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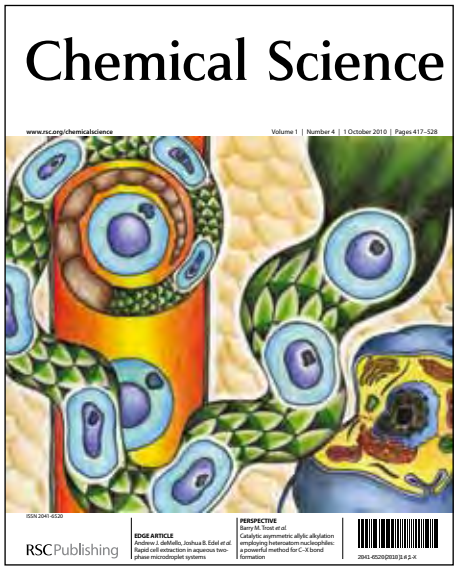

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ARTICLE TYPE

Metal-Templated Ligand Architectures for Trinuclear Chemistry: Tricopper Complexes and Their O_2 Reactivity

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A trinucleating framework was assmbled by templation of a heptadentate ligand around yttrium and lanthanides. The generated complexes orient three sets of two or three N-donors each for binding additional metal centers. Addition of three equivalents of copper(I) leads to the formation of tricopper(I) species. Reactions with dioxygen at low temperatures generate species whose spectroscopic features are consistent with a μ_3,μ_3-dioxo-tricopper complex. Reactivity studies were performed with a variety of substrates. The dioxo-tricopper species deprotonates weak acids, undergoes oxygen atom transfer with one equivalent of triphenylphosphine to yield triphenylphosphine oxide, and abstracts two hydrogen atom equivalents from tetramethylpiperidine-N-hydroxide (TEMPO-H). Thiophenols reduce the oxygenated species to a Cu^I_3 complex and liberate two equivalents of disulfide, consistent with a four-electron four-proton process.

Introduction

Enzyme active sites containing three metal centers perform diverse biological functions, including electron transfer, hydrolytic reactions, and O_2 reduction.[1] These enzymes display trimetallic moieties comprising of zinc, iron, magnesium, or copper.[2] In the context of O_2 reduction to water, the tricopper active sites of laccase and ascorbate oxidase (AO) have been studied extensively given the potential applications in fuel cell chemistry.[3] In these enzymes, a fourth copper center situated ~12 Å away provides an additional reducing equivalent.[4] Synthetic efforts have focused on modeling the tricopper site where O_2 activation occurs. Mononuclear diamine complexes have been shown to self-assemble upon reaction with O_2 to form a $Cu^{II}_2Cu^{III}(\mu_3\text{-}O)_2$ species.[5] Reduction of these trinuclear cores leads to dinuclear species, however, hindering attempts for developing catalytic versions of this reaction. An alternate strategy has been the employment of trinucleating frameworks.[6] Most systems investigated are rather flexible and do not faciliate cooperative trinuclear reactivity. Macrocyclic ligands have been shown to bind three Cu^{II} centers, but O_2 reactivity has not been reported with these systems.[7] Beyond tricopper models, recent ligand-design synthetic efforts have been reported on trinuclear complexes of manganese, iron, cobalt, and zinc.[8]

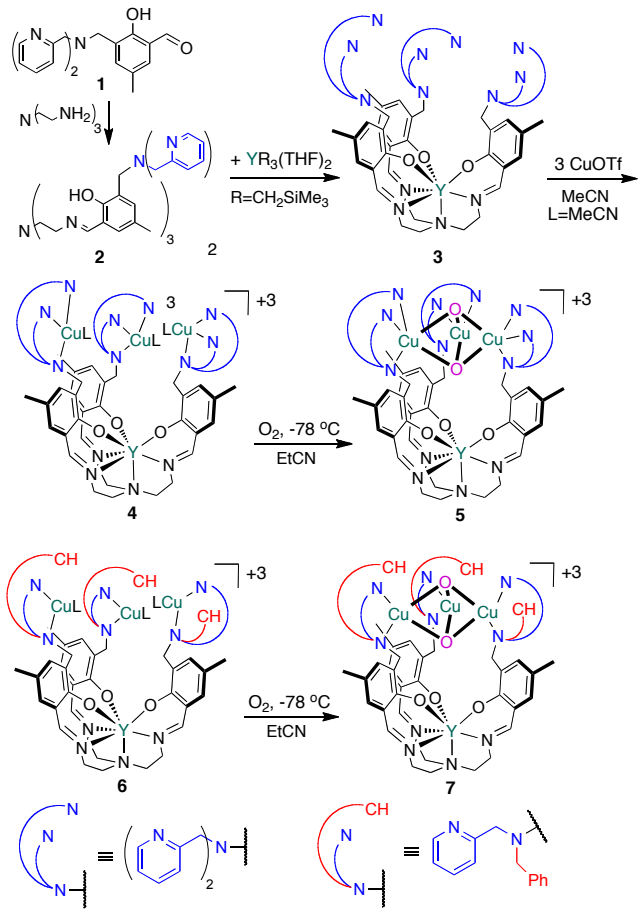
We have investigated 1,3,5-triarylbenzene frameworks, appended with a variety of donors, capable of supporting multimetallic systems.[8c, 9] The reaction of O_2 with a tricopper complex based on this framework was complicated in part because of the presence of alcohol groups which lead to a bridged alkoxide species upon oxidation to Cu^{II}.[9b] We report here a novel strategy for the generation of trimetallic moieties based on templating a ligand scaffold around yttrium or lanthanides to generate a seven-coordinate complex that displays three multidentate sites for binding of transition metals. The synthesis of tricopper complexes and their reactivity with O_2 is discussed.

Results and Discussion

Group 3 and lanthanide ions are known to bind heptadentate, tripodal $[O_3N_4]$-trisphenoxide-trisimine-amine ligands in a fashion that positions carbon substituents *ortho*- to the phenoxide oxygen about 3–4 Å apart from each other.[10] This separation is in the range observed for the copper centers in laccase and AO. Substitution with multidentate moieties at these positions are expected to allow for binding of three metal centers in close proximity. Additionally, these ligating moieties were selected to allow for orthogonal binding of different metals (e.g. first row transition metals vs lanthanides or yttrium) at the desired sites.

Toward assembling such multinucleating ligand architecture, a variant (**2**) of the $[O_3N_4]$-trisphenoxide-trisimine-amine framework with dipicolylamine substitutents was prepared via a condensation between tris(2-amino-ethyl)amine and three equivalents of previously reported aldehyde **1** (Scheme 1).[11] Metallation was perfomed via alkane elimination with an yttrium trialkyl precursor. NMR spectroscopic characterization shows a single phenoxide and pyridine environment, consistent with yttrium binding to the $[O_3N_4]$-trisphenoxide-trisimine-amine moiety to generate a high-symmetry species (**3**). Addition of three equivalents of Cu^I precursor ($Cu(CH_3CN)_4OTf$) dissolved in acetonitrile (MeCN) to a suspension of **3** in MeCN leads to the generation of a homogeneous mixture and to a color change from light yellow to gold. In contrast to **3**, the generated species is soluble in acetonitrile but not soluble in less polar solvents (e.g.: THF) suggesting the formation of an ionic complex. Single crystal X-ray diffraction studies show the formation of a tricationic Cu_3Y species, **4** (Figure 1), with the seven-coordinate yttrium center bound to the $[O_3N_4]$-trisphenoxide-trisimine-amine

site, the three copper centers bound to the dipycolylamine moieties, and three outer-sphere triflate anions. Acetonitrile molecules bind to the copper centers to complete distorted tetrahedral coordination environments. The selectivity for yttrium binding to the $[O_3N_4]$ motif, despite the presence of nine additional nitrogen donors is notable, and indicates that this strategy may be more general with respect to changes in the nature of chelating ligands and metals decorating the $[YO_3N_4]$ unit. In the solid-state, the copper centers are twisted away from each other leading to separations of ~9 Å. ^{1}H NMR studies show only one pyridine environment, despite the fact that the solid state structure is *pseudo*-C_3 symmetric. This indicates that in solution the conformation of the molecule is fluxional, with the copper centers potentially approaching closer orientations.



Scheme 1 Synthesis of ligands and tetrametallic, tricopper system complexes, and reactivity with O_2.

The reaction of compound **4** with O_2 was monitored by UV-Vis spectroscopy at low temperatures (Figure 2). A new species (**5**) is generated within a minute at -78 ºC and within seconds at -40 ºC. This species is stable for at least 24 hours at -78 °C; about 30% decay is observed over the same period at -40 °C and complete decay is observed within minutes at 25 °C. Volumetric measurements carried out with a Toepler pump indicate that 0.97±0.01 equivalents of O_2 are consumed per equivalent of **4**, supporting the formation of a complex with the stoichiometry "Cu_3O_2". This corresponds to the $Cu^{II}_2Cu^{III}(\mu_3\text{-}O)_2$ core previously reported with bidentate ligands: *N,N,N',N'*-tetraalkylcyclohexanediamines (**A**, for *N,N,N',N'*-tetramethylcyclohexanediamine) by Stack *et al.*, *N,N*-dimethyl-2-picolylethanamine (**B**) by Itoh *el al.,* and more recently 4-(2,2-dimethylhydrazino)-dimethylhydrazone-3-penten-2-one (**C**) by Tolman *et al.*[5, 12] These complexes were all self-assembled from concentrated solutions of monocopper(I) precursors supported by bidentate amines. To test the behavior of the present architecture with other donor sets, a ligand variant with only two nitrogen donors per copper-binding arm was synthesized for comparison – for each arm, one pyridyl group was replaced with phenyl. The related Cu_3Y complex, **6**, was prepared, and its reaction with O_2 led to a new species (**7**) with spectroscopic features similar to those of **6** (Figure 2). Spectroscopic comparison (UV-Vis and EPR, see also SI) with **A**, **B**, and **C** (Table 1) and the reaction stoichiometry support the assignment of species **5** and **7** as displaying the $Cu^{II}_2Cu^{III}(\mu_3\text{-}O)_2$ motif.[13] Additionally, no evidence of the presence of H_2O_2 was observed when a solution of **5** was treated with formic acid (5 equiv) and Ti(IV)oxysulfate solution.[12c, 14]

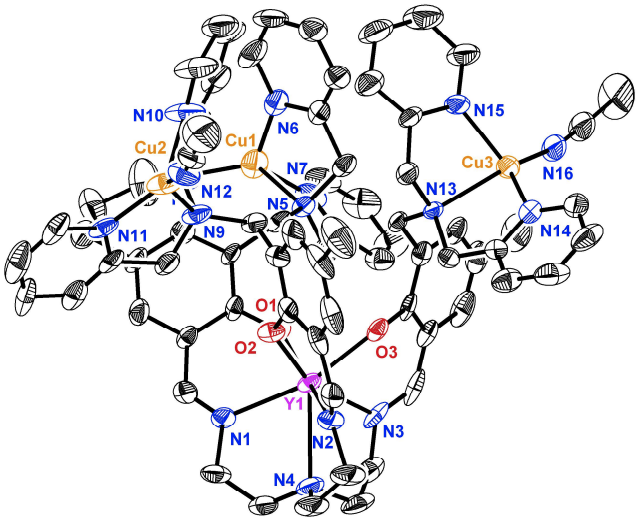
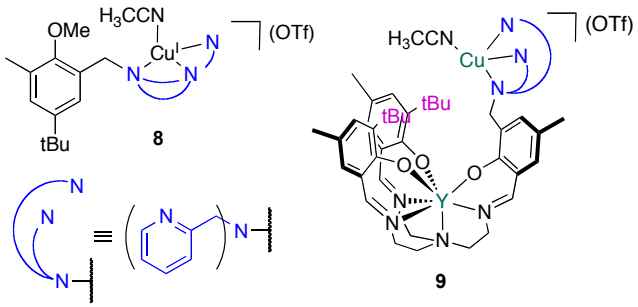


Figure 1. Solid-state structure of tricationic complex **4**. Thermal ellipsoids shown at 50% probability. Hydrogen atoms are omitted for clarity.

The synthesis of **5** and **7** is notable given the lack of precedent for preassembled trinuclear complexes that show similar reactivity with O_2. The generation of **5** is particularly noteworthy given that previous studies of copper-dipicolylamine complexes do not report trinuclear reactivity.[15] This difference in behavior indicates that the formation of the $Cu^{II}_2Cu^{III}(\mu_3\text{-}O)_2$ unit in this case may be a consequence of preassembling the three copper centers in close proximity. To further test this hypothesis, two related monocopper complexes were prepared, **8** and **9**, both displaying copper-dipicolylamine moieties (Scheme 2). The amine moiety in complex **8** is substituted with a methyl-aryl ether fragment, removing the yttrium binding site. Complex **9** is analogous to **4** by containing the Y-$[O_3N_4]$ motif, but displays a single dipicolylamine arm resulting in a monocopper complex. (see SI for ligand and complex syntheses) If intermolecular copper self-assembly reactivity upon reaction with O_2 was responsible for the spectroscopic features of **5** and **7**, mononuclear Cu^I complexes **8** and/or **9** were expected to undergo reactivity similar to **4** and **6** given the steric and electronic similarities. Reaction of either complex with O_2, however, leads to a species that has spectroscopic features different from **5** and **7** (Figure S32 in the Supporting Information). Even substantial increase in concentration (0.2-10.0 mM) does not lead to the signature of the $Cu^{II}_2Cu^{III}(\mu_3\text{-}O)_2$ core. In contrast, **5** and **7** are formed at concentrations as low as 0.05 mM. The literature intermolecular

examples are generated at concentrations of 10 mM (Stack, Itoh) or 1.0 mM (Tolman). These findings suggest that the reactivity of precursors **4** and **6** is intramolecular in copper and, moreover, the formation of the $Cu^{II}_2Cu^{III}(\mu_3\text{-}O)_2$ moiety is facilitated by the presence of the three Cu centers in close proximity on the same ligand framework.



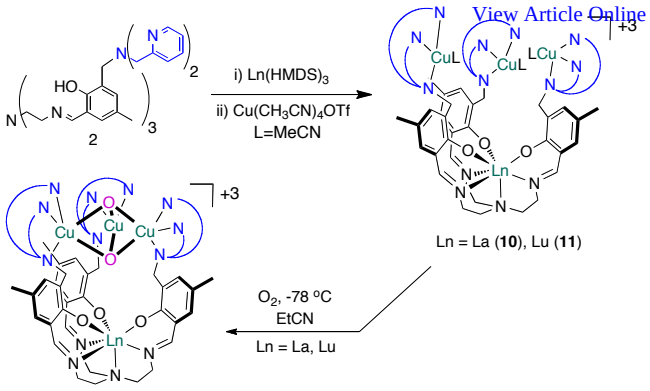
Scheme 2. Mononuclear Cu^{I} complexes for reactivity comparison to tri-copper Cu_3Y variants.

Table 1. Spectroscopic features of $Cu^{II}_2Cu^{III}(\mu_3\text{-}O)_2$ complexes.

A λ_{max} nm, (ε, $M^{-1}cm^{-1}$)	**B** λ_{max} nm, (ε, $M^{-1}cm^{-1}$)	**C** λ_{max} nm, (ε, $M^{-1}cm^{-1}$)	**5** λ_{max} nm, (ε, $M^{-1}cm^{-1}$)	**7** λ_{max} nm, (ε, $M^{-1}cm^{-1}$)
290 (12,500)	-		-	-
355 (15,000)	343 (12,000)	328 (10,700)	355 (12,400)	340 (11,500)
480 (1,400)	515 (1,000)	420 (1,500)	480 (1,910)	455 (2,160)
620 (800)	685 (800)	590 (835)	640 (800)	690 (760)

Facilitation of trinuclear cooperative reactivity by the tetrametallic, tricopper architecture in **4** has implications to the reaction of O_2 in biological systems, in which the protein scaffold keeps the three copper centers in close proximity. Furthermore, laccases and AOs bind the three copper centers using a total of eight histidines. Compound **5** displays nine N-donors for three coppers, which represents a more accurate model of biological systems (eight total nitrogen donors for three copper centers) than previous model complexes that a total of six nitrogen donors for the Cu_3O_2 moiety, although in the present case, coordination of all nitrogens has not been confirmed structurally. Although studies of multicopper proteins have not shown evidence of a $Cu^{II}_2Cu^{III}(\mu_3\text{-}O)_2$ moiety,[16] investigations of this moiety in a model system is expected to further our understanding of O_2 activation at tricopper sites.

In order to determine whether geometric changes in the ligand architecture would induce changes in reactivity, Cu_3Ln complexes analogous to **3** (Ln=La, **10**; Lu, **11**) were investigated. The size of the central Ln(III) ion affects the relative orientation of the three phenoxide arms, with the propeller-like turn of the aromatic rings varying from 27.3º to 47.7º vs the axial N-Ln vector.[17] Complexes **10-11** were prepared by protonolysis with suitable $Ln(HMDS)_3$ reagents (HMDS=hexamethydisilazide, Ln=La, Lu) followed by metalation with $Cu(CH_3CN)_4OTf$. Monitoring of O_2 reactivity of these complexes via UV-Vis spectroscopy revealed reactivity analogous to Cu_3Y complexes (Figure 2, bottom inset). The similar reactivity of complexes of lanthanides of different sizes – from largest, La, to smallest, Lu – further highlights the ability of the present architechture to engender cooperative reactivity among the three Cu centers regardless of the nature of the nature of the central, nucleating metal.



Scheme 3. Preparation and O_2 reactivity of Cu_3Ln complexes

Reactions of **5** and **7** with substituted ferrocenes were performed to estimate their reduction potentials, similarly to previous reports in the literature for products of O_2 activation by copper complexes.[5a, 18] In each case the 480 nm band decayed completely over 6 h upon treatment with decamethylferrocene ($E_{Fc^*/Fc^{*+}}$ = -0.05 V vs SCE)[19] at -40 °C. Treatment with 1,1'-dimethylferrocene ($E_{FcMe2/FcMe2+}$ = 0.34 V vs SCE)[19] over the same time period does not lead to decay of **5** or **7** beyond background decomposition. This indicates that the reduction potential of both **5** and **7** is between 0.34 and -0.05 V vs SCE. In contrast, the reduction potentials of previously reported Cu_3O_2 species supported by neutral ligands lie between 0.79 and 0.48 V vs. SCE as determined by analogous reactivity with ferrocene and acetylferrocene.[5a] Furthermore, several $Cu^{III}_2(\mu_2\text{-}O)_2$ species were reported to have a reduction potential near 0.5 V vs SCE.[20] Hence, **5** and **7** are significantly weaker oxidants. This may be due to the presence of electron rich phenoxide substituents on the nitrogen donors. Indeed, the Cu_3O_2 motif supported by more electron rich, anionic ligands recently reported by Tolman are unreactive toward decamethylferrocene.[12c]

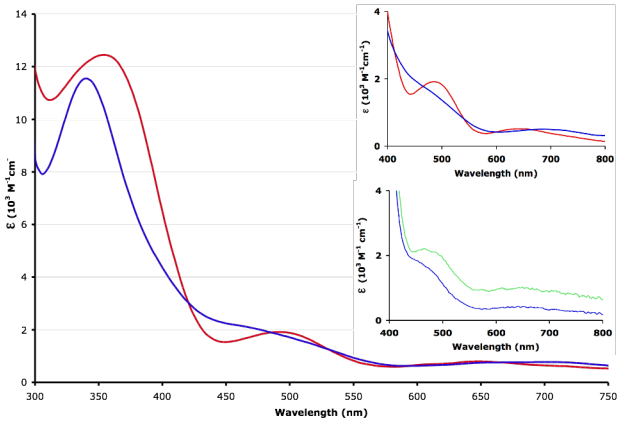


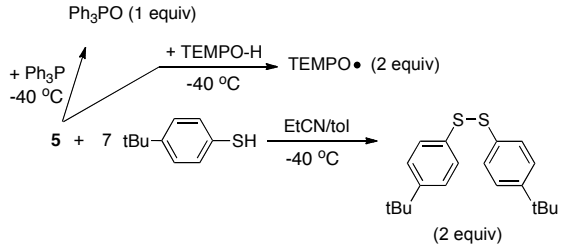
Figure 2. UV-Vis spectra of solutions of **5** (blue) and **7** (red) in 3:2 toluene/acetonitrile. Top inset: Expanded view of the 400-800 nm region. Bottom inset: spectra of oxygenated solutions of **10** (blue) and **11** (green) in 1:1 toluene/propionitrile at -78ºC.

Compound **5** reacts with 2,4-di-*tert*-butylphenol at -40 °C (UV-Vis spectroscopy). According to GC-MS and ^{1}H NMR spectroscopy, the phenol starting material is quantitatively recovered upon work-up. This behavior is in contrast to that of other Cu_3O_2 moieties supported by neutral ligands which generate biphenol.[5a, 5c] It has been previously proposed that the phenol coordinates to copper prior to dimerization.[5c] The higher

coordination number of **5** may block phenol binding to the copper centers. However, the analogous reaction of **7** – which has one fewer N-donor available per Cu center – with phenol also failed to yield dimerized product. This observation suggests that steric differences, rather than coordination number, may be the reason for the differences in reactivity between compounds **5** and **7** and other Cu_3O_2 moieties. Nonetheless, reaction with a less bulky phenol (4-tertbutylphenol) also showed no evidence of oxygenation or C–C coupling. Furthermore, H-atom abstraction by the Cu_3O_2 moiety was ruled out upon observing that reaction with 2,4,6-tri-*tert*-butylphenol does not give rise to the known 2,4,6-tri-*tert*-butylphenoxyl radical as observed by UV-Vis spectroscopy. Hence the observed reaction is proposed to involve only protonation of the Cu_3O_2 moiety. The reactivity of **5** with a variety of acids was studied. Treatment of **5** at -40 °C with triethylammonium triflate (pK_a=18.5 in acetonitrile)[21] causes complete decay of the 485 and 645 nm bands over 4 hours.[22] Treatment of **5** with weaker acids results in slightly slower reactions, as monitored by UV-Vis spectroscopy: 1,8-diazabicyclo[5.4.0]undec-7-enium triflate (pK_a=24.34)[21], and pyrrole (pK_a=34.6)[21], react with **5** to 50-70% completion in 6 hours. Although a pK_a value cannot be assigned to **5**, reaction with acids as weak as pyrrole is consistent with the interpretation of the reaction with phenols (pK_a>25)[21] also being protonation events.

The reactions of **5** with phosphine and H-atom transfer agents were investigated (Scheme 4). Compound **5** was found to react to completion with triphenylphosphine (5 eq) in 3 hours to give triphenylphosphineoxide (0.84 ± 0.10 equivalents, ^{31}P-NMR spectroscopy). In contrast, treatment of **7** with PPh_3 yielded ca. 2 equivalents of $(O)PPh_3$, suggesting that the lower possible coordination number of the Cu centers in **7** facilitates transfer of the second oxygen atom to phosphine. Decay of the spectroscopic signature of **5** was also observed upon treatment with *N*-hydroxy-2,2,6,6-tetramethylpiperidine (TEMPO–H, pK_a>41 in acetonitrile,[23] reaction complete in 4 hours). Integration of the electron paramagnetic resonance signal of the TEMPO–H reaction solution and comparison to a standard solution of TEMPO radical[49] indicates that two equivalents of TEMPO radical are generated per Cu_3O_2 moiety. Hence, compound **5** formally performs H-atom abstraction, rather than just deprotonation in this reaction. No reaction was observed with 9,10-dihydroanthracene or toluene. The observed trend in reactivity reflects the trend in X–H bond dissociation energies for these substrates (70 kcal/mol for TEMPO–H,[24] 74 kcal/mol for dihydroanthracene,[25] and 88 kcal/mol for toluene).[26]

The reactivity of complex **5** with thiol reducing agents was investigated. Upon treatment with 4-*tert*-butylthiophenol (Scheme 4) disappearance of the UV-Vis bands characteristic of **5** was observed within 1 min at -40 ºC. After anaerobic workup at room temperature, the reaction mixture contained two equivalents of the diaryldisulfide product (^{1}H NMR), corresponding to an overall transfer of four protons and four reducing equivalents by complex **5**. A reduced (diamagnetic) tricopper species was recovered in near-quantitative yield and was found to display thiophenol ligands (^{1}H NMR). Although structural characterization has eluded to date, the identity of the recovered tricopper complex (**4**•3ArSH) as a tricopper(I) adduct was supported by independent synthesis via addition of thiophenol to **4**. Therefore, unlike TEMPO-H, thiophenol is capable of delivering the four electrons and four protons necessary for full reduction of the $Cu^{II}_2Cu^{III}O_2$ core in **5** to Cu^{I}.[27] A solution of **5** that was allowed to warm to room temperature to yield the decomposition products of **5** still displayed reactivity with 4-*tert*-butylthiophenol, but only 50% of the expected disulfide product was obtained, and the reduced tricopper species was observed (~50% yield, ^{1}H NMR) but could not be isolated cleanly.



Scheme 4. Reactivity of complex **5**.

The present $Cu_3(\mu_3\text{-}O)_2$ moiety is a weaker oxidant relative to other dicopper and tricopper oxo species with reported reduction potentials. This may explain its lack of oxidative C–C coupling reactivity with alkylphenols.[28] X–H bond activation by **5** was observed only with substrates that have weak X–H bonds. Since X–H bond activation is controlled by both the reduction potential and basicity of the metal-oxo species,[29] it is not surprising that, despite a qualitatively basic center, reactivity with stronger X–H bonds is not observed, in view of the more negative reduction potential. This behavior is consistent with the function of tricopper sites in laccases and AOs, which are oxidases and hence do not perform C–H oxygenations. Oxygenation reactivity would likely be detrimental to these proteins, as it would lead to the functionalization of amino-acid side chains.

Conclusions

In summary, ligand frameworks displaying a total of sixteen or thirteen oxygen and nitrogen donors were selectively templated by yttrium(III) and lanthanides binding to a tripodal $[O_3N_4]$-trisphenoxide-trisimine-amine moiety. The remaining three pycolylamine-based metal binding sites coordinate copper(I). Reactions of these Cu^{I}_3Y complexes with O_2 generate $Cu^{II}_2Cu^{III}(\mu_3\text{-}O)_2$ motifs according to spectroscopic comparison to literature compounds and the measured reaction stoichiometry. Since two related mononuclear copperdipicolylamine complexes do not generate $Cu^{II}_2Cu^{III}(\mu_3\text{-}O)_2$ species, the preorganized tricopper core is necessary for this reactivity with O_2. Similarly to multicopper oxidases, the close arrangement of three metal centers leads to cooperative activation of O_2. Compound **5** is less oxidizing than previously reported $Cu^{II}_2Cu^{III}(\mu_3\text{-}O)_2$ complexes and does not perform phenol dimerization. Oxygenation of triphenylphosphine and activation of the weak O–H bond of TEMPOH were observed, however. Oxidation of thiol to generate two equivalents of diaryldisulfide show the ability of **5** to reduce to a tricopper(I) core using four electrons and four protons. Starting from **4**, the overall process corresponds to the reduction of O_2 to H_2O. The structural features that lead to these differences compared to previous systems are not clear at this time and further studies will explore the reactivity of this family of $Cu^{II}_2Cu^{III}(\mu_3\text{-}O)_2$ complexes. Future studies will focus in developing catalytic O_2 reduction systems and mechanistic studies of O_2 activation at tri- and tetranuclear cores based on the present type of complexes. The molecular architectures reported here are expected to be generally applicable to the assembly of

multimetallic complexes for a variety of transformations including multielectron redox processes and acid-base chemistry.

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Notes and References

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† Electronic Supplementary Information (ESI) available: experimental procedures, characterization data, and crystallographic details for **4** (CIF). See DOI: 10.1039/b000000x/

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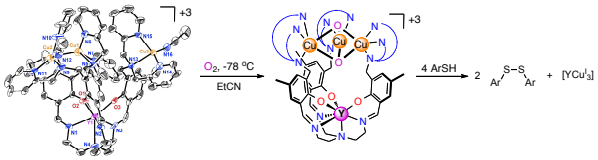
Table of Contents Graphic:



Three copper centres assembled in close proximity via ligand preorganization by yttrium or lanthanides perform intramolecular trimetallic dioxygen activation chemistry.