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Building Complexity in O_2-Binding Copper Complexes. Site-Selective Metalation and Intermolecular O_2-Binding at Dicopper and Heterometallic Complexes Derived from an Unsymmetric Ligand

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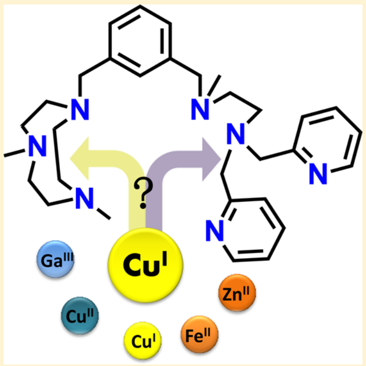
Supporting Information

ABSTRACT: A novel unsymmetric dinucleating ligand (L^{N3N4}) combining a tridentate and a tetradentate binding sites linked through a *m*-xylyl spacer was synthesized as ligand scaffold for preparing homo- and dimetallic complexes, where the two metal ions are bound in two different coordination environments. Site-selective binding of different metal ions is demonstrated. L^{N3N4} is able to discriminate between Cu^I and a complementary metal (M' = Cu^I, Zn^{II}, Fe^{II}, Cu^{II}, or Ga^{III}) so that pure heterodimetallic complexes with a general formula $[Cu^IM'(L^{N3N4})]^{n+}$ are synthesized. Reaction of the dicopper(I) complex $[Cu^I_2(L^{N3N4})]^{2+}$ with O_2 leads to the formation of two different copper-dioxygen (Cu_2O_2) intermolecular species (**O** and ^{T}**P**) between two copper atoms located in the same site from different complex molecules. Taking advantage of this feature, reaction of the heterodimetallic complexes $[CuM'(L^{N3N4})]^{n+}$ with O_2 at low temperature is used as a tool to determine the final position of the Cu^I center in the system because only one of the two Cu_2O_2 species is formed.



INTRODUCTION

Unsymmetric dinuclear active centers are commonly found in metalloproteins.[1] They can be either dimetallic centers where two metal ions of different nature act together to afford activity (e.g., FeZn purple acid phosphatases[2]) or homometallic sites in which the asymmetry originates from a markedly different coordination environment around each of the metal sites (hemerythrin[3]). Especially remarkable is the structural diversity found in O_2-activating enzymes relying on copper.[4,5] Some copper-containing dinuclear proteins have a heterometallic active site, so that a Cu center shares the active site with a second metal such as iron (cytochrome *c* oxidase)[6] or zinc (superoxide dismutase).[7] In addition, enzymes such as peptidylglycine-α-hydroxylating monooxygenase (PHM),[8] dopamine-β-hydroxylase (DβH),[8,9] and tyrosinase[10] bear two copper atoms in distinct coordination environments. While for PHM and DβH the residues coordinated to each of the copper ions are different, in the case of tyrosinase, the differences of the second coordination sphere render the two metal ions inequivalent. The lack of equivalence enables the two metals to perform different essential tasks in the enzymatic reaction.[8,9,11,12] The development of well-defined synthetic models with unsymmetrical bimetallic centers is highly desirable to understand these enzymatic processes, and it may be relevant for the development of catalytic systems.[13−18]

Modeling copper−dioxygen chemistry occurring in enzymes has attracted the attention of many research groups over the last three decades, and it is well-stablished that the ligand architecture surrounding the copper center determines the structure of the resulting Cu−dioxygen species.[5,19−24] However, the number of model systems featuring unsymmetric dinuclear sites is rather limited, most likely due to the difficulty in establishing control over the distribution of the two types of metals in the system.[1,13,25,26] Apart from the inherent difficulty in the challenging synthesis of unsymmetric dinucleating ligands, the preparation of heterometallic complexes might be hampered by the formation of homometallic complexes during the synthesis. One efficient strategy to overcome this problem is the design of dinucleating ligands with two differentiated binding sites that exhibit markedly distinctive affinities for the two metals involved.[26,27] Although the synthesis of these ligands is not straightforward, unsymmetric dicopper systems[28−30] and synthetic models of cytochrome c oxidase have been successfully prepared following this methodology.[31]

In this line, we recently described the preparation of a dicopper(I) complex bearing a dinucleating ligand that confers different coordination environments to the two metal centers.[32] Reaction of this dicopper complex toward O_2 afforded an unsymmetric *trans*-1,2-peroxodicopper(II) core, which exhibits reactivity patterns distinct from symmetric analogues.[33] Following these studies, in the present work we explore the coordination chemistry of a novel polyamine ligand scaffold designed with the aim to provide two distinct binding sites. The ligand was devised suitable for preparing well-defined heterometallic complexes combining copper(I) and another metal.

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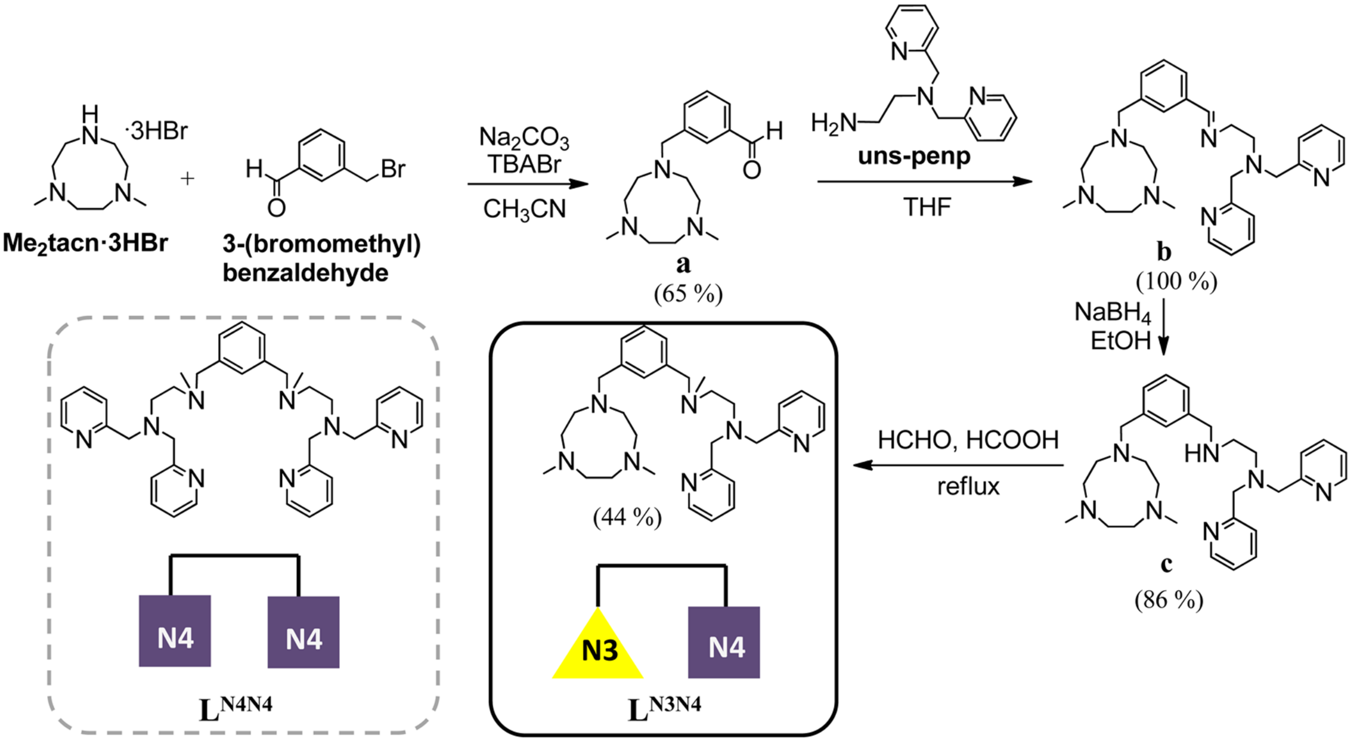
Scheme 1. Synthetic Route toward the Preparation of L^{N3N4} and Schematic Representation of L^{N4N4}



The designed ligand (L^{N3N4}) contains two distinct binding sites (N_3 and N_4) connected through a *meta*-xylyl moiety (Scheme 1). Both donor sets were used independently to support Cu^I/O_2 chemistry. The tridentate binding site (N_3) corresponds to a triazacyclononane ring (tacn), which forms highly stable complexes with a number of metals, which are chemically robust and resistant to oxidative degradation.[34] In this coordination environment, copper(I) is facially bound through the three aliphatic amines, and free coordination sites are available for interaction with other molecules. Tolman et al. have shown that the alkyl substituents in the nitrogen atoms of the triazacyclonane ring determine the outcome of the reaction of copper(I) with O_2. While *i*Pr-substituted tacn (*i*Pr_3tacn) leads to a mixture of bis(μ-oxo)dicopper(III) (**O**) and $\mu-\eta^2:\eta^2$-peroxodicopper(II) (^{S}**P**) species,[35] the less bulky benzyl or methyl substituents (Bn_3tacn and Me_3tacn) afford exclusively bis(μ-oxo)dicopper(III) (**O**) intermediates.[36−38] The second site (N_4) offers a tetracoordinating environment composed of two aliphatic nitrogen atoms and two pyridines (uns-penp). In contrast to tacn, uns-penp supports the formation of *trans*-1,2-peroxodicopper(II) (^{T}**P**) species upon reaction with O_2,[39,40] as occurs with other N-based tetradentate ligands.[41−44] The markedly different denticity of the two binding sites in L^{N3N4} is envisioned to translate into different binding constants that in turn should the preparation of heterobimetallic complexes combining copper(I) and another metal without contamination by the homometallic analogues.

Thus, in this work, we report the synthesis of the dinucleating ligand L^{N3N4} and we explore its ability to coordinate to copper(I) together with a second metal ion to give the corresponding heterobimetallic complexes $[Cu^IM'(L^{N3N4})]^{n+}$ (M′ = Cu^I, Zn^{II}, Fe^{II}, Cu^{II}, or Ga^{IIII}). Heterometallic complexes $[Cu^IM'(L^{N3N4})]^{n+}$ exhibit fast reactivity with O_2 to form tetrametallic $[(L^{N3N4})M'Cu(O_2)CuM'(L^{N3N4})]^{2n+}$ species where the O_2 molecule binds two copper centers. The nature of the Cu_2O_2 unit can be interrogated by its distinctive spectroscopic properties, and this in turn can be used to identify which is the binding site (N_3 or N_4) of Cu^I and M′ in the heterometallic complex. This analysis demonstrates that metal binding in L^{N3N4} is site-selective.

■ RESULTS AND DISCUSSION

Synthesis of L^{N3N4} and L^{N4N4}. L^{N3N4} was obtained after four reaction steps with moderate yields starting from Me_2tacn·3HBr and 3-(bromomethyl)benzaldehyde (Scheme 1, see Experimental Section for details). The *meta*-xylyl linker was chosen because it has been successfully applied in the past for the preparation of dicopper complexes that intramolecularly bind O_2 and that can be seen as models of O_2-activating dicopper proteins.[5] The use of the unsymmetric platform 3-(bromomethyl)benzaldehyde, prepared by reductive hydrolysis of the commercially available 3-(bromomethyl)benzonitrile,[45] enables the connection of two differentiated donor sets in the same molecule. The linkage of the N_3 set (tacn) occurs by reaction of 3-(bromomethyl)benzaldehyde with equimolar amounts of Me_2tacn·3HBr through a nucleophilic substitution reaction to give compound **a**. The N_4 coordination site is introduced by a condensation reaction between the aldehyde functionality and the primary amine of uns-penp to give an imine (**b**). Its hydrogenation and posterior methylation affords the final ligand L^{N3N4}, which is purified by column chromatography.

For the sake of comparison, we also synthesized the symmetric ligand L^{N4N4} (Scheme 1 and Supporting Information, Scheme S1) bearing two identical tetracoordinating binding sites connected through a *meta*-xylyl moiety. L^{N4N4} was prepared through a similar synthetic route as the one followed to obtain L^{N3N4} (see Supporting Information for further details).

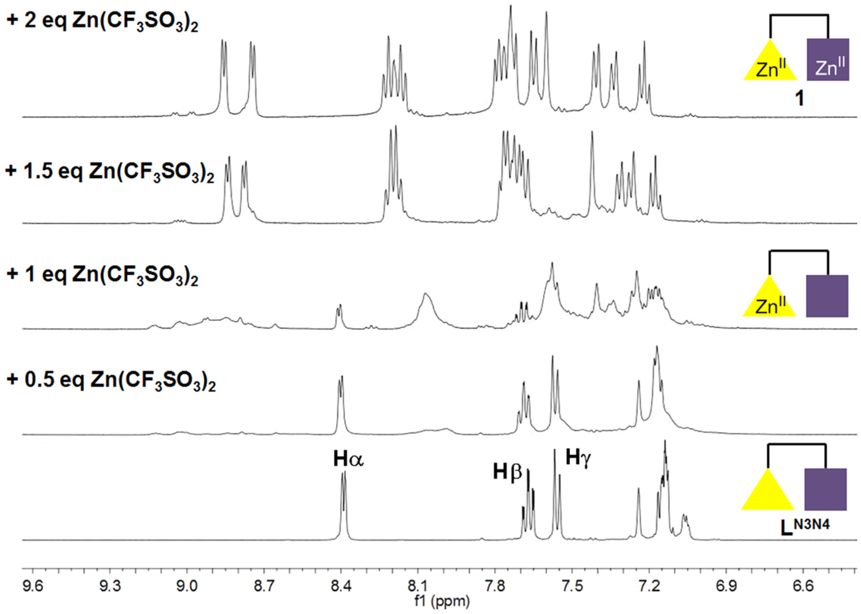


Figure 1. ^1H NMR monitoring of the titration of L^{N3N4} with $Zn(CF_3SO_3)_2$ in acetone-d_6 at 240 K. For clarity, only the aromatic region of the ^1H NMR spectrum is shown. The aliphatic region of the spectra is shown in Supporting Information, Figure S1. The tridentate and tetradentate sites are represented by a yellow triangle and a purple square, respectively.

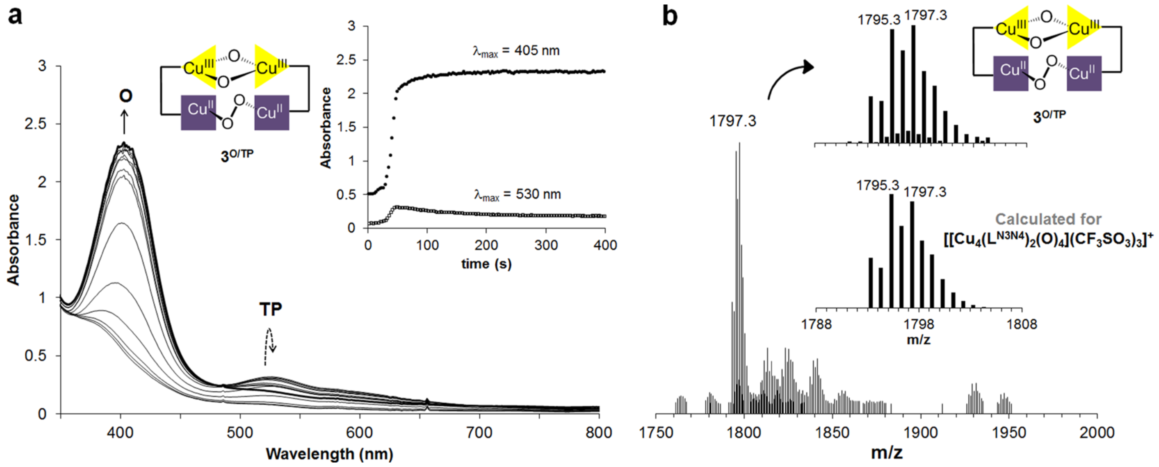


Figure 2. (a) UV–vis absorption spectra for the reaction of $[Cu^I_2(L^{N3N4})]^{2+}$ (**3**) (0.30 mM) and O_2 at −90 °C in acetonitrile/acetone 1:19. (inset) Time traces at 405 and 530 nm ($\mathbf{3}^{O/TP}$). (b) CSI-MS spectra at −90 °C for the reaction of **3** with O_2 in acetonitrile:acetone 1:19 leading to the formation of a dimeric species ($\mathbf{3}^{O/TP}$).

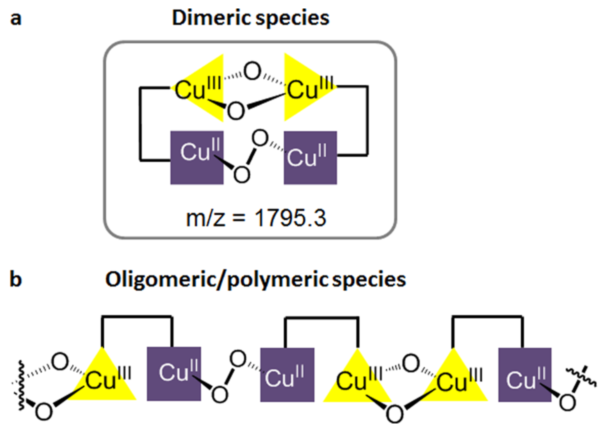
Homodimetallic Complexes. *Titration of L^{N3N4} with $Zn(CF_3SO_3)_2$.* To explore the ability of L^{N3N4} to selectively bind a metal ion in one of its two binding sites, we performed a ^1H NMR titration of the ligand in deuterated acetone (acetone-d_6) by adding small amounts of a metal salt (Figure 1). In particular, we chose $Zn(CF_3SO_3)_2$ because of its diamagnetic character and its stability under air enables its manipulation in the open atmosphere. The ^1H NMR spectrum of the free ligand (L^{N3N4}) in acetone-d_6 shows readily identifiable signals in the aromatic region corresponding to the two equivalent pyridine units in the tetradentate N_4 site (α, β, and γ protons) along with the less well-defined signals of the *meta*-xylyl moiety. Addition of 0.5 equiv of $Zn(CF_3SO_3)_2$ causes a broadening of these signals, but no apparent shift is observed, which suggests that Zn^{II} preferentially binds to the N_3 site and not to N_4. Addition of 0.5 equiv more of Zn^{II} causes severe broadening of the NMR lines, so that most likely some exchange of this metal ion is occurring between N_3 and N_4 sites. When more than 1 equiv of Zn^{II} is added the signals corresponding to H_α, H_β, and H_γ of the free ligand (L^{N3N4}) completely disappear, and new well-defined signals clearly arise (8.85, 8.74, and 8.18 ppm, Figure 1). Similar information can be extracted by analyzing the aliphatic region of the NMR spectrum (Supporting Information, Figure S1). Addition of a total of 2 equiv of Zn^{II} affords the homodimetallic complex $[Zn^{II}_2(L^{N3N4})]^{4+}$ (**1**), which was further characterized by high-resolution mass spectrometry (HR-MS) (Figure 1 and Supporting Information, Figure S2). Remarkably, the aromatic region of the ^1H NMR spectrum of **1** resembles that of the complex with the symmetric ligand $[Zn^{II}_2(L^{N4N4})](CF_3SO_3)_4$ (**2**) (Supporting Information, Figure S4). Thus, it seems that the first equivalent of zinc preferentially binds to the tacn ring (N_3) of L^{N3N4} and that the second equivalent binds to the N_4 binding site to form **1**. This observation suggests that L^{N3N4} can be potentially used to hold heterobimetallic complexes generated by sequential addition of two different metals.

*Synthesis of $[Cu^I_2(L^{N3N4})]^{2+}$ (**3**) and Its Reactivity with O_2.* The dicopper(I) complex $[Cu^I_2(L^{N3N4})]^{2+}$ (**3**) was prepared in the glovebox by reaction of L^{N3N4} with 2 equiv of $[Cu^I(CH_3CN)_4](CF_3SO_3)$ in acetonitrile affording a bright yellow solution. All attempts to isolate this compound by precipitation or crystallization using diethyl ether were unsuccessful due to the tendency of the resulting complex to disproportionate, as evidenced by a color change to deep green (Cu^{II}) and the formation of copper mirror (Cu^0) upon addition of diethyl ether into solutions of **3**. Synthesis of **3** in any solvent different from acetonitrile such as CH_2Cl_2, tetrahydrofuran (THF), or acetone also led to its immediate disproportionation. Thus, characterization of **3** was carried out in solution in acetonitrile-containing mixtures. The ^{1}H NMR spectrum of **3** exhibits broad signals even at 240 K (Supporting Information, Figure S5),[46] while HR-MS shows the expected peaks for this dicopper(I) complex (Supporting Information, Figure S6).

As **3** could not be isolated, studies of its reaction with O_2 were carried out starting from freshly prepared solutions by mixing L^{N3N4} with 2 equiv of the copper(I) source. A concentrated stock solution of **3** in acetonitrile (18 mM) was prepared, and after a 60-fold dilution with dry acetone, the reaction with O_2 was monitored by UV−vis spectroscopy at −90 °C. Upon exposure to O_2, two intense absorption bands concurrently developed within 1 min (Figure 2a): the absorption at λ_{max} 530 nm (ε = 2000 M^{-1} cm^{-1}) reached its maximum absorbance after 45 s of reaction, and then it decayed, while another band at λ_{max} 405 nm (ε = 15 000 M^{-1} cm^{-1}) was formed approximately over the same period of time, but it remained stable for at least 15 min at −90 °C. Remarkably, the latter quickly decomposed upon warming the solution, and none of the bands were detected when the reaction of **3** with O_2 was performed at room temperature. Finally, it is worth highlighting that the oxygenation of **3** was irreversible, as recovery of the starting dicopper(I) complex was not achieved when vacuum was applied after reaction with O_2.

The fact that these two bands follow completely different decomposition time courses indicates that they arise from two independent chromophores. The reported **O** species obtained upon reaction of two mononuclear $[Cu^I(Me_3tacn)]^+$ units with O_2 exhibits very characteristic absorption bands at 307 nm (ε = 16 000 M^{-1} cm^{-1}) and 412 nm (ε = 18 000 M^{-1} cm^{-1}),[37] while $^{\mathbf{T}}$**P** species originating from the reaction of $[Cu^I(\text{uns-penp})]^+$ with O_2 presents a UV−vis absorption at 535 nm (ε = 7000 M^{-1} cm^{-1}).[40] Comparison of these reported data with the observed reactivity of **3** with O_2 suggests that the unstable intermediate with λ_{max} = 530 nm may correspond to a $^{\mathbf{T}}$**P** species formed by interaction of two copper centers coordinated to the N_4 sites of two different molecules. Similarly, the intense band observed at 405 nm suggests the formation of an **O** species by interaction of copper centers located in the N_3 sites of two different molecules, giving rise to a complex structure containing two different Cu_2O_2 cores ($\mathbf{3}^{\mathbf{O/TP}}$). Because of the intermolecular character of O_2 binding in **3**, both a dimeric species or an oligomeric/polymeric structure are plausible structures for $\mathbf{3}^{\mathbf{O/TP}}$ (Scheme 2a,b, respectively). Cryospray ionization mass spectrometry (CSI-MS) turned out to provide conclusive information to distinguish between the two possibilities. Analysis of the initial stages of the reaction of **3** with O_2 by CSI-MS at 183 K (Figure 2b) clearly showed a major peak at *m/z* 1795.3 with a mass value and an isotopic pattern corresponding to $\{[(L^{N3N4})Cu^{II}Cu^{III}(\mu\text{-}O)_2(\mu\text{-}1,2\text{-}O_2)Cu^{II}Cu^{III}(L^{N3N4})](CF_3SO_3)_3\}^+$, which is consistent with the formation of a dimeric species in $\mathbf{3}^{\mathbf{O/TP}}$ (Scheme 2a). No peak that could be attributed to an oligomeric/polymeric species was detected.

Scheme 2. Representation of the Possible Structures of $\mathbf{3}^{\mathbf{O/TP}}$ [a]



[a] (a) Dimeric species. (b) Oligomeric/polymeric species.

To gain more evidence about the formation of a putative $^{\mathbf{T}}$**P** species by interaction of two copper(I) centers in two different N_4 sites, we synthesized the symmetric dicopper(I) complex using L^{N4N4} $[Cu^I_2(L^{N4N4})]^{2+}$ (**4**) (Scheme 1 and Supporting Information, Figure S7). Indeed, upon reaction of **4** with O_2 at −90 °C in acetonitrile/acetone 1:19 the exclusive formation of the band at λ_{max} = 530 nm (ε = 4400 M^{-1} cm^{-1}) was observed (Supporting Information, Figure S8).

Heterobimetallic Complexes. Despite the fact that both binding sites in L^{N3N4} are nitrogen-based, the coordination number, donor set, and binding constants were envisioned to be different enough to enable the preparation of heterobimetallic complexes in which each of the metal ions is selectively coordinated to one of the binding sites, that is, N_3 or N_4. In this line and as shown above, titration of L^{N3N4} with Zn^{II} indicates that this ligand is potentially a good candidate to hold heterobimetallic complexes.

*Synthesis of $[M^{II}Cu^I(L^{N3N4})]^{3+}$ (M = Zn (**5**), Cu (**6**), Fe (**7**)) and Their Reactivity with O_2.* To test the ability of L^{N3N4} to give well-defined heterobimetallic complexes, initial experiments were carried out by combining copper(I) and zinc(II). The use of these diamagnetic metal ions enables the proper characterization of the resulting complexes by ^{1}H NMR spectroscopy.

$[Zn^{II}Cu^I(L^{N3N4})]^{3+}$ (**5**) was prepared in the glovebox by sequential addition of 1 equiv of $[Cu^I(CH_3CN)_4](CF_3SO_3)$ and 1 equiv of $Zn(CF_3SO_3)_2$ in an acetonitrile solution of L^{N3N4}. No matter the order of addition of the two metals, in any case the ^{1}H NMR spectrum of the product was the same. The aromatic region of the ^{1}H NMR spectrum of **5** presents a great similarity with that of **1** and **2** (Figure 3 and Supporting Information, Figure S4), meaning that zinc coordinates to the N_4 site. If, instead, Cu^I were located in the pyridine site, broader NMR signals, like those observed in the ^{1}H NMR spectrum of **3** or **4**, would be observed (Figure 3 and Supporting Information, Figure S5). Thus, according to ^{1}H NMR, in compound **5** zinc binds to the N_4 site, while copper is bound to the N_3 unit. It is worth highlighting that the addition

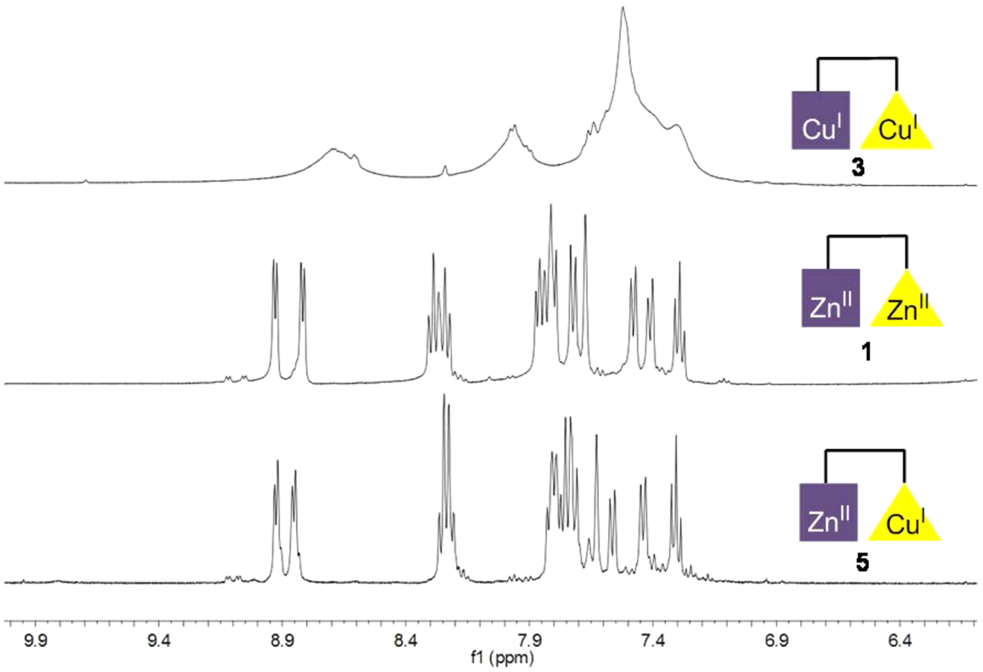


Figure 3. ^{1}H NMR spectrum of **1**, **3**, and **5** in CD_3CN/acetone-d_6 1:5 at 240 K. Only the aromatic region is shown for clarity.

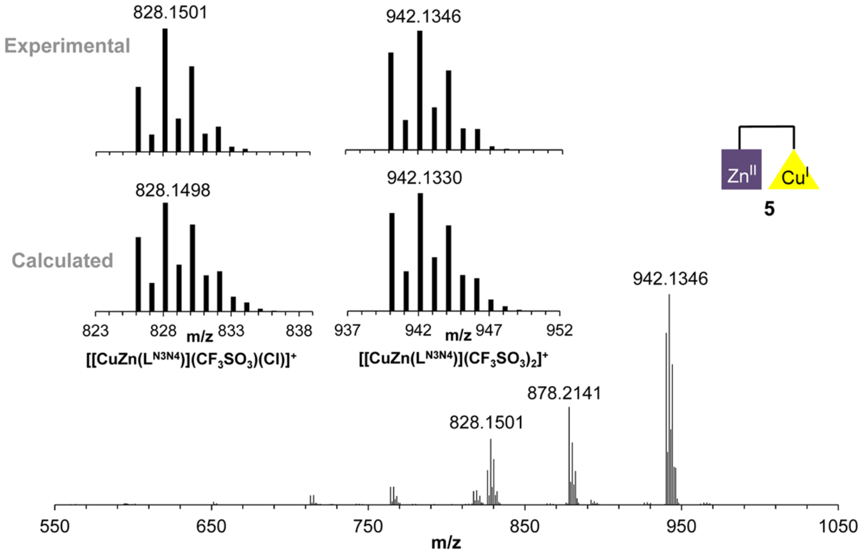


Figure 4. HR-MS spectrum of **5**. The peak at 878.2141 corresponds to the mononuclear $\{[\mathrm{Zn}(\mathrm{L^{N3N4}})](\mathrm{CF_3SO_3})_2\mathrm{H}\}^+$ complex ($\mathrm{L^{N3N4}} = \mathrm{C_{31}H_{45}N_7}$).

of 1 equiv of $\mathrm{Cu^I}$ after the addition of 1 equiv of $\mathrm{Zn^{II}}$ displaces the latter from the N_3 site to the N_4 site (as ascertained in the titration experiment, the first equivalent of zinc coordinates to N_3 site).

Compound **5** was also characterized by HR-MS (Figure 4). Two main peaks were observed at m/z = 828.1501 and 942.1346 with mass values and isotopic patterns fully consistent with the pure heterodimetallic species $\{[\mathrm{Cu^IZn^{II}}(\mathrm{L^{N3N4}})](\mathrm{CF_3SO_3})(\mathrm{Cl})\}^+$ and $\{[\mathrm{Cu^IZn^{II}}(\mathrm{L^{N3N4}})](\mathrm{CF_3SO_3})_2\}^+$. Remarkably, no peaks of the possible homodimetallic dizinc(II) or dicopper(I) complexes **1** and **3**, respectively, were detected.

To obtain more experimental evidence in favor of the heterobimetallic complex **5**, we studied its reactivity with O_2 at cryogenic temperatures. UV−vis monitoring of the reaction of **5** with O_2 at −90 °C in acetonitrile/acetone 1:19 showed the formation within 20 min of a new band at 405 nm (ε = 11 900 M^{-1} cm^{-1}) corresponding to the intermolecular **O** species $[(\mathrm{L^{N3N4}})\mathrm{Zn^{II}Cu^{III}}(\mu\text{-O})_2\mathrm{Cu^{III}Zn^{II}}(\mathrm{L^{N3N4}})]^{6+}$ ($\mathbf{5^O}$). No growth of any band at 530 nm characteristic of the $^{\mathrm{T}}\mathbf{P}$ species was observed, meaning that all the copper is located in the tacn tridentate binding site (Figure 5a). Remarkably, formation of $\mathbf{5^O}$ was observed independently of the order of addition of the two metallic salts to $\mathrm{L^{N3N4}}$ during the complex synthesis, which agrees with the formation of the same species as ascertained by NMR (see above).

The formation of $\mathbf{5^O}$ was further confirmed by CSI-MS at 183 K, which afforded a spectrum with peaks at m/z 2065.2049, 1951.2226, and 1839.2400 whose mass value and distribution pattern were consistent with $\{[(\mathrm{L^{N3N4}})\mathrm{Zn^{II}Cu^{III}}(\mu\text{-O})_2\mathrm{Cu^{III}Zn^{II}}(\mathrm{L^{N3N4}})(\mathrm{CF_3SO_3})_5\}^+$, $\{[(\mathrm{L^{N3N4}})\mathrm{Zn^{II}Cu^{III}}(\mu\text{-O})_2\mathrm{Cu^{III}Zn^{II}}(\mathrm{L^{N3N4}})](\mathrm{CF_3SO_3})_4\mathrm{Cl}\}^+$, and $\{[(\mathrm{L^{N3N4}})\mathrm{Zn^{II}Cu^{III}}(\mu\text{-O})_2\mathrm{Cu^{III}Zn^{II}}(\mathrm{L^{N3N4}})](\mathrm{CF_3SO_3})_3\mathrm{Cl_2}\}^+$, respectively

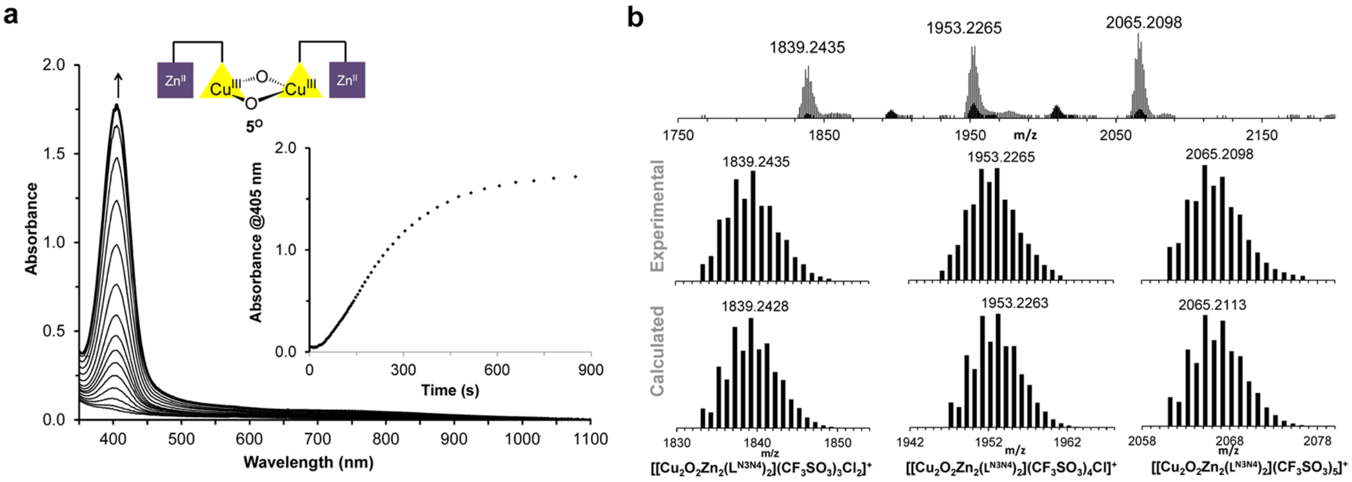


Figure 5. (a) UV−vis absorption spectra for the reaction of **5** (0.3 mM) with O_2 in acetonitrile/acetone 1:19 at −90 °C. (inset) Time trace at 405 nm. (b) CSI-MS spectra at −90 °C corresponding to the reaction of **5** with O_2 in acetonitrile/acetone 1:19 to give $\mathbf{5^O}$ ($L^{N3N4} = C_{31}H_{45}N_7$).

(Figure 5b). Remarkably all the identified peaks in the ESI-MS spectrum corresponded to pure heterobimetallic species containing both copper and zinc, which further renders L^{N3N4} as a privileged platform to selectively hold two different metals. Since both Zn^{II} and Cu^I have a d^{10} electronic configuration, none of them has stabilization of the crystal field according to the crystal field theory. Thus, it is remarkable that Cu^I is located in only one site, avoiding mixtures of **O** and $^{\mathbf{T}}\mathbf{P}$ species upon reaction with O_2.

Preparation of $[Cu^{II}Cu^I(L^{N3N4})]^{3+}$ (**6**) and $[Fe^{II}Cu^I(L^{N3N4})]^{3+}$ (**7**) was also achieved through the sequential addition of 1 equiv of $[Cu^I(CH_3CN)_4](CF_3SO_3)$ and then 1 equiv of $Cu^{II}(CF_3SO_3)_2$ or $[Fe^{II}(CF_3SO_3)_2(CH_3CN)_2]$ to L^{N3N4} in acetonitrile. These compounds could be characterized by HR-MS (Supporting Information, Figures S9 and S10). Attempts to characterize **6** and **7** by means of ^{1}H NMR proved unsuccessful, as only broad, not informative bands were observed in the spectra. UV−vis monitoring of the reaction of **6** and **7** with O_2 at −90 °C in acetonitrile/acetone 1:19 at −90 °C indicated the exclusive formation in both cases of an **O** species, $\mathbf{6^O}$ (λ_{max} = 405 nm, ε = 12 000 M^{-1} cm^{-1}), and $\mathbf{7^O}$ (λ_{max} = 405 nm, ε = 12 300 M^{-1} cm^{-1}), most likely arising from the intermolecular interaction between two copper(I) centers coordinated to N_3 sites of two different molecules (Figure 6 and Supporting Information, Figure S11). Interestingly, no heterometallic intramolecular O_2 activation occurred in $[Fe^{II}Cu^I(L^{N3N4})]^{3+}$ (**7**), where the redox active iron(II) center could potentially be involved in such activation processes.[47] Instead, formation of the intermolecular **O** species seems to be the thermodynamic driving force that dictates the fate of the O_2 activation. Overall, divalent metals such as Zn^{II}, Fe^{II} or Cu^{II} coordinate to the N_4 site in L^{N3N4} leaving the N_3 site available for copper(I), which gives intermolecular **O** species upon reaction with O_2.

Comparison of the formation and decay rates of the four bis(μ-oxo) species described in this manuscript ($\mathbf{3^{O/TP}}$, $\mathbf{5^O}$, $\mathbf{6^O}$, and $\mathbf{7^O}$) might give insight into the influence of the second metal in the formation of this Cu_2O_2 species. Interestingly, compounds **5**, **6**, and **7**, which contain Cu^I in the trivalent site (N_3) together with a divalent spectator metal such as Zn^{II}, Cu^{II}, and Fe^{II} in the tetradentate site (N_4), behave in an analogous fashion, and full formation of the corresponding bis(μ-oxo) species ($\mathbf{5^O}$, $\mathbf{6^O}$, and $\mathbf{7^O}$) is achieved after 10 min at −75 °C. In

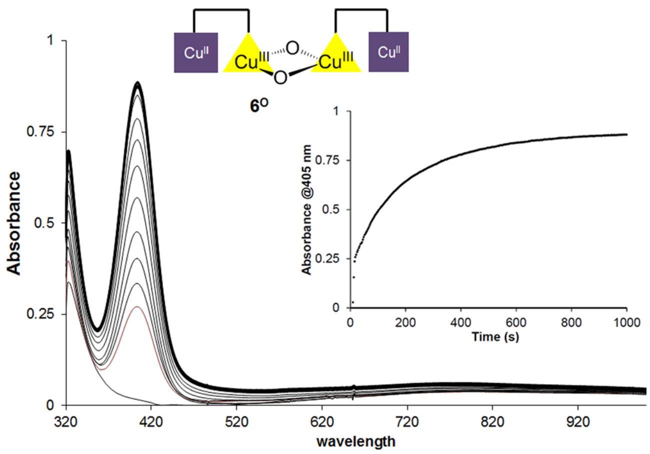


Figure 6. UV−vis absorption spectra for the reaction of $[Cu^ICu^{II}(L^{N3N4})]^{3+}$ (**6**) (0.15 mM) and O_2 at −90 °C in acetonitrile/acetone 1:19. (inset) Time trace at 405 nm ($\mathbf{6^O}$).

sharp contrast, formation of $\mathbf{3^{O/TP}}$ is much faster, and this species is fully developed only 1 min after starting the reaction of **3** with O_2 (Supporting Information, Figure S12a). On the other hand, the decay rates of $\mathbf{5^O}$, $\mathbf{6^O}$, and $\mathbf{7^O}$ are small (only 15% decomposition after 2 h at −60 °C) compared to the bis(μ-oxo) unit in $\mathbf{3^{O/TP}}$, which decomposes in only 20 min at −60 °C (Supporting Information, Figure S12b). The acceleration in the decay rate of $\mathbf{3^{O/TP}}$ might be related to the strain exerted by a putative interaction between the Cu^{II} centers resulting from the decomposition of the thermally unstable *trans*-peroxide unit. Such acceleration in the formation and decay rates of Cu_2O_2 species has been previously documented in Cu_2O_2 species derived from strained dinucleating ligands.[48] ESI-MS analyses of the final species derived from the thermal decomposition of $\mathbf{3^{O/TP}}$, $\mathbf{5^O}$, $\mathbf{6^O}$, and $\mathbf{7^O}$ showed the exclusive formation of metal-hydroxide species coordinated to the intact L^{N3N4} ligand. No ligand oxidation was detected in any case.

*Synthesis of $[Ga^{III}Cu^I(L^{N3N4})]^{4+}$ (**8**) and Its Reactivity with O_2.* The use of Ga^{III} completely changes the position of the copper center within ligand L^{N3N4}. $[Ga^{III}Cu^I(L^{N3N4})]^{4+}$ (**8**) was prepared analogously to the previously described heterometallic complexes but using $GaCl_3$ as the complementary metal source

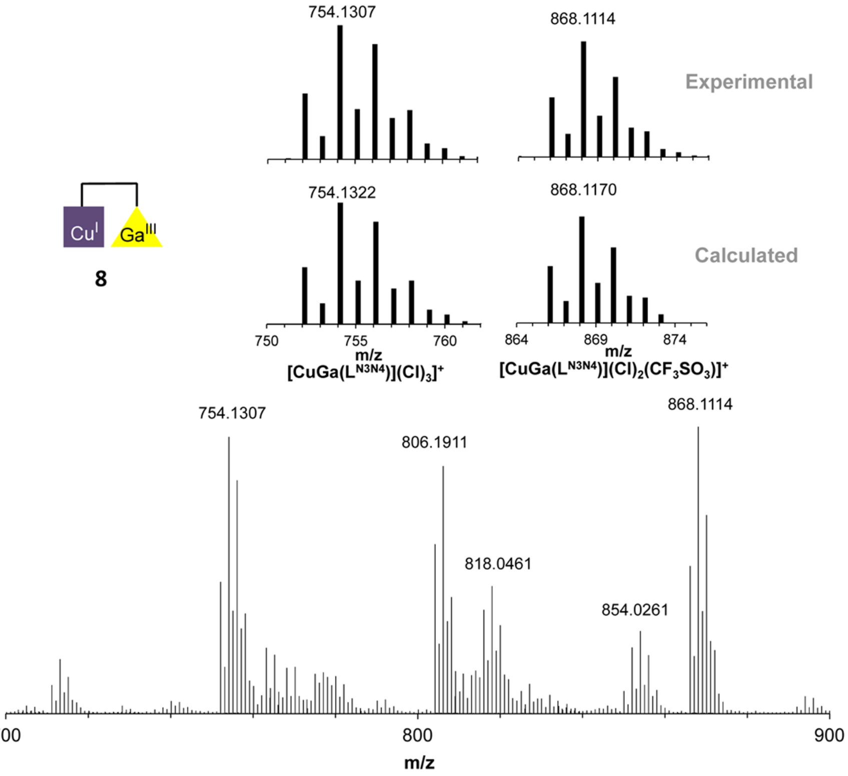


Figure 7. HR-MS spectrum of **8**. Peaks at 806.1911 and 818.0461 correspond to mononuclear Ga^{III} species (L^{N3N4} = $C_{31}H_{45}N_7$).

to copper(I). In the HR-MS spectrum of **8** peaks at *m/z* 754.1316 and 868.1114 corresponding to the heterodimetallic complex $\{[Cu^IGa^{III}(L^{N3N4})](Cl)_3\}^+$ and $\{[Cu^IGa^{III}(L^{N3N4})](Cl)_2(CF_3SO_3)\}^+$ were observed (Figure 7).

Interestingly, UV−vis monitoring of the reaction of this complex with O_2 at low temperature only exhibited the formation of the characteristic bands of ^{T}**P** species ($\mathbf{8^{TP}}$) with an absorption band centered at 530 nm (Figure 8). No trace of the band at 405 nm characteristic of the **O** compound was detected. Such result indicates that the trivalent metal is tightly bound to the tacn site blocking the access of copper(I) in the starting material, which is displaced to the N_4 site. Remarkably, the use of redox active trivalent metals such as Fe^{III} caused the immediate oxidation of the copper(I) site to copper(II), thus preventing further studies of O_2 activation.

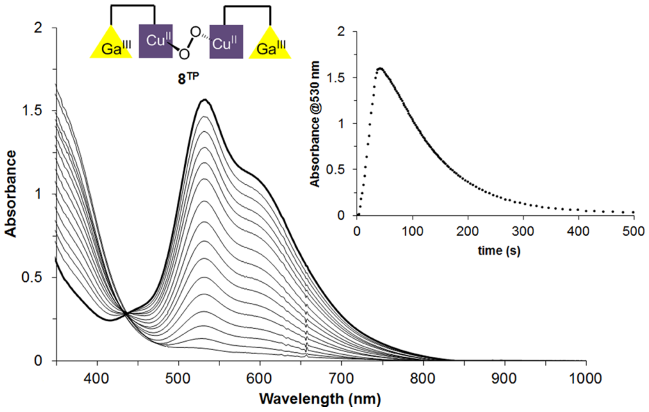


Figure 8. UV−vis absorption spectra for the reaction of $[Ga^{III}Cu^I(L^{N3N4})]^{4+}$ (**8**, 0.79 mM) with O_2 in acetonitrile/acetone 1:19 at −90 °C. (inset) Time trace at 530 nm ($\mathbf{8^{TP}}$).

■ CONCLUSIONS

In this work we have developed a novel dinuclear unsymmetric ligand scaffold (L^{N3N4}) that contains two highly differentiated coordination environments: a tridentate site (N_3) composed of a tacn ring and a tetradentate environment (N_4) offered by two aliphatic amines and two pyridines. It is shown that L^{N3N4} is potentially a good candidate for the synthesis of heterodimetallic complexes (Scheme 3). Reaction of the homodinuclear copper(I) complex (**3**) with O_2 at low temperature affords a mixture of **O** and ^{T}**P** species arising from the intermolecular interaction between two copper centers in the same binding environment but placed in two different complex molecules (Table 1). Taking advantage of the ligand asymmetry, a set of heterodimetallic complexes containing Cu^I and a divalent or trivalent complementary metal has been prepared as ascertained by ^{1}H NMR and HR-MS analyses. Since Cu^I forms kinetically labile complexes, its binding site in the heterometallic complexes is finally dictated by the donor set preferences of the complementary metal. Divalent metals such as Zn^{II}, Cu^{II}, or Fe^{II} bind preferentially at the N_4 site and force the coordination of Cu^I to the N_3 site. Instead, a trivalent metal such as Ga^{III} preferentially bind to the tacn site, thus positioning Cu^I in the N_4 site. Since the nature of the O_2-bound species at copper sites depends in their ligand donor set,[5,19,20] it follows that reaction between the heterodimetallic complexes (**5**−**8**) and O_2 afforded the exclusive formation of either **O** or ^{T}**P**, depending on the donor set of the Cu^I site (Scheme 3, Table 1). When Cu^I is bound at the tridentate site **O** species form upon reaction with O_2, while formation of ^{T}**P** species occurs upon reaction of O_2 with complexes where Cu^I is bound at the N_4 site. Indeed, the exclusive formation of **O** or ^{T}**P** when **5**−**8** react with O_2 could be regarded as evidence for site-selective binding to L^{N3N4}. Furthermore, the position of the

Scheme 3. Representation of the Complexes and the O_2-Bound Species Generated upon Reaction with O_2 Described in This Work

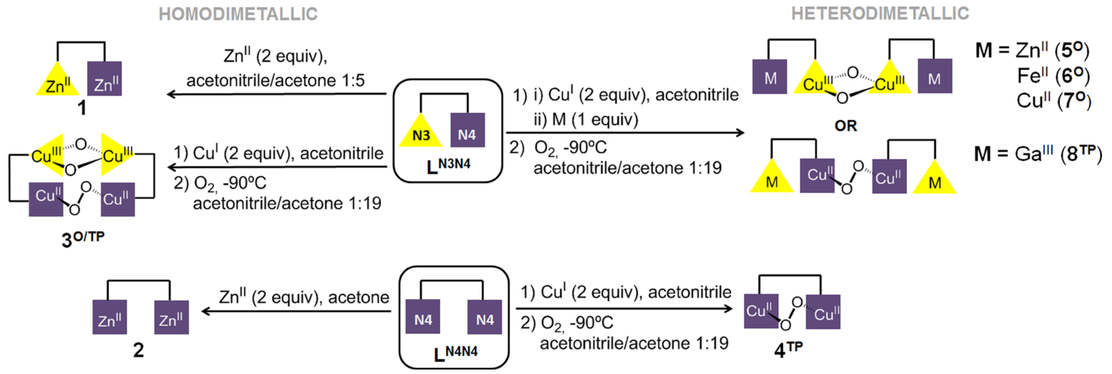


Table 1. Summary of the Spectroscopic Features of the O and ^{T}P Species Formed upon Reaction of $[M^{II/III}Cu^{I}(L)]^{3+/4+}$ with O_2 at −90°C in Acetonitrile/Acetone 1:19

ligand	compound	N_4 site	N_3 site	UV−vis features λ_{max}, nm (ε, M^{-1} cm^{-1})[a]	Cu_2O_2 species
L^{N3N4}	**3**	Cu^{I}	Cu^{I}	405 (15 000), 530 (2000)	**O** + ^{T}**P**
	5	Zn^{II}	Cu^{I}	405 (11 900)	**O**
	6	Cu^{II}	Cu^{I}	405 (12 000)	**O**
	7	Fe^{II}	Cu^{I}	405 (12 300)	**O**
	8	Cu^{I}	Ga^{III}	530 (4050)	^{T}**P**
L^{N4N4}	**4**	Cu^{I}	Cu^{I}	530 (4400), 600 (sh)	^{T}**P**

[a] ε values were calculated taking into account the expected maximum concentration of Cu_2O_2 unit.

copper(I) center within the ligand framework can be tuned by the complementary metal.

Thus, ligand L^{N3N4} has been proven to be a good platform for the synthesis of heterodimetallic complexes. The reactivity of some of the **O** and ^{T}**P** species described in this work is currently being investigated in our lab. Moreover, synthetic efforts are devoted to the preparation of new asymmetric ligand scaffolds that can force the intramolecular O_2 activation performed by two different metals akin to the reactivity exhibited by some enzymes.

■ EXPERIMENTAL SECTION

Instrumentation. All the spectroscopic and chromatographic analyses were carried out in Unitat d'Anàlisi Química i Estructural (UAQiE) or in the laboratories of the Bioinorganic and Supramolecular Chemistry Group (QBIS) at the University of Girona.

Elemental analyses were performed using a CHNS-O EA-1108 elemental analyzer from Fiscons. High-resolution mass spectra (HR-MS) were recorded on a Bruker MicrOTOF-Q II instrument using electrospray ionization (ESI) or cryospray ionization (CSI) sources at Serveis Tècnics of the University of Girona. Samples were introduced into the mass spectrometer ion source by direct infusion using a syringe pump and were externally calibrated using sodium formate. A cryospray attachment was used for CSI-MS. Temperature of the nebulizing and drying gases was set at −90 °C. The capillary voltage was set at −4500 V, and the collision energy at 8−10 eV. The instrument was operated in both positive and negative ion modes. NMR experiments were performed on a Bruker Ultrashield Avance III400 and Ultrashield DPX300 spectrometers. UV−vis spectroscopy was performed with an Agilent 50 Scan (Varian) UV−vis spectrophotometer with 1 cm quartz cells. Low-temperature control was achieved with a cryostat from Unisoku Scientific Instruments, Japan

Materials and Synthesis. Only the synthesis of the unsymmetric ligand L^{N3N4} is described below. A detailed synthesis procedure for the symmetric ligand L^{N4N4} can be found in the Supporting Information. Reagents and solvents used were of commercially available reagent quality unless otherwise stated. Solvents were purchased from Scharlab, Acros, or Sigma-Aldrich and were used without further purification.

Synthesis of L^{N3N4}. L^{N3N4} was obtained as a yellow oil after a total of four reaction steps with moderate yields starting from 1,4-dimethyl-1,4,7-triazacyclononane trihydrobromide salt ($Me_2tacn\cdot 3HBr$), (2-aminoethyl)bis(2-pyridylmethyl)amine (uns-penp), and 3-(bromomethyl)benzaldehyde. $Me_2tacn\cdot 3HBr$ was synthesized after three reaction steps starting from 1,4,7-tritosyl-1,4,7-triazacyclononane. 3-(bromomethyl)benzaldehyde and uns-penp were synthesized from commercially available reagents after one and two steps, respectively, following previously described procedures.[49,50] See Supporting Information for the correspondence of ^{1}H NMR and ^{13}C NMR signal assignments.

*Synthesis of **a***. $Me_2tacn\cdot 3HBr$ (1.26 g, 6.3 mmol) and 3-(bromomethyl)benzaldehyde (2.53 g, 6.3 mmol) were mixed in a two-necked flask in anhydrous CH_3CN (40 mL), leading to a yellow mixture. Na_2CO_3 (4.69 g, 44 mmol) and tetrabutylammonium bromide (TBABr, 0.05 g, 0.16 mmol) were then added directly as solids. Nitrogen atmosphere was established, and the mixture was refluxed for 20 h. Then it was cooled to room temperature, and a yellow solution with a suspended white solid was obtained. The solution was filtered to remove unreacted Na_2CO_3, and the filter cake was washed with CH_2Cl_2. The solvent from the combined filtrates was removed under reduced pressure, and an orange oil was obtained. NaOH (1 M, 15 mL) was added, and the product was extracted with CH_2Cl_2 (3 × 10 mL). The organic layers were combined and dried over $MgSO_4$, and the solvent was removed under reduced pressure. *n*-Pentane (50 mL) was added, and the mixture was stirred overnight. After filtration the solvent from the filtrates was removed under reduced pressure, and 1.13 g (4.1 mmol, 65%) of **a** were obtained. ^{1}H NMR ($CDCl_3$, 400 MHz, 298 K) δ, ppm: 10.02 (s, 1H, $\mathbf{H_j}$), 7.86 (s, 1H, $\mathbf{H_i}$), 7.76 (d, $J = 7.6$ Hz, 1H, $\mathbf{H_h}$), 7.66 (d, $J = 7.6$ Hz,1H, $\mathbf{H_f}$), 7.46 (t, $J = 7.6$ Hz, 1H, $\mathbf{H_g}$), 3.74 (s, 2H, $\mathbf{H_e}$), 2.80 (s, 4H, $\mathbf{H_b}$), 2.77−2.75 (m, 4H, $\mathbf{H_d}$), 2.68−2.65 (m, 4H, $\mathbf{H_c}$), 2.35 (s, 6H, $\mathbf{H_a}$). ^{13}C NMR ($CDCl_3$, 100 MHz, 298 K) δ, ppm: 192.55 ($\mathbf{C_l}$), 141.55 ($\mathbf{C_h}$), 136.43 ($\mathbf{C_f}$), 135.26 ($\mathbf{C_k}$), 130.14 ($\mathbf{C_g}$), 128.88 ($\mathbf{C_j}$), 128.45 ($\mathbf{C_i}$), 62.82 ($\mathbf{C_e}$), 57.11, 56.92 ($\mathbf{C_d}$,$\mathbf{C_c}$), 56.02 ($\mathbf{C_a}$), 46.66 ($\mathbf{C_b}$). ESI-MS (*m*/*z*): 276.2 $[M + H]^+$

*Synthesis of **b***. A measured quantity of uns-penp (786 mg, 3.2 mmol) was dissolved in THF (5 mL) and cooled to 0 °C. A solution of **a** (893 mg, 3.2 mmol) in THF (5 mL) was added dropwise. The mixture was left to attain room temperature, and it was stirred for 15 h. The solvent was removed under reduced pressure, and 1.95 g (3.88 mmol, >100%) of a pale yellow oil were obtained and used in the next step without further purification. ^{1}H NMR ($CDCl_3$, 400 MHz, 298 K)

δ, ppm:8.52 (d, J = 4.8 Hz, 2H, $\mathbf{H_q}$), 8.25 (s, 1H, $\mathbf{H_j}$), 7.66 (s, 1H, $\mathbf{H_f}$), 7.61–7.52 (m, 3H, $\mathbf{H_o+H_n+H_g}$), 7.45 (d, J = 7.8 Hz, 1H, $\mathbf{H_i}$), 7.37 (t, J = 7.8 Hz, 1H, $\mathbf{H_h}$), 7.14–7.11 (m, 2H, $\mathbf{H_p}$), 3.93 (s, 4H, $\mathbf{H_m}$), 3.83–3.78 (m, 2H, $\mathbf{H_k}$), 3.72 (s, 2H, $\mathbf{H_e}$), 2.98–2.92 (m, 6H, $\mathbf{H_l+H_b}$), 2.78 (br. s., 8H, $\mathbf{H_d+H_c}$), 2.40 (s, 6H, $\mathbf{H_a}$). ^{13}C NMR ($CDCl_3$, 100 MHz, 298 K) δ, ppm: 161.95 ($\mathbf{C_p}$), 159.84 ($\mathbf{C_i}$), 149.04 ($\mathbf{C_t}$), 140.15 ($\mathbf{C_h}$), 136.44 ($\mathbf{C_q/C_r}$), 131.57 ($\mathbf{C_k}$), 128.71, 128.45, 127.15 ($\mathbf{C_j}$, $\mathbf{C_g}$, $\mathbf{C_i}$), 125.53 ($\mathbf{C_f}$), 122.93 ($\mathbf{C_q/C_r}$), 122.02 ($\mathbf{C_i}$), 62.92 ($\mathbf{C_e}$), 60.79 ($\mathbf{C_o}$), 59.49 ($\mathbf{C_m}$), 56.42 ($\mathbf{C_n}$), 55.77 ($\mathbf{C_c+C_d}$), 54.89 ($\mathbf{C_b}$), 45.83 ($\mathbf{C_a}$). ESI-MS (m/z): 500.3 $[M + H]^+$, 276.2 [**a**+H]$^+$, 243.1 [uns-penp+H]$^+$.

Synthesis of **c**. Compound **b** (1.95 g, 3.9 mmol) was dissolved in absolute ethanol (50 mL), and sodium borohydride (0.16 g, 4.2 mmol) was added as a solid in little portions. The reaction was stirred for 12 h at room temperature, and then 10 mL of water was added to remove the unreacted $NaBH_4$. After removal of the solvent under reduced pressure, CH_2Cl_2 (15 mL) and H_2O (4 mL) were added. The mixture was treated with CH_2Cl_2 (2 × 8 mL). The organic layers were dried over $MgSO_4$, and the solvent was removed under reduced pressure to obtain 1.68 g (3.3 mmol, 86%) of a pale yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz, 298 K) δ, ppm: 8.51 (d, 2H, J = 4.3 Hz, $\mathbf{H_q}$), 7.64–7.60 (m, 2H, $\mathbf{H_o}$), 7.45 (d, 2H, J = 7.7 Hz, $\mathbf{H_n}$), 7.24–7.21 (m, 3H, $\mathbf{H_f+H_i+H_h}$), 7.15–7.12 (m, 3H, $\mathbf{H_g+H_p}$), 3.83 (s, 4H, $\mathbf{H_m}$), 3.66 (s, 2H, $\mathbf{H_j}$), 3.62 (s, 2H, $\mathbf{H_e}$), 2.79 (s, 4H, $\mathbf{H_b}$), 2.77–2.70 (m, 8H, $\mathbf{H_k+H_l+H_d}$), 2.65–2.63 (m, 4H, $\mathbf{H_c}$), 2.34 (s, 6H, $\mathbf{H_a}$). ^{13}C NMR ($CDCl_3$, 100 MHz, 298 K) δ, ppm: 159.67 ($\mathbf{C_p}$), 149.08 ($\mathbf{C_t}$), 140.26 ($\mathbf{C_f+C_h}$), 136.37 ($\mathbf{C_r}$), 128.75, 128.12, 127.63 ($\mathbf{C_g+C_j+C_k}$), 126.47 ($\mathbf{C_i}$), 122.94 ($\mathbf{C_q}$), 121.96 ($\mathbf{C_s}$), 63.26 ($\mathbf{C_e}$), 60.71 ($\mathbf{C_o}$), 57.07 ($\mathbf{C_c}$), 56.81 ($\mathbf{C_b}$), 55.90 ($\mathbf{C_d}$), 54.101 ($\mathbf{C_m}$), 53.80 ($\mathbf{C_l}$), 46.68 ($\mathbf{C_n}$). ESI-MS (m/z): 502.4 $[M + H]^+$, 251.6 $[M+2H]^{2+}$

Synthesis of L^{N3N4}. Compound **c** (1.68 g, 3.3 mmol) was dissolved in formic acid 98% (13 mL); formaldehyde 37% (25 mL) was added, and the mixture was refluxed for 24 h. The solvent was then removed under reduced pressure, and NaOH 3 M (5 mL) was added to the resultant yellow solid. The product was extracted with CH_2Cl_2 (3 × 50 mL). The organic phases were dried over $MgSO_4$, and the solvent was removed under reduced pressure. The resulting yellow oil was extracted with hexane overnight. After filtration, the solvent from the filtrates was removed under reduced pressure. The resulting yellow oil was purified by column chromatography over silica using a mixture of $CH_2Cl_2/MeOH/NH_3$ 80:20:4 as eluent. 770 mg (1.49 mmol, 44%) of a yellow oil was obtained. ^{1}H NMR ($CDCl_3$, 400 MHz, 298 K) δ, ppm: 8.52 (d, J = 4.6 Hz, 2H, H_q), 7.63 (td, J = 7.9 Hz, J' = 1.8 Hz, 2H, H_o), 7.52 (d, J = 7.9 Hz, 2H, H_n), 7.23–7.20 (m, 3H, $H_f+H_i+H_h$), 7.15–7.11 (m, 3H, H_p+H_g), 3.84 (s, 4H, H_m), 3.61 (s, 2H, H_e), 3.44 (s, 2H, H_j), 2.79 (s, 4H, H_b), 2.75 (t, J = 6.4 Hz, 2H, H_l), 2.72–2.68 (m, 4H, H_d), 2.65–2.58 (m, 6H, H_c+H_k), 2.34 (s, 6H, H_a), 2.12 (s, 3H, H_r). ^{13}C NMR ($CDCl_3$, 100 MHz, 298 K) δ, ppm: 160.07 (C_p), 149.11 (C_t), 140.15, 138.98 (C_f, C_h), 136.46 (C_r), 129.90, 128.10, 127.87, 127.63 (C_i, C_j, C_k, C_g), 123.00 (C_q), 121.99 (C_s), 63.44 (C_e), 62.77 (C_l), 60.95 (C_o), 57.11 (C_c), 56.83 (C_b), 56.02 (C_d), 55.58 (C_m), 52.36 (C_n), 46.62 (C_a), 42.65 (C_u). HR-MS (ESI time-of-flight) m/z calc. for $[M + H]^+$ 516.3809, found 516.3807.

Synthesis of Dimetallic Complexes. All the complexes containing copper(I) used in this work were synthesized in acetonitrile at room temperature under anaerobic conditions in a glovebox to avoid the oxidation of the initial Cu^I centers. Because of the high instability of these Cu^I centers, all the attempts to isolate the copper complexes failed. Thus, every day freshly prepared solutions of the complexes (~18 mM) were used. NMR samples were prepared in an analogous way directly in deuterated solvent in the glovebox. For the preparation of heterodimetallic complexes, a general procedure was followed: L^{N3N4} was dissolved inside the glovebox in acetonitrile, and 1 equiv of $[Cu(CH_3CN)_4](CF_3SO_3)$ was added directly as a solid. After 10 min of stirring, 1 equiv of the desired metallic salt ($Zn(CF_3SO_3)_2$, $Cu(CF_3SO_3)_2$, $Fe(CF_3SO_3)_2(CH_3CN)_2$, or $GaCl_3$) was directly added as a solid, leading to an 18 mM solution of the complex with the general formula of $[M^{II}/^{III}Cu^I(L^{N3N4})]^{3+/4+}$. From this solution, the desired concentration for characterization or reactivity experiments was obtained after dilutions with the appropriate amount of acetonitrile or acetone.

UV–vis Spectroscopy: Sample Preparation and Monitoring of the Formed Species at Low Temperature. All the UV–vis experiments were performed in acetonitrile/acetone 1:19 as the solvent mixture. The final complex concentration ranged between 0.3 and 0.9 mM. For the preparation of a 0.9 mM sample, a UV–vis cell was charged with 100 μL of the acetonitrile complex solution (~18 mM) and 1.9 mL of dry acetone in the glovebox. The quartz cell was capped with a septum, taken out of the box, and placed in a Unisoku thermostated cell holder designed for low-temperature experiments at 183 K. After reaching thermal equilibrium, a UV–vis spectrum of the starting complex was recorded. Dioxygen was injected into the cell with a balloon and a needle through the septum causing immediate reaction. For lower concentrations, the sample preparation was the same as described before, but in this case, the appropriate volume of the complex solution (~18 mM) was taken, and CH_3CN was added until the total volume of the aliquot was 100 μL.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Detailed synthesis of L^{N4N4}, NMR spectra of the different steps in the synthetic routes of L^{N3N4} and L^{N4N4}, aliphatic region of the ^{1}H NMR monitoring of the titration of L^{N3N4} with $Zn(CF_3SO_3)_2$, HR-MS spectra of **1–4**, **6**, and **7**, UV–vis monitoring of the reaction of **4** and **7** with O_2, comparison of the formation/decay rates of bis(μ-oxo) species ($\mathbf{3^{O/TP}}$, $\mathbf{5^O}$, $\mathbf{6^O}$, $\mathbf{7^O}$). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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