

## RESEARCH ARTICLE OPEN ACCESS

# Bridging Stability and Reactivity: Novel Dinucleating Ligand With Rigid Backbone Stabilizes a Cu<sub>2</sub>O<sub>2</sub> Side-On Peroxido Structure

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## ABSTRACT

Following the goal to move chemical reactions toward more sustainable approaches, this work focuses on selective oxidative conversions of organic substrates. Inspired by the enzyme tyrosinase, a copper model complex was designed and synthesized. The ligand design was derived from previous research within this group, resulting in a dinucleating tridentate bis(pyrazolyl)methane ligand with an aromatic group as the bridging unit. Oxygenation of the corresponding Cu(I) precursor complex leads to the formation of a Cu<sub>2</sub>O<sub>2</sub> species at room temperature. In addition to its catalytic activity towards selected phenolic substrates, this species exhibits remarkable stability towards temperature and water. Characterization via UV/Vis spectroscopy and mass spectrometry indicates the formation of a side-on  $\mu$ - $\eta^2$ : $\eta^2$ -peroxido species. The exceptional stability of this Cu<sub>2</sub>O<sub>2</sub> complex might pave the way for new and versatile applications of tyrosinase model complexes.

## 1 | Introduction

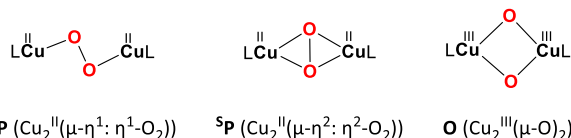
Moving processes and reactions toward enhanced sustainability displays one of the most significant recent goals in chemistry. According to the principles of green chemistry, increasing selectivity and yield while minimizing waste and operating under safe, nontoxic conditions leads to more efficient and sustainable chemical reactions [1, 2]. Since the oxidative conversion of organic substrates often requires the application of heavy metal-containing catalysts or the use of oxidants in stoichiometric amounts, finding a greener alternative presents a significant challenge, which is addressed in this work [3–5]. Therefore, the type III copper protein tyrosinase, which enables the usage of molecular oxygen for oxygenation and oxidation reactions within the synthesis of the pigment melanin, serves as the source of inspiration [6, 7]. Tyrosinase enables the hydroxylation of L-tyrosine to L-DOPA and the subsequent oxidation to L-DOPA quinone and thus exhibits monophenolase and diphenolase activity [7].

The enzyme's dinuclear site consists of two antiferromagnetically coupled copper ions that are each coordinated by three histidine residues [8]. The enzyme activates dioxygen by binding O<sub>2</sub> between its two copper centers in a side-on geometry (Cu<sub>2</sub><sup>II</sup>( $\mu$ - $\eta^2$ : $\eta^2$ -O<sub>2</sub>)) [9, 10]. Enzymes are highly optimized for efficiency and selectivity under mild conditions, a result of many decades of evolutionary optimization, making them an interesting source of inspiration for artificial catalysts [11]. Artificial complexes that are structurally inspired by a biological role model are referred to as model complexes. In the case of tyrosinase model complexes, the intricate protein matrix is replaced by structurally simplified mono- or dinucleating ligands [12, 13]. Tyrosinase model systems allow a better understanding of the mechanistic details of the enzyme's catalytic activity. Ligands for tyrosinase model complexes usually contain N-donors and are bi-, tri-, or tetradentate [13–20]. Depending on factors, such as the ligand's structure, solvent, temperature, and counterion, different binding modes of dioxygen can be observed for tyrosinase model systems

Dedicated to Prof. Dr. Siegfried Schindler on the occasion of his retirement.

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**SCHEME 1** | Different binding modes of dioxygen between the copper centers of tyrosinase models with different ligands [22, 25].

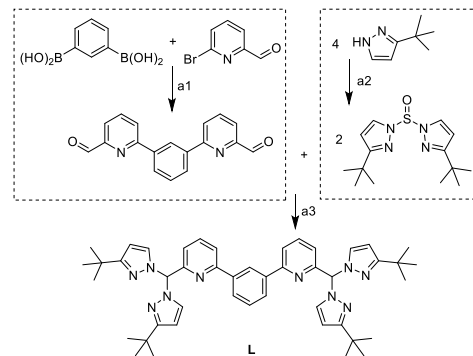
(Scheme 1) [18, 21, 22]. An end-on bound peroxide can be found in a trans-peroxido structure **TP** ( $\text{Cu}_2^{\text{II}}(\mu\text{-}\eta^1\text{:}\eta^1\text{-O}_2)$ ), which was observed for the first time by Karlin and coworkers in 1988 [19]. A side-on peroxido structure **SP** ( $\text{Cu}_2^{\text{II}}(\mu\text{-}\eta^2\text{:}\eta^2\text{-O}_2)$ ), as observed for the enzyme tyrosinase, was first observed by Kitajima et al. in 1989 [23], whereas the first (bis- $\mu$ -oxido) copper complex **O** ( $\text{Cu}_2^{\text{III}}(\mu\text{-O})_2$ ) was reported by Tolman and coworkers in 1996 [24].

Meanwhile, numerous copper complexes [12, 13, 15, 26–39] have been studied as tyrosinase models. The first tyrosinase model system exhibiting tyrosinase-like catalytic activity toward external substrates was reported by Bulkowski et al. for a copper complex with a tetraamine ligand, which transforms 18 equivalents of a phenolic substrate to the corresponding *o*-quinone, using triethylamine as an auxiliary base [40]. Réglier et al. reported catalytic activity of a dinuclear copper complex toward the substrate 2,4-di-*tert*-butylphenol with a turnover number (TON) of 16. The reaction conditions of adding 100 eq. substrate and 200 eq.  $\text{NEt}_3$  are referred to as Bulkowski–Réglier conditions [40, 41]. Since a **SP** structure was observed for tyrosinase, the investigation of model complexes stabilizing this peroxido species is of high interest. **SP** complexes are often stabilized by mono- or dinucleating ligands with aromatic or aliphatic amine donors [11, 22, 32]. In 1999, Koda and coworkers reported a molecular structure for a **SP** complex with a Cu–Cu distance of 3.6 Å and an O–O bond length of 1.4 Å [14]. **SP** complexes can be identified according to their characteristic transitions in the UV/Vis spectrum at  $\lambda = 340\text{--}380\text{ nm}$  ( $\epsilon \approx 18\,000\text{--}25\,000\text{ M}^{-1}\text{cm}^{-1}$ ) and at  $\lambda = 510\text{--}550\text{ nm}$  ( $\epsilon \approx 1000\text{ M}^{-1}\text{cm}^{-1}$ ) [22]. Previous research within this group showed that different bis(pyrazolyl)methane ligands stabilize catalytically active **SP** species [13, 27]. It was observed that a dinucleating ethylene-bridged bis(pyrazolyl)pyridinylmethane ligand significantly enhances the stability of the **SP** species, facilitating more detailed characterization [27]. Since the structure and the length of the bridging unit might have a significant impact on the peroxido's stability and activity, analogous to the studied **TP** species [39, 42], the goal herein is the design and synthesis of a similar ligand with a different bridge length to foster reactivity and stability of the resulting **SP** species, adding to the library of dinucleating ligands with aromatic linkers [15, 39]. Therefore, the ethylene bridge was replaced by a *meta*-phenylene bridge, varying both the bridging length and the rigidity.

## 2 | Results and Discussion

### 2.1 | Ligand Synthesis

Synthesis of the ligand **L** 1,3-bis(6-(bis(3-(*tert*-butyl)-1H-pyrazol-1-yl)methyl)pyridin-2-yl)benzene was performed based on



**SCHEME 2** | Synthetic approach for the dinucleating bis(pyrazolyl)pyridinylmethane ligand **L** (a1: Palladium tetra(triphenyl)phosphine,  $\text{Cs}_2\text{CO}_3$ , DMF, water [45]; a2: NaH,  $\text{SOCl}_2$ , THF,  $0^\circ\text{C}$  [44, 46]; a3:  $\text{CoCl}_2$ , THF,  $70^\circ\text{C}$  [44, 46]).

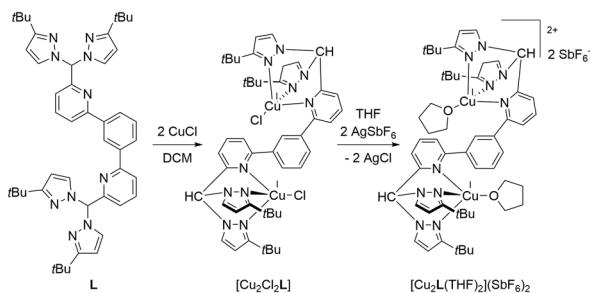
concepts for the synthesis of mono- and dinucleating bis(pyrazolyl)methane ligands within this group. Accordingly, a dialdehyde was synthesized, which was in the following converted to the target bis(pyrazolyl)methane ligand via a modified Peterson rearrangement (Scheme 2) [27, 43, 44].

The synthesis of 6,6'-(1,3-phenylene)dipicolinaldehyde was performed following a Pd-catalyzed Suzuki cross coupling reaction starting from 2-bromo-6-carbaldehydepyridine and *meta*-di(boronic acid)benzene [45, 47, 48]. The obtained dialdehyde was subsequently added to 1,1'-sulfinylbis(3-(*tert*-butyl)-1H-pyrazole) which was prepared by reaction of *tert*-butyl pyrazole with sodium hydride and thionyl chloride. The  $\text{CoCl}_2$ -catalyzed modified Peterson rearrangement leads to the formation of the target product [27, 43, 44]. Since several sensitive purification steps are required to isolate the ligand, the yields of the aldehyde ( $Y = 37\%$ ) and the target product ( $Y = 34\%$ ) are comparably low. It was also possible to obtain the molecular structure in the solid state of the ligand by single crystal X-ray diffraction (XRD) analysis (see Figures S1 and S13 and Table S5, full crystallographic data for **L** have been deposited with the Cambridge Crystallographic Data Centre, no. CCDC – 2466258).

### 2.2 | Complex Synthesis

After successful ligand synthesis and isolation, Cu(I) complexes were synthesized to investigate the ability of the dinucleating ligand to stabilize a  $\text{Cu}_2\text{O}_2$  species. Therefore, a Cu(I) precursor was synthesized according to an established method for mono- and dinucleating bis(pyrazolyl)methane ligands (Scheme 3) [13, 26, 27, 49].

First, copper(I)chloride was added to the ligand solution and stirred in order to form the Cu(I)Cl complex  $[\text{Cu}_2\text{Cl}_2\text{L}]$ . The coordinating chloride anion was then exchanged by the weakly coordinating hexafluoro antimonate anion, by adding  $\text{AgSbF}_6$  to the complex solution and allowing the silver chloride to completely precipitate. The molecular structure of  $[\text{Cu}_2\text{L}(\text{THF})_2](\text{SbF}_6)_2$  in the solid state was characterized via single crystal X-ray diffraction analysis, and the obtained molecular structure is depicted in Figure 1 (see also Figure S13 and Table S5). Each copper ion is coordinated in a distorted tetrahedron by three *N*-donors of the ligand and one



**SCHEME 3** | Synthesis of Cu(I) precursor  $[\text{Cu}_2\text{L}(\text{THF})_2](\text{SbF}_6)_2$  according to the established method by Herres-Pawlis and coworkers via synthesis of the  $\text{CuCl}$  complex  $[\text{Cu}_2\text{Cl}_2\text{L}]$  and subsequent anion exchange reaction by addition of  $\text{AgSbF}_6$  [13, 27, 49].

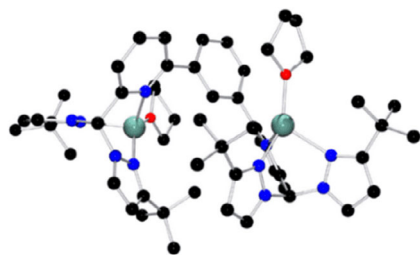


**FIGURE 1** | Molecular structure of  $[\text{Cu}_2\text{L}(\text{THF})_2]^{2+}$  in crystals of  $[\text{Cu}_2\text{L}(\text{THF})_2](\text{SbF}_6)_2$  (hydrogen atoms omitted for clarity) in the solid state. Full crystallographic data have been deposited with the Cambridge Crystallographic Data Centre (no. CCDC – 2466259).

O-donor of the molecule THF. Characteristic bond lengths and angles are summarized in Table 1 and are in the range of similar literature-reported systems [27, 51–54].

However, the enhanced rigidity of the system caused by the introduction of the *meta*-phenylene bridge is reflected in the molecular structure [27]. Accordingly, one  $\text{Cu}-\text{N}_{\text{Pz}}$  bond length is longer than the other one due to steric restrictions of the bridging unit.

**TABLE 1** | Important bond lengths and angles of  $[\text{Cu}_2\text{L}(\text{THF})_2](\text{SbF}_6)_2$ .

| Bond length, Å                                            | $[\text{Cu}_2\text{L}(\text{THF})_2](\text{SbF}_6)_2$ |
|-----------------------------------------------------------|-------------------------------------------------------|
| $\text{Cu}-\text{N}_{\text{Pz},1}$                        | 2.014(2), 2.017(2)                                    |
| $\text{Cu}-\text{N}_{\text{Pz},2}$                        | 2.202(2), 2.231(2)                                    |
| $\text{Cu}-\text{N}_{\text{Py}}$                          | 2.180(2), 2.195(2)                                    |
| $\text{Cu}-\text{O}(\text{THF})$                          | 2.0035(19), 2.0014(19)                                |
| Bond angle, °                                             |                                                       |
| $\text{N}_{\text{Pz},1}-\text{Cu}-\text{O}$               | 140.91(9), 145.15(8)                                  |
| $\text{N}_{\text{Pz},2}-\text{Cu}-\text{O}$               | 114.90(8), 118.56(8)                                  |
| $\text{N}_{\text{Py}}-\text{Cu}-\text{O}$                 | 118.85(8), 110.18(8)                                  |
| $\text{N}_{\text{Pz},1}-\text{Cu}-\text{N}_{\text{Pz},2}$ | 88.53(9), 89.18(9)                                    |
| $\text{N}_{\text{Pz},1}-\text{Cu}-\text{N}_{\text{Py}}$   | 88.80(8), 87.63(8)                                    |
| $\text{N}_{\text{Pz},2}-\text{Cu}-\text{N}_{\text{Py}}$   | 92.74(8), 92.25(8)                                    |
| $\tau_4^a$                                                | 0.74 and 0.68                                         |

$$^a \tau_4 = \frac{360^\circ - (\alpha + \beta)}{141} [50].$$

## 2.3 | Dioxygen Activation

The ability of the Cu(I) precursor complex to bind dioxygen was tested under various reaction conditions. Therefore, a solution of the complex was injected into dioxygen-saturated solvent, and the process was monitored via UV/Vis spectroscopy. As depicted on the right side in Figure 2, injection of the solution into dioxygen-saturated DCM at room temperature leads to the formation of a transition at  $\lambda = 355$  nm within 12 min. Addition of the precursor solution into dioxygen-saturated THF leads to a significantly slower formation of a similar transition. Therefore, changes in the spectra can still be observed after 5 h. Furthermore, the formation of a small shoulder at  $\lambda \approx 400$  nm can be observed (Figure 2). The small shoulder is not an indication of the presence of the bis( $\mu$ -oxido) species but is a charge transfer transition from the  $\pi^*$  of the pyrazolyl moiety to the Cu's d orbital [28, 30]. The formation of the characteristic transition at  $\lambda = 355$  nm indicates formation of a side-on  $\mu$ - $\eta^2$ : $\eta^2$ -peroxido species ( $^{\text{S}}\text{P}$ ) upon oxygenation of the precursor complex [22]. This transition is close to the one observed for the ethylene-bridged structural analog for which the side-on coordination geometry of dioxygen was confirmed by the molecular structure of the solid state obtained via XRD analysis, UV/Vis, and resonance Raman spectroscopy [27] and also other reported side-on  $\mu$ - $\eta^2$ : $\eta^2$ -peroxido species [15, 31]. However, the second and less intense transition (twenty times lower in intensity), which was observed for the ethylene-bridged species at around  $\lambda = 550$  nm [27], is not detectable, due to the incomplete formation and the considerably lower extinction coefficient. A similar observation was made for a  $^{\text{S}}\text{P}$  species with a mononucleating bis(pyrazolyl)methane ligand from our group [54]. Additionally, our DFT calculations show an almost planar  $\text{Cu}_2\text{O}_2$  core (vide infra), weakening the absorption feature further [55, 56]. Additional oxygenation test reactions, including acetonitrile as a solvent, did not show the formation of any transitions, indicating that acetonitrile impedes the coordination of dioxygen by coordinating to the copper itself and thus blocking the copper center for further coordination [49, 57]. Further characterization of the regarded  $\text{Cu}_2\text{O}_2$  species was performed via electron spray ionization mass spectrometry (ESI-MS) at room temperature. As depicted in Figure 3 and in Figure S2, both the dication and the cation with one hexafluoro antimonate anion of the complex were detected in the mass spectra, again proving the high stability of the oxygenated species at room temperature.

Furthermore, the influence of the temperature on the formation of the  $\text{Cu}_2\text{O}_2$  species was investigated. As depicted in Figure S3, the formation of  $^{\text{S}}\text{P}$  occurs significantly more slowly at  $-40^\circ\text{C}$ , and an additional shoulder at  $\lambda \approx 400$  nm was also observed in the UV/Vis absorption spectra. A slow increase in the temperature, as depicted in Figure S3, up to room temperature leads to an increase of the absorption maximum at  $\lambda = 355$  nm. These results indicate slower formation of a  $\text{Cu}_2\text{O}_2$  species at low temperature. Hence, all following oxygenation experiments were performed at room temperature if not stated differently. Therefore, stability of the L-stabilized  $\text{Cu}_2\text{O}_2$  species was investigated at room temperature over several hours as depicted in the inset in Figure 2. UV/Vis spectra recorded during this time do not show a significant decrease in the transition at  $\lambda = 355$  nm indicating high stability of the  $\text{Cu}_2\text{O}_2$  species over the course of the reaction time. In an analog experiment, the solvent was not

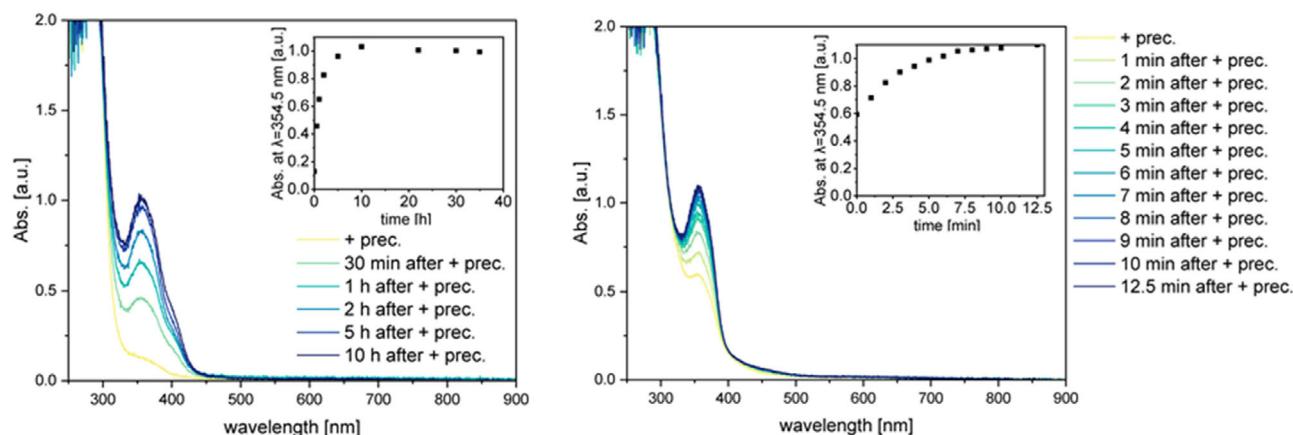


**FIGURE 2** | UV/Vis spectra monitoring the activation of dioxygen by the precursor (1 mM, regarding  $[\text{Cu}_2\text{L}(\text{THF})_2](\text{SbF}_6)_2$ , path length 1 mm) at room temperature (left, into THF (baseline correction), right: into DCM).

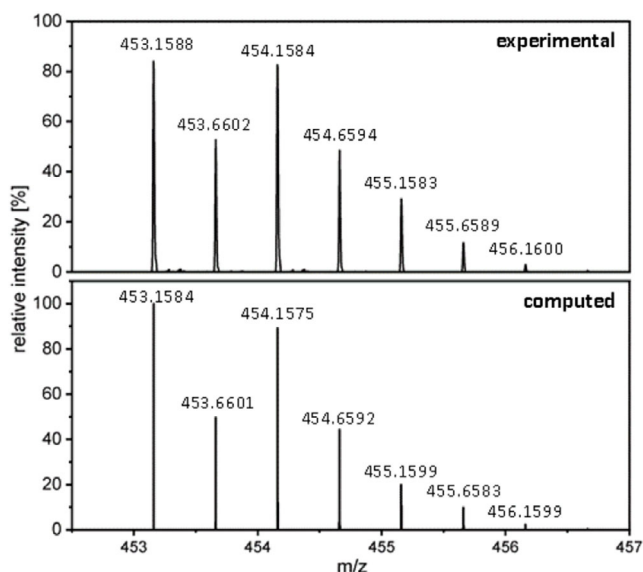


**FIGURE 3** | ESI-MS data of **L**-supported  $\text{Cu}_2\text{O}_2$  species  $[\text{Cu}_2\text{O}_2\text{L}]^{2+}$  (DCM, room temperature), experimental  $^{\text{S}}\text{P}$  (top) and calculated isotopic distribution (via envipat [51]).

purified beforehand. As depicted in Figure S4 on the right, formation of the  $\text{Cu}_2\text{O}_2$  species can be observed to be similar to the formation in anhydrous solvent. Furthermore, the absorption maximum only starts slowly to decrease after 4 h. These observations indicate an unusual stability of  $^{\text{S}}\text{P}$  towards water, which is an outstanding property of side-on peroxido complexes, enabling new potential applications for this system. Normally, this type of peroxido species is extremely sensitive to protons and water [12–14, 23, 26, 27, 32, 34, 43, 49, 52, 54, 58]. The addition of larger amounts of water to the oxygenated species (2 mL water into 6 mL of a 0.5 mM solution of **L**-supported  $\text{Cu}_2\text{O}_2$  species in DCM) leads to a decrease of the absorption maximum at  $\lambda = 355$  nm within 5 min, accompanied by a shift of the maximum to  $\lambda = 386$  nm as depicted in Figure S5. The baseline shift indicates the precipitation of a solid.  $^{\text{S}}\text{P}$  is resistant to the release of dioxygen under reduced pressure and  $\text{N}_2$  purging, emphasizing its robustness. Additionally, the stability of the  $\text{Cu}_2\text{O}_2$  species toward triethylamine was investigated to assess its suitability as an auxiliary base for catalytic substrate conversions. As shown in

Figure S5, the transition at  $\lambda = 355$  nm slowly decays after the addition of triethylamine, indicating the suitability of this base for further experiments. Two new transitions at  $\lambda = 386$  nm and at  $\lambda = 341$  nm form within 1 h after the addition of the base.

To obtain more information on the formation of the  $\text{Cu}_2\text{O}_2$  species, different titration experiments were performed. A titration with the ligand  $\text{Me}_6\text{tren}$  was performed to determine the quantity of formation of the **L**-supported  $\text{Cu}_2\text{O}_2$  species [22]. Upon addition of the  $\text{Me}_6\text{tren}$  solution, the absorption maximum at  $\lambda = 355$  nm decreases, accompanied by the formation of a new shoulder at  $\lambda \approx 330$  nm (Figure S6). As no further decrease of the absorption maximum could be observed after addition of 0.7 eq. of  $\text{Me}_6\text{tren}$ , incomplete formation of the oxygenated species is indicated, which can be further underlined by comparison to literature-reported extinction coefficients  $\epsilon$  for side-on peroxido species [13, 22, 27]. The overlap of the absorption maximum and the shoulder impedes calculation of completeness of the formation of the  $\text{Cu}_2\text{O}_2$  species and thus computation of a corrected  $\epsilon$ . However, titration with  $\text{Me}_6\text{tren}$  shows that 70% of the injected precursor formed the **L**-stabilized  $^{\text{S}}\text{P}$ , and applying Lambert–Beer law [59, 60] gives  $\epsilon = 15\,600 \text{ L mol}^{-1} \text{ cm}^{-1}$  for the absorption maxima at  $\lambda = 355$  nm. This estimated  $\epsilon$  is similar to the extinction coefficient for the previously reported ethylene-bridged analog [27].

## 2.4 | Density Functional Theory (DFT) Calculations

In order to obtain more information about the molecular structure of the **L**-stabilized  $^{\text{S}}\text{P}$  species and its electronic properties, DFT calculations were performed. Therefore, the triple- $\zeta$  basis set def2TZVP [61] and the TPSSH [62] functional with empirical dispersion correction were chosen in accordance to literature [13, 37, 63–65]. The bis( $\mu$ -oxido) and side-on  $\mu$ - $\eta^2$ : $\eta^2$ -peroxido cationic species were taken as starting points. Two  $\mu$ - $\eta^2$ : $\eta^2$ -peroxido **L**-stabilized  $\text{Cu}_2\text{O}_2^{2+}$  species were obtained: In one conformer, all six *N*-donors coordinate to the two copper ions ( $^{\text{S}}\text{P}_{\text{N}6}$ , Figure 4), and in the other conformer, one pyrazolyl unit is rotated out of the coordination plane and points into free space ( $^{\text{S}}\text{P}_{\text{N}5}$ , see Figure S7).

Since in the bis( $\mu$ -oxido) species the  $\text{Cu}_2\text{O}_2$  rhombus is more compressed compared with the  $\mu$ - $\eta^2$ : $\eta^2$ -peroxido species and a

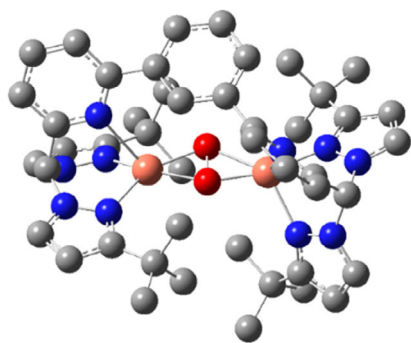


**FIGURE 4** | Calculated structure of  $^{\text{S}}\text{P}_{\text{N}6}$  (broken symmetry, TPSSh/def2TZVP/GD3BJ; H-atoms omitted for clarity). Atoms are labeled following the color scheme: gray – carbon, blue – nitrogen, red – oxygen, orange – copper.

**TABLE 2** | Important bond lengths and angles of  $^{\text{S}}\text{P}_{\text{N}6}$ .

| Cu...Cu vector and bond lengths, Å |                          |
|------------------------------------|--------------------------|
| Cu–Cu                              | 3.650                    |
| O–O                                | 1.436                    |
| Cu–O                               | 1.934/1.966//1.889/2.094 |
| Cu–N <sub>Pz</sub>                 | 2.030/2.040//1.976/2.091 |
| Cu–N <sub>Py</sub>                 | 2.421//2.212             |

bridging ligand is used here, only the species where five N-donors coordinate to the two copper ions and one pyrazolyl unit points into the free space was obtained. The  $^{\text{S}}\text{P}_{\text{N}6}$  is stabilized by 6.4 kcal/mol compared with the  $^{\text{S}}\text{P}_{\text{N}5}$  (Tables S3 and S4). The broken-symmetry approach for the  $^{\text{S}}\text{P}_{\text{N}6}$  results in further stabilization of 2.1 kcal/mol. The hypothetical bis( $\mu$ -oxido) species is less energetically stabilized by 19.3 kcal/mol than the broken-symmetry approach of the  $^{\text{S}}\text{P}_{\text{N}6}$ . The obtained optimized structure of the bis( $\mu$ -oxido) species possesses, due to the bridging ligand, not the typical values for the Cu...Cu distance and the O...O distance: The Cu...Cu distance is elongated to 3.036 Å (reported bis( $\mu$ -oxido) species: 2.8 Å) and the O...O distance to 2.015 Å (reported bis( $\mu$ -oxido) species: 1.8 Å) [15, 31]. Selected bond lengths of the  $^{\text{S}}\text{P}_{\text{N}6}$  are summarized in Table 2.

The Cu...Cu distance of 3.650 Å as well as the peroxide length of 1.436 Å are within the range of typical reported values for side-on  $\mu$ - $\eta^2$ : $\eta^2$ -peroxido species [22, 25, 27, 66, 67]. The slightly distorted geometry of the  $\text{Cu}_2\text{O}_2$  motif is caused by the restricting bridging unit. Another effect of this rigidity is the elongated bond length of one  $\text{N}_{\text{Py}}$ -donor to one of the copper centers. Starting from the optimized structure of the  $^{\text{S}}\text{P}_{\text{N}6}$ , the corresponding UV/Vis spectrum was calculated and compared with the experimental spectrum as depicted in Figure 5. Both spectra look similar, and the absorption maximum, which is within the same range for computed and experimental spectra, shows a slight red shift of the computed spectrum ( $\lambda = 380$  nm).

## 2.5 | Catalytic Properties

The catalytic properties of the L-stabilized  $^{\text{S}}\text{P}$  were investigated for *o*-hydroxylation activity and subsequent oxidation of different

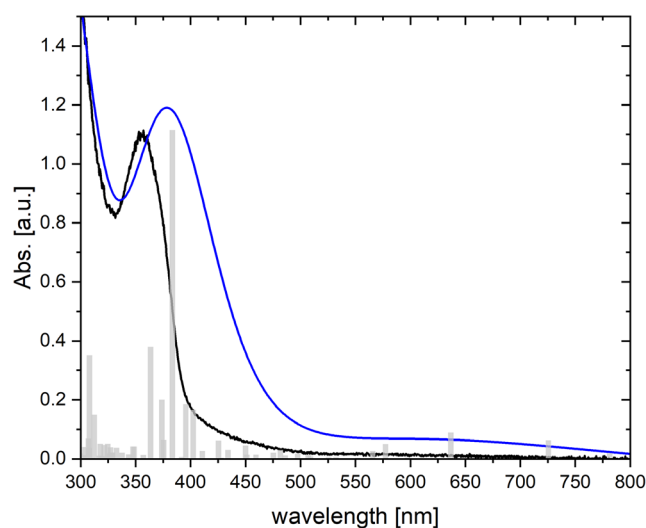
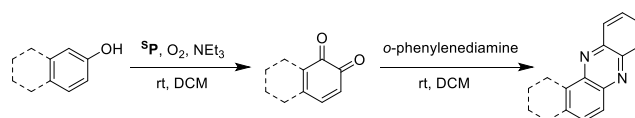


**FIGURE 5** | Experimental UV/Vis spectrum of  $^{\text{S}}\text{P}$  in DCM (black, 1 mM regarding  $[\text{Cu}_2\text{L}(\text{THF})_2](\text{SbF}_6)_2$ , path length 1 mm) and the calculated TD-DFT spectra of  $^{\text{S}}\text{P}_{\text{N}6}$  (broken- symmetry, TPSSh/def2TZVP/GD3BJ; blue) and the desired transitions (broken-symmetry, TPSSh/def2TZVP/GD3BJ; gray).

phenolic substrates following the standard protocol by Bulkowski and Réglér in DCM at room temperature using triethylamine as auxiliary base [40, 41]. Afterward, *o*-phenylenediamine (PDA) was added to form the more stable phenazine, enabling product characterization (see Scheme 4) [28].

To analyze a broad spectrum of substrates, catalysis experiments were performed with 1-naphthol, 2-naphthol, 2-hydroxycarbazole, *N*-acetyl-L-tyrosine-ethyl ester monohydrate (NATEE), 4-methoxycatechol, 4-methoxyphenol, 4-hydroxyindole, phenol, 2,4-di-*tert*-butyl phenol (2,4-DTBP), and 2-hydroxypyridine. During the conversion of 2-naphthol, fast formation of a transition at  $\lambda = 402$  nm was observed immediately after the addition of the substrate solution to a solution of the  $\text{Cu}_2\text{O}_2$  species (Figure 6). Using the complete reaction scheme, a catalytic conversion of 2-naphthol to the corresponding *o*-quinone was determined [68]. With 70% formation of the  $\text{Cu}_2\text{O}_2$  species and computing concentrations of the formed 1,2-naphthoquinone with the literature-reported extinction coefficient [69, 70], turnover number (TON) and turnover frequency (TOF) can be calculated for different reaction times (Figure 6, right). Stagnation at the beginning can be attributed to mixing effects following substrate addition. Afterward, the TON increases up to 24 after 30 min. A decrease in the product formation can be explained by different effects like catalyst deactivation or a decreasing substrate concentration. For the conversion of 4-methoxycatechol, the formation of a transition at  $\lambda \approx 417$  nm was observed in



**SCHEME 4** | Catalyzed by  $^{\text{S}}\text{P}$ , phenolic substrates are hydroxylated and subsequently oxidized to generate the corresponding *o*-quinone. The following double condensation reactions of the *o*-quinone with *o*-phenylenediamine form the phenazine product.

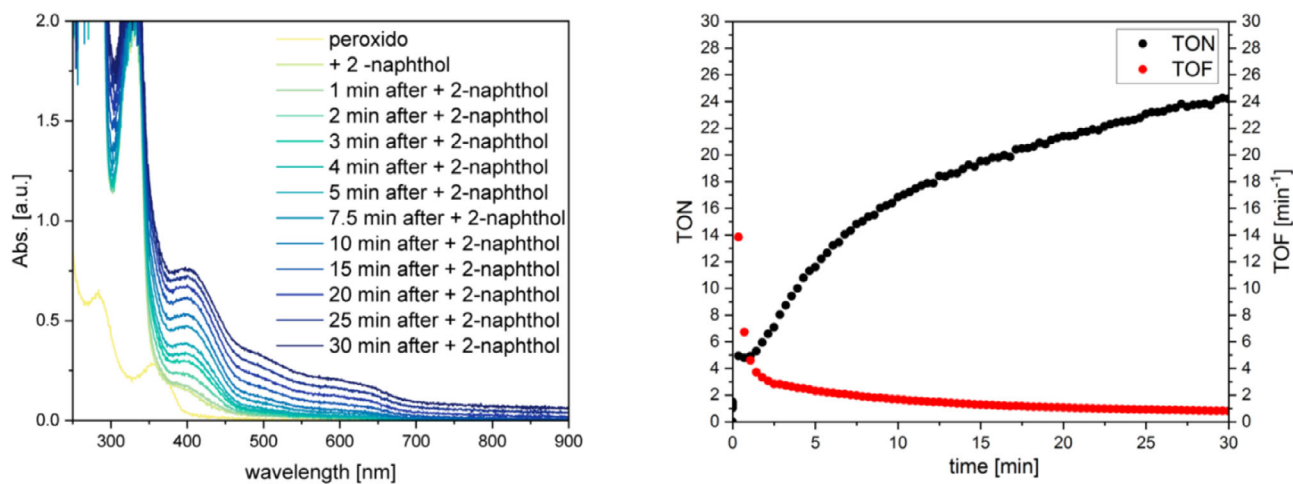


**FIGURE 6** | UV/Vis spectra monitoring the addition of 2-naphthol (50 eq.) and triethylamine (100 eq.) to L-supported  $\text{S}^{\text{P}}$  (0.25 mM, regarding  $[\text{Cu}_2\text{L}(\text{THF})_2](\text{SbF}_6)_2$ , path length 1 mm) in dioxygen-saturated DCM at room temperature (left, UV/Vis spectra; right, TON and TOF plotted versus time for conversion to 1,2-naphthoquinone [40]).

the UV/Vis spectra that was assigned to the corresponding quinone [54, 71]. A slight shift of this transition, which is accompanied by the formation of another absorption maximum at  $\lambda = 710$  nm, indicates further reaction of the quinone, which explains why the product cannot be isolated or characterized after the reaction (Figure S9). Furthermore, UV/Vis spectra indicate catalytic activity towards 2,4-DTBP as the formed transition at  $\lambda \approx 402$  nm can be assigned to the corresponding *o*-quinone (Figure S10). Again, the TON and TOF can be determined with the literature-reported extinction coefficient [72, 73]. Here, 30 min after substrate addition, the TON amounts to 12 and remains constant at 14 after 90 min (see Figure S10). The formation of a broad absorption band at  $\lambda = 584$  nm can likely be attributed to the aerobic oxidation of the substrate [38, 74]. Schneider et al. reported TONs of 8 after 5 h for  $[\text{Cu}(\text{MeCN})_4](\text{PF}_6)$  [75]. Conversions of 4-hydroxyindole, phenol, 2-hydroxycarbazole, and NATEE result in the formation of transitions or shoulders in the UV/Vis spectra, indicating the occurrence of a reaction. They could not be definitively assigned to a specific product (Figures S8–S11). However, the low stability of the corresponding quinones at the reaction conditions might hinder product detection for some substrates, as they decompose immediately after formation or undergo follow-up reactions [38, 66].

To confirm the conversion of 2-naphthol to benzo[*a*]phenazine, a catalytic experiment was performed on a larger scale, enabling product isolation and characterization. Therefore, the catalysis reaction was performed at room temperature with 0.1 mmol of the  $\text{Cu}_2\text{O}_2$  species and a substrate solution consisting of 25 eq. 2-naphthol and 50 eq. triethylamine was added. After a specific reaction time (2 h and 5 h), the condensation agent PDA (25 eq.) is added. After work-up, the reaction mixture was further purified via column chromatography to isolate, quantify, and characterize components of the mixture. For the different reaction times, the product benzo[*a*]phenazine was obtained in different yields and characterized via NMR spectroscopy [76, 77]. For reference,  $[\text{Cu}(\text{MeCN})_4](\text{PF}_6)$  itself generates benzo[*a*]phenazine with  $\text{TON} < 1$  [28]. For a reaction time of 2 h, the product was isolated with a yield of 18.5% and a TON of 7. Increasing the

reaction time to 5 h and the equivalents of 2-naphthol to 50 eq., leads to an isolated yield of 20% and a TON of 14.

### 3 | Conclusion

The herein discussed new dinucleating ligand shows that varying the bridging length from an ethylene to a *meta*-phenylene unit enhances the ligand's suitability as tyrosinase model system. UV/Vis spectroscopy as well as mass spectrometry indicate activation of dioxygen at room temperature by formation of a side-on  $\mu\text{-}\eta^2\text{:}\eta^2$ -peroxido species. Geometry optimization calculations also result in slightly distorted side-on  $\mu\text{-}\eta^2\text{:}\eta^2$ -peroxido coordination geometry of the  $\text{Cu}_2\text{O}_2$  rhomb. Next to remarkable stability at room temperature, the  $\text{Cu}_2\text{O}_2$  species shows an exceptional stability towards water which enables new applications for this system and thus makes it very interesting for further research. Additionally, catalytic activity was observed for selected substrates with TONs up to 24 after 30 min for 2-naphthol for example. The UV/Vis spectroscopic results were confirmed through product isolation.

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### Conflicts of Interest

The authors declare no conflicts of interest.

## Data Availability Statement

All synthetic details are described in the SI. Additional information on the synthesis of the target compounds and original analysis data files are available in the Chemotion repository (for corresponding links, see the SI). The optimized calculated structures were deposited in the repository RADAR4Chem by FIZ Karlsruhe – Leibniz-Institut für Informationsinfrastruktur and are published under an Open Access model (CC BY-NC-SA 4.0 Attribution-NonCommercial-ShareAlike) under this link: <https://www.radar-service.eu/radar/en/dataset/35t5h4hmfjx1ugbu>.

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## Supporting Information

Additional supporting information can be found online in the Supporting Information section. Experimental details, further UV/vis spectra of the dioxygen activation, titration experiment, catalytic experiments, mass spectrometric data, additional DFT data, and single crystal X-ray diffraction data are presented in the Supporting Information. Additional references are used within the Supporting Information [78–95].