Mechanistic Insight into Copper-Mediated Trifluoromethylation of Aryl Halides: The Role of Cul

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ACCESS Metrics & More Article Recommendations **SUPPORTING Information** Mechanistic map for Cu-mediated trifluoromethylation of ArX ABSTRACT: The synthesis, characterization, and reactivity of key intermediates $[Cu(CF_3)(X)]^-Q^+$ (X = CF₃ or I, Q = PPh₄) in [CuCF₂] Arl ArCF₃ + Cul fast copper-mediated trifluoromethylation of aryl halides were studied. [Cu(CF₃)(I)] -– Cul Qualitative and quantitative studies showed $[Cu(CF_3)_2]^-Q^+$ and $[Cu(CF_3)(I)]^-Q^+$ were not highly reactive. Instead, a much more $[Cu(CF_3)_2]^-$ Arl $ArCF_3 + [Cu(CF_3)(I)]^-$ slow reactive species, ligandless [CuCF₃] or DMF-ligated species CF_3Y [Cul₂] [(DMF)CuCF₃], was generated in the presence of excess CuI. Cul On the basis of these results, a general mechanistic map for CuI-[Cu(CF₃)(I)][−] Arl ArCF₃ + [Cul₂] slower promoted trifluoromethylation of aryl halides was proposed.

HOAc-promoted protocol for trifluoromethylation of aryl halides with $[Ph_4P]^+[Cu(CF_3)_2]^-$ was developed.

INTRODUCTION

Trifluoromethylated (hetero)arenes are privileged structural motifs in a considerable number of prescribed drugs and drug candidates in the pipelines of the pharmaceutical companies, owing to the unique steric and electronic properties of the trifluoromethyl group that might allow us to fine tune the molecule's biological properties including metabolic stability and lipophilicity.² Consequently, in the past decade, a wide variety of methods including transition-metal-catalyzed crosscoupling reactions or C-H trifluoromethylation that are capable of late-stage incorporation of the trifluoromethyl group into (hetero)arenes have emerged.³ More specifically, copper-mediated/-catalyzed trifluoromethylation of aryl halides represents one of the most practical approaches for the construction of the trifluoromethylated (hetero)arene units, largely ascribing to the copper catalyst's high reactivity, low cost, mild conditions, and broad functional group compatibility.⁴

Furthermore, on the basis of this mechanistic understanding, a

The first copper-mediated trifluoromethylation of aryl iodides by using CF₃I as the trifluoromethyl source was reported by McLoughlin and Thrower⁵ and later on by Kobayashi and Kumadaki in 1969.6 Mechanistically, it was proposed that reaction of copper powder with CF₃I generates [CF₃Cu], which then reacts with aryl iodide to give the corresponding CF₃Ar, even though the identity of [CF₃Cu] was not determined. From then on, a plethora of approaches for the generation of active [CF₃Cu] species were developed, including using trifluoromethyl metal reagent $(MCF_3)_{t}^{7}$ a combination of fluoride with in situ generated difluorocarbene from difluorocarbene precursors,8 Ruppert-Prakash reagent (Me_3SiCF_3) , CF_3CO_2Na , well as a few well-defined trifluoromethylcopper(I) complexes.¹³ More recently, copper-catalyzed trifluoromethylation of aryl halides under mild conditions was also reported.^{8c,14}

Even though widespread applications of this strategy in the preparation of trifluoromethylated drug candidates have been achieved, mechanistic studies,¹⁵ especially the experimental elucidation of the structures of active [CF₃Cu] species in copper-mediated/-catalyzed trifluoromethylation approaches, lag far behind. In 1986, the group of Burton reported the first spectroscopic studies of trifluoromethylcopper(I) species in this process (Scheme 1A).¹⁵ A characteristic peak with a chemical shift of -28.8 ppm (A) in the ¹⁹F NMR spectrum was generated upon mixing a solution of trifluoromethylzinc/ cadmium in DMF/HMPA with copper(I) salt at -50 °C. In the absence of HMPA, the peak disappeared at room temperature, and two new peaks at -32.3 ppm (B) and -35.5 ppm (C) in DMF were formed (Scheme 1A). It was found that both (A) and (B) were able to react with aryl iodides while species (C) was not active at all. Later on, these signals were proposed to be $[(CF_3)Cu] \cdot L$ (L = metal halide), $[(CF_3)_2Cu]^-$, and $[(CF_3)_4Cu]^{-16}$ In 2008, Kolomeitsev and co-workers reported that similar [CF₃Cu] species were generated when a mixture of CuBr, Me₃SiCF₃, and KF in a mixed solvent of DMF/DMI was stirred at 0 °C. In this case, these species were assigned as CF₃Cu·KBr (-28.8 ppm in DMF/DMI), $K^+[Cu(CF_3)_2]^-$ (-32.4 ppm in DMF/DMI),

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Scheme 1. Previous Efforts in Elucidation the Key Intermediates in Copper-Mediated Trifluoromethylation of Aryl Halides

A Burton. 1986 $\frac{\text{DMF}}{\text{-80 °C}} \text{ [CuCF_3] ([A])} \frac{\text{DMF}}{\text{rt}}$ CF₃CdX + CuBr -► [CuCF₃] ([**B**]) + [CuCF₃] ([**C**]) X = Br. Cl-28.8 ppm -32.3 ppm -35.5 ppm B Kolomeitsev, 2008 3 + CuBr KF (1.0 equiv.) (1.2 equiv.) DMF/DMI 0 °C, 1.5 h Me₃SiCF₃ + CuBr $CF_3Cu \cdot KBr + K[Cu(CF_3)_2] +$ $K[Cu(CF_3)_4]$ 76% 21% 3% -28.8 ppm -35.7 ppm -32.1 ppm C Yagupolskii, 2010 $\frac{\text{DMF}}{\text{rt. 2 h}} \text{Cu[Cu(CF_3)_2]} + \text{CuCF}_3 + \text{Cu[Cu^{III}(CF_3)_4]}$ Zn(CF₃)Br · DMF + CuBr · -28.4 ppm -32.0 ppm -35.1 ppm D well-defined complexes Mes Mes [Cu(CF₃)₂] PPh₄⁺[Cu(CF₃)₂]⁻ $Cs^{+}[Cu(CF_{3})_{2}]$ Shen (2019) Perez-Temprano (2019) Vicic (2008) Mes Meś

and an organocopper(III) species $K^+[Cu(CF_3)_4]^-$ (-35.7 ppm) (Scheme1B).¹⁷ Likewise, Yagupolskii and co-workers also reported, in 2010, that similar signals in the ¹⁹F NMR spectrum that corresponded to the [CF₃Cu] species were observed from treatment of CuBr with a solution of Zn(CF₃)Br·DMF in a molar ratio of 2:1 in DMF at room temperature. In this work, the signals were assigned as CuCF₃ (-32.0 ppm in DMF) and $Cu[Cu(CF_3)_2]$ (-28.4 ppm in)DMF) and Cu[Cu^{III}(CF₃)₄] (-35.1 ppm in DMF) (Scheme 1c).^{7b} Notably, while the assignment of the signal at -35.1ppm in ¹⁹F NMR spectra of the [CF₃Cu] species from three groups was consistent, the assignment of the other two signals was controversial, and the unambiguous structures of these species remained elusive. Moreover, Goossen and co-workers reported that when equimolar CuI and $K^{+}[CF_{3}B(OMe)_{3}]^{-}$ in DMF was stirred at room temperature, a species with a chemical shift of -28.1 ppm was generated, which was assigned as $[Cu(CF_3)(I)]^-$. Nevertheless, again, this species was not isolated and characterized.^{14b}

To elucidate the structure of the observed $[CF_3Cu]$ species, several groups have tried to characterize the proposed structure by independent synthesis. In 2008, Vicic and co-workers reported the synthesis and characterization of a well-defined cuprate complex, $[(SIMes)_2Cu]^+[Cu(CF_3)_2]^-$, with a chemical shift (-31.5 ppm in THF) close to those observed previously (Scheme 1D).^{13a} However, $[(SIMes)_2Cu]^+[Cu(CF_3)_2]^-$ reacted with aryl iodides sluggishly, and it was converted to more active neutral Cu(I) species [(SIMes)Cu(CF₃)] that reacted with aryl iodides efficiently (Scheme 1).¹⁸ In 2019, the groups of Pérez-Temprano and Shen independently reported the preparation, characterization, and reactivity studies of crystalline ionic cuprate complexes $Cs^{+}[Cu(CF_3)_2]^{-}(-31.1 \text{ ppm in})$ DMF)¹⁹ and $[Ph_4P]^+[Cu(CF_3)_2]^-$ (-31.4 ppm in THF or CDCl₃).²⁰ It was found that both complexes reacted with aryl iodides slowly at 50 or 100 °C (Scheme 1D). However, these reactions were accelerated dramatically when 1 equiv of CuI was added, and the scope of the reaction investigated by Shen's group showed that not only aryl iodides but also active heteroaryl bromides or aryl chlorides with an ortho-ester or -nitro directing group reacted to give the corresponding trifluoromethyl (hetero)arenes in good to excellent yields.²⁰ DFT calculation by Pérez-Temprano and co-workers proposed that the active copper species in the reaction was $[(DMF)-Cu(CF_3)]$, which was generated by thermal decomposition of $[Cu(CF_3)(I)]^{-.19}$

Despite these advances in attempting to elucidate the active species in the copper-mediated/-catalyzed trifluoromethylation of aryl halides, several questions remain. (1) Is the species at -28.4 ppm in DMF [Cu(CF₃)(I)]⁻? If so, is it the active copper(I) species that promotes the trifluoromethylation with aryl iodides? (2) Is the species at -32.4 ppm in DMF/DMI [Cu(CF₃)₂]⁻ since previous studies showed that it is not reactive to aryl iodides? If it is not the active species, how is it converted into the active species? (3) If both [Cu(CF₃)(I)]⁻ and [Cu(CF₃)₂]⁻ are not the active species in the reaction, what is the active species? (4) What is the role of CuI in promoting the trifluoromethylation with [Cu(CF₃)₂]⁻?

Herein, we report mechanistic studies of the coppermediated trifluoromethylation of aryl iodides and our discoveries, including: (1) $[Ph_4P]^+[Cu(CF_3)(I)]^-$ was prepared and fully characterized, including ¹H and ¹⁹F NMR spectroscopic study, X-ray diffraction of its single crystals, and elementary analysis. (2) ¹⁹F NMR spectroscopic study showed that $[Cu(CF_3)(I)]^-$ and $[Cu(CF_3)_2]^-$ were the species previously observed with a chemical shift at -28.8 and -32.3 ppm, respectively. (3) Both $[Cu(CF_3)(I)]^-$ and $[Cu(CF_3)_2]^-$ are not the most active trifluoromethylation species since stoichiometric reactions of both species with electron-rich aryl iodides gave the trifluoromethylated arenes in moderate yield even at 100 °C. However, kinetic studies showed that the reactivity of $[Cu(CF_3)_2]^-$ was about 2.3 times higher than that of $[Cu(CF_3)(I)]^-$. These reactivity studies also suggested that the active species was not generated from thermal decomposition of $[Cu(CF_3)(I)]^-$. (4) The most active Cu(I) species was determined to be ligandless $[Cu(CF_3)]$ or DMF-ligated $[(DMF)Cu(CF_3)]$, which was formed by reaction of $[Cu(CF_3)_2]^-$ with CuI, thus elucidating the role of CuI in the reaction. (5) Finally, an acetic acid promoted trifluoromethylation of aryl iodides by $[Ph_4P]^+[Cu(CF_3)_2]^$ was developed and various (hetero)aryl halides were

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trifluoromethylated in good to high yields under acidic conditions, which represents the first copper-mediated trifluoromethylation of aryl halides under acidic conditions.

RESULTS AND DISCUSSION

Preparation and Characterization of Trifluoromethyl Organocuprate(I) $[Ph_4P]^+[Cu(CF_3)(X)]^-$ (X = Cl, I, or CF₃). In 2019, we reported the preparation of $[Ph_4P]^+[Cu(CF_3)_2]^-$ (1a) by reaction of CuCl with excess Me_3SiCF_3 (3.5 equiv) in the presence of excess KF (6.5 equiv) in THF, followed by cationic exchange with [Ph₄P]⁺Cl⁻ at room temperature.²⁰ It was found that the reaction time (30 min) was key for the high-yielding formation of the complex 1a. Carefully monitoring the reaction by ¹⁹F NMR spectroscopy showed that a peak at -28.0 ppm in THF was initially formed within 5.0 min. Upon stirring the suspension at room temperature for another 15 min, the peak at -31.8 ppm in THF, which corresponded to $[Cu(CF_3)_2]^-$, emerged, suggesting that we might be able to isolate the species at -28.0 ppm by quenching the reaction within 15 min. Indeed, by controlling the reaction time to 13 min, the species at -28.0 ppm was isolated as $[Ph_4P]^+[Cu(CF_3)(Cl)]^-(1b)^{21}$ after recrystallization, albeit in low 7% yield (Scheme 2). The structure of $[Cu(CF_3)(Cl)]^{-1}$ was unambiguously confirmed by X-ray crystallography of its single crystals (see the Supporting Information for details).

Scheme 2. Strategies for the Preparation of Ionic Cuprate Cu(I) Complex $[Ph_4P]^+[Cu(CF_3)(I)]^-$ 1c



Considering that one of the potentially active species with a chemical shift of -28.8 ppm in THF in the copper-mediated trifluoromethylation of aryl iodides was proposed to be $[Cu(CF_3)(I)]^-$, and the only difference between this species and complex **1b** is the anionic halogen ligand, we therefore focused our initial efforts to synthesize $[Ph_4P]^+[Cu(CF_3)(I)]^-$ by employing the same strategy. Unfortunately, our attempts to synthesize $[Ph_4P]^+[Cu(CF_3)(I)]^-$ by reaction of CuI with excess TMSCF₃ and KF in various solvents at room temperature or at low temperature failed. It was found that CF₃H (-79 ppm in THF) was observed as the major product by monitoring of the reactions by ¹⁹F NMR spectroscopy when THF was used as the solvent. In other solvents such as DMF or DMSO, the formation of an inseparable mixture of

 $[Cu(CF_3)(I)]^-$ and $[Cu(CF_3)_2]^-$, as well as CF_3H (-79 ppm in THF). was observed (method A in Scheme 2). The failure in the isolation of the desired $[Cu(CF_3)(I)]^-$ by reaction of CuI with excess TMSCF₃ and KF led us to consider an alternative strategy by transmetalating one of the trifluoromethyl groups from $[Cu(CF_3)_2]^-$ to CuI since previously we discovered that the addition of CuI dramatically accelerated the trifluoromethylation reaction. It was found that stoichiometric reaction of $[Ph_4P]^+[Cu(CF_3)_2]^-$ and CuI in DMF at 100 °C after 1 h generated a new peak at -27.0 ppm in 53% yield. However, elongating the reaction time or changing the ratios of two reactants did not lead to full conversion of $[Ph_4P]^+[Cu(CF_3)_2]^-$. Consequently, efforts to isolate $[Cu(CF_3)(I)]^-$ from the mixture failed (method B in Scheme 2).

Previously, Vicic and co-workers reported that even though the reactivity of $[Cu(CF_3)_2]^-$ was not high, it reacted with aryl iodides slowly.¹⁸ We thus envisaged that pure $[Cu(CF_3)(I)]^$ could be prepared by consumption of $[Cu(CF_3)_2]^-$ in the mixture via its reaction with an appropriate aryl halide. As shown in Figure 1, addition of 1.0 equiv of iodobenzene to the



Figure 1. (a) Monitoring the stoichiometric reaction of $[Ph_4P]^+[Cu-(CF_3)_2]^-$ (1a) and CuI in DMF at 100 °C by ¹⁹F NMR spectroscopy. (b) Monitoring the stoichiometric reaction of $[Ph_4P]^+[Cu(CF_3)_2]^-$ (1a) and CuI in the presence of 1.0 equiv of iodobenzene in DMF at 100 °C by ¹⁹F NMR spectroscopy. (c) Monitoring the stoichiometric reaction of $[Ph_4P]^+[Cu(CF_3)_2]^-$ (1a) and CuI in the presence of 1.0 equiv of 2-bromopyridine in DMF at 100 °C by ¹⁹F NMR spectroscopy.

reaction mixture led to the consumption of both species. Nevertheless, addition of 1.0 equiv of 2-bromopyridine resulted in the complete conversion of $[Cu(CF_3)_2]^-$ into the corresponding 2-trifluoromethylated pyridine after 1.0 h at 100 °C, while $[Cu(CF_3)(I)]^-$ remained intact under these conditions (method C in Scheme 2). Further optimization of the reaction conditions enabled us to isolate the well-defined organocuprate(I) complex $[Ph_4P]^+[Cu(CF_3)(I)]^-$ (1c) in 13% yield after recrystallization, for the very first time, by treating $[Ph_4P]^+[Cu(CF_3)_2]^-$ with 1.0 equiv of CuI and 2.0 equiv of 2-bromo-6-trifluoromethylpyridine in DMF at 100 °C for 2 h (Scheme 3).

Ionic cuprate complex $[Ph_4P]^+[Cu(CF_3)(I)]^-$ (1c), a white crystalline solid, is sensitive to air and moisture. A solution of 1c in CDCl₃ has a characteristic peak with a chemical shift at





-27.8 ppm in ¹⁹F NMR spectroscopy, which is identical to that of $[Ph_4P]^+[Cu(CF_3)(Cl)]^-$. In DMF, the peak slightly shifts to -27.0 ppm. The ³¹P NMR spectrum of complex 1c in $CDCl_3$ showed a singlet peak with a chemical shift of -24.3ppm. To further establish the structure of complex 1c. single crystals of complex 1c was obtained by slow diffusion of methyl tert-butyl ether to a solution of complex 1c in THF at -35 °C. X-ray diffraction studies of the single crystals showed the bond angle of C-Cu-I is 171.4°, suggesting that the ionic cuprate complex adopts approximately a linear geometry. The bond length of $Cu-C(CF_3)$ in complex 1c is 2.10 Å, which is much longer than the $Cu-C(CF_3)$ bond length in complex $[Cu(CF_3)_2]^-$ (1.93 Å) and $[Cu(CF_3)CI]^-$ (1.66 Å), respectively. The longer bond length of $Cu-C(CF_3)$ in complex 1c than those in complexes 1a and 1b is due to the stronger trans influence of the iodide anion than chloride and trifluoromethyl anion (Figure 2).



Figure 2. ORTEP diagram of $[Ph_4P]^+[Cu(CF_3)(I)]^-$ 1c. Ellipsoids are shown at the 30% level, and selected bond lengths and bond angles: Cu(1)-C(25): 2.111(18) Å; Cu(1)-I(1): 2.2646(14); C-Cu-I: 171.4°.

Are $[Cu(CF_3)_2]^-$ and $[Cu(CF_3)(I)]^-$ the Key Intermediates in the Copper-Mediated Trifluoromethylation of Aryl Halides? Having successfully prepared and characterized both $[Cu(CF_3)_2]^-$ and $[Cu(CF_3)(I)]^-$, we set out to study whether these two species were the proposed key intermediates in copper-mediated trifluoromethylation of aryl halides. To determine whether the species is one of the proposed key intermediates, we decided to add the isolated cuprate complex $[Cu(CF_3)_2]^-$ 1a and $[Cu(CF_3)(I)]^-$ 1c to a mixture of previously proposed active copper species that was generated from reaction of CuI and TMSCF₃ in the presence of KF and then examine the mixture by ¹⁹F NMR spectroscopy. If complex $[Cu(CF_3)_2]^-$ 1a or $[Cu(CF_3)(I)]^-$ 1c is the proposed key intermediate, the signals in the ¹⁹F NMR spectroscopy should overlap and show a single peak. Otherwise, we would observe two different signals. As shown in Figure 3, upon treatment of CuI (1.2 equiv) with Me₃SiCF₃ (1.0 equiv) and KF (1.0 equiv) in DMF/DMI (v/v = 10:1) at 0 °C for 15 min, two proposed species, CF₃Cu·KX and $[Cu(CF_3)_2]^-$ with a chemical shift at -28.9 and -31.4 ppm, respectively, were observed by ¹⁹F NMR spectroscopy, respectively, despite a slight deviation of chemical shifts of the two species reported in Kolomeitsev's work due to the replacement of CuBr to CuI¹⁷ (Figure 3a). To the mixture was added a solution of complex $[Ph_4P]^+[Cu(CF_3)(I)]^-$ (1c) in DMF at 0 °C. Clearly, a superimposed peak with a chemical shift at -28.2 ppm in DMF/DMI was observed, indicating the proposed CF₃Cu·KX has the authentic structure of [Cu(CF₃)- $(I)^{-}$ (Figure 3b). Likewise, addition of a solution of complex $[Ph_4P]^+[Cu(CF_3)_2]^-$ 1a in DMF at 0 °C also showed a superimposed peak at -31.4 ppm in DMF/DMI, suggesting $[Cu(CF_3)_2]^-$ is another key intermediate in copper-catalyzed/ mediated trifluoromethylation (Figure 3c). These results provided strong evidence that $[Cu(CF_3)_2]^-$ and $[Cu(CF_3)_-$ (I)]⁻ are the key intermediates observed previously in coppermediated trifluoromethylation of (hetero)aryl halides.

Comparison of the Reactivities of [Cu(CF₃)(I)]⁻, $[Cu(CF_3)_2]^-$, and $[Cu(CF_3)_2]^-$ + Cul. To evaluate the reactivities of complexes $[Cu(CF_3)(I)]^-$ and $[Cu(CF_3)_2]^-$, as well as the combination of $[Cu(CF_3)_2]^-$ with CuI, we studied stoichiometric reactions of these complexes with aryl halides with different substituents including electron-rich 4methoxylphenyl iodide, electron-neutral phenyl iodide, electron-poor methyl 4-iodobenzoate, and a heteroaryl bromide 2bromopyridine. Specifically, a set of parallel experiments were conducted in which aryl halides were allowed to react with 1.0 equiv of cuprate complex $[Cu(CF_3)_2]^-$ 1a or $[Cu(CF_3)(I)]^-$ 1c as well as the combination of $[Cu(CF_3)_2]^-$ with CuI in DMF at 100 °C for 3.0 h. The yields of the corresponding trifluoromethyl (hetero)arenes were then determined by ¹⁹F NMR spectroscopy in the presence of an internal standard. As shown in Table 1, it was found that complex $[Cu(CF_3)(I)]^-$ 1c reacted in lower yields than complex $[Cu(CF_3)_2]^-$ 1a, while a combination of $[Cu(CF_3)_2]^-$ 1a with CuI reacted in much higher yields than both $[Cu(CF_3)_2]^-$ 1a and $[Cu(CF_3)(I)]^-$ 1c. For instance, reaction of complex $[Cu(CF_3)(I)]^-$ 1c with 4-methoxylphenyl iodide in DMF occurred in less than 5% yield after 3 h at 80 °C and in 22% yield after 3 h at 100 °C, while reaction of $[Cu(CF_3)_2]^-$ 1a with 4-methoxylphenyl iodide gave 4-methoxy-1-trifluoromethylbenzene in 30% yield after 3 h at 80 °C and 57% yield after 3 h at 100 °C. Importantly, reaction of $[Cu(CF_3)_2]^-$ 1a with 4-methoxylphenyl iodide in the presence of 1.0 equiv of CuI occurred in much higher yields of 82% and quantitative yield, respectively, under the same reaction conditions. A similar trend was also observed for reactions of phenyl iodide and 2-bromopyridine. In addition, electron-poor aryl iodides generally reacted much faster and in higher yields than electron-rich aryl iodides, which is consistent with previous observations in copper-mediated trifluoromethylation of aryl halides. For instance, reaction of electron-poor methyl 4-iodobenzoate with complex [Cu- $(CF_3)_2$ ⁻ 1a occurred to full conversion after 3.0 h at 80 °C to give the methyl 4-trifluoromethylbenzoate in quantitative yield. On the contrary, reactions of electron-neutral phenyl iodide or electron-rich 4-methyl phenyl iodide with complex $[Cu(CF_3)_2]^-$ 1a occurred in less than 70% yields after 3.0 h at 100 °C. Furthermore, we also observed that reaction of 2-



Figure 3. (a) ¹⁹F NMR spectrum for reaction of CuI/KF/Me₃SiCF₃ in DMF/DMI at 0 °C for 15 min. (b) ¹⁹F NMR spectrum of the reaction mixture with $[Cu(CF_3)(I)]^-$ 1c. (c) ¹⁹F NMR spectrum of the reaction mixture with $[Cu(CF_3)_2]^-$ 1a.

Table 1. Comparison of the Reactivities of $[Cu(CF_3)(I)]^-$, $[Cu(CF_3)_2]^-$, and $[Cu(CF_3)_2]^-$ in the Presence of 1.0 equiv of CuI with a Variety of (Hetero)aryl Halides^{*a,b*}

$Ar - X + [Cu] \xrightarrow{DMF} Ar - CF_3$ X = Br, I (1.0 equiv.) $T^{/o}C$, 3 h						
[Cu(CF ₃)]	[Cu(CF₃)(I)] [_]		[Cu(CF ₃) ₂] [−]		[Cu(CF ₃)₂]⁻ + Cul	
	Temp	Yield	Temp	Yield	Temp	Yield
ArX	(°C)	(%)	(°C)	(%)	(°C)	(%)
	100	22	80	30	80	82
	100	22	100	57	100	quant.
	100	29	80	41	80	94
	100	50	100	65	100	quant.
	100	86	80	quant.	80	quant.
	100	100 80	100	quant.	100	quant.
Br	100	nd	80	7	80	87
N →N	100	n.u.	100	42	100	quant.

^{*a*}Reaction conditions: (hetero)aryl halide (0.025 mmol), Cu(I) complex (0.025 mmol), DMF (0.50 mL) at 80 or 100 °C for 3 h under argon. ^{*b*}Yields were determined by ¹⁹F NMR spectra with 1-fluoronaphthalene as internal standard; nd = not detected, quant = quantitative yield.

bromopyridine generally occurred much more slowly and gave much lower yields than that of aryl iodides, likely due to the stronger C–Br bond in 2-bromopyridine than the C–I in aryl iodides. These qualitative reactivity studies disclosed that (1) complex $[Cu(CF_3)_2]^-$ 1c is less reactive than complex $[Cu(CF_3)_2]^-$ 1a; (2) in the presence of 1.0 equiv of CuI, the reactivity of $[Cu(CF_3)_2]^-$ 1a improved significantly and a new active species might be generated; and (3) reactions of (hetero)aryl halides with different electron properties might proceed via different reaction pathways. Quantitative Comparison of the Reactivities of $[Cu(CF_3)(I)]^- 1c$ and $[Cu(CF_3)_2]^- 1a$. To assess quantitatively the reactivities of complexes $[Cu(CF_3)(I)]^- 1c$ and $[Cu(CF_3)_2]^- 1a$, we studied the kinetics of the complex $[Cu(CF_3)(I)]^- 1c$ and $[Cu(CF_3)_2]^- 1a$ with 10.0 equiv of methyl 4-iodobenzoate. More specifically, a solution of complex $[Cu(CF_3)_2]^- 1a$ with 10.0 equiv of methyl 4-iodobenzoate in DMF in a J. Young NMR tube was placed in the NMR probe which was preheated to 60 °C, and the progress of the reaction was monitored by ¹⁹F NMR spectroscopy (Figure 4A). The decay of the signal correspond-



Figure 4. (a) Plot of the decay of the concentration of $[Cu(CF_3)_2]^- 1a$ over reaction time for the reaction of $complex[Cu(CF_3)_2]^- 1a$ (0.050 mM) with methyl 4-iodobenzoate (0.5 mM) in DMF at 60 °C. (b) Effect of initial concentration of 1a on the rate constants. (c) Plot of initial rates versus initial concentration of methyl 4-iodobenzoate for the reaction of $[Cu(CF_3)_2]^- 1a$ (0.050 mM) with methyl 4-iodobenzoate in DMF at 40 °C. (d) Plot of the decay of the concentration of $[Cu(CF_3)(I)]^- 1c$ over reaction time for reaction of $[Cu(CF_3)(I)]^- 1c$ (0.050 mM) with methyl 4-iodobenzoate (0.5 mM) in DMF at 60 °C.

ing to complex $[Cu(CF_3)_2]^-$ 1a over the reaction time was then plotted, and it was found that the concentration of $[Cu(CF_3)_2]^-$ decreased exponentially, indicating a pseudofirst-order dependence of the rate on the concentration of complex $[Cu(CF_3)_2]^-$ 1a. Accordingly, the rate constant k_{obs1} for this reaction was determined to be $(1.26 \pm 0.12) \times 10^{-3}$ s^{-1} . In addition, we found that variation of the initial concentration of 1a did not obviously influence the k_{obs1} , thus providing further evidence that the reaction is first order (Figure 4B). Furthermore, the initial rates for reactions of complex $[Cu(CF_3)_2]^-$ 1a with methyl 4-iodobenzoate at different concentrations at 40 °C were also studied, and it was found that the initial rates were in a linear correlation with the concentrations of complex $[Cu(CF_3)_2]^-$ 1a, thus suggesting the reaction is also first order on the concentration of methyl 4-iodobenzoate (Figure 4C). These results illustrated that the reaction of complex $[Cu(CF_3)_2]^-$ 1a with methyl 4iodobenzoate is a typical second-order reaction and rate constant for the reaction in DMF at 60 °C is $(1.26 \pm 0.12) \times$ 10^{-2} L·(mol·s)⁻¹. Likewise, kinetic study for the reaction of $[Cu(CF_3)(I)]^-$ 1c with 10.0 equiv of methyl 4-iodobenzoate in DMF at 60 °C also exhibited a first-order kinetic behavior, an

average observed rate constant k_{obs2} was determined to be $(3.86 \pm 0.21) \times 10^{-4} \text{ s}^{-1}$, and the rate constant of the reaction between $[\text{Cu}(\text{CF}_3)(\text{I})]^- \text{1c}$ and methyl 4-iodobenzoate in DMF at 60 °C was $(3.86 \pm 0.21) \times 10^{-3} \text{ L} \cdot (\text{mol} \cdot \text{s})^{-1}$ (Figure 4D). Thus, a quantitative comparison of the reactivities of complexes $[\text{Cu}(\text{CF}_3)(\text{I})]^- \text{1c}$ and $[\text{Cu}(\text{CF}_3)_2]^- \text{1a}$ revealed that complex $[\text{Cu}(\text{CF}_3)_2]^- \text{1a}$ showed a 3.3-fold higher reactivity than complex $[\text{Cu}(\text{CF}_3)(\text{I})]^- \text{1c}$ when they reacted with electron-poor aryl iodides $((1.26 \pm 0.12) \times 10^{-2} \text{ L} \cdot (\text{mol} \cdot \text{s})^{-1} \text{ vs} (3.86 \pm 0.21) \times 10^{-3} \text{ L} \cdot (\text{mol} \cdot \text{s})^{-1}).$

Mechanistic Studies of Trifluoromethylation of Aryl lodides with $[Ph_4P]^+[Cu(CF_3)_2]^-$. Because it was found that reaction of electron-poor aryl iodides with $[Ph_4P]^+[Cu-(CF_3)_2]^-$ 1a does not required the addition of CuI, we wanted to investigate the mechanism of this reaction in more detail. Therefore, we focused on the kinetics of the reaction of $[Cu(CF_3)_2]^-$ with excess methyl 4-iodobenzoate in DMF at 60 °C. It was found that reaction of $[Cu(CF_3)_2]^-$ with methyl 4iodobenzoate gave 4-trifluoromethylbenzoate as well as $[Cu(CF_3)(I)]^-$ slowly. Because we knew that $[Cu(CF_3)(I)]^$ reacted with methyl 4-iodobenzoate much more slowly than $[Cu(CF_3)_2]^-$, the reaction of $[Cu(CF_3)_2]^-$ with methyl 4iodobenzoate could be considered as a typical continuous reaction. Indeed, we observed the initial accumulation of $[Cu(CF_3)(I)]^-$ and then consumption slowly after reaching the highest concentration within 25 min when the reaction of $[Ph_4P]^+[Cu(CF_3)_2]^-$ 1a with 10.0 equiv of methyl 4-iodobenzoate in DMF at 60 °C was monitored by ¹⁹F NMR spectroscopy (Figure 5). Fitting the relative concentration of



Figure 5. Plot of the relative concentration of $[Cu(CF_3)(I)]^-$ from reaction of $[Cu(CF_3)_2]^-$ **1a** (0.050 mM) with 10.0 equiv of methyl 4-iodobenzoate (0.5 mM) in DMF at 60 °C.

 $[Cu(CF_3)(I)]^-$ vs time using kinetic model for continuous reaction gave an equation of $([[Cu(CF_3)(I)]^-]/[[Cu-(CF_3)_2]^-]_0 = 1.15 [exp(-2.00 \times 10^{-4}t) - exp(-1.56 \times 10^{-3}t)])$, which allowed the extraction of the pseudo rate constants of $k_{obs1}' = (1.56 \pm 0.10) \times 10^{-3} \text{ s}^{-1}$ and $k_{obs2}' = (2.00 \pm 0.13) \times 10^{-4} \text{ s}^{-1}$ for reactions of $[Cu(CF_3)_2]^-$ and $[Cu(CF_3)(I)]^-$ with methyl 4-iodobenzoate, respectively.

Accordingly, the rate constants for both reactions could be determined to be $(1.56 \pm 0.10) \times 10^{-2} \text{ L} \cdot (\text{mol} \cdot \text{s})^{-1}$ and $(2.00 \pm 0.13) \times 10^{-3} \text{ L} \cdot (\text{mol} \cdot \text{s})^{-1}$, which are within the acceptable ranges when compared with the k_{obs1} and k_{obs2} obtained in the previous quantitative experiments $((1.26 \pm 0.12) \times 10^{-2} \text{ L} \cdot (\text{mol} \cdot \text{s})^{-1} \text{ vs} (3.86 \pm 0.21) \times 10^{-3} \text{ L} \cdot (\text{mol} \cdot \text{s})^{-1}$, respectively).

Quantitative Comparison of the Reactivities of $[Cu(CF_3)_2]^-$ 1a with a Combination of $[Cu(CF_3)_2]^-/Cul$. Previous studies from the groups of Pérez-Temprano and Shen independently determined that the addition of 1 equiv of CuI would significantly accelerate the trifluoromethylation of $[Cu(CF_3)_2]^-$ with aryl iodides.^{19,20} To quantitatively compare the reactivity of the combination of $[Cu(CF_3)_2]^-/CuI$ with $[Cu(CF_3)_2]^-$, we studied the kinetics of their reactions with electron-poor methyl 4-iodobenzoate. As shown in Figure 6, reaction of equimolar of $[Cu(CF_3)_2]^-/CuI$ with 1.0 equiv of 4iodobenzoate occurred to full conversion of the in situ generated [CuCF₃] after 780 s at 60 °C ($t_{1/2}$ = 314 s), while reaction of $[Cu(CF_3)_2]^-$ with 1.0 equiv of 4-iodobenzoate in the absence of CuI occurred to 50% conversion after 7800 s $(t_{1/2} = 7800 \text{ s})$. From these experiments, we concluded that the reactivity of a combination of $[Cu(CF_3)_2]^-/CuI$ is estimated to be at least 24 times faster than that of $[Cu(CF_3)_2]^{-1}$.

Identification of the Active Species in a Combination of $[Cu(CF_3)_2]^-$ with Cul. To identify the active species in a combination of $[Cu(CF_3)_2]^-$ with CuI, we carried out the stoichiometric reaction of $[Cu(CF_3)_2]^-$ 1a with CuI. An equimolar amount of $[Cu(CF_3)_2]^-$ 1a with CuI in DMF with an internal standard in a J-Young NMR tube was heated at 100



Figure 6. Comparison of reactivity between $[Cu(CF_3)_2]^-$ and a combination of $[Cu(CF_3)_2]^-$ with CuI.

°C for 15 min. The mixture was then cooled to room temperature and analyzed by ¹⁹F NMR spectroscopy. A new peak with a chemical shift at -27.4 ppm which was assigned as $[Cu(CF_3)(I)]^-$ and a broad peak with a chemical shift between -25.0 and -26.5 ppm were observed. Based on the stoichiometry of the reaction between $[Cu(CF_3)_2]^-$ 1a with CuI, we suspected that the broad peak should be $[CuCF_3]$ and the broadening of the peak is due to a rapid equilibrium of the ligand association/dissociation process between a ligandless [CuCF₃] and a DMF-coordinated copper species [(DMF)-CuCF₃]. To probe if this is the case, we conducted lowtemperature ¹⁹F NMR experiments with the hope that the ligand association/dissociation process could slow down at low temperature and we would be able to observe the proposed copper species [(DMF)CuCF₃] directly. To our delight, the peak became narrower and sharper when the temperature was lowered from 25 °C to 0, -25, and -35 °C, respectively (Figure 7). At -35 °C, a singlet peak with a chemical shift at -25.8 ppm was observed. Previously, Grushin reported that a ligandless [CuCF₃] which was generated from reaction of CuCl with fluoroform (CF_3H) in DMF in the presence of 2.0 equiv of KO^tBu, followed by the addition of 1 equiv of Et_3N . 3HF to quench the excess KO^tBu, has a chemical shift of -26.3 ppm in ¹⁹F NMR spectroscopy.^{11a} Accordingly, we assigned the peak with a chemical shift at -25.8 ppm we observed at -35° C to be [(DMF)CuCF₃].

To examine whether $[(DMF)CuCF_3]$ is the active species, we studied and compared its reactivity with those of $[Cu(CF_3)(I)]^-$ and $[Cu(CF_3)_2]^-$. Reaction of a 1:1 mixture of $[Cu(CF_3)_2]^-$ and CuI in DMF occurred in 56% conversion after 1.0 h at 100 °C to generate [(DMF)CuCF₃] and $[Cu(CF_3)(I)]^-$ in 53% yield, respectively. To the mixture was added 1.0 equiv of 2-bromopyridine, and the resulting mixture was allowed to react at 100 °C for an additional 1.0 h. It was found that the peak at -25.8 ppm disappeared and a new peak at -68.1 ppm appeared, which corresponded to 2-trifluoromethylpyridine generated in quantitative yield. In contrast, under these conditions, $[Cu(CF_3)_2]^-$ was only partially reacted while $[Cu(CF_3)(I)]^-$ remained intact (Scheme 4). These results clearly suggest that [(DMF)CuCF₃] which could be generated from the reaction of $[Cu(CF_3)_2]^-$ with CuI, is much more reactive than that of $[Cu(CF_3)(I)]^-$ or $[Cu(CF_3)_2]^-$, and it is the active species in the copper-mediated trifluoromethylation reaction.

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Figure 7. Low-temperature ¹⁹F NMR spectra for the solution of the stoichiometric reaction between $[Cu(CF_3)_2]^-$ 1a and CuI after 15 min at 100 °C.

Scheme 4. Comparison of Reactivity of the in Situ Generated $[CuCF_3]$ with $[Cu(CF_3)_2]^-$ and $[Cu(CF_3)(I)]^-$

[Cu(CF ₃) ₂] ⁻ + Cul <u>1a</u> 1a	[Cu(CF ₃) ₂] ⁻ 1a (44%) + [Cu(CF ₃)(1)] ⁻ 1c (53%) + CuCF ₃ tive species (2-BrPy 2-CF ₃ Py <u>53%</u> 100 °C, 2 h	[Cu(CF ₃) ₂] [−] 1a + [Cu(CF ₃)(I)] [−] 1c + CuBr ↓
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Role of [Cul₂]⁻ in Copper-Mediated Trifluoromethylation of Aryl lodides. We have now determined that even though $[Cu(CF_3)(I)]^-$ is not the active species in the coppermediated trifluoromethylation reactions, $[Cu(CF_3)(I)]^-$ reacted with aryl iodides slowly to give trifluoromethylated arenes. From the stoichiometry of the reaction $[Cu(CF_3)(I)]^$ with aryl iodide, an ionic cuprate $[CuI_2]^-$ along with ArCF₃ should be generated. Previously, Pérez-Temprano and coworkers proposed that $[CuI_2]^-$ might undergo decomposition to give I⁻ and CuI, which is the activator in the reaction.¹⁹ To clarify if this is the case, we conducted two sets of experiments. In the first experiment, we studied the reaction of CuI with 1 equiv of ⁿBu₄NI. It was found that the reaction occurred so fast that $[^{n}Bu_{4}N]^{+}[CuI_{2}]^{-}$ 1d was generated after the mixture of CuI and "Bu₄NI was shaken in CH₂Cl₂ for 30 s, and complex 1d was isolated as a light yellow solid in 76% yield ater evaporation of the solvent (Scheme 5, eq 1).²² This experiment suggests that reaction of I⁻ with CuI occurs very quickly, and the reverse reaction for generation of CuI from thermal decomposition of $[^{n}Bu_{4}N]^{+}[CuI_{2}]^{-}$ should be unfavorable. In the second experiment, we studied the reaction $[^{n}Bu_{4}N]^{+}[CuI_{2}]^{-}$ with $[Cu(CF_{3})_{2}]^{-}$. A solution of equimolar $[Cu(CF_3)_2]^-$ and $[^nBu_4N]^+[CuI_2]^-$ in DMF reacted quickly at room temperature to generate $[Cu(CF_3)(I)]^-$ until an

Scheme 5. Preparation and Reaction of $ Cul_2 $ Anio	Scheme 5	heme S	e 5. Preparation	and Reaction	of (Jul	Anion
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Cul +
$$nBu_4NI$$
 $\xrightarrow{CH_2CI_2}$ $nBu_4N^{+}[Cul_2]^{-}$ (1)
30 s 76%
[Cu(CF_3)_2]^{-+} [Cul_2]^{-} $\underbrace{K_{eq} = 2.01}_{[Cu(CF_3)(I)]^{-}}$ (2)

equilibrium with an equilibrium constant of 2.01 was established after 5 min (Scheme 5, eq 2). These experiments clearly showed that the generation of CuI from $[CuI_2]^-$ under the copper-mediated trifluoromethylation conditions is unlikely, since $[CuI_2]^-$ would prefer to react with excess $[Cu(CF_3)_2]^-$ in the reaction system to give less reactive $[Cu(CF_3)(I)]^-$.

Proposed Mechanism for Copper-Mediated Trifluoromethylation of Aryl lodides. Based on our mechanistic studies, we proposed an overall mechanistic map for the copper-mediated trifluoromethylation of aryl iodides. First, reaction of CuI with a trifluoromethyl source generates two cuprates, $[Cu(CF_3)_2]^-$ and $[Cu(CF_3)(I)]^-$, quickly. In the presence of excess CuI, reaction of $[Cu(CF_3)_2]^-$ with CuI occurs at elevated temperature to give the active species ligandless [CuCF₃] or DMF-ligated [(DMF)CuCF₃], which then reacts with aryl iodides to give the desired trifluoromethylarenes and regenerate CuI (pathway A in Figure 8). Under these conditions, pathway A is the major productforming pathway. Alternatively, in the absence of CuI, both $[Cu(CF_3)_2]^-$ and $[Cu(CF_3)(I)]^-$ react with aryl iodides but much more slowly than that of ligandless $[CuCF_3]$ to afford ArCF₃, and pathway B is the major product-forming pathway (pathways B and C in Figure 8). There are three points worthy of further discussion. (1) It is known that it is difficult to trifluoromethylate various nitrogen-containing heteroaryl halides under the copper catalyst. On the basis of our mechanistic

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Figure 8. Mechanistic map	for copper-mediated	trifluoromethylation	of aryl iodides.
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map, nitrogen-containing substrates may coordinate to ligandless $[CuCF_3]$ to form much less reactive $[(substrate)-CuCF_3]$ and, consequently, shut down the trifluoromethylation reaction. Under these circumstances, it would be better to conduct the reaction that does not require excess CuI or CuI could be fully consumed during the step for the generation of the cuprates. (2) We found that reaction of electron-poor aryl iodides with $[Cu(CF_3)_2]^-$ occurred smoothly and quickly at 50-60 °C. Therefore, for those substrates, it is not necessary to add any activator. (3) Iodide anion is harmful for the reaction since it is going to react with CuI to generate $[CuI_2]^-$, which is going to further react with $[Cu(CF_3)_2]^-$ to give less reactive $[Cu(CF_3)(1)]^-$.

Comments on Frequently Applied Copper-Mediated Trifluoromethylation of Aryl lodides. In the Introduction, we mentioned that the reactivities of the $[CuCF_3]$ species generated under various conditions differ significantly. Having elucidating the $[CuCF_3]$ species and their reactivities in the copper-mediated trifluoromethylation reaction, we could now explain the divergent reactivities of these systems.

CuX/TMSCF₃/MF System.^{9a} Copper-mediated trifluoromethylation of aryl iodides using Ruppert-Prakash reagent $(TMSCF_{2})$ as the trifluoromethyl source represents one of the most common methods for the preparation of trifluoromethylated arenes. The reaction using TMSCF₃ for trifluoromethylation of aryl halides was first reported by Fuchikami and co-workers in 1991.^{9a} Interestingly, during their optimization of the reaction conditions, it was found that the amount of CuI was crucial for the yield of the reaction. While reaction using 1.0 equiv of CuI led to the formation of ArCF₃ in 85% yield, the same reaction with 1.5 equiv of CuI gave ArCF₃ in quantitative yield. Our mechanistic studies now clearly showed that excess CuI in the reaction system facilitates the transformation of $[Cu(CF_3)_2]^-$ species to more reactive ligandless CuCF₃ and, consequently, gave the trifluoromethylated arenes in higher yield.

In addition, Fuchikami and co-workers also found that by switching the copper salt from CuI to CuBr the yield of the reaction decreased to 58%. We now know that reaction of CuBr with TMSCF₃ and KF conducted by Kolomeitsev and co-workers generated $[Cu(CF_3)(Br)]^-$ and $[Cu(CF_3)_2]^-$ with a ratio of 3.6:1. Our study showed that the ratio of $[Cu(CF_3)(I)]^-$ and $[Cu(CF_3)_2]^-$ for the reaction of CuI with TMSCF₃ and KF in DMF was 1.44:1. Since $[Cu(CF_3)_2]^-$ is at least 2.3 times more reactive than $[Cu(CF_3)(X)]^-$, the higher ratio of the $[Cu(CF_3)_2]^-$ in the reaction system suggests faster reaction and higher yields since longer reaction time may lead to decomposition of the trifluoromethylated copper species.

Trifluoromethylation Using Chen's Reagent (FSO₂CF₂CO₂Me).⁸ Copper-mediated trifluoromethylation of aryl halides using FSO₂CF₂CO₂Me as the trifluoromethyl source is another frequently applied method for the preparation of trifluoromethyl arenes because FSO₂CF₂CO₂Me is cheap and available on bulk scale. To probe the reactive species in this system, we studied the stoichiometric reaction of FSO₂CF₂CO₂Me and CuI in DMF at 80 °C. ¹⁹F NMR spectroscopic study of the reaction mixture of the stoichiometric reaction of FSO₂CF₂CO₂Me and CuI in DMF after 1.0 h at 80 °C showed the formation of $[Cu(CF_3)(I)]^-$, $[Cu(CF_3)_2]^-$, and $[Cu(CF_3)_4]^-$ in a ratio of 5.9:1.4:1, while the formation of ligandless CuCF3 was not observed. The high ratio presence of $[Cu(CF_3)(I)]^-$ suggests that the reactivity of the reaction system is not high and typically high temperature and long reaction time are required for full conversion. Nevertheless, there is one advantage for this reaction system. The iodide anion generated in the reaction mixture would nucleophilically attack the methyl group of the reagent to generate MeI and diminish the concentration of [CuI₂]⁻, which we have determined to be deleterious to the active species in the reaction.

HOAc-Promoted Copper-Mediated Trifluoromethylation of (Hetero)aryl Halides $Q^{+}[Cu(CF_3)_2]^{-}$ 1a. Our mechanistic studies showed that the ligandless [CuCF₃] or DMF-ligated $[(DMF)CuCF_3]$ is the active species that promotes the trifluoromethylation with aryl iodides, while the initial formed copper species for the reaction of CuX with TMSCF₃ and KF are the mixture of $[Cu(CF_3)(I)]^-$ and $[Cu(CF_3)_2]^-$. To overcome such a dilemma and considering that the solubility of CuI in DMF is not high, we envisaged to improve the reaction by the addition of an alternative additive other than CuI that can "abstract" one of the -CF₃ groups in $[Cu(CF_3)_2]^-$ to generate the ligandless $[CuCF_3]$ or DMFligated [(DMF)CuCF₃] effectively. It is well-known that the C-F bond in a trifluoromethylated metal species could be easily activated by a protonic acid or a Lewis acid because of the strong π -back donation of $d_{\pi} \rightarrow \sigma^*(C-F)$ in the trifluoromethylated metal species.²³ We therefore chose several Lewis acids and Brønsted acids to examine whether they could remove one of the trifluoromethyl groups in $[Cu(CF_3)_2]^-$ via abstraction of the fluorine in the trifluoromethyl group and subsequent decomposition of the metal-bound difluorocarbene.²⁴ After extensive screening, it was found that HOAc was able to serve as the activator to effectively activate [Cu- $(CF_3)_2$ ⁻ to generate the ligandless CuCF₃. In general, reactions of 1.5 equiv of $Q^+[Cu(CF_3)_2]^-$ 1a and 1.5 equiv of HOAc with a variety of (hetero)aryl iodides, bromides, and chlorides proceeded smoothly at room temperature to 80 °C to give the trifluoromethyalted (hetero)arenes in good yields

(Scheme 6). More specifically, reactions of electron-poor aryl iodides such as 4-nitrophenyl iodide and methyl 4-



"Reaction conditions: aryl halide (0.50 mmol), 1a (0.75 mmol), acetate acid (0.75 mmol) in DMF (5.0 mL) at room temperature to 80 °C for 16–48 h under argon. ^bYields were determined by 19 F NMR spectrum by using fluorobenzene as internal standard; Isolated yields were shown in parentheses.

iodobenzoate occurred after 24 h at room temperature to give the desired products 2a and 2b in 91% and 82% yield, respectively, while reactions of electron-rich aryl iodides 4-iodo-*N*,*N*-dimethylaniline and *N*-(4-iodophenyl)acetamide required reaction at 50–80 °C for 16–24 h for full conversion (Scheme 6, 2a–d). As a comparison, previous conditions using CuI as the activator typically required reaction at 100 °C for full conversion for electron-rich aryl iodides.²⁰ Electron-poor heteroaryl bromides also showed good reactivities (2h–j), while aryl bromide (2g), electron-rich heteroaryl bromide (2i), and (hetero)aryl chlorides (2k–l) were trifluoromethylated in moderate to excellent yields with the assistance of a directing group at the *ortho*-position. The accelerating effect of an *ortho*-ester or nitro group was consistent with the reaction that used CuI as the activator.²⁰

CONCLUSIONS

In summary, in this work, we report the identification of the previously proposed key intermediates $[Ph_4P]^+[Cu(CF_3)-(X)]^-(X = Cl, I \text{ or } CF_3)$ in copper-mediated trifluoromethylation by independent synthesis. These complexes were fully characterized by NMR spectroscopy and microanalysis and further confirmed by X-ray diffraction of their single crystals.

Nevertheless, our studies disclosed that the reactivities of both $[Cu(CF_3)_2]^-$ and $[Cu(CF_3)(I)]^-$ are not high, and a much more reactive species, ligandless CuCF₃ or DMF-ligated $[(DMF)CuCF_3]$, is generated when excess CuI is presented. Quantitative studies showed that ligandless CuCF₃ or DMFligated [(DMF)CuCF₃] is roughly 24 times more reactive than $[Cu(CF_3)_2]^-$ and 80 times more reactive than $[Cu(CF_3)(I)]^-$. An overall mechanistic map was then provided on the basis of these systematic studies. In the presence of excess CuI, reaction of $[Cu(CF_3)_2]^-$ with CuI occurs at elevated temperature to give the active species ligandless $[CuCF_3]$ or DMF-ligated $[(DMF)CuCF_3]$, which then reacts with aryl iodides to give the desired trifluoromethylarenes and regenerate CuI. Alternatively, in the absence of CuI, both $[Cu(CF_3)_2]^-$ and $[Cu(CF_3)(I)]^-$ react with any iodides but much more slowly than that of ligandless [CuCF₃] or DMFligated $[(DMF)CuCF_3]$ to afford ArCF₃. Under these conditions, reaction with $[Cu(CF_3)_2]^-$ is faster than that with $[Cu(CF_3)(I)]^-$. Based on these mechanistic studies, we uncovered a new activator HOAc which could effectively abstract one of the trifluoromethyl groups in $[Cu(CF_3)_2]^-$ to generate more reactive ligandless [CuCF₃] or DMF-ligated [(DMF)CuCF₃]. Under these conditions, a broad range of aryl iodides, bromides, and chlorides were trifluoromethylated under mild conditions. Furthermore, our studies also suggest that the halide anion generated from the aryl halides is deleterious to the reaction by conversion $[Cu(CF_3)_2]^-$ to less reactive $[Cu(CF_3)(I)]^-$ or by quenching the activator CuI to generate $[CuI_2]^-$. Efforts to develop efficient copper-catalyzed trifluoromethylation of aryl halides by effectively removing the halide anion from the reaction mixture are currently underway in our laboratory.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.1c07408.

Experimental details and kinetic profiles; ¹H, ¹⁹F, and ¹³C NMR spectra of **1a-c** and **2a-l** (PDF)

Accession Codes

CCDC 2096993 and 2096996 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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