess oxidant is necessary for efficient CF_3 transfer, as is the case in many previous reports of Cu-mediated trifluoromethylation. The SET mechanism might be present in other copper-catalyzed C(sp^2)-H functionalization reactions. This will be the topic of our future investigations.

Supporting Information

The authors have cited additional references within the Supporting Information.[59-79]

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Keywords: Arenes, Copper, Electron transfer, Fluorine, Trifluoromethylation

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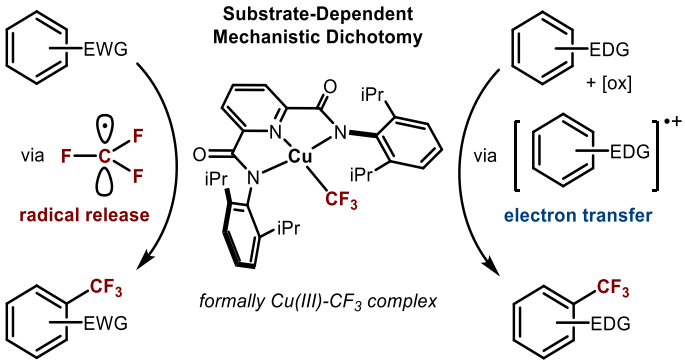
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Copper(II) and copper(III) trifluoromethyl complexes were used to elucidate the mechanism of Cu-mediated C(sp^2)-H trifluoromethylation. For electron-rich substrates, a previously unidentified single electron transfer (SET) mechanism is followed, whereas electron-poor substrates follow CF_3 radical release/electrophilic aromatic substitution (S_EAr).

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