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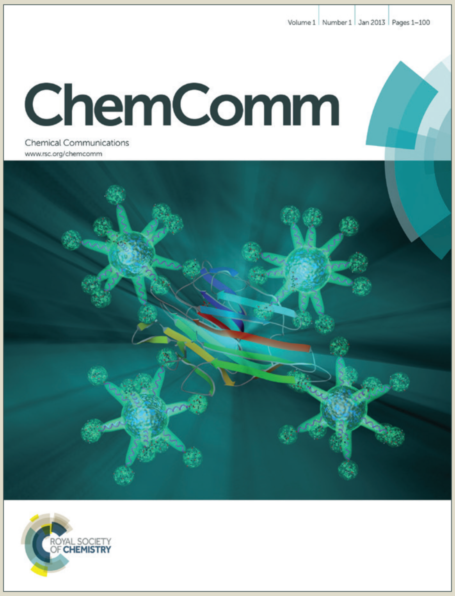

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Iminosemiquinone radical ligand enables access to well-defined redox-active Cu^{II}–CF_3 complex

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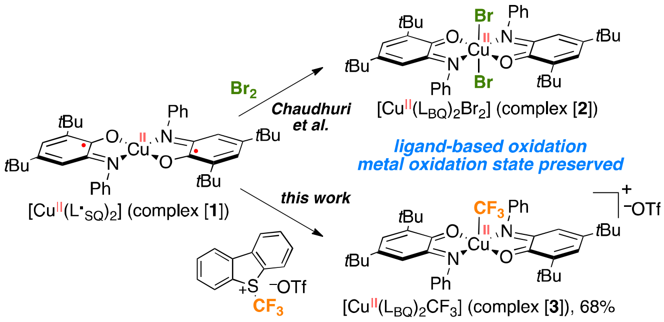
Jérémy Jacquet,[a] Elise Salanouve,[a] Maylis Orio,[b] Hervé Vezin,[b] Sébastien Blanchard,[a] Etienne Derat,[a] Marine Desage-El Murr*[a] and Louis Fensterbank*[a]

Reaction of a copper complex bearing iminosemiquinone ligands with a CF_3^+ source provides an unprecedented Cu^{II}–CF_3 complex through ligand-based oxidation. Reactivity of this complex leads to nucleophilic trifluoromethylation of the ligand, suggesting an electronic interplay that results in a formal *umpolung* of the initial CF_3^+.

The widespread benefits of fluorinated molecules in drug design, materials and imaging to name a few have triggered acute development of transition metal-catalyzed methods to introduce fluorinated motifs in molecules,[1] among which trifluoromethylation is a fast developing area. Specifically, copper catalyzed trifluoromethylation, relying on a cheaper and more earth-abundant metal than palladium, iridium and ruthenium has attracted chemists' attention.[2] Copper-catalyzed methods have been developed using nucleophilic (CF_3^-), electrophilic (CF_3^+), and radical ($CF_3^\bullet$) sources. However, the field has suffered from high catalyst loadings (often stoichiometric), harsh conditions and limited scope. Recent improvements have relied on the development of ligand-stabilized well-defined copper complexes such as [$PhenCuCF_3$] (Phen: phenanthroline), reported in 2011 by the Hartwig group and coined Trifluoromethylator^{TM} for its striking performances.[3] Other significant developments have emerged from the combined use of copper catalysis and *in situ* generation of CF_3 radicals, thus avoiding costly CF_3 sources.[4]

Redox non-innocent ligands[5] have been identified as promising partners in the development of catalytic methods using non-noble metals by circumventing their tendency to engage in monoelectronic redox events and promoting instead their capacity to perform two-electrons elementary steps. In line with our interests in application of non-innocent ligands to catalytically relevant methods,[6] we were interested to see if such ligands could be used to stabilize a Cu–CF_3 species and possibly influence its chemical behaviour through electronic participation. Among redox non-innocent ligands, the amidophenolate motif has been widely explored as chemists seek to take advantage of its privileged redox properties. Indeed, this ligand scaffold can accommodate two successive monoelectronic oxidation steps through a redox chemical interplay involving three distinct oxidation states (amidophenolate, iminosemiquinone and iminobenzoquinone). Such ligands have been successfully applied to several metal–catalyzed or –mediated processes associated with a variety of metals such as iridium for hydrogen oxidation[7] and cobalt for Negishi cross-coupling.[8] All these examples were found to involve ligand-based redox events. Specifically, copper complexes bearing amidophenolate ligands[9] behave as mimics of galactose oxidase enzyme and were shown to oxidize primary alcohols into aldehydes under aerobic conditions.[10]



Scheme 1 Reaction of complex [1] with oxidants Br_2 [12] and CF_3^+ induces a ligand-based oxidation.

Seeking to introduce a trifluoromethyl ligand on the copper, we first tried to react the original deep-green [$Cu^{II}(L^\bullet_{SQ})_2$] (complex[1]) with a nucleophilic CF_3 source ($TMSCF_3$). No reaction occurred[11] and this observation is consistent with the fact that complex [1] has been shown to behave rather as a nucleophile.[12] Accordingly, switching to an electrophilic trifluoromethylating agent proved successful as reaction of [1] with one equivalent of Umemoto reagent[13] in CH_2Cl_2 at room temperature under Ar induced a color change from deep green to deep red. A dark red precipitate was filtered and presence of dibenzothiophene was detected in the filtrate, providing the promising hint that the CF_3 group had been abstracted from the Umemoto reagent. The isolated complex (68% yield) was analyzed by ESI mass spectrometry confirming the incorporation of a CF_3 group with a molecular peak corresponding to that expected for a [$Cu(L_{BQ})_2CF_3$]$^+$ complex

[**3**]. No clear NMR spectra could be obtained thus indicating that this species is probably paramagnetic. In UV-vis spectroscopy (SI), the inter valence charge transfer band (IVCT) at λ=795 nm, related to the diradical character of CuL_{SQ2} is not observed for [**3**]. This has been similarly observed when bromine was reacted onto this complex,[12] and can be related to the oxidation of both L_{SQ}^{-} ligand to the quinone L_{BQ} form during the reaction.

To further assess the electronic structure of the product, the X-band EPR spectrum was recorded at 10 K in frozen CH_2Cl_2 (Fig. S2). This spectrum is clearly different from that of the starting complex and exhibits a quasi axial symmetry with some rhombic distorsion and $^{63/65}Cu$ hyperfine splittings characteristic of a single ion Cu^{II} complex featuring an unpaired electron occupying a d_{x2-y2} magnetic orbital, with no radical ligands involved.[9] Interestingly, while the g- and A^{Cu}-values (g_i=2.225, 2.065, 2.000 and A_i^{Cu}= (182,13.5,9.5)x $10^{-4}cm^{-1}$) are very similar to that of parent complex [**2**] ($[CuL_{BQ2}Br_2]$), (g_i=2.205, 2.085, 2.02 and and A_i^{Cu}= (138,3,24)x $10^{-4}cm^{-1}$), no nitrogen superhyperfine couplings could be observed in our case. This could be related to the difference in geometry between the *trans*–Br_2 hexacoordinated complex and complex [**3**]. Thus, as was the case for the Br_2 oxidation product, these results strongly suggest the presence of a Cu^{II} center in [**3**] coordinated with diamagnetic L_{BQ} ligands. Cyclic voltammogram of [**3**] was recorded in CH_2Cl_2 with 0.1M of $TBABF_4$ as supporting electrolyte (Fig. 2). The open circuit potential is around 0.8V/SCE. Upon reduction, the first two waves appear composite and not fully reversible, while the two most negative waves are quasi reversible and correspond to that of $[Cu(L_{SQ})_2]$. Again, this is very similar to the results obtained with complex [**2**] and the first two reduction steps are likely to be electrochemical chemical (EC) processes, with probable decoordination of the CF_3 ligand upon successive monoreduction of each ligand yielding the $[Cu(L_{SQ})_2]$ form and its electrochemical signature, with recoordination of the CF_3 moiety upon reoxidation of $[Cu(L_{SQ})_2]$ (see SI).

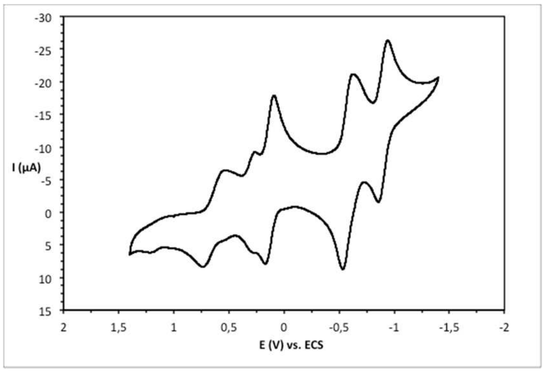


Fig. 2. Cyclic voltammogram of [**3**] in CH_2Cl_2.

Thus, all evidence here points toward a similar reactivity of [**1**] with bromine and Umemoto reagent, *ie* oxidation of the iminosemiquinone ligands to iminobenzoquinone with reduction of the reagent, forming either two bromide ions coordinated to a Cu^{II} center or a trifuoromethyl anion linked to the copper. Pulsed EPR has been widely applied to material sciences and biological systems to gain insight into the surrounding of paramagnetic centers, and more recently to understand the reactivity of molecular systems.[14] Thus, to confirm the presence of the trifluoromethyl ligand, pulsed EPR experiments were conducted on frozen CH_2Cl_2 samples of [**3**] (Fig. 3) using 2D hyperfine-sublevel correlation experiment (2D-HYSCORE, see SI for details),[15] which enables proper assignment of various couplings with a large number of nuclei (^1H, ^{13}C, ^{14}N, or ^{19}F).

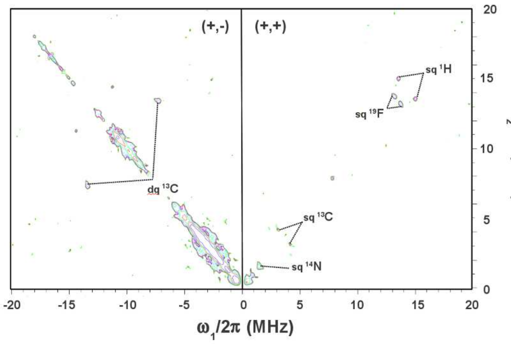


Fig. 3. 2D-HYSCORE spectra of [**3**]. Experimental conditions: frozen CH_2Cl_2 sample of [**3**], T = 5K. Spectrum recorded for the B = 3357 G value of the ESE detected field sweep spectrum. The time delay was set to 136 ns and a pulse length of 12 ns was used for π/2 pulses with 256*256 points along t_1 and t_2 directions.

Besides the detection in the (+,+) quadrant of weakly coupled ^1H, ^{13}C, ^{14}N from the ligands (see SI, fig. S5), of much more significance here is the presence of a pair of cross-peaks centered at ν = 13.4 MHz in the (+,+) quadrant which are assigned to the ^{19}F Larmor nuclear frequency. These symmetric cross-peaks indicate a weak hyperfine coupling that is estimated at 0.9 MHz and evidence the interaction between ^{19}F centers of the putative CF_3 group with the unpaired electron of the system. This is further confirmed by analyzing the specific features of the HYSCORE pattern in the (+,-) quadrant that indicates a *strong* hyperfine coupling from a ^{13}C nuclei, estimated at 22 MHz from the antidiagonal peak. This last result supports the presence of a carbon center being *directly* attached to the copper ion in [**3**], as expected if a CF_3 ligand is being formed upon the reaction with Umemoto reagent. These experimental data thus directly show the coordination of the CF_3 group through a metal-carbon bond in complex [**3**].

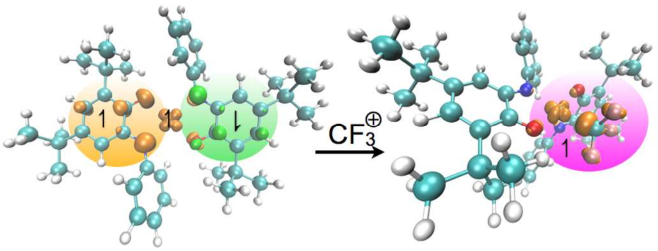
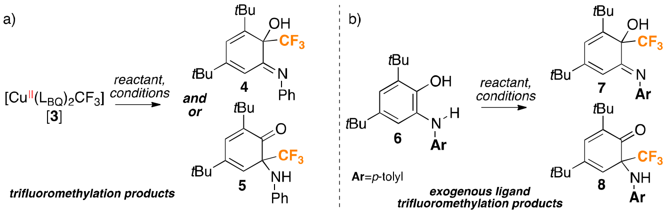


Fig. 4. DFT structures and spin density isosurfaces for complexes [**1**] and [**3**].

DFT calculations were undertaken to clarify the electronic structure of the new copper adduct. Complex [**1**] is known to be an open-shell species exhibiting an anti-ferromagnetic coupling between the ligand-based radicals, while one unpaired electron is localized on copper (Fig. 4). Upon incorporation of CF_3^+, the electronic description is totally modified: ligands are closed-shell and copper is the only atom bearing a significant amount of spin density (the remaining being on the CF_3 group). Thus, [**3**] can be described as a Cu^{II} adduct in which electrons responsible for Cu–CF_3 bonding originate from the ligand.

Although $Cu^{I}CF_3$[2d,3,16] and $Cu^{III}CF_3$[17] complexes[18] have been reported, complex [**3**] would be, to the best of our knowledge, the first example of a $Cu^{II}CF_3$ complex and we were therefore curious to probe its reactivity. Stability tests (SI, table S1) revealed that, upon standing in CH_3CN at rt for 18 h, a product identified as **4** (Scheme 2) was formed in 35% yield. Heating complex [**3**] in CH_3CN at 70 °C for 9 h resulted in isolation of distinct trifluoromethylated adduct **5** in 54% yield. Full analysis of these products by NMR ^{1}H, ^{13}C, ^{19}F and MS established that these products were trifluoromethylated quaternary analogues of the ligand in which a CF_3 group has been transferred to an electrophilic site. Independent heating of **4** in CH_3CN at 70 °C results in full conversion to **5** in 3 h, therefore suggesting that the CF_3 transfer occurs selectively at the electrophilic site of the carbonyl and that complex [**3**] could promote nucleophilic trifluoromethylation while originating from a CF_3^{+}source. This unexpected finding prompted us to explore reactivity towards selected partners. However, reaction with electrophiles (Tables S2–S3) did not afford any trifluoromethylated adducts. Reaction with aldehyde or imine produced **4** (45%) or **5** (54%) respectively (Table S2). Heating [**3**] in DCE in the presence of 2,2,6,6-tetramethyl-1-piperidinyloxyl (TEMPO) did not yield TEMPO–CF_3,[19] indicating that $[Cu(L_{BQ})_2CF_3]$ is not a source of CF_3 radicals. Switching to $PhBF_3K$ as nucleophilic partner resulted in formation of **4** at rt (22%) and **5** at 70°C (69%) (Table S4).

Hypothesizing that failure in trifluoromethylation of external partners might be linked to the geometry of the complex, we performed the reaction with exogenous ligand **6** as substrate, differing from the ligand by a tolyl group (Scheme 2, right). Under those conditions, both **7** (8%) and **8** (27%), could be isolated along with **4** (2%) and **5** (8%), indicating that trifluoromethylation of external substrate probably requires ligand exchange at the copper center.



Scheme 2. Trifluoromethylated products. a) CH_3CN, rt or 70 °C, b) **6** (1 equiv.), Umemoto reagent (1 equiv.), [**1**] (20 mol%), Et_3N (2 equiv.), AcOEt, 70 °C.

In summary, a new $[Cu^{II}(L_{BQ})_2CF_3]$ complex was prepared reacting $[Cu^{II}(L^{\cdot}_{SQ})_2]$ with an electrophilic CF_3^{+} source. The resulting two-electrons oxidation is sustained by the redox-active ligands while the copper oxidation state is preserved. Evidence for a Cu–CF_3 bond and detailed electronic structure have been assessed by combined *cw* and pulsed EPR spectroscopic measurements together with DFT studies. This complex promotes trifluoromethylation at electrophilic sites while originating from a CF_3^{+} source, performing a formal *umpolung* of the CF_3 moiety. Although still limited in scope, this reactivity is a proof-of-concept that redox-active ligands show potential for future applications in trifluoromethylation.

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Notes and references

[a] UPMC, CNRS, UMR 8232, Institut Parisien de Chimie Moléculaire (IPCM), F-75005, Paris (France).

[b] Laboratoire de Spectrochimie Infrarouge et Raman, UMR CNRS 8516 Bâtiment C5, 59655 Villeneuve d'Ascq Cedex (France).

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