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Copper Mediated Intramolecular vs. Intermolecular Oxygenations: The Spacer makes the Difference!

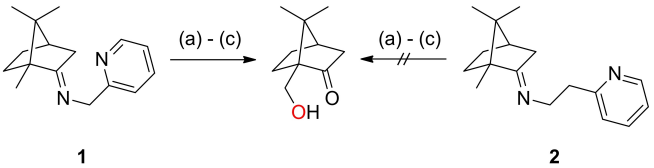
Alexander Petrillo,[a] Alexander Hoffmann,[b] Jonathan Becker,[a] Sonja Herres-Pawlis,[b] and Siegfried Schindler*[a]

Copper complexes in combination with dioxygen are important as potential catalytic systems for regio- and stereoselective aerobic oxygenations of aromatic and aliphatic C–H bonds at ambient temperatures. In that context we herein describe a copper(I) complex with an imine ligand derived from (+)-camphor and 2-(2-aminoethyl)pyridine that forms a bis(μ-hydroxido) dicopper complex upon reaction with dioxygen at room temperature. It is detectable by UV-vis for several hours up to a few days, depending on the solvent and could be structurally characterized. In contrast to previous observations this complex rather oxygenates acetone or thioanisole as external substrates instead of undergoing an intramolecular ligand hydroxylation.

Introduction

Copper enzymes such as tyrosinase or dopamine-β-monoxygenase catalyze[1] reactions that are potentially highly desirable for chemical industry.[2,3] The active species responsible for these oxygenations often are investigated by applying model complexes which are usually short lived and often only accessible at low temperatures (around −80 °C).[4] So far only a few examples of copper "dioxygen adduct" species are known, which are persistent at room temperature for an extended time range.[5,6] Especially copper complexes with tetradentate and tridentate ligands have been investigated in that regard. They demonstrated a large influence of chelate ring size as well as substituents on nitrogen donor atoms on the reactivity of the complexes towards dioxygen.[7,8] Less reports have been published on complexes with bidentate ligands that tend to form either side-on peroxido or bis(μ-oxido) dicopper copper complexes. Groups by Itoh, Karlin, Tolman and Stack, as well as us, demonstrated the large influence of the ligand system with regard to the outcome of the reaction.[9,10]

Previously, Baran, Garcia-Bosch and co-workers successfully hydroxylated an aminomethylpyridine based imine ligand **1** in high yields (up to 94%) according to Scheme 1.[11,12]

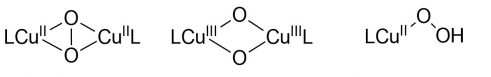


1 **2**

Scheme 1. (a) 1) 2.3 eq. $[Cu(MeCN)_4]PF_6$, 3 eq. Na ascorbate, acetone, 2) O_2, 50 °C, 6 h, 3) Na_4EDTA workup; (b) 1) 1.1 eq. $Cu(NO_3)_2 \cdot 3\,H_2O$, THF, 2) 15 eq. H_2O_2, 50 °C, 4.5 h, 3) Na_4EDTA workup; (c) 1) 1 eq. $[Cu(MeCN)_4]PF_6$, acetone, 2) 15 eq. H_2O_2, r.t., 4.5 h, 3) Na_4EDTA workup.

To compare reactivities we investigated the closely related copper system with literature known ligand **2** (Scheme 1)[13,14] at room temperature, which only differs by applying 2-(2-aminoethyl)pyridine instead of aminomethylpyridine. However, despite the minor difference in the ligand system, no intramolecular ligand γ-hydroxylation was observed with **2** (Figure S22–Figure S24).

Hydroxylation reactions of this type, a so called "clip and cleave" concept,[10,15,16] in general proceed either via copper hydroperoxido complexes or 2:1 copper dioxygen species (e.g. bis(μ-oxido) or μ-η^2:η^2-peroxido dicopper complexes) as key intermediates (Scheme 2), or via a dioxygen mediated series of electron transfers between the ligand and copper ultimately opening the ligand for nucleophilic attack by water to yield the hydroxylation product.[10,12,15,17] If such a reaction takes place and which path it takes is determined by very subtle structural and electronic changes in the ligand structure.[10,18]



μ-η^2:η^2-peroxido bis(μ-oxido) η^1-hydroperoxido

Scheme 2. Common intermediates in copper mediated ligand hydroxylations.

[a] *A. Petrillo, Dr. J. Becker, Prof. Dr. S. Schindler*
Institute of Inorganic and Analytical Chemistry,
Justus-Liebig-University Giessen
Heinrich-Buff-Ring 17, 35392 Giessen, Germany
E-mail: siegfried.schindler@anorg.chemie.uni-giessen.de
https://www.uni-giessen.de/fbz/fb08/Inst/iaac/schindler
[b] *Dr. A. Hoffmann, Prof. Dr. S. Herres-Pawlis*
Institute of Inorganic Chemistry,
RWTH Aachen University
Landoltweg 1a, 52074 Aachen, Germany
https://www.bioac.ac.rwth-aachen.de/go/id/ictk/

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Results and Discussion

To gain better insight into these reactions in general, we investigated the reaction of the copper complex with ligand **2** in more detail. Intriguingly, in contrast to most imines, ligand **2** resists hydrolysis during aqueous workup and could be crystallized in its protonated form under air (molecular structure and crystallographic data are reported in SI 3.5.6).

The 1:1 copper(I) complex of **2** crystallized as a dimer with two linear coordinated copper centers bridging two ligands (Figure 1). Similar molecular structures were reported e.g. by Specht *et al.* for a related ligand, where (+)-camphor is substituted by cyclohexanone, and by Ray and co-workers.[10,19] In contrast to our complexes, the copper(I) complexes of the methylene bridged ligand **1** and complexes of the related ligands by Specht *et al.* were crystallized as trigonal planar mono copper complexes with one acetonitrile ligand or as 2:1 ligand:copper ratio coordinated complexes.[12] Both species were detectable for copper complexes with ligand **2** as well by ESI-MS, indicating equilibria between the three copper(I) species (Figure S32). The $[Cu(\mathbf{2})_2]^+$ species is unreactive towards dioxygen (Figure S8), we therefore propose that this species plays no significant role during dioxygen activation. Despite several attempts to crystallize this copper(I) species, only the copper(II) analogue could be structurally characterized (SI 3.5.2). However, even though the dimer was the most prominent species in the ESI-MS spectrum, thorough NMR analysis confirmed that the mono acetonitrile coordinated species $[Cu(\mathbf{2})(MeCN)]PF_6$ is the preferred species in solution (Figure S14–Figure S21).

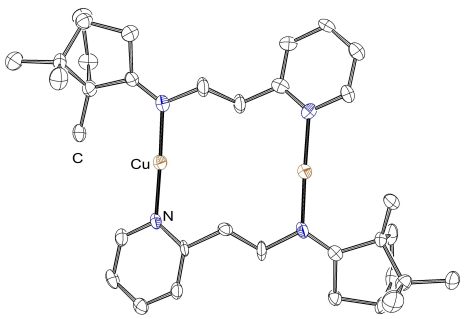

Figure 1. ORTEP Plot of the molecular structure of $[Cu_2(\mathbf{2})_2](PF_6)_2$. Anions and hydrogen atoms are omitted for clarity. Ellipsoids are drawn at 50% probability.

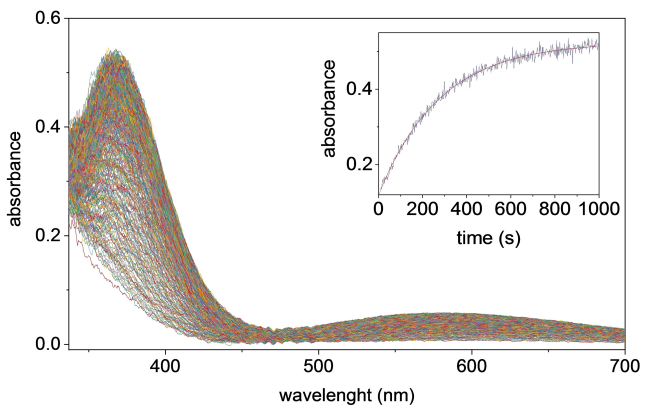

Figure 2. Time-resolved UV-vis spectra of the reaction of $[Cu(\mathbf{2})(MeCN)]PF_6$ ($4.7 \cdot 10^{-4}$ mol · L^{-1}) with dioxygen ($5.7 \cdot 10^{-3}$ mol · L^{-1})[3] in acetone at −7 °C over a period of 1000 s. The inset displays the time dependent change in absorbance at 365 nm (blue: experimental, red: exponential fit, first-order rate constant $k_{obs} = 3.6 \cdot 10^{-3}$ s^{-1}).

Stopped-flow measurements in acetone (Figure 2) were carried out to investigate the reaction of $[Cu(\mathbf{2})(MeCN)]PF_6$ with dioxygen to detect the formation of reactive intermediates. No reactions were observed at low temperatures (−93 °C). Furthermore, oxygenation in acetonitrile afforded only a very slow color change to purple (within days) and no observable LMCT bands within hours. Stopped-flow measurements in acetone: MeCN (2.5% V/V MeCN) revealed a strong inhibition of the reaction by the presence of small amounts of MeCN. The significance of de-coordination of additional ligands (such as MeCN) during or prior to dioxygen activation has been thoroughly studied in the past.[20]

Time resolved UV-vis spectra were collected in acetone between −10 °C and +10 °C. Absorbance maxima were observed at 365 nm and at 570 nm, which would be the typical region for μ-η^2:η^2-peroxido dicopper complexes.[21] Furthermore, similar spectra were assigned to bis(μ-oxido) dicopper complexes in the past.[6,22] However, the product complex formed was stable enough to be crystallized and turned out to be the bis(μ-hydroxido) dicopper complex $[Cu_2(\mathbf{2})_2(\mu\text{-}OH)_2](PF_6)_2$ (Figure 3). We were able to confirm that the UV-vis spectrum can be assigned to the bis(μ-hydroxido) by isolation of the complex and the measurement of a UV-vis spectrum at room temperature. Additionally, DFT calculations (see below and SI 1.5) supported this assignment.

The crystallization of two conformers of the bis(μ-hydroxido) dicopper complex was achieved (Figure 3). The presence of such bis(μ-hydroxido) conformers in solution was supported by Ray and co-workers using helium tagging infrared photodissociation spectroscopy.[19] It is a common decomposition product of μ-η^2:η^2-peroxido and bis(μ-oxido) complexes and was also clearly detectable by ESI-MS (SI 3.4).[15,19,23]

Ray and co-workers recently reported the formation of a bis(μ-oxido) complex that subsequently reacts to a reactive bis(μ-hydroxido) with similar UV-vis features that we

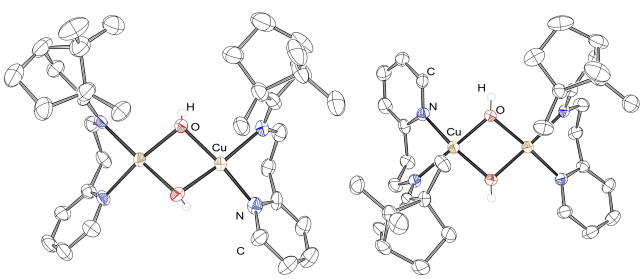

Figure 3. ORTEP Plots of the molecular structures of the C_1 and C_2 form of $[Cu_2(\mathbf{2})_2(\mu\text{-}OH)_2](PF_6)_2$. Anions and carbon bound hydrogen atoms are omitted for clarity. Ellipsoids are drawn at 50% probability.

observed.[19] However, they could not crystallize their complex. In contrast we did not observe the formation of the presumed bis(μ-oxido) complex, but obtained instead a stable bis(μ-hydroxido) complex. The temperature range and the time of full formation of the band at 365 nm of approximately 1000 s (Figure 2) is quite exceptional for copper dioxygen species and demonstrates the high stability of the copper(I) complexes of **2**. It is known that copper(I) complexes can be stabilized by six membered chelate rings.[8,10] Furthermore, it was observed in the past that the bite angle of a ligand can determine which type of adduct forms.[24]

The observed adduct does not decompose significantly at room temperature (Figure 4a–d). It is even detectable by UV-vis in DCM for at least 5 d (Figure 4b). Considering that the copper(I) complexes of **1** undergo intramolecular hydroxylation via a copper hydroperoxido complex within hours, makes [Cu(**2**)(MeCN)]PF_6 an outstanding example for the influence of chelate ring size and bite angle on the reactivity of copper(I) complexes towards dioxygen.

Bis(μ-oxido) dicopper complexes are common intermediates for intramolecular ligand hydroxylations, which makes it particularly interesting how our "substrate" ligand forms copper dioxygen species without subsequent oxygenation.[10,15,16,25] Anyhow, the molecular structure of the bis(μ-hydroxido) complex reveals a γ-H···O distance of 2.34–2.50 Å, which could potentially be too far for an insertion of O into the C–H bond or even radical H abstraction, under the assumption that similar distances are present in the actual dioxygen adduct.

The temporal evolution of the absorbance at 365 nm (inset Figure 2) can be fitted by a single exponential function, indicating pseudo first order kinetics. Furthermore, kinetic measurements in dependency O_2 concentration confirmed the first order kinetics with respect to $c(O_2)$ leading to the overall rate law:

$$\frac{dc([Cu_2(\mathbf{2})_2(\mu{-}OH)_2](PF_6)_2)}{dt} = k \cdot c([Cu(\mathbf{2})(MeCN)]^+) \cdot c(O_2)$$

Thus, the initial formation of a 1:1 Cu:O_2 superoxido species should be representing the rate determining step followed by fast consecutive steps to the final product. Despite the small temperature range we calculated the activation parameters $\Delta H^{\ddagger} = +21.9 \pm 0.7\ kJ\,mol^{-1}$ and $\Delta S^{\ddagger} = -166 \pm 2\ J\,K^{-1}\,mol^{-1}$ from an Eyring plot (Figure S4; Table S2). The quite negative activation entropy is in line with an associative mechanism (substitution of MeCN) that also explains the suppression of the reaction if the concentration of MeCN is raised.

Density functional theory (DFT) calculations were performed to investigate the nature of the Cu_2O_2 species that forms prior to the bis(μ-hydroxido) complex and confirmed the overall reaction mechanism. The calculations reveal the bis(μ-oxido) species as favored by app. 9 kcal mol^{-1} over the peroxido species (Figure S10; Table S5). As the UV-vis spectrum together with the observation of no characteristic Cu_2O_2 modes in the Raman spectrum of this species indicates the formation of the

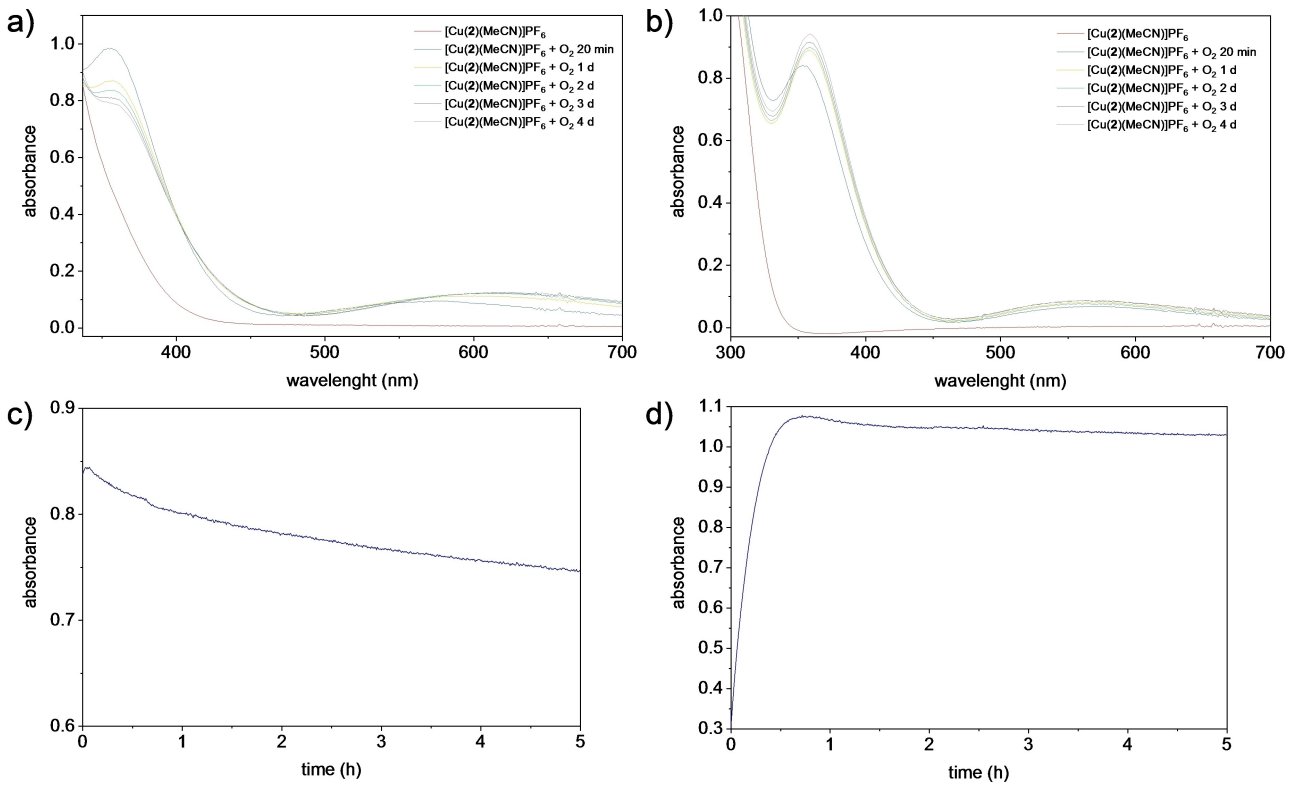

Figure 4. UV-vis spectra of the reaction of [Cu(**2**)(MeCN)]PF_6 with O_2 a) in acetone over 4 d and b) in DCM over 4 d; c) Time trace of the absorption at 365 nm in acetone; d) Time trace the absorption at 365 nm of the reaction in DCM.

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hydroxido species, it was also investigated via DFT calculations. The key parameters of the triplet hydroxido species (favored by 14.1 kcal/mol compared to the singlet hydroxido species; Table S6) agree very well with the bond length and angles determined by single crystal X-ray crystallography (Table S8). Furthermore, the time-dependent (TD) DFT UV-vis spectrum of the triplet hydroxido species corresponds to the experimental spectrum (Figure S13). Therefore, the bis(μ-hydroxido) most likely forms from a bis(μ-oxido) core by hydrogen atom abstraction from the acetone, as observed by Ray and co-workers.[19]

This was further confirmed by the formation of a dinuclear copper complex with an acetate and hydroxide bridge (Figure 5), upon oxygenation of [Cu(**2**)(MeCN)]PF_6 in acetone after a few days at room temperature (A species which was not observable by ESI-MS measurements). Furthermore, the bis(μ-hydroxido) must play a role in oxygen mediation during acetone oxidation, since it slowly decomposes in acetone, but not in DCM (Figure 4c, Figure 4d).

The molecular structure demonstrates that the dioxygen adduct is able to oxidize substrates after all. Acetic acid is a typical product from oxygenation of acetone to methyl glyoxal and subsequent oxidative decomposition.[26] Anyhow, this process seems to be very slow, which is why the acetate bridged complex was not observable by ESI-MS. The stability of the complex in DCM thus can be easily explained by the lack of the observed acetone oxidation.

Stereoselective oxygenations of prochiral substrates with dioxygen as oxidant are mostly carried out utilizing enzyme catalysis, which have the drawback of high substrate specificity and therefore relatively narrow substrate scope.[27] However, some non-enzymatic examples are known, but to the best of our knowledge no prochiral substrates were enantioselectively oxygenated applying copper dioxygen chemistry.[28] Thioanisole

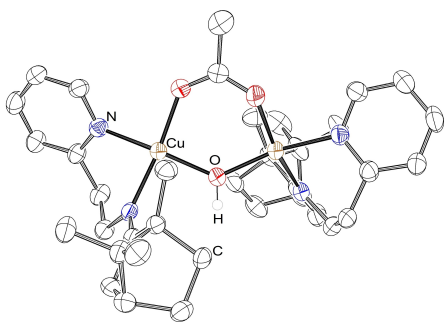
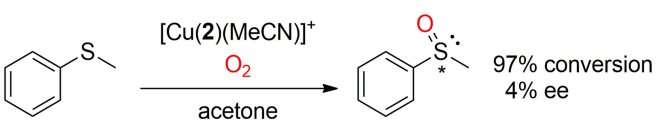


Figure 5. ORTEP Plot of the molecular structure of [Cu_2(**2**)$_2$(μ-OAc) (μ-OH)](PF_6)$_2$. Anions and carbon bound hydrogen atoms are omitted for clarity. Ellipsoids are drawn at 50% probability.



Scheme 3. Oxygenation of thioanisole to the chiral methyl phenyl sulfoxide.

was chosen as a target substrate to test potential stereoselective oxygenations by [Cu_2(**2**)$_2$($OH)_2$]$^{2+}$, since aryl sulfides are enantioselectively oxidizeable to their corresponding sulfoxides (Scheme 3).[29,30] Chiral sulfoxides are particularly interesting due to their biological activity, but this reaction is rather a proof of concept to demonstrate that copper "dioxygen adduct" complexes can be designed to be stereoselective oxygen mediators.[29,31]

Conversions up to 97% were achieved using one equivalent of the copper(I) complex, yielding almost exclusively the sulfoxide and ee's up to 4%. Furthermore, $^{18}O_2$ experiments revealed that dioxygen is the sole oxygen source for the oxygenation. Since the thioanisole oxidation is a 2 e^- process a conversion up to 50% (with respect to copper(I)) was expected. The higher conversion could indicate a catalytic reaction with two turnovers. However, attempts to run the reaction with catalytic amounts (5% and 10%) of copper(I) failed. Furthermore, considering the fact that the reactions have the best outcome in acetone and that the dioxygen complex clearly reacts with acetone (Figure 5), the direct oxygenation of thioanisole by the bis(μ-hydroxido) species, as observed by Ray and co-workers, seems likely. However, the *in situ* formation of H_2O_2 and formation of a copper hydroperoxido species as active oxidizing species, as observed by the Baran and Garcia-Bosch groups, cannot be completely excluded.[12,19] The presence of the bis(μ-hydroxido) complex in the C_2 and C_1 symmetric form (crystallographic characterization) in solution causes many possible transition states during oxygenation that most likely do not yield the same enantiomer, which could be a reason for the lack of enantioselectivity. Furthermore, the (+)-camphor moieties might not be sufficiently bulky to induce higher ee's for this type of reaction. Despite the low ee's this reaction proofs that with further optimization and according ligand design enantioselective oxygenations utilizing chiral copper dioxygen adducts as oxygen mediators could potentially be developed.

Conclusion

Our observations are a concise example for the often observed stabilization of copper(I) complexes by six membered chelate rings, an effect that was previously elucidated.[8,10] However, such a dramatic effect of the chelate ring size on the ultimate reactivity of copper(I) towards dioxygen (hydroperoxido vs. bis(μ-oxido) and bis(μ-hydroxido)) was not expected here. The methyl bridged ligand readily undergoes intramolecular ligand hydroxylation in high yields (up to 94%) when reacted with copper(I) and O_2 or H_2O_2. Complexes of the ethyl bridged ligand on the other hand oxygenates the solvent rather than the γ-C–H bond and is able to selectively oxygenate thioanisole to its according sulfoxide.

Chiral copper dioxygen adducts are rare (only one has been crystallized so far).[32] Further investigations on simple chiral ligands are required for the development of useful enantioselective non-enzymatic oxygenations using dioxygen as oxidant and chiral copper(I) complexes as catalysts.

Experimental Section

Materials and Methods: Solvents and reagents were purchased from common suppliers. $[Cu(MeCN)_4]PF_6$ and $[Cu(MeCN)_4]OTf$ were prepared according to literature procedures and stored in an argon filled glove box.[33] The used solvents were purchased as anhydrous solvents under nitrogen atmosphere and were distilled under argon prior to transferring them into an argon filled glove box. ^1H and ^{13}C NMR spectra were measured on a Bruker Avance II 400 MHz or Bruker Avance III 400 MHz HD. The NMR analysis of the copper(I) complex was carried out on a Bruker Avance III 600 MHz HD NMR-spectrometer. Elemental analysis was carried out on a Thermo FlashEA–1112 Series CHN-analysator. Reactions under inert conditions were carried out in an argon 5.0 filled glove box (MBraun, Garching, Germany). UV-vis measurements were carried out using an Agilent 8453 spectrometer at 20 °C. GC-MS measurements were carried out using an Agilent Technologies 5977B mass detector with a 7820 A GC system. Chiral HPLC was carried out using a CHIRALPAK IC column and a Dionex UVD 170 U detector (eluent mixture: 70% n-hexane, 30% IPA). ESI-MS was measured using a Bruker Daltonics micrOTOF. SC-XRD analysis was carried out on a Bruker D8 Venture system, which was equipped with an IμS microfocus Mo-K_α and Cu-K_α X-ray source. Moreover, the system was equipped with an OXFORD CRYOSYSTEMS 700 low temperature system and a PHOTON100 CMOS-detector. The molecular structures were solved and refined using SHELXT2014/5[34] and SHELXL2018/3[35], respectively.

Preparation of Ligand 2: A modified version of a literature known synthesis was used to obtain **2**.[13] (+)-Camphor (2.119 g, 13.92 mmol) was added to a round bottom flask and dissolved in anhydrous toluene (50 mL). Afterwards 2-(2-pyridyl)-ethylamine (1.711 g, 14.01 mmol) and $BF_3 \cdot Et_2O$ (0.1 mL, 0.8 mmol) were added to the solution and the flask was attached to a Dean-Stark apparatus equipped with a reflux condenser and a drying tube filled with $CaCl_2$. The mixture was refluxed overnight. After cooling to room temperature the solvent was removed *in vacuo* and the crude product was purified by Kugelrohr distillation. The pure product was obtained as a colorless oil (2.022 g, 7.886 mmol; 57%). ^1H NMR(400 MHz, $CDCl_3$): δ (ppm) = 8.48 (d, J = 4.5 Hz, 1H), 7.51 (tt, J = 7.7, 1.7 Hz, 1H), 7.13 (d, J = 7.7 Hz, 1H), 7.05 (t, J = 7.6 Hz, 1H), 3.71–3.51 (m, 2H), 3.15–3.00 (m, 2H), 2.18 (dt, J = 17.0, 3.9 Hz, 1H), 1.79 (t, J = 4.6 Hz, 1H), 1.77–1.66 (m, 1H), 1.6 (d, J = 16.9 Hz, 1H), 1.53 (td, J = 12.0, 4.2 Hz, 1H), 1.21–1.10 (m, 1H), 1.01–0.91 (m, 1H), 0.90 (s, 3H), 0.83 (s, 3H), 0.53 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) = 182.6, 160.6, 149.2, 136.0, 124.0, 121.1, 53.5, 52.3, 46.7, 43.7, 38.4, 35.5, 32.2, 27.3, 19.3, 18.9, 11.5; HRMS (ESI): *m/z* calcd for $C_{17}H_{24}N_2 + H^+$: 257.2013 $[M+H]^+$, found: 257.2014.

Preparation of [Cu(2)(MeCN)]PF_6: In an argon filled glovebox $[Cu(MeCN)_4]PF_6$ (1.480 mg, 3.971 mmol) was dissolved in anhydrous acetone (20 mL). Ligand **2** (1.016 mg, 3.963 mmol) was also dissolved in anhydrous acetone (15 mL) and added dropwise while stirring the copper(I) solution. The pale yellow solution was stirred at room temperature for 2 h. Subsequently anhydrous diethyl ether (250 mL) was added to precipitate the colorless copper complex. The suspension was stirred overnight. The colorless solid was filtered off and washed with anhydrous diethyl ether (3 · 10 mL). The product was dried *in vacuo*. A colorless solid was obtained as final product (1.705 mg, 3.370 mmol, 85%). ^1H NMR(600 MHz, acetone-*d6*): δ (ppm) = 8.70 (d, J = 5.4 Hz, 1H), 8.10 (t, J = 7.5 Hz, 1H), 7.78 (d, J = 7.5 Hz, 1H), 7.58 (t, J = 5.8 Hz, 1H), 4.18–4.04 (m, 1H), 4.04–3.93 (m, 1H), 3.63 (s, 2H), 2.69 (dt, J = 18.4, 3.8 Hz, 1H), 2.30 (s, 3H), 2.09 (d, J = 18.4 Hz, 1H), 2.02 (t, J = 4.5 Hz, 1H), 1.90–1.82 (m, 1H), 1.79 (td, J = 12.2, 3.7 Hz, 1H), 1.50 (s, 3H), 1.32–1.23 (m, 1H), 1.17–1.08 (m, 1H), 0.95 (s, 3H), 0.66 (s, 3H); ^{13}C NMR (151 MHz, acetone-*d6*) δ (ppm) = 195.9 (q, broad), 161.0 (q), 150.6 (CH), 140.9 (CH), 126.5 (CH), 124.7 (CH), 118.7 (q, MeCN), 56.2 (q), 54.0 (CH_2), 49.3 (q), 44.3 (CH), 40.8 (CH_2, broad), 39.1 (CH_2), 32.6 (CH_2), 27.3 (CH_2), 19.7 (CH_3), 19.1 (CH_3), 13.0 (CH_3), 1.8 (CH_3); elemental analysis calcd (%) for $C_{19}H_{27}CuF_6N_3P$: C 45.10, H 5.38, N 8.31; found: C 45.02, H 5.55, N 8.16.

Crystallization of [Cu(**2**)(MeCN)]PF_6 was attempted in MeCN, acetone and DCM. However, the copper(I) complex always crystallized as the $[Cu_2(\mathbf{2})_2](PF_6)_2$ dimer complex (SI 3.5.1), whether the isolated complex [Cu(**2**)(MeCN)]PF_6 was used or the complex was generated *in situ* by careful addition of **2** to $[Cu(MeCN)_4]PF_6$.

Stopped-Flow UV-vis Spectroscopy: Stopped-Flow measurements were carried out on a commercial HI-TECH SF-61SX2 stopped-flow unit (TgK Scientific, Bratford-on-Avon, UK). The collected data was processed using Kinetic Studio version 5.02 Beta. The procedure for kinetic measurements was described in detail in previous work.[36]

UV-vis Experiments: A $8.1 \cdot 10^{-4}$ mol · L^{-1} solution of $[Cu(\mathbf{2})(MeCN)]^+$ was prepared by mixing equimolar amounts of $[Cu(MeCN)_4]PF_6$ and **2** in anhydrous degassed acetone or DCM in an argon filled glovebox. A UV-vis spectrum of the copper(I) complex was recorded at 20 °C. Afterwards dioxygen was led through the solution for about 4 min. Spectra were recorded after further 16 min, 1 d, 2d, 3 d and 4 d. The experiment was repeated in both solvents and the intensity at 365 nm was traced over 5 h at 20 °C.

Oxygenation Reactions: The oxygenation of thioanisole by the bis(μ-hydroxido) complex was investigated, to test if the complex is suitable for enantioselective oxygenations. In an argon filled glovebox [Cu(**2**)(MeCN)]PF_6 (216.7 mg; 0.4283 mmol) was dissolved in anhydrous acetone (20 mL). Subsequently, thioanisole (50 μL; 0.43 mmol) was added to the solution under stirring. Pure dioxygen was lead through the solution for 5 min at r.t. causing the solution to turn to a deep purple color. The solution was stirred at r.t. for 4 h and quenched by the addition of 1 mol · L^{-1} NH_3 solution (30 mL). The acetone was removed *in vacuo* and the aqueous layer was washed with DCM (4 · 15 mL). The combined organic layers were dried over Na_2SO_4. After removal of the drying agent, the solvent was removed *in vacuo* and the product mixture was analysed by GC-MS and chiral HPLC. The procedure was repeated in DCM and THF (DCM: green solution after oxygenation; THF: purple suspension that turned into a blue solution after oxygenation).

Crystallizations

$[Cu_2(\mathbf{2})_2](PF_6)_2$: One equivalent of $[Cu(MeCN)_4]PF_6$ and one equivalent of **2** were dissolved in small amounts of anhydrous degassed acetone in separate vials. The ligand solution was carefully added to the copper salt solution resulting in a highly concentrated pale yellow complex solution. Colorless crystals were obtained by slow ether diffusion over a few days at room temperature.

$[Cu(\mathbf{2})_2](BF_4)_2 \cdot 2\ C_3H_6O$: One equivalent of $[Cu(MeCN)_4]BF_4$ and one equivalent of **2** were dissolved in small amounts of anhydrous degassed DCM in separate vials. The ligand solution was carefully added to the copper salt solution resulting in a highly concentrated pale yellow complex solution. Approximately 10 equivalents of S_8 were added in an attempt to crystallize potential sulfido complexes. The solution was stirred overnight and filtered using a syringe filter resulting in a purple solution. Red crystals were obtained by slow pentane diffusion over three months at −30 °C. The sulfur most likely oxidized the Cu(I) complex to the observed $[Cu(\mathbf{2})_2](BF_4)_2$. However the crystallization of sulfido complexes remained unsuccessful.

$[Cu_2(\mathbf{2})_2(\mu\text{-}OH)_2](PF_6)_2 \cdot 2$ THF (C_2): One equivalent of $[Cu(MeCN)_4]PF_6$ and one equivalent of **2** were dissolved in small amounts of anhydrous degassed THF in separate vials. The ligand solution was

carefully added to the copper salt solution resulting in a highly concentrated pale yellow complex solution. Dioxygen gas was passed through the solution at room temperature for 2 min resulting in a deep purple colored solution. Blue crystals were obtained by slow pentane diffusion over 10 d at −30 °C.

$[Cu_2(2)_2(\mu\text{-}OH)_2](PF_6)_2 \cdot 2\ C_3H_6O$ (C_1): One equivalent of $[Cu(MeCN)_4]PF_6$ and one equivalent of **2** were dissolved in small amounts of anhydrous degassed acetone in separate vials. The ligand solution was carefully added to the copper salt solution resulting in a highly concentrated pale yellow complex solution. One equivalent of NaBArF was added in an attempt to exchange the anion. Dioxygen gas was passed through the solution at room temperature for 2 min resulting in a deep purple colored solution. Blue crystals were obtained by slow ether diffusion over a week at room temperature.

$[Cu_2(2)_2(\mu\text{-}OAc)(\mu\text{-}OH)](PF_6)_2$: One equivalent of $[Cu(MeCN)_4]PF_6$ and one equivalent of **2** were dissolved in small amounts of anhydrous degassed acetone in separate vials. The ligand solution was carefully added to the copper salt solution resulting in a highly concentrated pale yellow complex solution. Dioxygen gas was passed through the solution at room temperature for 2 min resulting in a deep purple colored solution. Blue crystals were obtained by slow ether diffusion over a week at room temperature.

2-$H_2(OTf)_2 \cdot H_2O$: One equivalent of $Cu(OTf)_2$ and one equivalent of **2** were dissolved in small amounts of DCM in separate vials. The ligand solution was carefully added to the copper salt solution resulting in a highly concentrated green complex solution. The solvent was removed and the complex was re-dissolved in acetone. Colorless crystals were obtained by slow ether diffusion over a few days at room temperature.

Computational Details: Density functional theory (DFT) calculations were performed with Gaussian 16, Revision B01[37]. The geometry optimizations were optimized by using the TPSSh functional[38] and with the Ahlrichs type basis set def2-TZVP[39] basis set as implemented in Gaussian 16, Revision B01.[37] As solvent model, we used the Polarizable Continuum Model (PCM) as implemented in Gaussian 16. As empirical dispersion correction, we used the D3 dispersion with Becke–Johnson damping as implemented in Gaussian16, Revision B.01.[40]

Deposition Numbers 2118500 (for $[Cu_2(\mathbf{2})_2(\mu\text{-OAc})(\mu\text{-OH})](PF_6)_2$), 2118501 (for **2**-$H_2(OTf)_2 \cdot H_2O$), 2118502 (for $[Cu_2(\mathbf{2})_2(\mu\text{-OH})_2](PF_6)_2 \cdot C_3H_6O$), 2118503 (for $[Cu_2(\mathbf{2})_2](PF_6)_2$), 2118504 (for $[Cu_2(\mathbf{2})_2(\mu\text{-OH})_2](PF_6)_2 \cdot 2$ THF), 2118505 (for $[Cu(\mathbf{2})_2](BF_4)_2 \cdot 2\ C_3H_6O$) contain the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service at www.ccdc.cam.ac.uk/structures.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Keywords: Chiral · Copper · DFT · Dioxygen · Oxygenations

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