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# Reactivity of Copper Complexes with Tripodal Tetradentate Ligands based on Camphoric Acid towards Dioxygen

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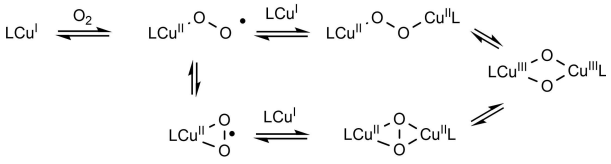
The reaction of dioxygen with copper(I) complexes containing camphor-derived ligands was investigated. Stopped-flow measurements revealed the formation of bis($\mu$-oxido) copper complexes at low temperatures. However, these intermediates were not stable enough to be isolated and decomposed quickly. Sterically more demanding alkyl groups slowed the formation of the bis($\mu$-oxido) copper complexes. A kinetic analysis was performed and showed - in line with previous reports - that the rate-determining step could be assigned to forming a mononuclear superoxido copper complex. For one of the reactions investigated, a product could be structurally characterized and turned out to be a copper(II) complex with an additional hydroxide as a ligand (most likely caused by a C–H abstraction from the solvent acetone). One of the complexes oxidized thioanisole to the corresponding sulfoxide (conversion of 34% according to GC-MS) with no byproducts. Chiral GC gave an enantiomeric excess of 14%.

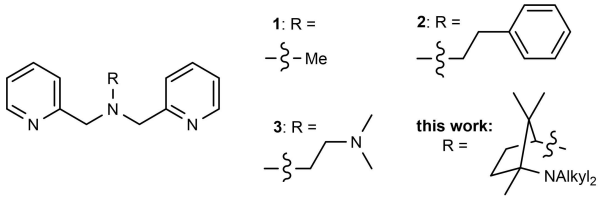
## Introduction

Activation of molecular dioxygen is an essential topic in bioinorganic chemistry for possible applications in synthetic chemistry, the selective oxygenation of organic substrates.[1,2–4] For example, the copper enzyme tyrosinase, a monooxygenase, can hydroxylate the amino acid tyrosine leading to consecutive reactions to L-DOPA.[5] Furthermore, methane monooxygenase, based on either iron or copper ions in the active site, catalyzes methane oxidation to methanol.[6] So far, many model complexes containing copper(I) ions have been synthesized with different ligand systems to activate dioxygen.[3,4] In the reaction with $O_2$, a wide variety of so-called "copper-oxygen-adduct complexes" were characterized.[2,3,7] Several of these, often highly reactive species, can be used to oxidize diverse substrates with dioxygen as the oxidant.[8,9,10–13] The dioxygen binding mode depends on the ligands' geometric/steric and electronic properties. Some of the possible reactions leading to their formation of different intermediates are presented in Scheme 1.[2–4,14,15]

*Astner et al.* showed that the copper(I) complexes of the ligand Me-bpa **1** (Scheme 2) did not show an observable formation of an oxygen species.[16] In contrast, *Itoh* and coworkers reported a copper(I) complex with ligand **2** (Scheme 2), where the methyl group is exchanged for a phenethyl group.[17] This ligand can stabilize copper(I) by d-$\pi$ interaction of the phenyl residue to the copper center. This copper(I) complex's reaction with dioxygen led to a bis($\mu$-oxido) copper complex in acetone. However, this oxygen intermediate decomposed even at low temperatures and led to an intramolecular hydroxylation of the phenylethyl sidearm.[17]



**Scheme 1.** Possible reaction pathways of the reaction of copper(I) complexes with dioxygen.[15]



**Scheme 2.** Derivatives of bispicolylamine (R = H), the ligands Me-bpa **1**, $^{Phe}L^{Pym2}$ **2**, and $Me_2$-uns-penp **3** used in previous work and the new ligands described herein.

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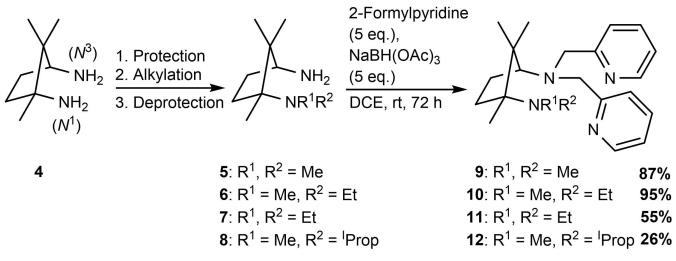
With an aminoethyl group for R (Scheme 2), the tripodal ligand uns-penp[18] was obtained, and derivatives of this ligand were applied successfully for stabilizing copper oxygen intermediates. For example, the ligand $Me_2$-uns-penp (**3**) formed a dimeric copper (*trans*-1,2-peroxido) complex.[13,19] With tetraphenylborate as an anion, it was possible to stabilize this usually unstable intermediate even at room temperature. With this peroxido species, the oxidation of toluene could be achieved.[13] More recently, we described the immobilization of a copper(I) complex with derivatives of uns-penp on silica for the oxidation of toluene.[20] The results of this work could become important for future applications of oxygenation reactions in a flow reactor.

As we were interested in enantioselective oxygenations, we started investigating the reactions of copper(I) complexes containing camphor-derived ligands[21] with dioxygen.[11,15] Camphor-based systems have also been reported previously by Garcia-Bosch and co-workers.[22] As a precursor, we applied camphor related bisamine **4** (Scheme 3), which can be easily prepared from camphoric acid.[23] The ligands could be easily modified, and the resulting copper(I) complexes showed good properties in stabilizing oxygen intermediates. Thus we could obtain a bis($\mu$-oxido) copper complex that was structurally characterized.[11] We decided to further functionalize the bpa system by introducing a camphor derivative as the R group with different alkyl residues (Schemes 2 and 3).

## Results and Discussion

### *Synthesis and Characterization of Ligands and Copper Complexes*

The educts **5**–**7** (Scheme 3) of the final ligand systems were prepared by literature procedures.[11] The synthesis of amine **8** is described in the supporting information. However, the alkylation of the nitrogen $N^1$ with more bulky groups (for example, $R_1$=$^i$Prop, $R_2$=Et) was not successful, presumably because of the high steric hindrance in this position (details are given in the supporting information). The ligands **9**–**12** were synthesized by adapting the reaction conditions with slight modifications of the synthesis of the ligand acetyl-uns-penp.[18] After purification using column chromatography, the pure ligands were obtained.




**4**

**5**: $R^1$, $R^2$ = Me
**6**: $R^1$ = Me, $R^2$ = Et
**7**: $R^1$, $R^2$ = Et
**8**: $R^1$ = Me, $R^2$ = $^i$Prop

**9**: $R^1$, $R^2$ = Me **87%**
**10**: $R^1$ = Me, $R^2$ = Et **95%**
**11**: $R^1$, $R^2$ = Et **55%**
**12**: $R^1$ = Me, $R^2$ = $^i$Prop **26%**

**Scheme 3.** Synthesis of the ligand systems using reductive amination conditions.

Crystallographic data for ligands **9** and **10** are given in the supporting information.

Attempts to crystallize copper(I) complexes of these ligands failed. In all cases, only yellow-colored oils were obtained. Therefore, copper(I) complexes obtained in an in situ 1:1 mixture of $[Cu(CH_3CN)_4]OTf$ and the corresponding ligand in deuterated acetone were characterized by NMR (acetone was used because the reactivity with dioxygen was only observed in acetone, *vide infra*; NMR data are reported in the supporting information).

In contrast to copper(I) complexes, it was possible to structurally characterize copper(II) complexes of the ligands **9**, **10**, and **11**. To understand if the alkylated nitrogens $N^1$ of the ligands can also coordinate with copper ions, we decided to use a mixture of $CuCl_2$ and $Cu(ClO_4)_2$ in a 0.5 to 0.5 ratio for the complexation reaction. With $Cu(ClO_4)_2$ alone, no crystals could be obtained. In the case of ligand **9** ($R^1$, $R^2$=Me) and **11** ($R^1$, $R^2$=Et), blue-colored crystals were obtained, which could be structurally characterized (Figure 1). For both complexes, $[Cu(\mathbf{9}\text{-H})Cl](ClO_4)_2$ and $[Cu(\mathbf{11}\text{-H})Cl](ClO_4)_2$, the alkylated nitrogen got protonated, presumably caused by the solvent methanol. Using aprotic solvents, the crystallization failed.

The implementation of the ligands **10** ($R^1$=Me, $R^2$=Et) and **11** ($R^1$, $R^2$=Et) with $CuCl_2$ led to the formation of green-colored crystals, which were structurally characterized. In both cases, only the bpa unit binds to the copper center in a square pyramidal fashion (Figure 2). Chloride effectively competes with

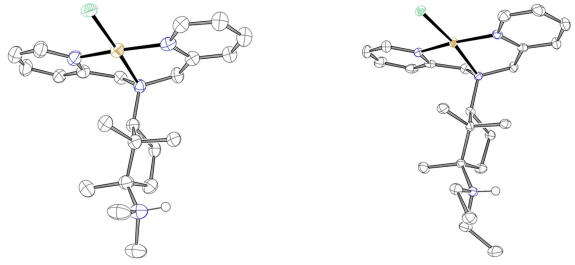


**Figure 1.** Molecular structures of $[Cu(\mathbf{9}\text{-H})Cl](ClO_4)_2$ (left) and $[Cu(\mathbf{11}\text{-H})Cl](ClO_4)_2$ (right). Hydrogen atoms (except N–H), solvent molecules, and perchlorate anions are omitted for clarity. Anisotropic displacement ellipsoids are set to 50% probability.

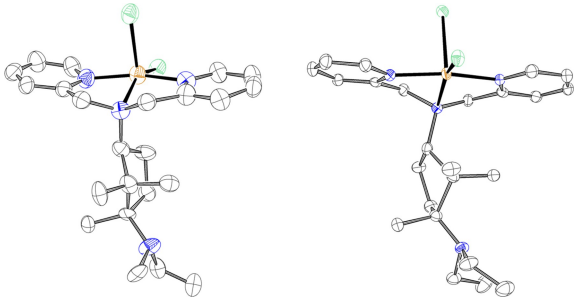


**Figure 2.** Molecular structures of $[Cu(\mathbf{10})Cl_2]$ (left) and $[Cu(\mathbf{11})Cl_2]$ (right). Hydrogen atoms are omitted for clarity. Anisotropic displacement ellipsoids are set to 50% probability.

coordinating the alkylated nitrogen that can bind to the copper(II) ions, as described below.

### *Reactivity of the Copper(I) Complexes with Dioxygen and Kinetic Investigations*

The first benchtop experiments with the complex solutions of the ligands **9**–**12** with $[Cu(CH_3CN)_4]OTf$ were performed in DCM at −80 °C. A slow color change from yellow to green was observed when bubbling dry oxygen through this solution. This could be caused by the oxidation of Cu(I) to Cu(II). When the reaction was monitored with stopped-flow techniques, no intermediate, e.g. an oxido/peroxido species, was observed. This indicates that in DCM, a possible oxygen intermediate cannot sufficiently be stabilized, and the color change indicates the oxidation of copper(I) to copper(II). However, in contrast to the related complexes reported by *Itoh* and co-workers (described above),[17] no disproportionation reactions were observed.

However, when the reactions of the different complex solutions were performed in acetone at −80 °C, a color change to a dark brown color occurred (Figure 3). In the case of the complex solution with the double methylated ligand **9**, the occurrence was much faster (instantaneously) in contrast to the other ligands and the brown color switched to green after approximately one minute. When using the other ligands **10**–**12**, the brown color appeared much slower (minute range) and stayed much longer. After warming to room temperature, the color changed to green in all cases. We previously observed similar color changes when a copper(I) complex with a tetramethylated diamine ligand reacted with dioxygen.[11]

The reaction was monitored with low-temperature stopped-flow techniques to verify the occurrence of an "oxygen adduct" complex. While investigating the double methylated ligand **9**, the formation of a band at 389 nm was observed, which indicates the formation of the postulated bis($\mu$-oxido) copper complex (Figure 4).[2,11,25] The typical appearance of the band near 300 nm cannot be observed because of the limitation of our detector for measurements lower than 330 nm and the absorbance of the solvent acetone in that region. A decrease of the absorbance maximum at 389 nm could be detected after approximately one minute, completely in line with our observation in the benchtop experiment.

The absorbance vs. time trace measured under pseudo first order conditions (dioxygen concentration in excess) can be

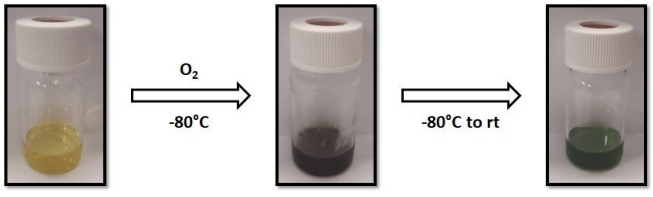



**Figure 3.** The copper(I) complex solutions react with dioxygen at −80 °C.

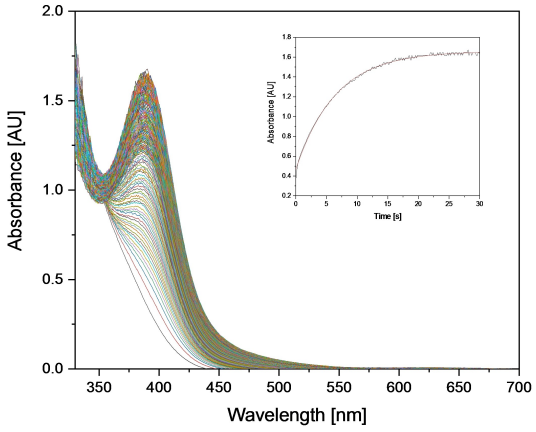



**Figure 4.** Time-resolved UV/Vis spectra of the reaction of $[Cu(CH_3CN)_4]OTf$ and **9** ($c = 0.6 \times 10^{-3}$ mol/L) with dioxygen ($c = 5.7 \times 10^{-3}$ mol/L) in acetone at −75 °C over 30 s. The inset shows the absorbance vs. time at $\lambda = 389$ nm.

fitted to a single exponential function. Therefore, the copper complex's concentration is first order in the rate law. The plot of $k_{obs}$ vs. the concentration of dioxygen yielded a linear correlation (Figure 5) with an intercept. This shows that the consumption of $O_2$ is also first order in the rate law. The intercept indicates a reversible reaction in the rate-determining step, the dioxygen binding. This was observed previously in a related study on the formation of a copper peroxido complex by *Lerch et al.* using the ligand $Pim^{iPr2}$. A detailed description of the kinetic analysis is described herein.[24]

In line with this publication and previous work on forming other bis($\mu$-oxido) copper complexes[12,15,25], a proposed mechanism for the overall reaction is presented in Scheme 4. The rate-limiting step is assigned to the formation of a superoxido complex (eq. 1). However, as described previously through extensive DFT calculations using guanidine-containing ligands, it is not possible to spectroscopically detect this intermediate

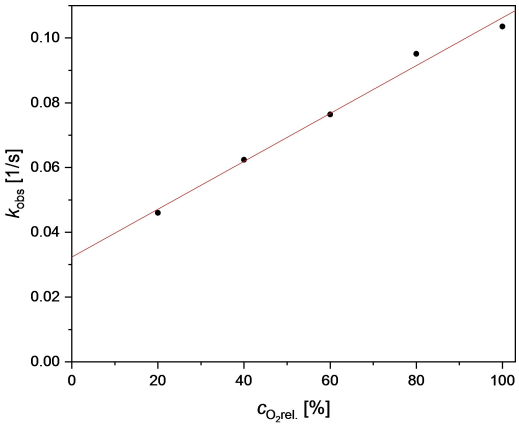
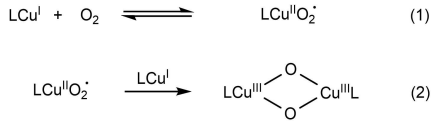



**Figure 5.** Plot $k_{obs}$ *vs.* relative concentration of dioxygen using the double methylated ligand **9**. The measurements were done in acetone at −75 °C with the copper salt $[Cu(CH_3CN)_4]OTf$.




**Scheme 4.** Proposed formation of the bis($\mu$-oxido) copper complexes.

due to the much faster formation of the observed bis($\mu$-oxido) copper complex (eq. 2).[25]

Additionally, a temperature-dependent series of measurements allowed to calculate the activation parameters ($\Delta H^{\neq} =$ 18.5 kJ/mol; $\Delta S^{\neq} = -165$ J/(mol·K) from an Eyring plot (see supporting information). The highly negative value for the activation entropy has been observed by us previously for a related complex system[15] and indicates an associative mechanism. This supports the coordination of the alkylated nitrogen of the ligand system, as discussed below. Dioxygen binds at the copper ion while the alkylated nitrogen atom is still coordinated, followed by the formation of the bis($\mu$-oxido) copper complex in a consecutive reaction while breaking the bond to the alkylated nitrogen atom with the bulky group. Thus leading to a bis($\mu$-oxido) copper complex similar to the copper(II) complexes in Figure 2, with the two chloride ions replaced by the two bridging oxido anions.

Due to the intermediates' short lifetime, obtaining them as solids (crystals) for complete characterization was impossible. Therefore, it was tried to crystallize one of the products after the reaction. From the oxidation of $[Cu(CH_3CN)_4]PF_6$ and the ligand **9**, a few blue-colored crystals were obtained that could be picked and structurally characterized. The molecular structure of this complex is presented in Figure 6 (crystallographic data are reported in the supporting information).

The molecular structure of the copper(II) complex clearly shows that the amine nitrogen atom $N^1$ can be coordinated as well. This is what we assume for the copper(I) complexes with this ligand series. The coordinated hydroxide ion most likely is caused by a C–H abstraction from the solvent acetone. The decomposition of bis($\mu$-oxido) copper complex to copper hydroxido complexes is well known by us and others.[8,26,27]

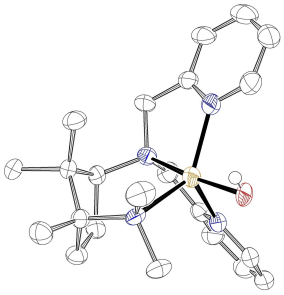


**Figure 6.** Molecular structure of the copper-hydroxido complex with ligand **9**. Hydrogen atoms (except O–H) and $PF_6$ anion are omitted for clarity. Anisotropic displacement ellipsoids are set to 50% probability.

However, these complexes are potentially helpful for the oxidation of substrates.[26,27] Unfortunately, we failed in selectively synthesizing this complex for applications in oxidation reactions.

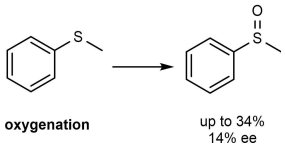
As described above, copper(I) complexes with the ligands **10, 11**, and **12** reacted nearly the same way as with ligand **9**; however, by a factor of about ten slower (data for the kinetic investigations with these complexes are reported in the supporting information). From the comparison of the activation parameters (Table 1), it is clear that the activation enthalpies cause differences in reaction rates.

### *Oxidation of external substrates*

The oxidation of external substrates with bis($\mu$-oxido) copper complexes is well known, - e.g., Herres-Pawlis and co-workers described the oxidation of 2-naphthol to the corresponding *ortho* quinone.[28] Trials to oxidize this substrate with the copper complexes reported herein only led to the formation of BINOL. This was not surprising because the oxidative coupling reaction is already described in the literature using copper(II) amine complexes.[29] Attempts to oxidize the non-activated substrate cyclohexane failed. The oxidation of toluene, described by Karlin[10] using a bis($\mu$-oxido) copper species, did not lead to the formation of benzyl alcohol or benzaldehyde. Only the oxidation of thioanisole to the corresponding sulfoxide (Scheme 5) could be detected. While using the double methylated ligand **9**, the sulfoxide was detected with a conversion of 34% using GC-MS with no visible byproducts. Chiral GC gave an enantiomeric excess of 14%. Using the complex solutions of the other ligands, the corresponding sulfoxide could be detected only in traces. Most likely, this is a consequence of the sterically more demanding alkyl groups in ligands **10**–**12** suppressing a close approach of the substrate molecule. Casella and co-workers also performed asymmetric oxidation of thioanisole. Using a binuclear copper complex containing a chiral diamino-

**Table 1.** Activation parameters for the reaction of dioxygen with all copper(I) complexes described herein.

| Cu(I)L | $\Delta H^{\neq}$/kJ/mol | $\Delta S^{\neq}$/J/(mol K) | $k_{(obs)}$ at $-73 \pm 1$ °C/ $1\ s^{-1}$ |
|---|---|---|---|
| **9** | $+18.5 \pm 0.3$ | $-165 \pm 1$ | 0.146 |
| **10** | $+24.7 \pm 0.6$ | $-153 \pm 3$ | 0.015 |
| **11** | $+25.7 \pm 0.1$ | $-148 \pm 1$ | 0.016 |
| **12** | $+24.9 \pm 0.1$ | $-154 \pm 2$ | 0.013 |




**Scheme 5.** Oxygenation of thioanisole to the corresponding sulfoxide.

*m*-xylene tetra(benzimidazole) ligand, a comparable enantiomeric excess of 12% of the corresponding sulfoxide was observed.[30] Furthermore, *Gamba et al.* described catalytic sulfoxidation. A dicopper peroxido complex was assigned as the reactive intermediate.[31] In our previous work, we also showed that bis($\mu$-hydroxido) dicopper complexes can oxidize thioanisole.[26] However, only small *ee*'s up to 4 % were detected. Due to the high interest in chiral sulfoxides, for example, in drug research, these results could play a role in future synthetic concepts.[32]

### *Summary and Conclusion*

A series of camphor-derived ligands had been prepared, and copper(II) complexes with some of these ligands were structurally characterized. The reaction of dioxygen with the copper(I) complexes led to the formation of bis($\mu$-oxido) copper complexes as reactive intermediates that could be detected spectroscopically. A kinetic analysis, applying low temperature stopped-flow measurements allowed us to postulate a reaction mechanism that was in line with previous investigations by us and others. In contrast to previous work, it was not possible to isolate and structurally characterize one of the bis($\mu$-oxido) copper complexes formed due to the instability of these compounds, even at low temperatures. One of the complexes turned out to oxidize thioanisole (in a low conversion) selectively to the corresponding sulfoxide with an enantiomeric excess of 14%, a promising result for future work in this area. Detecting a copper(II) complex with an additional hydroxide as a ligand could indicate the involvement of hydroxido complexes as possible oxidants.

## Experimental Section

**General**: Chemicals and solvents were purchased from commercial sources (AcrosOrganics, Alfa Aesar, Merck, and Sigma Aldrich). The solvents were distilled and, if necessary, dried using standard procedures. Oxygen-free solvents were obtained by redistillation under argon. Preparation under anaerobic conditions was carried out in a glovebox (MBraun) under Argon atmosphere. Column chromatography was performed using Silica 60, 0.04–0.063 mm (MACHEREY-NAGEL). $^{1}$H and $^{13}$C spectra were measured on a Bruker Avance II 400 MHz and Bruker Avance III HD 400 MHz spectrometer. Complex solutions were measured on a Bruker Avance III HD 600 MHz spectrometer. The $^{1}$H- and $^{13}$C-NMR spectra were calibrated against the residual proton and carbon signals of chloroform ($\delta = 7.26$ and $\delta = 77.2$) and acetone ($\delta = 2.05$ and $\delta = 29.8$).[33] HRMS(ESI) was measured with an ESI-MS Bruker Micro-TOF. Elemental analysis was performed by a Thermo FlashEA-1112 Series. GC-MS analysis was carried out using an Agilent Technologies 7820 A GC System coupled with an Agilent Technologies 5977B MSD. Chiral GC was performed with a HP 5890 SERIES II GAS CHROMATOGRAPH with Hydrodex ß-TBDAc column.

**Stopped-Flow measurements**: The copper(I) complex solutions were prepared in a glove box by adding the copper salt solution to the ligand solution under stirring and were filled in glass syringes. Saturated solutions of dioxygen were prepared by bubbling dry oxygen through dry acetone in a syringe for 10 minutes. The saturated dioxygen concentration in acetone is $11.4 \times 10^{-3}$ mol/L at 25 °C.[34] The measurements were performed by a commercial HI-TECH SF-61SX2 instrument (TgK Scientific, Bradford-on-Avon, UK) at different temperatures. Detailed descriptions of the stopped-flow measurements and fitting of the kinetic data have been described previously.[24,25,35]

**Ligand synthesis**: The amines **5**–**7** were synthesized using literature procedures.[11] The synthesis of amine **8** is described in the supporting information. The final ligands were obtained by reductive amination reactions:

**(1*R*,3*S*)-*N*$^{1}$-Dimethyl-*N*$^{3}$-bis(2-pyridinylmethyl)-1,2,2-trimethylcyclopentane-1,3-diamine (9)**: Amine **5** (0.76 g; 4.5 mmol) was dissolved in 30 ml DCE. Pyridine-2-carbaldehyde (2.13 ml, 22.4 mmol) and $NaBH(OAc)_3$ (4.75 g, 22.4 mmol) were added. The mixture was stirred under nitrogen over three days. The mixture was made basic with 50 ml NaOH solution (~15 wt.%) and extracted with DCM (3x50 ml). The organic phases were combined and the solvent was removed. The residue was purified by flash column chromatography (DCM:MeOH 9/1 (to remove the impurities), then diethyl ether, 2% $NEt_3$; silica). The product was obtained as a colorless solid (1.37 g; 3.90 mmol; 87%). Crystals suitable for SC-XRD were obtained by dissolving the solid in a minimal amount of DCM followed by diethylether diffusion at −20 °C. $^{1}$H NMR (400 MHz, $CDCl_3$) δ [ppm] 8.54–8.49 (m, 2H), 7.66 (td, $J = 7.6$, 1.8 Hz, 2H), 7.62–7.56 (m, 2H), 7.18–7.10 (m, 2H), 3.96 (d, $J = 14.7$ Hz, 2H), 3.76 (d, $J = 14.7$ Hz, 2H), 3.21 (t, $J = 9.4$ Hz, 1H), 2.17 (s, 6H), 1.89–1.59 (m, 3H), 1.57–1.48 (m, 1H), 0.95 (s, 3H), 0.83 (s, 3H), 0.78 (s, 3H). $^{13}$C NMR (101 MHz, $CDCl_3$) δ [ppm] 160.7, 149.1, 136.4, 123.3, 122.0, 68.3, 66.2, 59.6, 48.6, 40.2, 37.0, 23.7, 18.5, 18.4, 11.3. HRMS (ESI): calcd. for $C_{22}H_{32}N_4$ [M + H$^+$] 353.2700, found 353.2703. $C_{22}H_{32}N_4$: calcd. C 74.96, H 9.15, N 15.89; found C 74.75, H 9.37, N 15.55.

**(1*R*,3*S*)-*N*$^{1}$-Ethyl-*N*$^{1}$-methyl-*N*$^{3}$-bis(2-pyridinylmethyl)-1,2,2-trimethylcyclopentane-1,3-diamine (10)**: Amine **6** (0.71 g; 3.9 mmol) was dissolved in 30 ml DCE. Pyridine-2-carbaldehyde (1.80 ml, 18.9 mmol) and $NaBH(OAc)_3$ (4.10 g, 19.3 mmol) were added. The mixture was stirred under nitrogen over three days. The mixture was made basic with 50 ml NaOH solution (~15 wt.%) and extracted with DCM (3×50 ml). The organic phases were combined and the solvent was removed. The residue was purified by flash column chromatography (DCM:MeOH 9/1 (to remove the impurities), then diethyl ether, 2% $NEt_3$; silica). The product was obtained as a light yellowish oil (1.36 g; 3.70 mmol; 95%) which crystallized after some time. The crystals were suitable for SC-XRD. $^{1}$H NMR (400 MHz, $CDCl_3$) δ [ppm] 8.54–8.47 (m, 2H), 7.66 (td, $J = 7.6$, 1.8 Hz, 2H), 7.62–7.55 (m, 2H), 7.17–7.09 (m, 2H), 3.96 (d, $J = 14.7$ Hz, 2H), 3.75 (d, $J = 14.7$ Hz, 2H), 3.14 (t, $J = 9.4$ Hz, 1H), 2.50–2.37 (m, 1H), 2.22–2.10 (m, 1H), 2.08 (s, 3H), 1.85–1.56 (m, 3H), 1.55–1.45 (m, 1H), 0.95 (t, $J = 7.1$ Hz, 3H), 0.89 (s, 3H), 0.84 (s, 3H), 0.77 (s, 3H). $^{13}$C NMR (101 MHz, $CDCl_3$) δ [ppm] 160.8, 149.0, 136.3, 123.3, 121.9, 68.2, 66.8, 59.6, 48.7, 45.9, 36.9, 35.6, 24.2, 18.8, 18.3, 14.3, 12.9. HRMS (ESI): calcd. for $C_{23}H_{34}N_4$ [M + H$^+$] 367.2856, found 367.2861. $C_{23}H_{34}N_4$: calcd. C 75.37, H 9.35, N 15.29; found C 75.29, H 9.41, N 15.52.

**(1*R*,3*S*)-*N*$^{1}$-Diethyl-*N*$^{3}$-bis(2-pyridinylmethyl)-1,2,2-trimethyl-cyclopentane-1,3-diamine (11)**: Amine **7** (1.30 g; 6.55 mmol) was dissolved in 40 ml DCE. Pyridine-2-carbaldehyde (3.10 ml, 32.6 mmol) and $NaBH(OAc)_3$ (6.96 g, 32.8 mmol) were added. The mixture was stirred under nitrogen over three days. The mixture was made basic with 50 ml NaOH solution (~15 wt.%) and extracted with DCM (3×50 ml). The organic phases were combined and the solvent was removed. The residue was purified by flash column chromatography (DCM:MeOH 9/1 (to remove the impurities), then diethyl ether, 2% $NEt_3$; silica). The product was obtained as a yellowish oil (1.37 g; 3.60 mmol; 55%). $^{1}$H NMR (400 MHz,

$CDCl_3$) δ [ppm] 8.55–8.48 (m, 2H), 7.66 (td, $J$ = 7.6, 1.8 Hz, 2H), 7.60 (dt, $J$ = 7.9, 1.2 Hz, 2H), 7.18–7.10 (m, 2H), 3.96 (d, $J$ = 14.7 Hz, 2H), 3.76 (d, $J$ = 14.7 Hz, 2H), 3.09 (t, $J$ = 9.5 Hz, 1H), 2.55–2.34 (m, 4H), 1.93–1.80 (m, 1H), 1.79–1.55 (m, 2H), 1.50–1.41 (m, 1H), 0.96 (t, $J$ = 7.1 Hz, 6H), 0.89 (s, 3H), 0.86–0.81 (m, 6H). $^{13}$C NMR (101 MHz, $CDCl_3$) δ [ppm] 160.9, 149.1, 136.3, 123.3, 121.9, 68.2, 67.7, 59.6, 49.1, 45.0, 36.0, 24.3, 19.2, 18.6, 17.0, 16.5. HRMS (ESI): calcd. for $C_{24}H_{36}N_4$ [M + $H^+$] 381.3013, found 381.3014. $C_{24}H_{36}N_4$: calcd. C 75.74, H 9.53, N 14.72; found C 75.41, H 9.25, N 14.38.

**(1*R*,3*S*)-*N*$^1$-Isopropyl-*N*$^1$-methyl-*N*$^3$-bis(2-pyridinylmethyl)-1,2,2-trimethylcyclopentane-1,3-diamine (12)**: Amine **8** (0.44 g; 2.22 mmol) was dissolved in 30 ml DCE. Pyridine-2-carbaldehyde (0.85 ml, 8.9 mmol) and $NaBH(OAc)_3$ (1.89 g, 8.89 mmol) were added. The mixture was stirred under nitrogen over three days. The mixture was made basic with 70 ml NaOH solution (~15 wt.%) and extracted with DCM (3x70 ml). The organic phases were combined and the solvent was removed. The residue was purified by flash column chromatography (DCM:MeOH 19/1 (to remove the impurities), then diethyl ether, 1% $NEt_3$; silica). The product was obtained as a yellowish oil (0.22 g; 0.58 mmol; 26%). $^1$H NMR (400 MHz, $CDCl_3$) δ [ppm] 8.54–8.47 (m, 2H), 7.65 (td, $J$ = 7.6, 1.8 Hz, 2H), 7.62–7.56 (m, 2H), 7.17–7.09 (m, 2H), 3.95 (d, $J$ = 14.8 Hz, 2H), 3.75 (d, $J$ = 14.8 Hz, 2H), 3.19–3.06 (m, 2H), 2.05 (s, 3H), 1.88–1.44 (m, 4H), 0.96–0.82 (m, 15H). $^{13}$C NMR (101 MHz, $CDCl_3$) δ [ppm] 160.8, 149.0, 136.3, 123.2, 121.9, 68.2, 67.4, 59.6, 49.3, 47.5, 36.5, 28.5, 24.2, 21.2, 21.0, 19.0, 18.3, 16.3. HRMS (ESI): calcd. for $C_{24}H_{38}N_4$ [M + $H^+$] 381.3013, found 381.3011.

**[Cu(9-H)Cl](ClO$_4$)$_2$**: Ligand **9** (50.0 mg; 0.142 mmol) was dissolved in approx. 2 ml MeOH. The solution was added to a mixture of $CuCl_2$ (9.5 mg, 0.071 mmol) and $Cu(ClO_4)_2$x6$H_2O$ (26.3 mg; 0.0710 mmol). A blue solid was formed which was filtered off. Slow evaporation of the solvent led to the formation of some crystals, which were structurally characterized.

**[Cu(11-H)Cl](ClO$_4$)$_2$**: Ligand **11** (55.9 mg; 0.147 mmol) was dissolved in approx. 2 ml MeOH. The solution was added to a mixture of $CuCl_2$ (9.9 mg, 0.074 mmol) and $Cu(ClO_4)_2$x6$H_2O$ (27.2 mg; 0.0734 mmol). A blue solid was formed which was filtered off. Slow evaporation of the solvent led to the formation of some crystals, which were structurally characterized.

**[Cu(10)Cl$_2$]**: Diethyl ether diffusion to a solution of ligand **10** (32.4 mg; 0.0884 mmol) and $CuCl_2$ (11.8 mg; 0.0878 mmol) in approx. 1 ml MeOH led to the formation of green crystals (suitable for SC-XRD). The crystals were filtered off, washed with diethyl ether (3x ~ 5 ml) and dried in vacuum. The complex was obtained as green powder (20.6 mg; 0.0411 mmol; 47%). $C_{23}H_{34}N_4CuCl_2$: calcd. C 55.14, H 6.84, N 11.18; found C 55.13, H 6.84, N 11.09.

**[Cu(11)Cl$_2$]**: Diethyl ether diffusion to a solution of ligand **11** (34.8 mg; 0.0914 mmol) and $CuCl_2$ (12.0 mg; 0.0893 mmol) in approx. 1 ml MeOH led to the formation of green crystals (suitable for SC-XRD). The crystals were filtered off, washed with diethyl ether (3x ~ 5 ml) and dried in vacuum. The complex was obtained as green powder (11.9 mg; 0.0231 mmol; 26%). $C_{24}H_{36}N_4CuCl_2$: calcd. C 55.97, H 7.05, N 10.88; found C 55.99, H 6.96, N 10.65.

**[Cu(9)OH](PF$_6$)**: In a glove box $[Cu(CH_3CN)_4](PF_6)$ (23.8 mg; 0.0639 mmol) in approx. 0.5 ml acetone was added to Ligand **9** (22.1 mg; 0.0627 mmol) in approx. 0.5 ml acetone. Dry dioxygen was bubbled through the solution at −80 °C for two minutes. After warming to rt, diethyl ether diffusion led to the formation of a small amount of blue colored crystals, which were suitable for SC-XRD.

**General Procedure for the Oxidation Experiments**: $[Cu(CH_3CN)_4]$OTf (0.05 mmol) dissolved in approx. 1 ml acetone was added to the ligand (0.05 mmol) in approx. 1 ml acetone under stirring. The substrate (0.05 mmol) dissolved in approx. 0.1 ml acetone was added. Dry dioxygen was bubbled through the solution for 10 min at −80 °C. After 24 h the solution was warmed to rt and diluted with aqueous ammonia (~20 ml) and was extracted with DCM (~20 ml). The organic phase was concentrated in vacuum and analyzed using GC-MS and chiral GC (in the case of thioanisole oxidation).

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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.

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