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Redox-ligand sustains controlled generation of CF_3 radicals by well-defined copper complex†

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A well-defined copper complex bearing iminosemiquinone ligands performs single electron reduction of an electrophilic CF_3^+ source into $CF_3^{\cdot}$ radicals. This redox behavior is enabled by the ligand which shuttles through two different redox states (iminosemiquinone and iminobenzoquinone) while the copper center is preserved as a Cu(II). This system was used in the trifluoromethylation of silyl enol ethers, heteroaromatics and in the hydrotrifluoromethylation of alkynes. This is the first example of cooperative redox catalysis for the controlled generation of $CF_3^{\cdot}$ radicals.

Introduction

Cooperative redox catalysis steps away from the established organometallic paradigm involving redox events occurring at the metal center by introducing ligand-based electronic participation. Drawing inspiration from the redox relays involved in enzymatic processes,[1] this area of catalysis hinges upon a participative role of the non-innocent ligand in catalytic elementary steps in order to achieve multielectronic transformations with base metals.[2–8]

While redox non-innocence in biological settings has long been familiar to bioinorganic chemists, the use in a broader context of "synthetic" redox ligands as surrogates of the original biological radicals is emerging as a catalytic tool of its own. These privileged molecular scaffolds have been shown to actively participate in catalytic events through reversible delocalization of spin density.[4] This redox interplay between ligand and metal can provide attractive alternative mechanistic venues for catalyst development. Among expected benefits, the enabling potential of these ligands towards first-row transition metals or redox silent metals could enlarge their chemistry and unravel unprecedented reactivities. This area of catalysis is currently on the fast track for the development of alternative catalytic approaches circumventing the use of precious noble metals.[5]

Seeking to enlarge the scope of applications, we have been focusing on a well-known family of metal complexes exhibiting non-innocent behavior: copper complexes with iminosemiquinone ligands. Originally developed as enzyme mimics,[9] these complexes are of particular interest due to the versatile ligand scaffold which can accommodate two successive monoelectronic oxidation steps through a redox chemical interplay between three oxidation states: amidophenolate (AP), iminosemiquinone (SQ) and iminobenzoquinone (BQ). These systems are now being developed in broader (catalytic) contexts[10] with several metals including iridium,[11] cobalt,[12,13] palladium[14,15] and copper.[16,17] Previous work allowed us to establish that the interaction of complex **1** $[Cu(II)(L^{SQ})_2]$ with an electrophilic source of CF_3 triggers CF_3 uptake by the complex through ligand-based bis-electronic redox participation while preserving the metal Cu(II) oxidation state.[18] The resulting $[Cu(II)(L^{BQ})_2CF_3]^+$ complex **2** exhibits a nucleophilic intramolecular CF_3 reactivity, thus suggesting that redox involvement of ligands can sustain formal umpolung of the CF_3 moiety (Fig. 1).

Transfer of trifluoromethyl groups through metal-catalyzed processes is currently a topic of acute interest as this group belongs to the privileged moieties in synthetic chemistry. Its introduction in a biologically active scaffold enhances metabolic stability and favors permeation of drugs through the blood

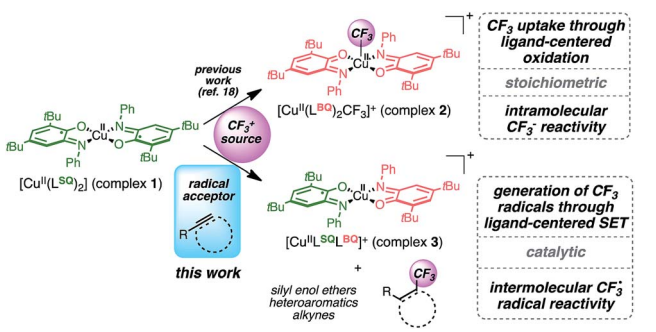

Fig. 1 Ligand-based redox reactivity of complex **1** with an electrophilic CF_3^+ source.

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brain barrier among other upsides.[19–23] The widespread benefits of the introduction of trifluoromethyl groups also pervade through materials chemistry and agrochemistry. Accordingly, numerous strategies have been devised by chemists for the introduction of this chemical functionality.[24–26] The wide range of available nucleophilic, electrophilic and radical trifluoromethylating sources provides varied catalytic manifolds opportunities, which plays no mean part in the success of this flourishing area. The wealth of CF_3 sources available has allowed flexibility in the development of a variety of approaches differing from the electronics involved.[27–30] In this matter, several metals have proven valuable to the chemists among which copper[31] and palladium.[32–34] Strategies involving the addition of CF_3 moieties across multiple bonds have also been developed and these efficient approaches allow building of molecular complexity.[35–37]

Recently, among these strategies, major focus has been placed on synthetic application of systems implying $CF_3^{\cdot}$ radicals[38] and recent elegant contributions rely on photoredox catalytic manifolds as means to generate such radicals in a clean and controlled fashion.[39–44] Radical trifluoromethylation of unsaturated moieties is inherently challenging because of competing radical-atom transfer and several methods have sought to take advantage of this reactivity in order to develop hetero- and carbotrifluoromethylation.[45–50] However, direct hydrotrifluoromethylation of multiple bonds, thus generating simple trifluoromethylated alkenes and alkanes, has been less explored and is an emerging application.[51–56] While these methods are an elegant and efficient way to produce $CF_3^{\cdot}$ radicals in a controlled fashion, they mostly imply expensive and less sustainable noble metals such as ruthenium and iridium and/or also often imply the use of additives playing the role of sacrificial electron donors and redox relays.

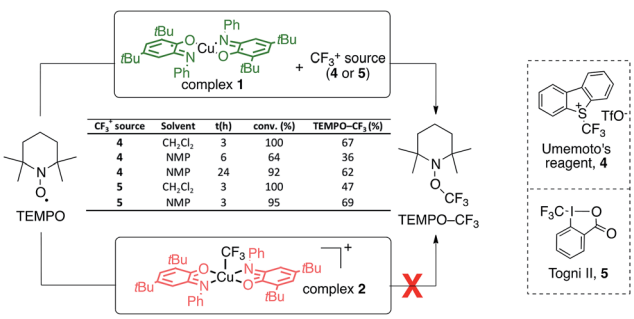
On the cheaper end of the metal spectrum, copper is a metal that has enjoyed recent exciting applications in trifluoromethylation of various organic substrates.[31,57] Notably, an efficient Cu(I)-photocatalyzed trifluoromethylation of alkenes was recently reported.[58] Another generation of $CF_3^{\cdot}$ radicals by Cu(I) salts from an electrophilic CF_3^+ source (**5**) in the trifluoromethylation of unactivated olefins to generate allylic trifluoromethylated products has been reported by Wang *et al.*[59] using CuCl and by Buchwald *et al.*[60] using $[(MeCN)_4Cu]PF_6$. A similar transformation was reported by Fu and Liu[61] using electrophilic source **4** and CuTC ((thiophene-2-carbonyloxy) copper) and the authors postulated the involvement of a Cu(III)–CF_3 species. The use of simple copper salts in these reactions is convenient but the lack of ligands that could stabilize the active copper species generates less controlled reactive intermediates and is a drawback for mechanistic elucidation. Moreover, these protocols often require between 10 and 20 mol% catalyst loading in order to provide good results.

Here, we show that well-defined complex **1** can be used in conjunction with an electrophilic CF_3^+ reagent as a catalytic source of $CF_3^{\cdot}$ radicals through SET sustained by the redox-active ligand scaffold. This cost-effective alternative way to generate $CF_3^{\cdot}$ radicals offers broad scope in transformations including trifluoromethylation of heteroaromatics, silyl enol ethers, and hydrotrifluoromethylation of alkynes.

Results and discussion

Initial experiments showed that reacting complex **1** with an electrophilic CF_3^+ source (Umemoto **4** or Togni II **5** reagents) in the presence of TEMPO (2,2,6,6-tetramethylpiperidine-*N*-oxyl radical, Scheme 1) led to the formation of the TEMPO–CF_3 adduct, as evidenced by NMR ^{19}F spectroscopy ($\delta = -55.7$ ppm). This reactivity was evaluated in CH_2Cl_2 and NMP with two CF_3^+ sources (**4** and **5**) and was found to proceed in fairly good yields (up to 69%). These results suggest that complex **1** can promote the generation of $CF_3^{\cdot}$ radical from a CF_3^+ source in the reaction medium. An independent equimolar mixture of TEMPO and complex **1** was followed by UV-vis and no reaction was found to occur, thus ruling out the possibility of direct electronic transfer between complex **1** and TEMPO and subsequent ionic CF_3 transfer. Also, no formation of the TEMPO–CF_3 adduct occurs in the absence of complex **1**, which is thus mandatory.[49] This reactivity is in sharp contrast with that of the fully oxidized complex **2** $[Cu(II)(L^{BQ})_2CF_3]^+$ which was found to be inert to reaction with TEMPO as no transfer of the CF_3 moiety was observed.

During the trifluoromethylation of TEMPO, the reaction medium turns from dark green to dark purple (source **4**) or dark orange (source **5**). We thus decided to investigate the locus of the electronic transfer by UV-vis spectroscopy. The initial green colour of the solution mainly corresponds to that of $[Cu(L^{SQ})_2]$ complex **1**, as attested by the presence on the spectra of its two characteristic bands around 300 nm and 800 nm,[62] and as can be seen in Fig. 2 (green curve). At the end of the reaction, these two characteristic bands have disappeared, while broad new features appear with maxima at 425 nm, 525 nm and 725 nm (Fig. 2, brick red curve). Interestingly, very similar bands have been reported for the electrochemically synthesized $[Cu(L^{SQ})(L^{BQ})]^+$ complex **3**, arising from single electron oxidation of complex **1**.[62] We therefore independently synthesized complex **3** *via* mediamutation of an equimolar mixture of $[Cu(L^{SQ})_2]$ complex **1** and its related dicationic complex **6** $[Cu(L^{BQ})_2]^{2+}$ (see ESI† for preparation) and recorded its absorption spectrum (Fig. 2, sky blue curve). Indeed, an



Scheme 1 TEMPO trapping experiments for the generation of CF_3 radicals with complexes **1** and **2**. NMP: *N*-methylpyrrolidinone.

excellent match between this reference spectrum and that of the reaction medium at the end of the reaction is observed. An almost perfect match is even obtained upon addition of one equivalent of dibenzothiophene, which is released in the reaction medium upon trifluoromethylation with Umemoto's reagent **4** (Fig. 2, purple curve).

These results strongly suggest that $[Cu(L^{SQ})(L^{BQ})]^+$ complex **3**, the monooxidized product of $[Cu(L^{SQ})_2]$ complex **1**, is formed during the reaction and point towards a SET process involved in the reaction and sustained by the redox ligand.

Since complex **3** seems to be a cornerstone for the reactivity examined here, its electronic structure was evaluated through DFT calculations. These calculations were performed with Turbomole v6.4, using the B3LYP functional complemented by the D3 dispersion scheme and with the Def2-SV(P) basis set. In Fig. 3 can be seen the optimized structure together with the total spin density. It appears that one unpaired electron remains on the metallic center (in the $dx^2 - y^2$ orbital) while the second one is dispatched over the two ligands, with an antiferromagnetic coupling between the two. Thus, while we formally write that complex **3** is bearing two different ligands (one SQ and one BQ), the picture emerging from DFT calculations shows that the unpaired electron is fully delocalized on both ligands. The corresponding UV-vis spectrum of complex **3** was calculated using the same DFT level (Fig. 4). In the 400–800 nm range, the experimental and calculated spectra appear to be very similar. Two groups of transitions, centered around 425 nm and 600 nm, can be associated with the 425 nm and 525 nm bands, while an additional band around 790 nm may be associated with the 725 nm shoulder. Overall, the calculated spectrum fits well with the experimental data. Thus, all the data collected allow us to confirm the nature of complex **3** as $[Cu(L^{SQ})(L^{BQ})]^+$.

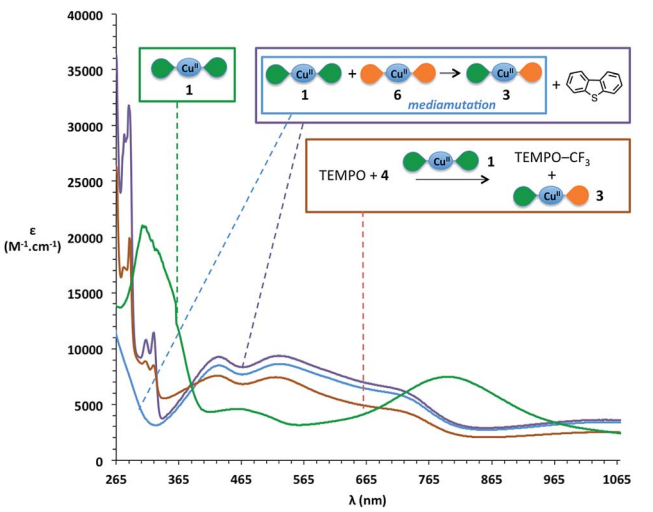


Fig. 2 Comparison of UV-vis spectra in CH_2Cl_2 of: green: $[Cu(L^{SQ})_2]$ **1**; brick red: reaction with Umemoto's source **4**; sky blue: *in situ* generated $[Cu(L^{SQ})(L^{BQ})]^+$ **3**; purple: *in situ* generated $[Cu(L^{SQ})(L^{BQ})]^+$ **3** with added dibenzothiophene. Color code for ligands: green petal is SQ ligand and orange petal is BQ ligand.

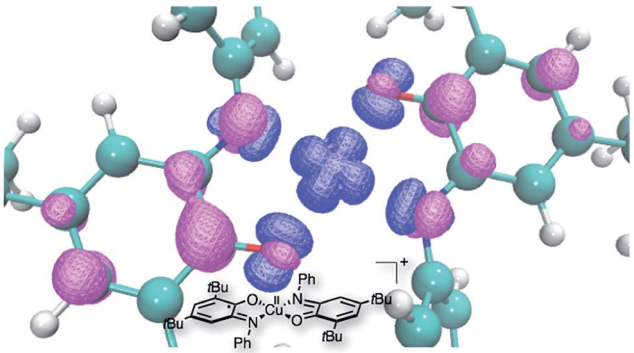


Fig. 3 DFT optimized structure for complex **3**, together with a spin density isosurface (plotted at $0.005e^- Å^{-3}$).

When using Togni's reagent **5**, the spectrum at the end of the reaction displays maxima around 300 nm, 390 nm and 500 nm (Fig. 5, brick red curve), which differs notably from the spectrum of $[Cu(L^{SQ})(L^{BQ})]^+$ complex **3**. We wondered if the iodobenzoate released from Togni's reagent might interact with the final copper complex and to our delight, adding the corresponding carboxylate to independently generated $[Cu(L^{SQ})(L^{BQ})]^+$ complex **3** induces a change in its UV-vis spectrum, which then displays a very good match with the spectrum observed at the end of the reaction (Fig. 5, purple curve).

Thus, in the case of Togni's reagent **5**, a SET from one of the iminosemiquinone ligands of $[Cu(L^{SQ})_2]$ complex **1** to form $[Cu(L^{SQ})(L^{BQ})]^+$ complex **3** also appears very likely. These experiments strongly support a SET occurring between complex **1** and the CF_3^+ source, in which the CF_3^+ source is reduced to form a $CF_3^{\cdot}$ radical while the concomitant oxidation of complex **1** into complex **3** is ligand-based and sustained by oxidation of an iminosemiquinone ligand into an iminobenzoquinone ligand.

These observations led us to probe the reactivity of this system and evaluate the possibility of CF_3 uptake in various

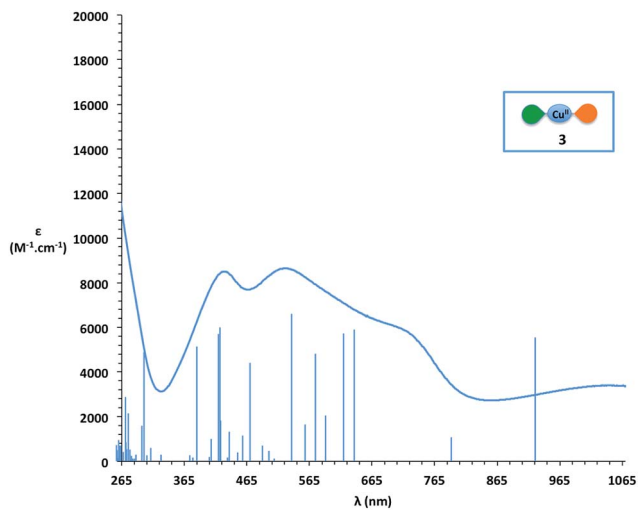


Fig. 4 Comparison of DFT calculated peak positions (blue peaks) and experimental (blue curve) UV-vis spectrum of complex **3**.

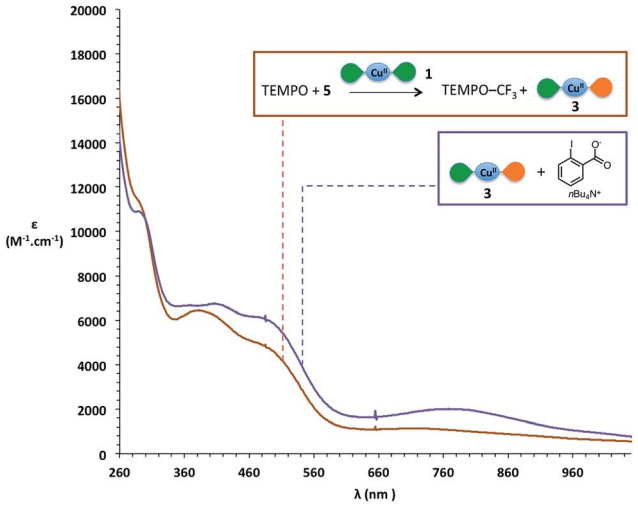


Fig. 5 Comparison of UV-vis spectra in CH_2Cl_2 of: brick red: reaction with Togni II's source **5**; purple: *in situ* generated $[Cu(L^{SQ})(L^{BQ})]^+$ **3** with added *o*-iodobenzocarboxylate. Color code for ligands: green petal is SQ ligand and orange petal is BQ ligand.

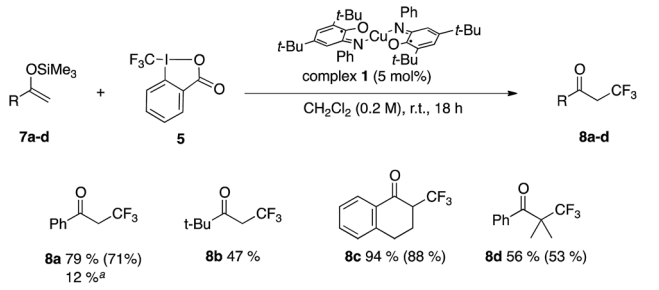
families of radical acceptors. Photoredox[63] and copper-catalyzed[64] catalytic trifluoromethylation of silyl enol ethers to generate α-trifluoromethyl ketones have been reported and this family of substrates was used as benchmark reactivity for our system.

We were pleased to see that reaction of silyl enol ethers **7a–d** with reagent **5** in the presence of 5 mol% of complex **1** yielded the corresponding trifluoromethylated adducts **8a–d** in promising to good yields from 47 to 94% (Table 1). However, substituting source **4** for **5** provided lower yields. The reaction proceeds within 18 hours at room temperature, which compares well with reported conditions (24 h at rt[63] and 12 h at rt to 50 °C[64]).

Introduction of CF_3 motifs in heteroaromatics is also a topic of interest and several radical-based methods have been reported.[40,65,66] Efficiency of the redox catalyst **1** was probed with indole, pyrrole and furane derivatives (Table 2, **9a–f**). The yields range from 59 to 87% and the regioselectivity obtained for **10b** is consistent with reported radical trifluoromethylation conditions.[40] Lowering the catalyst loading to 2 mol% resulted in decreased yields. Furthermore, the structure of compound **10c** was confirmed by X-ray crystallography. Successful preparation of **10c** and **10e** also demonstrates the mildness of our reaction conditions towards electrophiles such as aryl iodides, which are typically reactive under photoredox conditions[67,68] and could in our approach be used as synthetic handles for further functionalization by classic methods.

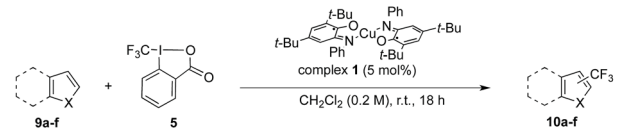
Having established the catalytic activity of complex **1** with well-known radical acceptors, we turned our attention towards hydrotrifluoromethylation of alkynes or alkenes. Since a seminal study from Kitazume in 1985 reporting the ultrasound-promoted hydrotrifluoromethylation of alkynes with trifluoroalkylcuprates, generated *in situ* from CF_3I or CF_3Br, zinc powder and substoichiometric amounts of CuI,[69] only a handful of strategies for selective hydrotrifluoromethylation have been

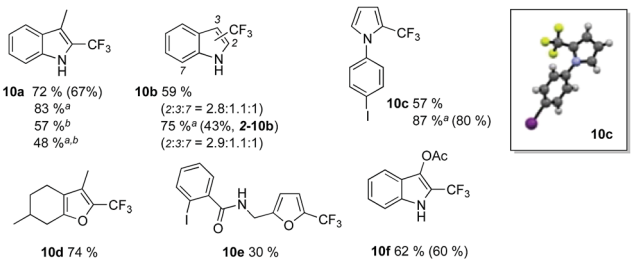
Table 1 Trifluoromethylation of silyl enol ethers



Yields were determined by ^{19}F NMR analysis, reaction conditions: 1 equiv. silyl enol ether, 1.5 equiv. reagent **5**. [a] Reaction was performed with **4** instead of **5**. Isolated yields in brackets.

Table 2 Trifluoromethylation of heteroaromatics



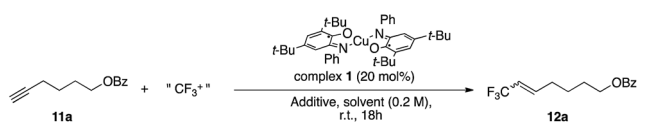


Yields were determined by ^{19}F NMR analysis, reaction conditions: 1 equiv. heteroaromatic, 1.5 equiv. reagent **5**. [a] Reaction conditions: 5 mol% complex **1**, 4 equiv. heteroaromatic, 1 equiv. reagent **5**. [b] 2 mol% catalyst loading. Isolated yields in brackets.

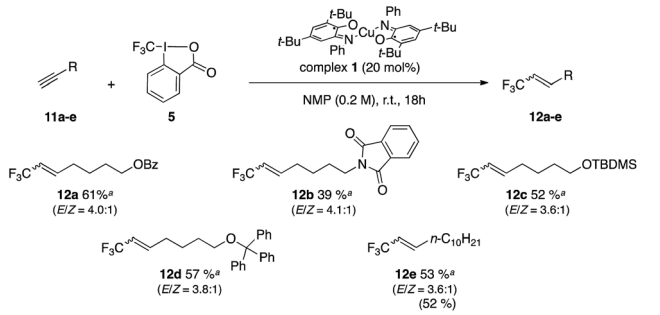
reported.[70] These involve inorganic electride,[51] silver-catalyzed[52] or organic[53,54] and organometallic[55,56] photoredox systems.

Cho and co-workers have reported the controlled trifluoromethylation of alkynes with CF_3I, *fac*-$[Ir(ppy)_3]$ as catalyst and DBU (10 equiv.) as reductive quench and H source.[56] The Gouverneur group has reported a method for alkynes and alkenes using photoredox catalyst $[Ru(bpy)_3]^{2+}$ in conjunction with Umemoto reagent **4** as CF_3^+ source and methanol as H source.[55] An organic photoredox system was reported for alkynes by Scaiano and co-workers using reagent **5** along with organic photocatalyst Methylene Blue and DBU (2 equiv.).[54] We selected alkyne **11a** as a model for optimization studies and established that the best conditions involved the use of complex **1** and reagent **5** in NMP (Table 3, entry 2). Introduction of additive such as CHD (1,4-cyclohexadiene) as H atom donor did not improve the yields (entries 3 and 4). The scope of the reaction was evaluated and provided the corresponding trifluoromethylated alkenes in yields between 39 and 61%. These results prove competitive towards the literature with 68%

Table 3 Hydrotrifluoromethylation of alkynes



Entry	CF_3^+ source	Solvent	Additive	12a[a]
1	**4**	NMP	—	11%
2	**5**	NMP	—	61%
3	**5**	NMP	CHD (1 equiv.)	35%
4	**5**	CH_2Cl_2	CHD (1 equiv.)	25%

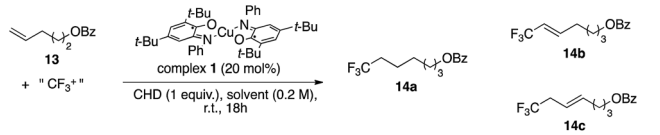


CHD: 1,4-cyclohexadiene. Reaction conditions: alkyne (4 equiv.), CF_3^+ source (1 equiv.), solvent, additive, rt, 18 h. [a] Yields were determined by ^{19}F NMR analysis. Isolated yields in brackets.

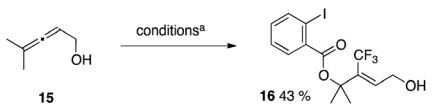
yield reported for alkene **12a** (conditions: 10 mol% $[Ru(bpy)_3Cl_2 \cdot 6H_2O]$, visible light, 1.8 equiv. of **4** in methanol at 25 °C for 24 h).[55]

Hydrotrifluoromethylation of alkene **13** (Table 4) was attempted but failed to deliver any expected hydrotrifluoromethylated product **14a**. Vinyl–CF_3 **14b** and allyl–CF_3 **14c** compounds were obtained instead. This could be due to the fact that the alkyl radical generated upon addition of $CF_3^{\cdot}$ onto

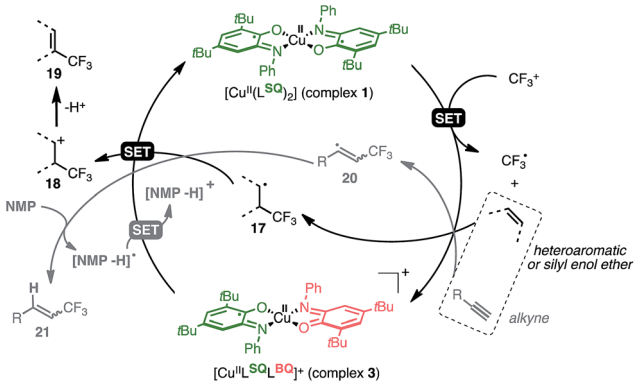
Table 4 Attempted hydrotrifluoromethylation of alkenes and trifluoromethylation of allenes



Entry	CF_3^+ source	14a	14b	14c
1	**4**	Traces	Traces	Traces
2	**5**	—	19%	29%



1,4-CHD = 1,4-cyclohexadiene. Reaction conditions: alkene (4 equiv.), CF_3^+ source (1 equiv.), 1,4-CHD (1 equiv.), NMP, rt, 18 h. Yields were determined by ^{19}F NMR analysis. [a] Reaction conditions: 5 mol% complex **1**, 1.5 equiv. reagent **5**, CH_2Cl_2, r.t., 18 h.



Scheme 2 Proposed mechanism for the controlled generation of $CF_3^{\cdot}$ radicals sustained by redox ligand. [NMP–H] corresponds to the species resulting from H atom abstraction, more likely at the CH_2 position adjacent to the nitrogen.[76]

the alkene (Scheme 2) is easier to oxidize than its vinylic counterpart – generated upon addition of $CF_3^{\cdot}$ on the alkyne – and thus undergoes oxidation to the alkyl cation followed by proton loss to generate the allylic CF_3 product more quickly than H transfer. This observation also extends to allene **15** which was found to undergo oxytrifluoromethylation to yield product **16** presumably arising from trapping of the cationic intermediate by 2-iodobenzoate generated in the reaction upon reduction of reagent **5**.[71]

Based on literature precedents, mechanistic possibilities for this transformation include organometallic, ionic or radical pathways. An organometallic route was proposed by Beller and co-workers[72] and by Sanford and co-workers[41] for the copper-catalyzed trifluoromethylation of vinyl boronic acids with $CF_3^{\cdot}$ radicals generated by *t*-BuOOH and CF_3SO_2Na or CF_3I and photocatalyst $Ru(bpy)_3Cl_2 \cdot 6H_2O$ respectively. Both involved a Cu^{III}–CF_3 intermediate releasing the final product through reductive elimination. Investigating the copper-catalyzed allylic trifluoromethylation of alkenes with reagent **4**, Fu and Liu postulated a similar mechanism based on DFT calculations.[61] This mechanism can be ruled out in our system since the corresponding Cu–CF_3 complex **2** resulting from CF_3 uptake by complex **1** has been isolated and cannot transfer its CF_3 moiety.[18] An ionic pathway seems unlikely as the presence of the catalyst is mandatory and this route would be in contradiction with the TEMPO trapping experiments (Scheme 1). Indeed, adding TEMPO to a solution of complex **1** does not change the UV-vis profile, therefore suggesting that no electronic transfer occurs between TEMPO and complex **1**.[73]

In light of these considerations, we propose a mechanism (Scheme 2) implying the generation of $CF_3^{\cdot}$ radicals by SET from complex **1** to the CF_3^+ source[74] and subsequent addition of this radical onto the unsaturated moieties. The resulting alkyl–CF_3 radical **17** (Scheme 2, black pathway) could then undergo another SET thereby regenerating complex **1** along with the oxidized cation **18** and closing the catalytic cycle. Proton loss provides the expected product **19**. In the case of alkynes (Scheme 2, grey pathway), vinyl–CF_3 radical **20** obtained presumably undergoes hydrogen transfer with NMP,[52] thereby

providing trifluoromethylated alkene **21**. The resulting NMP radical is then oxidized to the cation, thus regenerating complex **1**. Also, performing the reaction of complex **3** instead of complex **1** with TEMPO in the presence of reagent **5** only provides TEMPO–CF_3 adducts in trace amounts (<3%) thus indicating that only reduced complex **1** is capable of reducing the CF_3^+ source.[75]

Conclusions

We have shown that a well-defined copper(II) complex can promote generation of $CF_3^{\cdot}$ radicals by reduction of an electrophilic CF_3^+ source. This unusual behavior is enabled by a redox dialogue between the CF_3^+ source and the complex, mediated by the redox-active ligand which enables SET through ligand-centered oxidation. This strategy offers milder conditions and complementarity to photoredox catalytic manifolds as well-defined molecular complexes performing controlled generation of $CF_3^{\cdot}$ radicals. This method circumvents changes in the redox state of the copper center by promoting electronic transfer at the ligand instead, thus limiting uncontrolled reactivities at the metal center, and was successfully applied to the trifluoromethylation of silyl enol ethers, heteroaromatics and hydrotrifluoromethylation of alkynes. To the best of our knowledge, this is the first example of hydrotrifluoromethylation of alkynes catalyzed by a well-defined copper complex and overall of controlled generation of $CF_3^{\cdot}$ radicals by cooperative redox catalysis. This reactivity opens the way towards new developments in the field of redox ligand-based cooperative catalysis as possible mild alternatives to expensive noble metals such as iridium and ruthenium. Among other foreseeable broad catalytic perspectives, the participative nature of these ligands could allow them to stabilize high and/or disfavored metallic oxidation states, which is a prospect we are currently pursuing.

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