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Key Intermediate in Copper-Mediated Arene Trifluoromethylation [nBu₄N][Cu(Ar)(CF₃)₃]: Synthesis, Characterization and C(sp²)-CF₃ Reductive Elimination

Zehai Lu,[a] He Liu,[a] Shihan Liu,[b] Xuebing Leng,[a] Yu Lan*[b] and Qilong Shen*[a]

Abstract: The synthesis, characterization and C(sp²)-CF₃ reductive elimination of stable aryl(tris(trifluoromethyl))cuprate(III) complexes [nBu₄N][Cu(Ar)(CF₃)₃] were described. Mechanistic investigations including kinetic studies, the effect of temperature and solvents, the effect of the *para*-substitution of the aryl group and DFT calculations suggest that C(sp²)-CF₃ reductive elimination process proceeds via a concerted carbon-carbon bond-forming pathway.

The trifluoromethyl group (CF₃-) represents one of privileged structural motif in drug molecules due to its unique size and strong electron withdrawing property that may dramatically improve the drug molecule's pharmacokinetics including lipophilicity and metabolic stability.[1] Consequently, incorporation of the trifluoromethyl group into the drug candidates has become a widely employed tactic in new drug discovery.[2] The importance of the trifluoromethyl group has thus attracted great interests to develop trifluoromethylating methods, and, in the past 10 years, a plethora of new efficient methods that are capable of site-specifically installing the trifluoromethyl group into the target molecules have been reported.[3]

In particular, copper-mediated or -catalyzed trifluoromethylation represents one of the most prominent reactions that may have potentially widespread applications.[4] In general, these protocols can be divided into two different types: copper-mediated trifluoromethylation of aryl halides with different trifluoromethyl sources (Fig. 1, Type I)[5] and copper-catalyzed trifluoromethylation of aryl boronic acids with an electrophilic or nucleophilic trifluoromethylating reagent (Fig. 1, Type II).[6] Mechanistically,[7] for type I reaction, it was proposed that an active Cu(I) species [CuCF₃] is initially formed, which then reacts with aryl halide to generate a copper(III) intermediate [Ar-Cu(III)-CF₃]. Reductive elimination from this intermediate forms trifluoromethylarene (Fig. 1, left).[8] Likewise, for type II reaction, it was proposed that a Cu(I) species [Cu^I-Ar] is initially generated
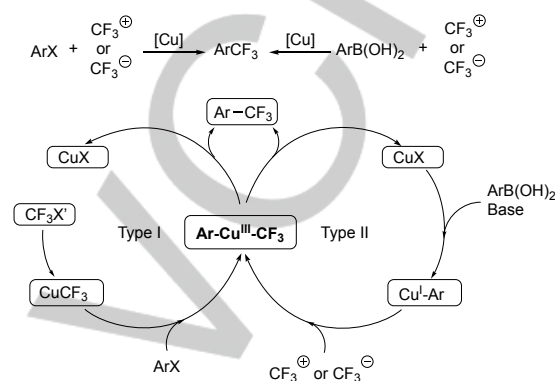

Figure 1. Proposed mechanism for copper-mediated formation of trifluoromethylated arenes.

through transmetallation of aryl boronic acid to CuX in the presence of a base. The trifluoromethyl group is then oxidatively added to [Cu^I-Ar] to give the key intermediate [Ar-Cu(III)-CF₃], followed by reductive elimination to generate the trifluoromethylarene (Fig. 1, right).

In both mechanisms, a trifluoromethylated organocopper(III) intermediate [Ar-Cu^{III}-CF₃] that reductive eliminates to give the final trifluoromethylated product was proposed. Nevertheless, this putative key product-forming Cu(III) intermediate [Ar-Cu^{III}-CF₃] has never been observed or isolated previously.[9-12] Consequently, the elementary step that forms the aryl-CF₃ bond from Cu(III) complex [Ar-Cu^{III}-CF₃] remains elusive. Thus, preparation of well-defined organocopper(III) [Ar-Cu^{III}-CF₃] and investigation of their C(sp²)-CF₃ bond-forming reductive-elimination process will not only provide fundamental insights into factors that govern the C(sp²)-CF₃ bond-forming process, but can also provide a guide for the development of new trifluoromethylation reactions. Herein, we reported the preparation of a family of stable square planar aryl(tris(trifluoromethyl))cuprate(III) complexes [nBu₄N][Cu(Ar)(CF₃)₃] that underwent reductive elimination to generate trifluoromethylarenes in high yields.[13] Mechanistic investigations including kinetic studies, the effect of temperature and solvents, the effect of the *para*-substitution of the aryl group and DFT calculations indicated that C(sp²)-CF₃ reductive elimination occurred a concerted bond-forming process via a three-membered ring transition state.

Our initial synthetic approach for the preparation of the proposed Cu(III) intermediate [Ar-Cu^{III}-CF₃] was inspired by Grushin's recent report on the synthesis of [(bpy)Cu(CF₃)₃] **1** from [nBu₄N][Cu(CF₃)₄],[14] with the hope that an aryl group could replace the bipyridine ligand under certain conditions. Indeed, two new peaks at -31.35 ppm and -34.64 ppm with a 2:1 integral ratio in ¹⁹F NMR spectrum that are presumptively corresponding to

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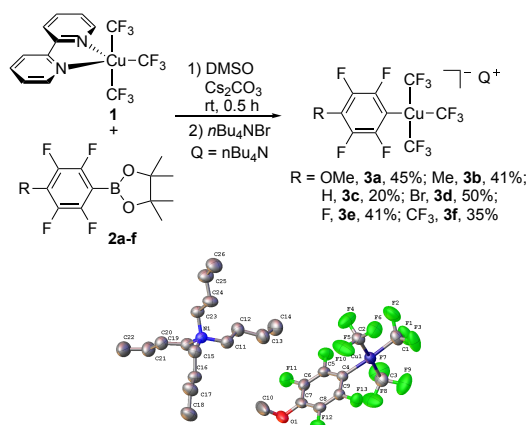   Supporting information for this article is available on the WWW under
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Figure 2. Preparation of [nBu_4N][Cu(Ar)(CF$_3$)$_3$] **3a-f** and ORTEP diagrams of [nBu_4N][Cu(4-MeOC$_6$F$_4$)(CF$_3$)$_3$] **3a**. Ellipsoids are shown at the 50% level.

Scheme 1. Reductive elimination of [nBu_4N][Cu(Ar)(CF$_3$)$_3$] **3a-f**.

entry	R	complex 3	additive	yield (%)	t$_{1/2}$ (min)
1	OMe	**3a**	-	99%	25.3
2	OMe	**3a**	TEMPO	79%	-
3	OMe	**3a**	1,4-dinitrobenzene	81%	-
4	Me	**3b**	-	97%	18.3
5	H	**3c**	-	95%	31.5
6	Br	**3d**	-	82%	46.7
7	F	**3e**	-	90%	53.5
8	CF$_3$	**3f**	-	86%	61.6

anionic [Cu(Ar)(CF$_3$)$_3$] species appeared upon addition of an aryl borate derived from 4-biphenylpinacolyl boronate and nBuLi to [(bpy)Cu(CF$_3$)$_3$] **1** in DMSO at room temperature. The species was not stable enough to be isolated but decomposed at room temperature within 80 min to give 4-trifluoromethylbiphenyl in 54% yield. To our delight, by switching the borate to electron-poor 4-methoxytetrafluorophenyl-substituted borate **2a** and exchanging the lithium cation with nBu$_4$NBr, the putative copper(III) complex [nBu$_4$N][Cu(Ar)(CF$_3$)$_3$] **3a** (Ar = 4-methoxytetrafluoro phenyl) which was stable in solution at room temperature, was formed in 57% yield, as determined by ^{19}F NMR spectroscopy. Moreover, complex **3a** was successfully isolated in 45% yield when [(bpy)Cu(CF$_3$)$_3$] was treated with 4-methoxytetrafluorophenyl pinacolyl boronate in the presence of 2.0 equiv. of Cs$_2$CO$_3$ at room temperature for 0.5 h, followed by cation exchange with nBu$_4$NBr. Likewise, analogous complexes **3b-f** with different aryl groups were prepared in 20-50% yields according to the same procedure (Fig. 2). Complexes **3a-f** were fully characterized by ^{1}H and ^{19}F NMR, as well as elemental analyses and the structures of **3a-f** were further confirmed by X-ray diffraction of their single crystals. Complexes **3a-f**, that are air/moisture stable white crystalline compounds, to the best of our knowledge, represent the first isolable organocopper(III) complexes bearing an aryl group and a trifluoromethyl group at the same copper metal center.

With complexes **3a-f** in hand, we then proceeded to study their reductive elimination under various conditions. Heating the solution of complex **3a** in ClCH$_2$CH$_2$Cl at 95 °C for 4 h led to a clean reductive elimination to generate 1-methoxy-4-trifluoromethyltetrafluorobenzene **4a** in quantitative yield (Scheme 1, entry 1). Likewise, organocopper(III) complexes **3b-f** underwent reductive elimination to give the corresponding trifluoromethylated arenes in 82-97% yields (Scheme 1, entries 4-8). We further studied the thermal reactions of complex **3a** in different solvents such as CDCl$_3$, THF, acetone, PhCN, DMF or DMSO and found that these reactions occurred smoothly to give compound **4a** in 90-99% yields. The isolation of stable organocopper(III) complexes that underwent Ar-CF$_3$ bond reductive elimination is remarkable since it is well-known that metal-perfluoroalkyl (M-R$_f$) bonds are much more thermally stable
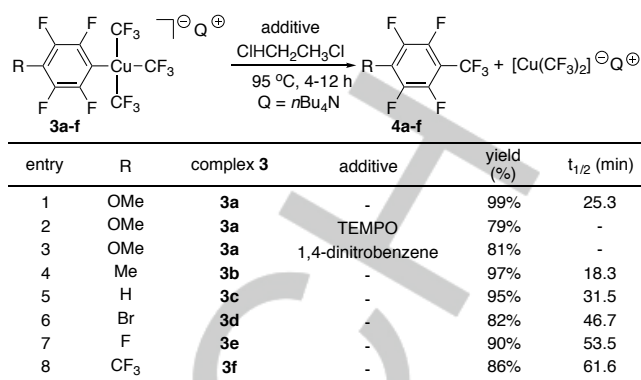
than analogues containing hydrocarbon alkyl (M-R) linkages[15] and few trifluoromethylated complexes that were able to reductive eliminate Ar-CF$_3$ have been reported previously.[16]

To probe whether the C(sp^2)−C(CF$_3$) reductive elimination from [nBu$_4$N][Cu(Ar)(CF$_3$)$_3$] **3** occurs by a radical mechanism (Pathway A in Fig. 3), we studied the reductive elimination reaction in the presence of a radical or single-electron-transfer (SET) inhibitor. Reactions in the presence of 2.0 equivalent of TEMPO or 1,4-dinitrobenzene occurred smoothly to give reductive elimination product **4a** in 79% and 81% yield, respectively (Eq. 1). The slightly decreased yields suggest the reaction is not prohibited by a radical or SET inhibitor, thus rendering a radical pathway unlikely. To gain more evidences against the radical pathway, we studied the reductive elimination reaction of **3a** with electron paramagnetic resonance (EPR) spectroscopy. Experimentally, an aliquot of reaction mixture was drawn periodically and was then analyzed by EPR spectroscopy. Notably, no EPR signal was observed. Interestingly, upon addition of a spin trapping reagent N-tert-butyl-α-phenylnitrone (PBN), the EPR spectrum of the resulting mixture showed the formation of CF$_3$-PBN spin trap. Control experiments showed that it was the Cu(CF$_3$)$_2^-$ species generated from reductive elimination that reacted with PBN to form CF$_3$-PBN (See supporting information for details). Furthermore, DFT calculation showed that even though homolytical cleavage of the Cu-CF$_3$ bond from [Cu(Ar)(CF$_3$)$_3$] is feasible ($\Delta G^{\ddagger}$ = 20.6 kcal/mol), the activation free energy barrier ($\Delta G^{\ddagger}$ = 53.8 kcal/mol) to reach the three-member ring transition state **12-ts** that generates reductive elimination product is much higher than that in Pathway D (Fig. 5). These results clearly suggest that a pathway that involving a homolytical cleavage of the Cu-CF$_3$ bond from complex **3a** to form a CF$_3$ radical (CF$_3$•) and a [Cu(II)(CF$_3$)(Ar)] species, followed by reductive elimination is disfavored.

To assess the effect of the temperature on the reductive elimination reaction, we studied the kinetics of the aryl-CF$_3$ bond-forming reductive elimination from complex **3a** in two different solvents (ClCH$_2$CH$_2$Cl vs PhCN) from 90 to 110 °C. These studies disclosed that reductive elimination from complex **3a** followed first-order kinetics and the rate constants did not change with different initial concentrations of complex **3a**. Furthermore, it was found that the rates of reductive elimination from complex **3a** in ClCH$_2$CH$_2$Cl with temperature ranging from 85 to 110 °C resulted
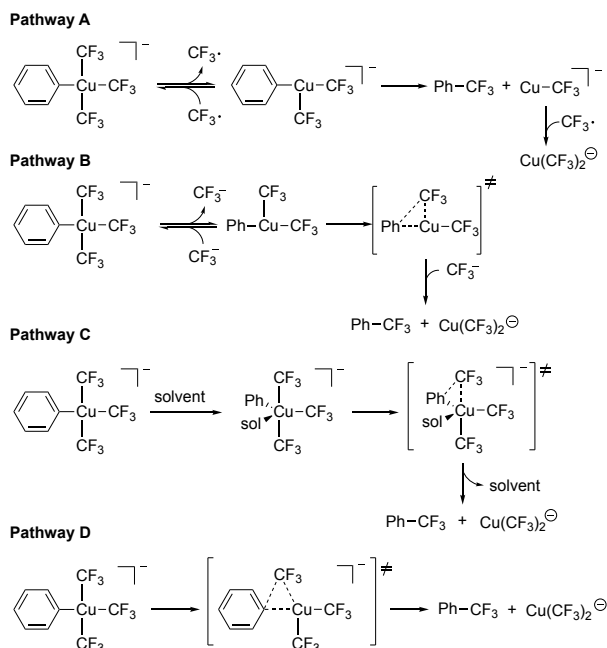
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Pathway A

Pathway B

Pathway C

Pathway D

Figure 3. Possible mechanistic pathways for C(sp^2)-CF$_3$ reductive elimination from [nBu$_4$N][Cu(Ar)(CF$_3$)$_3$].

Figure 4. (a) Effect of temperature on reductive elimination of complex **3a** in ClCH$_2$CH$_2$Cl. (b) Effect of temperature on reductive elimination of complex **3a** in PhCN. (c) Effect of the polarity/coordination property of the solvents on reductive elimination of complex **3a**.

in a linear correlation. Eyring analysis gave activation parameters of $\Delta H^\ddagger = 29.56 \pm 0.72$ kcal/mol and $\Delta S^\ddagger = 6.20 \pm 1.97$ e.u. (Fig. 4a). Likewise, a linear dependency of the rates of the elimination from complex **3a** in a coordination solvent PhCN was observed and two activation parameters of $\Delta H^\ddagger = 27.64 \pm 0.94$ kcal/mol and $\Delta S^\ddagger = 0.26 \pm 2.56$ e.u. were obtained (Fig. 4b). The small activation entropies in both solvents are against a dissociation pathway (Pathway B in Fig. 3) for the aryl-CF$_3$ bond-forming reductive elimination from complex **3a**. Computationally, it was found that dissociating a trifluoromethyl anion to form a three-coordinated copper(III) intermediate **6** is an endothermic process with a barrier of 40.3 kcal/mol, which is much higher than that from Pathway D ($\Delta G^\ddagger = 27.6$ kcal/mol) (Fig. 5). Thus, a dissociation pathway for the Ar−C(CF$_3$) bonding-forming reductive elimination from complex **3a** was ruled out.

It is well-known that the rate of a reductive elimination reaction can be greatly affected by the reaction medium since the transition states are stabilized relative to the corresponding ground states by the solvents, or *vice versa*.[17] Alternatively, the solvent may coordinate to the transition metal center to stabilize the complex. To evaluate the influence of the solvent polarity on the reductive elimination from complex **3a**, we studied the kinetics of the reductive elimination of complex **3a** in six solvents with different polarity (ClCH$_2$CH$_2$Cl, CDCl$_3$, THF, acetone, DMF and DMSO) and a coordinating solvent PhCN. Interestingly, reductive elimination in these solvents occurred in high yields (90-99%). Nevertheless, the magnitude of differences between the rates in the solvents with different polarities is small (Fig. 4c). Interestingly, reductive elimination in a nonpolar, no-coordinating solvent ClCH$_2$CH$_2$Cl was slightly faster than that in a polar, coordinating solvent PhCN ($4.57 \pm 0.09 \times 10^{-4}$ s^{-1} vs $3.43 \pm 0.07 \times 10^{-4}$ s^{-1}, respectively). These results revealed that both the polarity and the coordinating property of the solvents do not have a significant
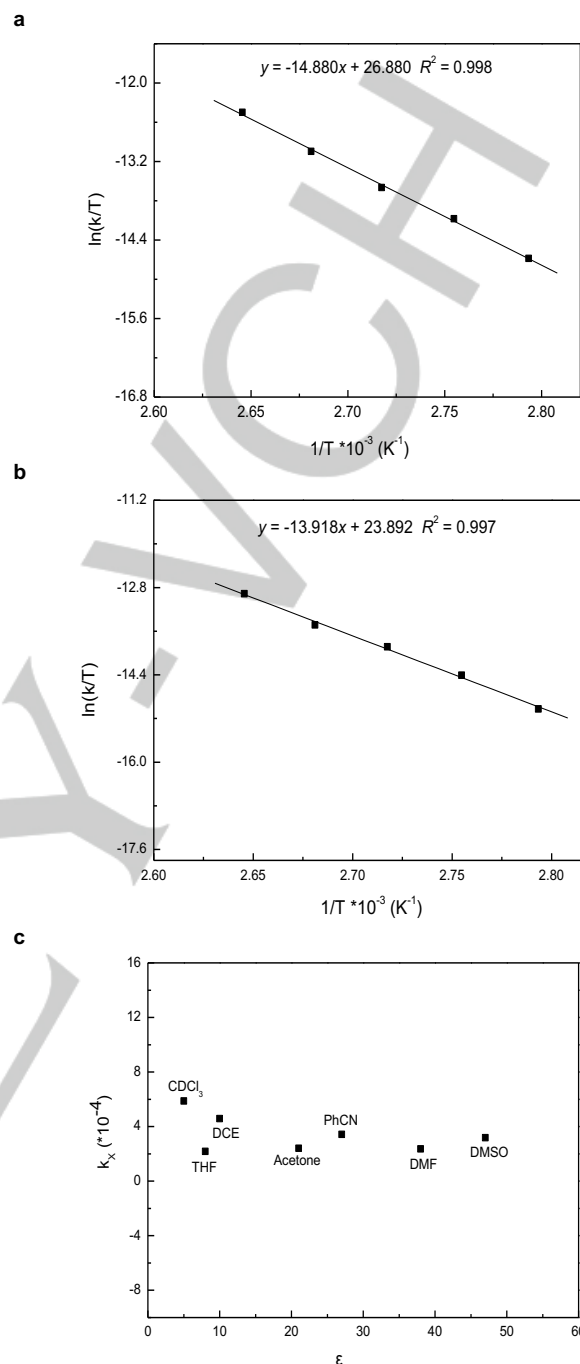
effect on the rates of the reductive elimination of complex **3a**. More importantly, the small differences of the rates of reductive elimination in solvents with different polarities are against an association pathway. Furthermore, if the reductive elimination proceeds via an association pathway, reactions in a coordinating solvent such as PhCN would significantly accelerate the reaction (Pathway C in Fig. 3). The fact that reaction in PhCN was slightly slower than that in ClCH$_2$CH$_2$Cl renders the association pathway unlikely.
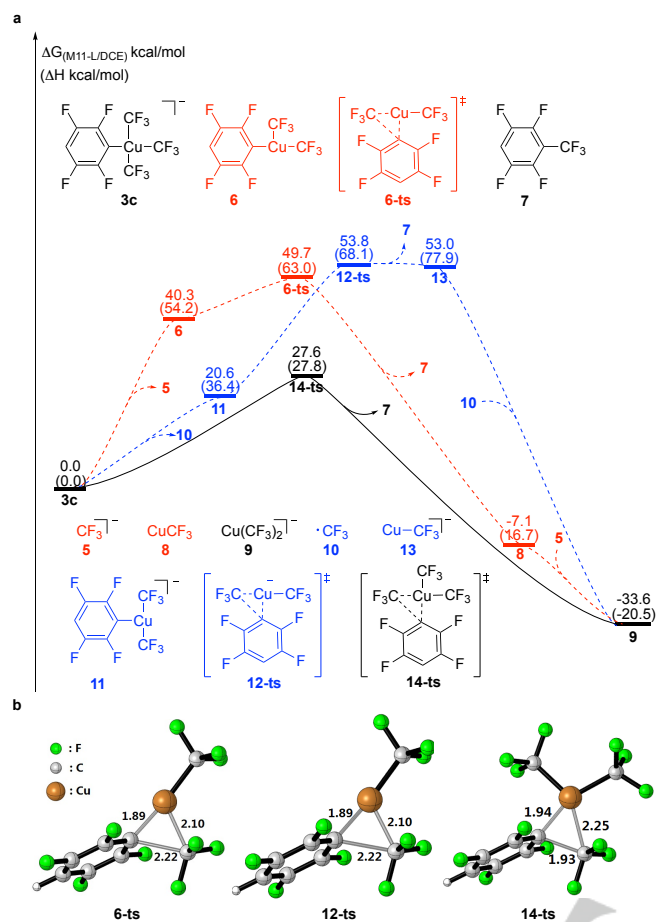
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Figure 5. (a) The calculated activation free energies for the C(sp²)-CF₃ reductive elimination of [nBu₄N][Cu(Ar)(CF₃)₃]. (b) Optimized structures for the transition states **6-ts**, **12**-ts and **14-ts** are shown. Selected bond distances [Å] are provided.

Collectively, both experimental results and DFT calculation suggest that the mechanism for the C(sp²)-CF₃ reductive elimination from complex **3** occurs through a classic concerted bond-forming process via a three-membered ring transition state, as shown in pathway D, Figure **3**.

In summary, we have synthesized, for the first time, a family of stable square planar aryl(tris(trifluoromethyl))cuprate(III) complexes [nBu₄N] [Cu(Ar)(CF₃)₃] **3a-f**, that might act as key intermediates in copper-mediated trifluoromethylation reactions. The thermal reactions of these complexes were then studied in detail. These results combined with DFT calculation indicate that the C(sp²)-CF₃ reductive elimination from complexes [nBu₄N][Cu(Ar)(CF₃)₃] proceeds through a concerted carbon-carbon bond-forming pathway from the four-coordinated Cu(III) metal center via a three-membered ring transition state. The results of this study reveal the extraordinary reactivity of the organocopper(III) complexes bearing both an aryl and a trifluoromethyl group, which has not been described previously, despite the long history of Cu-mediated trifluoromethylation reactions. Further characterization of high-valent trifluoromethylated organocopper species and studies of their fundamental organometallic chemistry are undergoing currently in our laboratory.

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[17] The rates for carbon-carbon reductive elimination from Pd(II) complex in solvents with different polarity differed greatly. A solvent association pathway was proposed. See: A. Gillie, J. K. Stille, *J. Am. Chem. Soc.* **1980**, *102*, 4933.

[18] CCDC 1881168-1881173 contain the supplementary crystallographic data for the compound **3a-f** reported in this article. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif or pm application to CCDC, 12 Union Road, Cambridge CB2 1 EZ, UK [fax: +44-1223/336-033; email: deposit@ccdc.cam.ac.uk].

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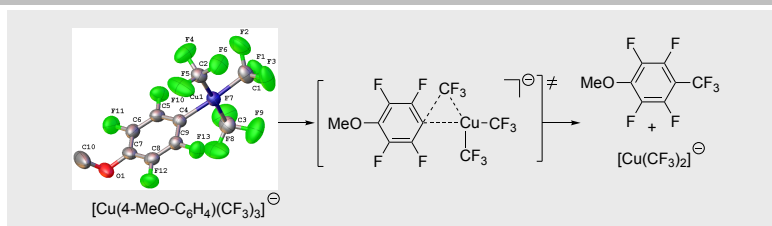
$[Cu(4\text{-}MeO\text{-}C_6H_4)(CF_3)_3]^{\ominus}$

The synthesis, characterization and $C(sp^2)$-CF_3 reductive elimination of stable aryl(tris(trifluoromethyl))cuprate(III) complexes [nBu$_4$N][Cu(Ar)(CF$_3$)$_3$] were described. Mechanistic investigations including kinetic studies, the effect of temperature and solvents and DFT calculations indicate that $C(sp^2)$-CF_3 reductive elimination process proceeds via a concerted bond-forming pathway.

Zehai Lu, He Liu, Shihan Liu, Xuebing Leng, Yu Lan* and Qilong Shen*

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Key Intermediates in Copper-Mediated Arene Trifluoromethylation [*n*Bu₄N][Cu(Ar)(CF₃)₃]: Synthesis, Characterization and C(sp²)-CF₃ Reductive Elimination