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Guanidines strike back: Exceptional Substrate Diversity in Oxygenation Reactions Catalyzed by a Bis(*μ*-oxo) Copper Complex

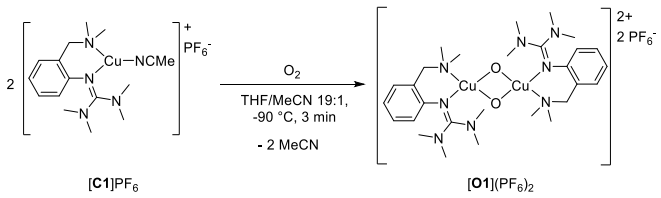
Melanie Paul[a], Melissa Teubner[a,b], Benjamin Grimm-Lebsanft[b], Christiane Golchert[a], Yannick Meiners[a], Laura Senft[c], Kristina Keisers[a], Patricia Liebhäuser[a], Thomas Rösener[a], Florian Biebl[b], Sören Buchenau[b], Maria Naumova[d], Vadim Murzin[d], Roxanne Krug[e], Alexander Hoffmann[a], Jörg Pietruszka[e,f], Ivana Ivanović-Burmazović[c], Michael Rübhausen[b], Sonja Herres-Pawlis*[a]

Abstract: *The enzyme tyrosinase contains a reactive side-on peroxo dicopper(II) center as catalytically active species in C-H oxygenation reactions. The tyrosinase activity of the isomeric bis(μ-oxo) dicopper(III) form has been discussed controversially. We describe the synthesis of bis(μ-oxo) dicopper(III) species [Cu$_2$(μ-O)$_2$(**L1**)$_2$](X)$_2$ ([**O1**](X)$_2$, X = PF_6^-, BF_4^-, OTf^-, ClO_4^-), stabilized by the novel hybrid guanidine ligand 2-{2-((dimethylamino)methyl)phenyl}-1,1,3,3-tetramethylguanidine (**L1**), and its characterization via UV/Vis, Raman and XAS spectroscopy as well as cryo-UHR-ESI mass spectrometry. We highlight selective oxygenation of a plethora of phenolic substrates mediated by [**O1**](PF$_6$)$_2$, which results in mono- and bicyclic quinones and provides an attractive strategy for designing new phenazines. We predict the selectivity using the Fukui function which is hereby introduced into tyrosinase model chemistry. Our bioinspired catalysis harnesses molecular dioxygen for organic transformations and achieves a substrate diversity reaching far beyond the scope of the enzyme.*

The use of dioxygen as a readily available oxidizing agent is crucial for many biological and biomimetic oxidation processes as well as industrial applications.[1] Natural copper enzymes such as tyrosinase or particulate methane monooxygenase successfully activate molecular dioxygen.[2] Tyrosinase, in particular, is essential in living organisms catalyzing phenol oxidation in melanin biosynthesis.[3] It converts phenols, for instance L-tyrosine, via an electrophilic aromatic substitution via its catechol form to the final quinone form.[4] Although structure and reactivity of tyrosinases were studied extensively, many details of the oxidation mechanism are still under debate.[5] Recently, second shell residues at the active site (approx. 5.5-16 Å distance to Cu ions) were considered to direct the reactivity of the enzyme.[2b,6]

For understanding the mechanism of activation and transfer of O_2, synthetic model systems were developed mimicking enzymatic properties. Some well-studied Cu/O_2 species represent μ-η^2:η^2-peroxo Cu(II) [**P**] and bis(μ-oxo) Cu(III) [**O**] complexes, which exist in a dynamic equilibrium due to a small isomerization barrier.[2b,7] In many functional tyrosinase systems, **[P]** cores are found,[8] but an increasing number of examples of functional [**O**] species has also been reported.[9] However, only few Tyrosinase model systems feature catalytic oxygenation reactivity.[10] Réglier *et al.* presented the first system using the imine-pyridine ligand BiPh(impy)$_2$,[11] followed by Casella *et al.* using the benzimidazole ligand L66,[12] which both stabilize binuclear Cu catalysts. Later, Tuczek *et al.* reported on the mononucleating benzimidazole ligand L^{impy} promoting catalytic conversion of 2,4-di-*tert*-butyl phenol.[13] Over the years, Lumb *et al.* have focused on the chemo- and regioselectivity of tyrosinase-like reactions using the amine DBED giving rise to several quinones, oxidative coupling and cyclization products.[14] More complex phenolic substrates were oxygenated by Herres-Pawlis *et al.* using bis(pyrazolyl)methane and guanidine ligands.[15]

Herein, we report on the synthesis and characterization of hybrid guanidine-stabilized bis(μ-oxo) complex [Cu$_2$(μ-O)$_2$(**L1**)$_2$]$^{2+}$ ([**O1**]$^{2+}$, Scheme 1) along with its high catalytic activity in oxygenation and oxidation reactions of phenolic substrates and subsequent condensation reactions, offering a facile synthetic pathway to new phenazines.



Scheme 1. Synthesis of bis(μ-oxo) species [**O1**](PF$_6$)$_2$.

Guanidines feature high basicity and strong N-donor abilities, enabling stabilization of metal ions with high oxidation states.[16] For instance, TMG_3tren is known to stabilize highly reactive Cu(II) superoxo complexes.[17] By using [**O1**](PF$_6$)$_2$, it is possible to promote selective C-H functionalization of complex phenolic substrates. To the best of our knowledge, no activity of

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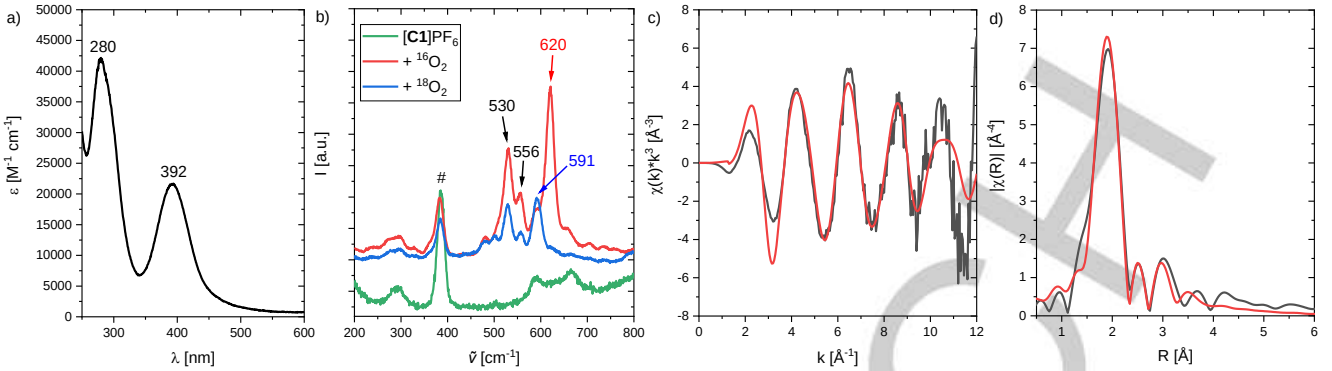

Figure 1. a) UV/Vis spectrum of [**O1**](PF$_6$)$_2$ (0.5 mM) in THF at –90 °C, b) resonance Raman spectra of [**O1**](PF$_6$)$_2$ in THF with excitation at 420 nm (blue: $^{18}O_2$, red: $^{16}O_2$, green: [**C1**]PF$_6$, #: solvent), c) k^3-weighted Cu-K-edge EXAFS of [**O1**](PF$_6$)$_2$, d) phase-corrected Cu-K-edge Fourier transform of EXAFS of [**O1**](PF$_6$)$_2$.

tyrosinases towards complex phenolic substrates was reported before. [**O1**](PF$_6$)$_2$ highlights a beneficial interplay of steric and electronic factors of the ligand regarding substrate accessibility of [Cu$_2$O$_2$] core leading to a remarkable extension of the substrate scope. Using a variety of phenolic substances allows the synthesis of new quinones. In a consecutive reaction, quinones can condense with 1,2-phenylenediamine to phenazines, which feature antibacterial, antimalarial and antitumor activities and are used in dyes and pesticides.[18] We targeted to selectively obtain bent phenazines as special benefit of the [**O1**](PF$_6$)$_2$ mediated hydroxylation, since the calculation of the Fukui function of the hydroxylation products indicated preferential formation of the corresponding quinone.

Inspired by a propylene-bridged hybrid guanidine ligand system that showed promising phenolase activity,[9k-l] we developed a related ligand system with a more rigid aromatic backbone. 2-{2-((dimethylamino)methyl)phenyl}-1,1,3,3-tetramethylguanidine (**L1**) was synthesized in a three-step reaction and isolated in high yield (Supporting Information). Synthesis of the colorless, air- and moisture-sensitive Cu(I) complex [**C1**]PF$_6$ was achieved by mixing equimolar amounts of **L1** and [Cu(MeCN)$_4$]PF$_6$ in acetonitrile at room temperature. Oxygenation of [**C1**]PF$_6$ in THF at -90 °C led to the formation of the khaki-colored species [**O1**](PF$_6$)$_2$ (Scheme 1).[19] [**O1**](PF$_6$)$_2$ showed ligand-to-metal-charge transfer (LMCT) features at 280 nm (ε = 40000 M^{-1} cm^{-1}) and 392 nm (21000 M^{-1} cm^{-1}) in the UV/Vis spectrum[20] (Figure 1a), which are characteristic for bis(μ-oxo) dicopper(III) species.[8, 21] Similar UV/Vis features were obtained using different weakly coordinating anions (BF$_4^-$, ClO$_4^-$, OTf$^-$) (Figure S17; Table S3). Incorporated O$_2$ of [**O1**](PF$_6$)$_2$ was resistant to cycles of evacuation and purging with N$_2$. Laser excitation at 420 nm led to a resonance Raman spectrum with a characteristic vibration at 620 cm^{-1}, which was attributed to the symmetrical Cu$_2$O$_2$ core expansion (breathing mode), thus evidencing the formation of a bis(μ-oxo) species (Figure 1b). $^{16}O_2$/$^{18}O_2$ isotope exchange measurements in THF exhibited a shift to 591 cm^{-1}, which is in good agreement with theoretical calculations (Table S13). The signal at 530 cm^{-1} is caused by the N(amine)-Cu vibration.

Theoretical studies on [**O1**](PF$_6$)$_2$ were performed to investigate geometry and Raman features (Figure 2). The calculations show that the **O** species is favored by 10 kcal mol^{-1} over the **P** species (Table S11). Key bond lengths around the Cu atoms were determined by Cu-K-edge EXAFS (Figure 1c-d, Supporting Information) and agree well with the theoretical model. Moreover, the edge position is in accordance with the assignment as Cu(III). For quantification of the formation of [**O1**](PF$_6$)$_2$, spectrophotometric back-titration of [**O1**](PF$_6$)$_2$ was performed using ferrocene monocarboxylic acid (FcCOOH).[9k-l] Following the decay of the LMCT band at 392 nm, titration of [**O1**](PF$_6$)$_2$ with FcCOOH revealed >90% formation of [**O1**](PF$_6$)$_2$ (Figures S18-19). To elucidate the Cu-O$_2$ stoichiometry of [**O1**](PF$_6$)$_2$, cryo-UHR-ESI mass spectrometry was performed (Figure S20). The isotopic pattern and corresponding m/z values are in accordance with the calculated spectrum of the monocationic species [**O1**](PF$_6$)$^+$ with a 2:1 Cu-O$_2$ ratio.

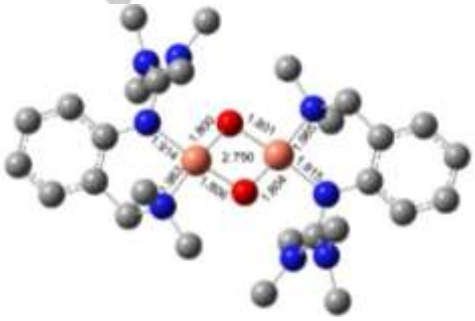

Figure 2. DFT model of [**O1**]$^{2+}$ (TPSSh/def2-TZVP, THF-PCM), selected bond lengths [Å] and Cu···Cu vector [Å].

Thermal decomposition kinetics of [**O1**](PF$_6$)$_2$ revealed a first-order decay at low temperatures (Figures S21-22). Half-life times of [**O1**](PF$_6$)$_2$ in THF of 1 h at –80 °C and 5 min at –74 °C were determined. Thermal decomposition products of [**O1**](PF$_6$)$_2$ were identified by crystallization as a dicationic μ-alkoxo-μ-hydroxo copper(II) complex [**H1**](PF$_6$)$_2$ with a Cu···Cu distance of 2.953(1) Å (Figure 3). Each copper atom is coordinated in a distorted square-planar fashion. The average Cu-O bond length (1.92 Å) is shorter compared to that in the mixed phenolato hydroxo-bridged dicopper(II) species (1.96 Å) reported by Karlin *et al.*[22] Concomitant formation of yellow blocks was observed, which contain the protonated ligand [(**L1**)H$_2$](PF$_6$)$_2$.

Bis(μ-hydroxo) species are commonly observed as decay products[9,18a] and often resulted from intramolecular hydroxylation of C-H bonds in α- or β-position of N-donor groups.[23] Inter-

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estingly, [**H1**]$^{2+}$ is the first example of a trinuclear μ-alkoxo-μ-hydroxo copper(II) complex cation. Only few examples of alkoxo-hydroxo copper(II) species were reported so far.[23] Mechanistic studies on intramolecular hydroxylation of the supporting ligand upon warming of the bis(μ-oxo) species were proposed by Itoh, Tolman *et al.*, stating a mixed alkoxo-hydroxo copper(II) complex as intermediate species to form thermodynamically stable bis(μ-hydroxo) and bis(μ-alkoxo) complexes.[23a,24] In case of [**H1**]$^{2+}$, the chemoselective attack of the equatorially located methyl groups of the guanidine moiety over the axially disposed aminomethyl groups is favored due to geometric constraints, analogously to observations made by Tolman *et al*.[23c,25]

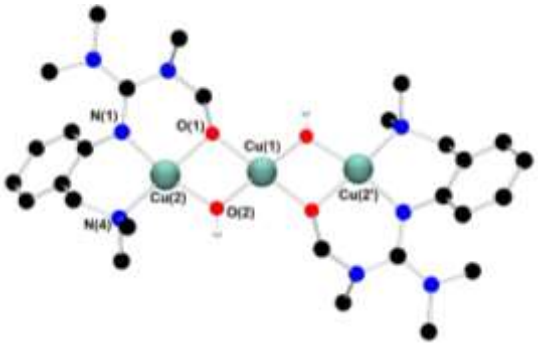
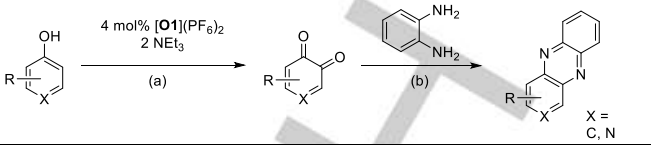


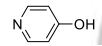
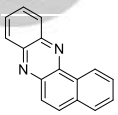
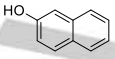
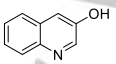
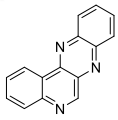
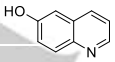
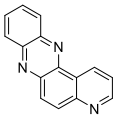
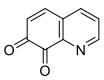
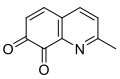
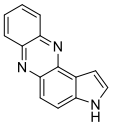
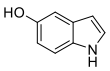
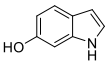
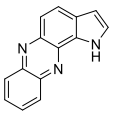
Figure 3. Molecular structure of [**H1**]$^{2+}$ in crystals of [**H1**](PF$_6$)$_2$. H atoms except for the H atom of μ-OH groups, counterions and solvent molecules are omitted for clarity. Selected interatomic distances [Å] and angles [°]: Cu(1)-O(1) 1.912(2), Cu(1)-O(2) 1.893(2), Cu(2)-O(1) 1.923(2), Cu(2)-O(2) 1.932(2), Cu(1)···Cu(2) 2.953(1), Cu(2)-N(1) 1.986(2), Cu(2)-N(4) 2.019(3), N(1)-Cu(2)-N(4) 94.9(1), O(1)-Cu(2)-O(2) 76.8(1), Cu(2)-O(1)-Cu(1) 100.7(1), Cu(2)-Cu(1)-Cu(2') 180.0.

Aiming to expand the commonly used substrate scope of simple phenols, catalytic hydroxylation activity of [**O1**](PF$_6$)$_2$ was evaluated towards a variety of challenging phenolic substrates, including phenols, pyridinols, naphthols, quinolinols and indolols (Table 1, and Supporting Information), whose quinones and phenazines are biologically relevant and difficult to synthesize. We report on the hydroxylation of a multitude of these substrates by [**O1**](PF$_6$)$_2$ along with transformation of the quinone into a phenazine. Remarkably, until now, catalytic conversion of phenols was mostly reported for side-on peroxo copper complexes as catalytically active species.[11-13,15] Oxygenation reactions were performed following a protocol established by Bulkowski and modified by Tuczek *et al.* using 25 eq. of substrate and 50 eq. NEt_3 (Table 1, Reaction (a)).[13a,26] Reaction (a) was monitored by UV/Vis spectroscopy at –90 °C for 1 h as optical spectra remained constant after that time. Reactive quinones were subsequently converted in a one-pot step into their corresponding phenazines at room temperature by using 1,2-phenylenediamine (Table 1, Reaction (b)).

When simple phenols are used, [**O1**](PF$_6$)$_2$ showed, besides the expected hydroxylation activity, also C-O coupling chemistry (Table S8, entries 1-4). UV/Vis spectra showed a low intensity absorption band at 510 and 530 nm (Figures S39-40). EPR measurements revealed the hyperfine splitting pattern typical for a radical-free, metal-centered Cu(II) species (Figure S41), ruling out the formation of a semiquinone species.[27]

Table 1. (a) Catalytic oxygenation of phenolic substrates[a] (b) subsequent condensation of the quinone using 1,2-phenylenediamine.[b]



entry	substrate	conv. [%]	product (quinone/phenazine)		yield[c] [%]	TON[d]
1		>99		(**Q1**)	[e]	[f]
2		>99		(**Q1**)	[e]	[f]
3		80		(**P1**)	22	11
4		89		(**P1**)	31	16
5		95		(**P2**)	32	16
6		87		(**P2**)	21	11
7		>99		(**P3**)	30	15
8		28		(**Q2**)	-	14[g]
9		24		(**Q3**)	-	12[g]
10		81		(**P4**)	19	10
11		88		(**P4**)	26	13
12		92		(**P5**)	27	14
13		84		(**P5**)	31	16

[a] conditions: THF, -90 °C, 1 h. [b] conditions: THF, -90 °C, then rt, overnight. [c] isolated yield after column chromatography. [d] based on isolated yield in correlation with conc. of [**O1**](PF$_6$)$_2$. [e] quinone too reactive to be isolated. [f] no extinction coefficient of the quinone reported. [g] determined after reaction (a) via UV/Vis spectra and based on conc. of [**O1**](PF$_6$)$_2$.

An interesting substrate for the catalytic oxygenation is 8-quinolinol.[15,28] While 7,8-quinolinedione (**Q2**) was formed with 14 turnovers (entry 8), methyl-substitution in 2-position resulted in a TON of 12 (**Q3**, entry 9). However, formation of the respective phenazine was observed in neither case (Figures S50-51), presumably due to the smaller Fukui function f+ at the corresponding C atoms of **Q2** and **Q3** (Table S15). Conversion of other quino-

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linols was not reported before in Cu/O_2 chemistry. 3- and 4-quinolinol were transformed into their quinone (absorption band at 370 nm, Figures S47-48) and isolated as quinolino[3,4-b]quinoxaline (**P2**) (entries 5-6). 6-Quinolinol was oxidized into 5,6-quinolinedione (entry 7), which showed absorption bands at 325, 340 and 370 nm (Figure S49). Pyrido[3,2-a]phenazine (**P3**) was isolated in 15 turnovers after column chromatography and sublimation, and crystallized from DMSO (see Supporting Information).

In contrast to reactions with phenols and 8-quinolinol, no conversion of pyridinols was reported so far. When 3- and 4-pyridinol (entries 1-2) are used, an intense absorption band at 375 nm, similar to that in 3- and 4-quinolinol, was observed in both cases within less than one minute (Figures S42-43), indicating formation of 3,4-pyridoquinone (**Q1**). A fast drop in intensity illustrates high reactivity of the quinone even at low temperatures, leading to C-O coupled dimers (see Supporting Information).[29] Theoretical studies revealed lesser stability of 3,4-pyridoquinone compared to its most stable 2,5-isomer.[30] However, no other study exists that reports on pyridoquinones.

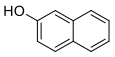
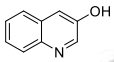
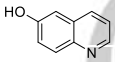
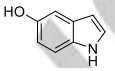
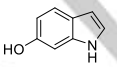
Naphthoquinones are accessible from 1- and 2-naphthol in the presence of an oxidizing agent.[31] Both naphthols were converted via [**O1**](PF$_6$)$_2$ into the corresponding quinone, which resulted in the formation of benzo[a]phenazine[31c] (**P1**) upon treatment with 1,2-phenylenediamine (entries 3-4, Figures S44-45). **P1** was purified via column chromatography and isolated with a TON of 11-16. Consistent with observations made by Krohn *et al.*, no formation of the linear phenazine was observed.[31c] The control experiment using 1-methyl 2-naphthol (Table S8, entry 7) showed no product formation as was expected (Figure S46), since the 1-position is occupied by the methyl substituent inhibiting the oxygenation process.

While related bicyclic indolols possess an easily accessible pyrrole ring, C-H functionalization of the phenyl ring remains challenging.[32] When [**O1**](PF$_6$)$_2$ was used, 4- and 5-indolol were converted into 4,5-indoledione, which was captured as pyrrolo[3,2-a]phenazine (**P4**) in 10-13 turnovers (entries 10-11, Figures S52-53). Similarly, 6- and 7-indolol (Figures S54-55) were transformed into pyrrolo[2,3-a]phenazine (**P5**, TON = 14-16) and crystallized from hexane (entries 12-13). The control experiment revealed no oxygenation activity on 6-indolol in the absence of supporting ligand **L1** (Figure S36), thus evidencing the necessity of the stabilizing ligand system.

The accompanying DFT calculations based on the negative Fukui function are used to determine the location of the electrophilic attack, which are in good accordance with the observed products (for substrates with two product possibilities, Table 1-2, see Supporting Information). The Fukui function describes the electron density in a frontier orbital, in this case $\mathbf{f_k^-}$ denotes the initial part for an electrophilic reaction. A large value for $\mathbf{f_k^-}$ indicates the preferred site for an electrophilic attack – in this case the tyrosinase-like hydroxylation. In all cased studied here, the Fukui function points to the experimentally observed hydroxylation site finally yielding the bent phenazines.

It has to be highlighted that the phenazines **P3**, **P4** and **P5** are new and fully characterized.[33] Thus, the combination of tyrosinase-like hydroxylation reactivity with the condensation of quinones with diamines allows synthetic access to a multitude of new phenazines.

Table 2. Summary of calculated Fukui function (f_k^-) of phenolic substrates with two possible products.

entry	substrate	Fukui function (f_k^-)	C-atom position
1		21.14 0.74	1 3
2		1.38 15.17	2 4
3		23.93 0.91	5 7
4		19.93 1.05	4 6
5		2.03 11.99	5 7

While tyrosinase (from *Aspergillus oryzae*) oxidizes phenol quantitatively,[34] the enzyme exhibited no reactivity towards naphthols, quinolinols and indolols (Table S10). Thus, the bis(μ-oxo) species [**O1**](PF$_6$)$_2$ demonstrates an exceptional broad substrate scope, to which the enzyme itself gave no access.

In summary, we established the synthesis of the aromatic hybrid guanidine-stabilized bis(μ-oxo) species [**O1**]$^{2+}$, which was clearly evidenced by its spectroscopic properties. [**O1**](PF$_6$)$_2$ revealed a moderate stability at low temperatures with a distinguished activity towards a large variety of phenolic substrates. DFT calculations enabled a prognosis of the hydroxylation position via Fukui function, which fully agreed with experimental results. The Fukui function was introduced as new predictive tool for Cu/O_2 chemistry. Moreover, our present findings clearly show efficient C-H activation of mono- and bicyclic phenolic substrates, stating an atom-economic strategy to design new phenazines. A bio-inspired model system such as [**O1**](PF$_6$)$_2$ indicates tyrosinase-like activity of **O** cores and exceeds evidently the enzymatically limited substrate scope. This study opens the door to future developments on tyrosinase model systems with high relevance to atom-economic oxygen transfer reactions with synthetic importance.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: copper catalysis • dioxygen activation • guanidines • phenazines • tyrosinase

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Entry for the Table of Contents

Layout 2:

COMMUNICATION

We describe the synthesis and characterization of bis(*μ*-oxo) dicopper(III) species $[Cu_2(\mu\text{-}O)_2(\mathbf{L1})_2](X)_2$ ([**O1**](X)$_2$, X = PF_6, BF_4, OTf, ClO_4) via UV/Vis, Raman and XAS spectroscopy as well as cryo-UHR-ESI mass spectrometry, stabilized by an aromatic hybrid guanidine ligand. We highlight selective oxidation of a plethora of phenolic substrates mediated by [**O1**]$(PF_6)_2$, that results in mono- and bicyclic quinones far beyond the enzyme's scope and provides an attractive strategy to design new phenazines.

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Guanidines strike back: Exceptional Substrate Diversity in Oxygenation Reactions Catalyzed by a Bis(*μ*-oxo) Copper Complex