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Enzyme Mimics

Bioinspired Copper(I) Complexes that Exhibit Monooxygenase and Catechol Dioxygenase Activity

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Abstract: New tripodal ligand **L2** featuring three different pyridyl/imidazolyl-based N-donor units at a bridgehead C atom, from which one of the imidazolyl units is separated by a phenylene linker, was synthesized and investigated with regards to copper(I) complexation. The resulting complex [(**L2**)Cu]OTf (**2**^{OTf}), the known complex [(**L1**)Cu]OTf (**1**^{OTf}; **L1** differs from **L2** in that it lacks the phenylene spacer) and [(**L3**)Cu]OTf (**3**^{OTf}), prepared from a known chiral, tripodal, N-donor ligand featuring pyridyl, pyrazolyl, and imidazolyl donors, were tested as catalysts for the oxidation of sodium 2,4-di-*tert*-butylphenolate (**NaDTBP**) with O_2. Indeed, they mediated **NaDTBP** oxidation to give mainly the corresponding catecholate and quinone (**Q**). None of the complexes **1**^{OTf}, **2**^{OTf}, and **3**^{OTf} is superior to the others, as yields were comparable and, if the presence of protons is guaranteed by concomitant addition of the phenol **DTBP**, the oxidation can also be performed catalytically. For all complexes stoichiometric oxidations under certain conditions (concentrated solutions, high **NaDTBP** content) were found to also generate products typical for metal-mediated intradiol cleavage of the catecholate with O_2. As shown representatively for **1**^{OTf} this dioxygenation sets in at a later stage of the reaction. Initially a copper species responsible for the monooxygenation must form from **1**^{OTf}/**NaDTBP**/O_2, and only thereafter is the copper species responsible for dioxygenation formed and consumes **Q** as substrate. Hence, under these circumstances complexes **1**^{OTf}–**3**^{OTf} show both monooxygenase and catechol dioxygenase activity.

Introduction

The degradation of phenols is an important part of several metabolic pathways. One of them includes hydroxylation of phenol to catechol, which is further transformed into non-aromatic products by C–C cleavage reactions. The oxygenation of phenols to catechols can be catalyzed by the copper monooxygenase tyrosinase,[1] while dioxygenases are responsible for the C–C cleavage. These mostly contain iron cores in their active subunits,[2] although also one such copper enzyme, namely, flavonol-2,4-dioxygenase, is known.[3,1b]

During the last 25 years tyrosinase has been the subject of intense research, and the results of studies on the natural system in combination with reactivity investigations on synthetic model compounds have provided a consistent, commonly accepted view of the general catalytic mechanism; some details still remain a matter of debate, though.[1]

Because tyrosinase contains a dinuclear copper core in which each metal atom is coordinated by three histidine residues, the ligands designed for the development of model complexes often contain N-heterocyclic donors related to histidine, such as imidazole or pyridine, and it proved possible to synthesize complexes that show monooxygenase, that is, tyrosinase activity, in the sense that they mediate the oxygenation of phenolates to give catechols or, after further oxidation, quinones.[4] The nature of the ligands has much influence on the reactivity toward O_2 of the systems. Whereas for tyrosinase the reaction with O_2 leads to a side-on peroxo intermediate, bio-inspired model complexes, depending on the electronic and steric characteristics as well as on the solvent used, were observed to also yield end-on peroxo and bis(μ-oxo) intermediates.[1,5]

Although model complexes known so far mimic certain aspects of the enzyme reactivity, most suffer from deficiencies such as 1) ligand instead of substrate oxygenation, 2) rather low activities (turnover numbers, TONs) compared to the natural system, and even 3) limitation to a stoichiometric ratio between L_xCu_2 ($x = 1,2$) and phenol derivative. Hence, there is still scope for improvement, and further ligand design is a tool to reach new discoveries. Besides recently published systems prepared in situ from Cu^I salts and simple (di)amines,[6] to the best of our knowledge only five well-defined complexes have been described that show monooxygenase activity similar to that of tyrosinase and promote the respective reactions as catalysts with TONs of more than 1 up to 32.[4a,c,d,7] Here we describe Cu^I complexes that show not only monooxygenase, but at the same time also dioxygenase activity.

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Results and Discussion

Reaction pockets of enzymes are always chiral due to the presence of optically active amino acids and lack of symmetry. This suggests the use of chiral ligands also in model compounds. Recently, we described the Cu^{I} system [(**L1**)Cu]X in which **L1** is a chiral tripodal ligand (see Figure 1) and showed that its reac-

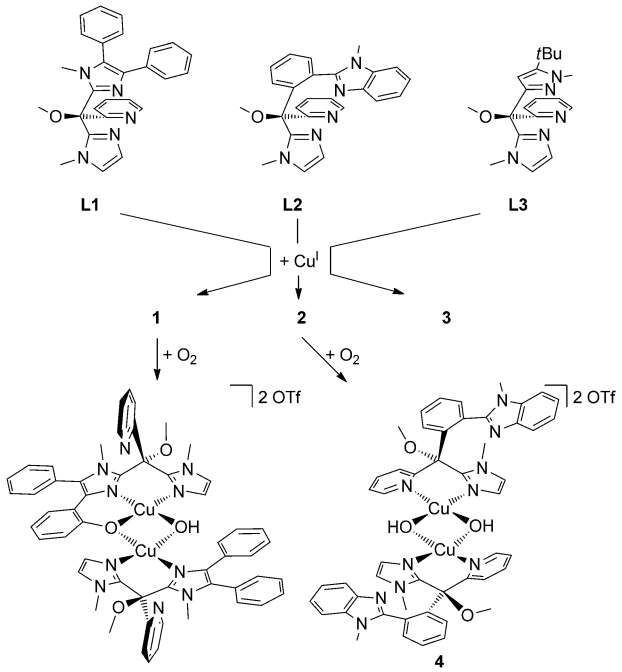


Figure 1. Chiral ligands **L1**, **L2**, and **L3** and the formation of copper(I) and μ-hydroxo copper(II) complexes.

tivity towards dioxygen depends on the anion and solvent. Intramolecular tyrosinase-like activity was observed for [(**L1**)Cu]OTf ($\mathbf{1}^{\mathbf{OTf}}$), which reacts with O_2 by oxygenation of a phenyl residue at the ligand framework (→$\mathbf{L1}^{\mathbf{ox}}$), so that a dinuclear copper(II) complex with bridging phenolate and hydroxide ligands was obtained (see Figure 1).[8]

This work focuses on the reactivity of $\mathbf{1}^{\mathbf{OTf}}$ and $\mathbf{1}^{\mathbf{PF6}}$ towards exogenous substrates. In this context the novel copper complexes [(**L2**)Cu]OTf ($\mathbf{2}^{\mathbf{OTf}}$), [(**L2**)Cu]$PF_6$ ($\mathbf{2}^{\mathbf{PF6}}$), [(**L3**)Cu]OTf ($\mathbf{3}^{\mathbf{OTf}}$) and [(**L3**)Cu]$PF_6$ ($\mathbf{3}^{\mathbf{PF6}}$) containing chiral, tripodal, N-donor ligands were also studied (Figure 1).

Ligand **L2** (for the synthesis route see Supporting Information) differs from **L1** in that it contains a phenylene linker between the C atom of one of the benzimidazole donor units and the bridgehead C atom, and thus the chelating properties of the system are significantly altered. Ligand **L3** can be derived from **L1** by replacing the diphenylimidazolyl donor unit by a *tert*-butylpyrazolyl moiety and has been described previously.[9]

Complexes $\mathbf{1}^{\mathbf{OTf}}$–$\mathbf{3}^{\mathbf{OTf}}$ and $\mathbf{1}^{\mathbf{PF6}}$–$\mathbf{3}^{\mathbf{PF6}}$ were obtained by treating the corresponding ligands **L1**, **L2**, and **L3** in form of their racemic mixtures with $[Cu(MeCN)_4]X$ (X = OTf or PF_6). It has already

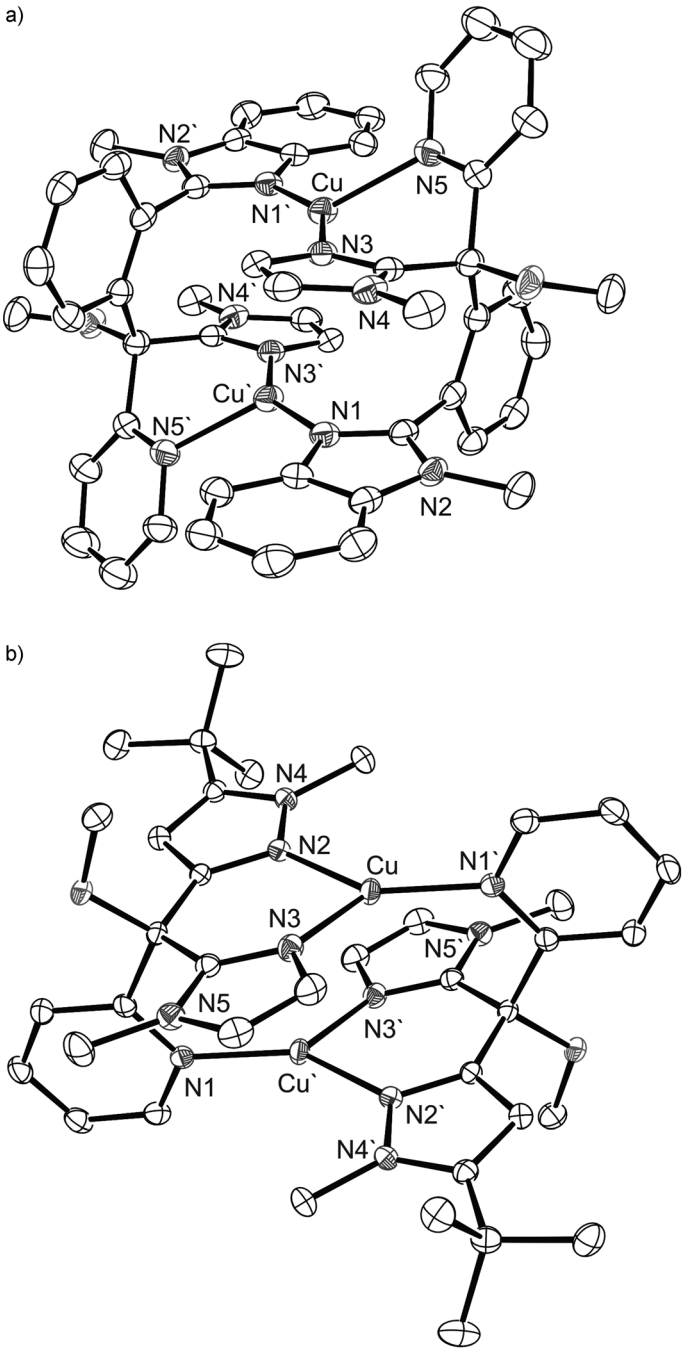


Figure 2. Molecular structures of a) the cation $[(\mathbf{L2})Cu]_2^{2+}$ and b) the cation $[(\mathbf{L3})Cu]_2^{2+}$, as revealed by a single-crystal X-ray diffraction analysis of $\mathbf{2}^{\mathbf{OTf}}$ and $\mathbf{3}^{\mathbf{PF6}}$, respectively. Hydrogen atoms and cocrystallized solvent molecules are omitted for clarity. Selected bond lengths [Å] and angles [°]: a) N3–Cu 1.936(3), N5–Cu 2.160(3), N1′–Cu 1.910(3); N3-Cu-N5 88.93(12), N5-Cu-N1′ 119.52(12), N3-Cu-N1′ 148.41(13) and b) N1′–Cu 1.9308(14), N2–Cu 1.9649(14), N3–Cu 1.9902(15), N5-Cu-N2 93.30(6), N3-Cu-N1 125.36(6), N2-Cu-N1 141.08(6).

been shown that both $\mathbf{1}^{\mathbf{OTf}}$ and $\mathbf{1}^{\mathbf{PF6}}$ have a dinuclear structure in the solid state, and X-ray analyses of $\mathbf{2}^{\mathbf{OTf}}$ and $\mathbf{3}^{\mathbf{PF6}}$ revealed similar structures (Figure 2).

In both complexes the ligands **L2** and **L3** coordinate through two N-donor units to one Cu^{I} center. The third donor unit, in the case of $\mathbf{2}^{\mathbf{OTf}}$ the benzimidazole and in the case of

$\mathbf{3}^{PF6}$ the pyridyl residue, binds to a second LCu^{I} entity, the copper atom of which is in turn coordinated by two N-donor units of a second ligand molecule binding through the third donor unit to the first copper atom. Consequently, both ligands form bridges between the two copper atoms. In an $[LCu]_2^{2+}$ unit one of the ligands has the *R* configuration, and the other the *S* configuration. In $\mathbf{2}^{OTf}$ and $\mathbf{3}^{PF6}$ the copper atoms are coordinated by the corresponding three nitrogen atoms in an almost trigonal-planar fashion. It has been shown previously that dimeric $\mathbf{1}^{OTf}$, as found in the crystal, splits for the most part into monomers on dissolution in acetonitrile,[8] and the same was verified for $\mathbf{2}^{OTf}$ and $\mathbf{3}^{PF6}$ by DOSY NMR spectroscopy at room temperature (see Supporting Information).

Investigations on other copper systems have shown that typically dinuclear copper(II) complexes with bridging peroxo ligands[10,7b,4e] or bis(μ-oxo) dicopper(III) compounds[11] are responsible for the oxygenation of phenolates. However, a mononuclear copper superoxo complex has been reported to show oxygenating ability, too.[12] The intermediately formed Cu/O_2 species could be detected for some systems, but mostly only at temperatures of −78 °C or below. Complexes **1**–**3** do not react with O_2 at such temperatures. For $\mathbf{1}^{OTf}$, a color change of acetonitrile solutions from colorless to green is observed only at −35 °C, while solutions in dichloromethane even require a temperature of −10 °C. Unfortunately, no evidence for the formation of a Cu/O_2 species has been obtained, since no specific absorptions became visible in the UV/Vis spectra after addition of O_2 to 0.1 mM solutions of $\mathbf{1}^{OTf}$, $\mathbf{2}^{OTf}$, or $\mathbf{3}^{PF6}$ in acetonitrile (−30 °C) and propionitrile or acetone (−80 °C). Only on exposure of a 10 mmolar solution of $\mathbf{1}^{OTf}$ in acetonitrile at −35 °C to an O_2 atmosphere did new absorptions evolve intermediately, but the extinction coefficients were untypically low (see Supporting Information). Although, accordingly, the investigations of the reactions of **1**–**3** with O_2 were unsuccessful with respect to the identification of an active Cu/O_2 species, it is likely that such intermediates are formed, considering the isolation of $[(\mathbf{L1})Cu(OH)Cu(\mathbf{L1}^{ox})](OTf)_2$ as described previously[8] (see Figure 1), and in fact a related dicopper(II)bis(μ-hydroxo) complex was also obtained on employing **L2**: after reaction of $\mathbf{2}^{OTf}$ with O_2 in acetonitrile, $[(\mathbf{L2})Cu(OH)_2Cu(\mathbf{L2})](OTf)_2$ (**4**) was isolated in good yield from the reaction mixture (Figure 1; for crystal structure, see Supporting Information). Such copper μ-hydroxo complexes are often formed when reactive dinuclear oxygen intermediates abstract H atoms from the environment, and hence it is reasonable to assume that both $\mathbf{1}^{OTf}$ and $\mathbf{2}^{OTf}$ react with O_2 to give an intermediate, dinuclear, O_2-bound species, which, however, is not detectable in UV/Vis experiments at the comparatively high temperatures to which the investigations are constrained.

Monooxygenation

Two principle routes have been established in the past to test copper complexes for potential tyrosinase-like activity: 1) Generating the active Cu/O_2 species (often a $Cu^{II}(\mu\text{-}O_2)Cu^{II}$ species) at low temperature by reaction of a Cu^{I} complex with O_2 and subsequently treating it with phenolate. 2) Alternatively, the Cu^{I} complex is first treated with phenolate before it is exposed to O_2. Since the Cu/O_2 species that likely form during the reactions of **1**–**3** with O_2 eluded detection, we followed route 2 to test for monooxygenase activity and added sodium 2,4-di-*tert*-butylphenolate (**NaDTBP**) prior to exposure to O_2 (the sodium salt of 2,4-di-*tert*-butylphenol (**DTBP**) was used in all reactions because this has already proved to be of value in testing for oxygenation reactions in the past).[1] Conversions with $\mathbf{1}^{OTf}$, $\mathbf{2}^{OTf}$, and $\mathbf{3}^{OTf}$ were examined with 0.5 and 1 equivalent of **NaDTBP** in 7.5 mmolar solutions of $\mathbf{1}^{OTf}$–$\mathbf{3}^{OTf}$ in acetonitrile. The reactions led mainly to the formation of 3,5-di-*tert*-butyl-1,2-benzoquinone (**Q**), 3,5-di-*tert*-butylcatechol (**C**), and 3,3′,5,5′-tetra-*tert*-butylbiphenyl-2,2′-diol (**BP**; see Figure 3, in which the percentages refer to the averaged yields of three independent experiments, and Scheme 1). These are the products typically observed when **NaDTBP** is used as the

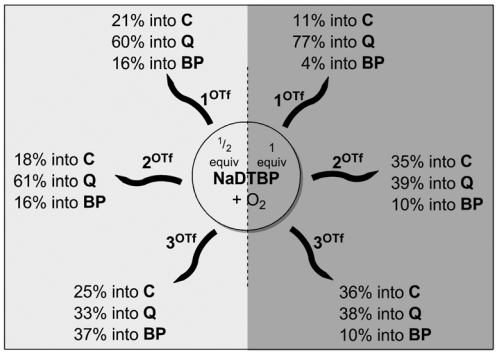
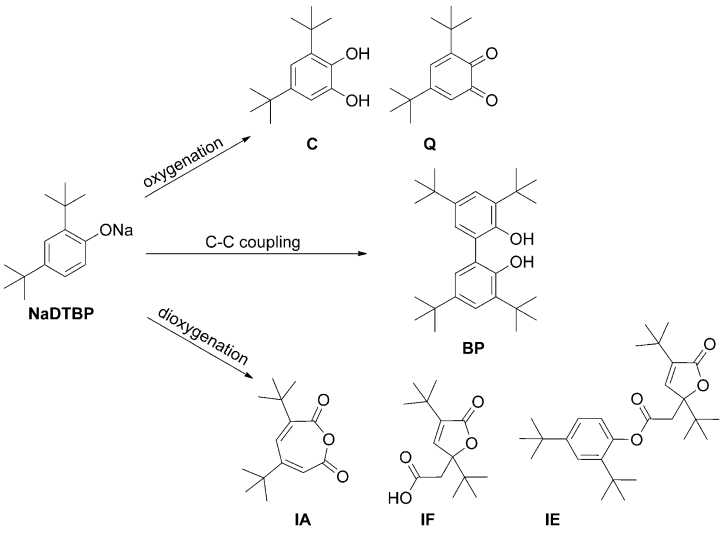


Figure 3. Yields of the main products resulting from systems composed of $\mathbf{1}^{OTf}$ – $\mathbf{3}^{OTf}$, 0.5 or 1 equivalent of **NaDTBP** and O_2 in 7.5 mmolar acetonitrile solutions after 40 min (yields are given in percent and refer to converted **NaDTBP**).



Scheme 1. Oxidation products detected after conversion of **NaDTBP** and O_2 with $\mathbf{1}^{OTf}$–$\mathbf{3}^{OTf}$ after workup.

substrate to investigate the activity of tyrosinase model systems.[1,4c,d] Compound **C** is the desired product associated with tyrosinase activity, while **Q** is generated by further oxidation of **C**, a reaction catalyzed by tyrosinase as well (more specifically by catechol oxidase). **BP** is an undesired product in this context, as it is usually formed by outer-sphere oxidation and radicals that do not occur in the mechanism of tyrosinase. An independent experiment showed that **BP** can be produced via a further route: **NaDTBP** and **Q** partly react under an O_2 atmosphere to give **BP** and **C** (within 10 min reaction time, up to 10% of the employed substrate can be transformed into **BP** and **C** at room temperature under the conditions considered here). Hence, this must be borne in mind as a possible side reaction once **Q** has been formed in relevant amounts.

In case of the reactions with 0.5 equivalents of **NaDTBP**, complex $\mathbf{1}^{OTf}$ shows the best oxygenation yield of 81% (**C**+**Q**), followed by $\mathbf{2}^{OTf}$ (79% **C**+**Q**). In comparison, treating $\mathbf{1}^{OTf}$–$\mathbf{3}^{OTf}$ with one equivalent of **NaDTBP** and O_2 led to slightly higher yields ("yield" refers to converted phenolate) of the monooxygenation products **C** and **Q** (for $\mathbf{1}^{OTf}$ 88%, for $\mathbf{2}^{OTf}$ and $\mathbf{3}^{OTf}$ 74%) and lower yields of coupling product **BP** were observed, that is, on coordination of one phenolate substrate ligand per copper center, *ortho*-hydroxylation is favored and side reactions are suppressed. The amounts of **BP** (4–10%) formed in these conversions can be explained by the above-mentioned reaction of **NaDTBP** and **Q** with O_2.

Additionally, the results of the reactions of $\mathbf{1}^{OTf}$–$\mathbf{3}^{OTf}$ with one equivalent of **NaDTBP** and O_2 allow for an interesting inference: Assuming a dinuclear active CuO_2Cu species, this should be capable of oxygenating only 0.5 equivalents of **NaDTBP**. The fact that, on addition of one equivalent of **NaDTBP**, more than 50% was oxidized thus means that either 1) an intermediately formed $Cu(O)_2Cu$ unit shows catalytic activity or 2) monooxygenation is due to a different reactive species, for example, a $Cu(O_2)$ moiety. The results outlined below indicate that option 1 is correct.

As described in previous literature concerning tyrosinase model compounds, significant catalytic activity requires the presence of protons to enable the formation of water. Consequently, catalytically active tyrosinase models have been treated with phenol and NEt_3 to form phenolate and $HNEt_3^+$, as the latter is then able to act as a H^+ source. In this context recent results of investigations concerning the potential of NEt_3 and other amines as ligands in such conversions are of interest. It was found that di-*tert*-butylethylenediamine/$[Cu(MeCN)_4]PF_6$ mediated the aerobic oxidation of monosubstituted phenols to give phenoxy-substituted *o*-quinones in very good yields[6a] and that 2,4-substituted phenols can be oxidized selectively to the corresponding *o*-quinones by $[Cu(MeCN)_4]PF_6$ in the presence of an excess of NEt_3 if molecular sieves are added to effectively remove all water generated.[6b] To address the need for protons in our system, we proceeded differently and developed an experimental procedure that does not require the use of NEt_3 and allows for the conversion of **NaDTBP** to **Q** by complexes $\mathbf{1}^{OTf}$–$\mathbf{3}^{OTf}$ with notable turnovers. The corresponding copper complex, **NaDTBP** (ideally 2 equiv), and an excess of **DTBP** (70 equiv) as proton and successive phenolate deliverer were treated with O_2. This led in 20 h to **Q** with 22 turnovers by $\mathbf{1}^{OTf}$, 19 turnovers by $\mathbf{2}^{OTf}$, and 21 turnovers by $\mathbf{3}^{OTf}$ (calculated for a potential dinuclear active species). However, **BP** was also formed in almost equal amounts, as also found for the above-mentioned $[Cu(MeCN)_4]PF_6/NEt_3$ system, if the water formed was not removed by molecular sieves.[6b]

For further confirmation of the catalytic activity of $\mathbf{1}^{OTf}$, $\mathbf{2}^{OTf}$, and $\mathbf{3}^{OTf}$ also results obtained setting out from the Cu^{II} complex of, examplarily, **L1** were rather revealing. After treating an equimolar mixture of **L1**, $Cu(OTf)_2$, and **NaDTBP** with O_2 for 40 min, 34% of the employed phenolate was converted to **BP** and 66% to **Q**. Assuming that the oxygenation reaction starts from Cu^I, which can in this case only be generated by the reaction of the Cu^{II} complex with **NaDTBP** leading to **BP** and Cu^I, the results of this experiment indicate a catalytic reaction: A maximum of 34% of the Cu^{II} ions employed can have been reduced to Cu^I, and if these form a dinuclear active Cu/O_2 species, a stoichiometric reaction with **NaDTBP** would be expected to provide a maximum of 17% oxygenation product (a mononuclear Cu/O_2 intermediate would result in formation of **Q** with a maximum yield of 34%). The fact that 66% of **Q** was isolated means that, during the conversion of **NaDTBP** to **Q**, the reducing equivalents of catecholate formed initially are utilized to generate further (**L1**)Cu^I species that allow for further turnover (→catalysis), independent of the nature of the active Cu/O_2 species.

Attempts to identify the active species formed in contact with O_2 with the aid of UV/Vis spectroscopic investigations, as mentioned above, were repeated in the presence of **NaDTBP**. However, after treatment of $\mathbf{1}^{OTf}$, $\mathbf{2}^{OTf}$, or $\mathbf{3}^{PF6}$ at very low concentrations with **NaDTBP,** in course of the O_2 addition only the evolution of absorption bands at 410 nm, indicating the formation of **Q**, and a simultaneous decrease of absorptions in the range of 200–280 nm in case of $\mathbf{1}^{OTf}$ and at about 310 nm in case of $\mathbf{3}^{PF6}$, resulting from the conversion of phenolate, were observed (see Supporting Information). In none of the three UV/Vis experiments could an active intermediate be detected.

However, since there are indications that the O_2 reactions of the copper complexes $\mathbf{1}^{OTf}$ and $\mathbf{2}^{OTf}$ lead to dinuclear intermediates (formation of dinuclear copper(II) end products featuring μ-hydroxide bridges) and investigations on the enzyme and on the majority of functional model complexes evidenced the intermediate formation of dinuclear species, too, even when mononuclear precursors were employed, the same is proposed for the monooxygenation reactions of $\mathbf{1}^{OTf}$–$\mathbf{3}^{OTf}$ with **NaDTBP** and O_2.

Dioxygenation

The detailed analysis of minor oxidation products formed during the above-mentioned reactions of $\mathbf{1}^{OTf}$–$\mathbf{3}^{OTf}$ with 0.5 and 1 equivalent of **NaDTBP** and O_2 surprisingly led to the detection of three compounds that are typical products of the metal-mediated intradiol cleavage of catechol **C** with O_2, namely, 3,5-di-*tert*-butyl-1-oxacyclohepta-3,5-diene-2,7-dione (**IA**), 3,5-di-*tert*-butyl-5-(carboxymethyl)-2-furanone (**IF**), and a product of the esterification of the furanone **IF** with **DTBP**,

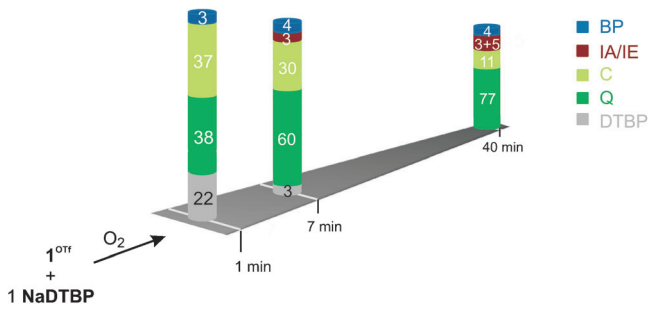
namely, **IE** (Scheme 1).[2] **IA** is a *tert*-butyl derivative of the anhydride of muconic acid, the characteristic product generated by iron-based intradiol-cleaving catechol dioxygenases, and **IF** is a corresponding cyclization product of this acid.

Whereas the employment of 0.5 equivalents of **NaDTBP** reduces the yield of byproducts originating from intradiol cleavage to a maximum of 5% (**IF** in the case of $\mathbf{2}^{OTf}$ and **IA** in the case of $\mathbf{3}^{OTf}$, Table 1), the change to one equivalent of **NaDTBP** resulted in an increase in dioxygenated product (15% **IE** in the case of $\mathbf{2}^{OTf}$, 16% **IE**+**IA** in the case of $\mathbf{3}^{OTf}$). Furthermore, raising the overall concentration of the solution for the reaction of $\mathbf{1}^{OTf}$/**NaDTBP** with O_2 from 7.5 to 30 mmolar increases the yield of **IE** from 3 to 12%.

Table 1. Yields of products formed in the reactions between $\mathbf{1}^{OTf}$–$\mathbf{3}^{OTf}$, O_2, and 0.5 equivalents/one equivalent of **NaDTBP** in acetonitrile solutions after 40 min (yields are given in percent and refer to converted **NaDTBP**).

Complex	*c* [mM]	C	Q	BP	IE	IA	IF
			+0.5 **NaDTBP**				
$\mathbf{1}^{OTf}$	7.5	21	60	16	–	3	–
$\mathbf{2}^{OTf}$	7.5	18	61	16	–	–	5
$\mathbf{3}^{OTf}$	7.5	25	33	37	–	5	–
			+1 **NaDTBP**				
$\mathbf{1}^{OTf}$	7.5	11	77	4	3	5	–
$\mathbf{2}^{OTf}$	7.5	35	39	10	15	–	1
$\mathbf{3}^{OTf}$	7.5	36	38	10	6	10	–
			change of concentration				
$\mathbf{1}^{OTf}$	30	10	66	6	12	6	–

It is known that Cu^{II} catecholate compounds can disproportionate in contact with protons (after workup) into semiquinone (SQ) complexes.[13] In this context it is conspicuous that, after 1 min reaction time, the ratio of **C** and **Q** is approximately 1:1 (just like in the corresponding reactions with $\mathbf{2}^{OTf}$ and $\mathbf{3}^{OTf}$ after 40 min), which suggests the formation of a SQ that disproportionates in course of workup. Indeed an EPR spectrum recorded for a frozen solution of $\mathbf{1}^{OTf}$/1 **NaDTBP** and O_2 after 1 min reaction time hinted at the presence of a Cu^{I}–SQ complex in equilibrium with a Cu^{II} compound, possibly, a Cu^{II} catecholate complex (see Supporting Information).



Scheme 2. Time dependence of the reaction of $\mathbf{1}^{OTf}$ with one equivalent of **NaDTBP** and O_2 in a 7.5 mmolar acetonitrile solution. Product yields were determined after workup, are given in percent, and refer to converted **NaDTBP**.

Time-dependent analysis of the reaction of $\mathbf{1}^{OTf}$ and one equivalent of **NaDTBP** with O_2 in 7.5 mmolar acetonitrile solutions showed that firstly the monooxygenation products **C** and **Q** are generated (Scheme 2). After this, due to the catechol oxidase activity of the copper complex, **C** is oxidized to **Q**, and simultaneously the dioxygenation products **IA** and **IE** are formed.

Former studies on the reactivity of $\mathbf{1}^{OTf}$ towards O_2 had shown that in the absence of a substrate the ligand **L1** experiences intramolecular oxygenation at the phenyl residue (see above, Figure 1). However, the same complex cation $[(\mathbf{L1})Cu]^+$ with PF_6^- as counteranion reacted only to a small extent through oxygenation.[8] To reveal a possible anion dependence also of the reactivity with external substrates, the anion-exchanged analogues of $\mathbf{1}^{OTf}$–$\mathbf{3}^{OTf}$, $\mathbf{1}^{PF6}$–$\mathbf{3}^{PF6}$, were tested with respect to their potential to convert an equimolar amount of **NaDTBP** and O_2. Indeed, anion dependence could be observed (see Supporting Information). This finding, which fits to the results of a recent comparison of $[Cu(MeCN)_4]PF_6$ and CuCl as precatalysts,[6b] suggests that the anions, which will be located close to the complex cations to compensate their charge, open or block certain reaction channels, depending on their size and orientation. For instance, it is known that steric interactions between substrate and ligand residues can influence the product distribution very sensitively, as they disfavor inner-sphere O-atom transfer and instead promote formation of free radicals. At the same time, the results provide further support that the oxygenation reactions indeed occur in the coordination spheres of the metal atoms. Any discussion beyond that would be highly speculative.

The increased dioxygenation yields in the reactions of $\mathbf{1}^{OTf}$–$\mathbf{3}^{OTf}$ on employment of one equivalent instead of half an equivalent of phenolate and the dependence of product distributions on the concentration raised the question whether the yield of the intradiol products can be enhanced even further if more equivalents of **NaDTBP** are used in a highly concentrated solution. Therefore 30 mmolar acetonitrile solutions of $\mathbf{1}^{OTf}$–$\mathbf{3}^{OTf}$ were treated with two equivalents of **NaDTBP**, and indeed (in absence of protons) more than half of the employed phenolate was converted to the intradiol cleavage product **IE** (Table 2). Lowering the concentration of $\mathbf{1}^{OTf}$ to 1.5 mM led to a decrease of the yield in **IE** to 23%.

While there are numerous examples of copper complexes showing tyrosinase-like monooxygenase activity, representatives that oxygenate phenols and subsequently cleave the bond between the two C(O) atoms of the formed catecholate

Table 2. Yields of products of the reaction $\mathbf{1}^{OTf}$/$\mathbf{2}^{OTf}$/$\mathbf{3}^{PF6}$+2 **NaDTBP** with O_2 in acetonitrile solutions after 15 min (yields are given in percent and refer to converted **NaDTBP**).

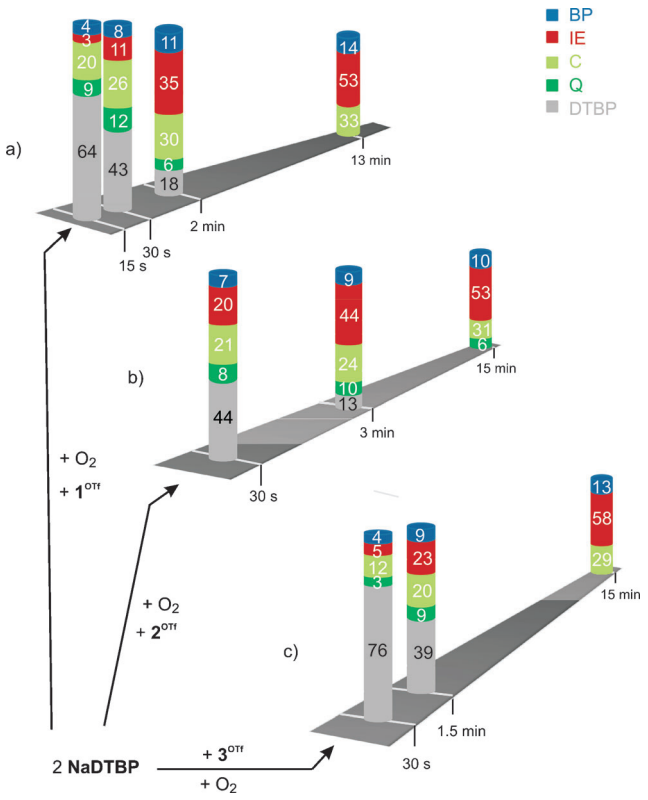
Complex	*c* [mM]	C	Q	BP	IE
$\mathbf{1}^{OTf}$	30	33	–	14	53
$\mathbf{1}^{OTf}$	1.5	16	30	31	23
$\mathbf{2}^{OTf}$	30	31	6	10	53
$\mathbf{3}^{OTf}$	30	29	–	13	58

are rather rare. To our knowledge, only one example has been published: in 1976, phenol was reported to react with a mixture of two equivalents of CuCl, pyridine, methanol and dioxygen to selectively give the intradiol cleavage product monomethyl muconate.[14] The rarity of copper complexes showing tyrosinase and at the same time dioxygenase activity raises questions on the prerequisites and the relevant mechanism.

Requirements for dioxygenation

NMR studies on the reaction of **NaDTBP** with $\mathbf{1}^{OTf}$ in varying stoichiometries and in the absence of O_2 showed that one copper center can interact at least with two equivalents of phenolate (see Supporting Information). Since, on reaction of $\mathbf{1}^{OTf}$/3 **NaDTBP** with O_2 the product distribution in comparison to the conversion of two equivalents of **NaDTBP** was hardly altered but one equivalent of **NaDTBP** remained unconsumed, we assume that in fact two equivalents are bound per copper(I) center. To get more insight into the reactions of $\mathbf{1}^{OTf}$–$\mathbf{3}^{OTf}$ with two equivalents of phenolate in the presence of O_2, again time-dependent analyses were performed.

As shown in Scheme 3, in the first seconds of the reactions of the copper complexes with two equivalents of **NaDTBP** mainly catecholate and quinone are formed, that is, they show



Scheme 3. Time dependence of the reactions of a) $\mathbf{1}^{OTf}$, b) $\mathbf{2}^{OTf}$, and c) $\mathbf{3}^{PF6}$ with two equivalents of **NaDTBP** and O_2. In case of $\mathbf{1}^{OTf}$ the reaction had finished after 13 min; in cases of $\mathbf{2}^{OTf}$ and $\mathbf{3}^{PF6}$ the reaction time was 15 min. Product yields were determined after workup, are given in percent, and refer to converted **NaDTBP**.

mainly monooxygenase reactivity, as often observed for functional Cu^{I} complexes and revealed already by monitoring the 1:1 reaction of $\mathbf{1}^{OTf}$/1 **NaDTBP** with O_2, as shown in Scheme 2. An important additional finding is that the amount of quinone rises first and then decreases again after a few minutes. **IE** is formed only in small amounts within this initial reaction period; it becomes the major reaction product only towards the end.

Keeping the focus on the reaction of $\mathbf{1}^{OTf}$, it is remarkable that the quinone formed in the beginning could no longer be detected after 13 min, which suggests that it is cleaved between the two C(O) atoms. If this were the case, **Q** would be an intermediate in the formation of **IE**, which would suggest that **Q** and **NaDTBP** react with $\mathbf{1}^{OTf}$ to form **IE**. This was tested in an independent experiment in which **Q**, **NaDTBP**, and $\mathbf{1}^{OTf}$ were treated in an equimolar ratio with O_2. As the conversions were unselective and the presence of **Q** right from the start seemed to even deteriorate the monooxygenation/dioxygenation potential of the system, it became clear that the species formed from **Q**, $\mathbf{1}^{OTf}$, and **NaDTBP** is not the one that generates predominantly **IE** in the presence of O_2.[15]

The question remained how **Q** is consumed during the reaction. Assuming that an active copper species with dioxygenating potential must first form in the absence of **Q**, a further experiment was carried out in which $\mathbf{1}^{OTf}$ was treated with 2 **NaDTBP** and O_2 first before 0.4 equivalents of **Q** were added. Remarkably, after 13 min not only had **NaDTBP** been consumed quantitatively, but also almost half of the **Q** employed, to mainly yield **IE**, as can be seen in Table 3 (entry 2), in which

Table 3. Yields of products of the reaction $\mathbf{1}^{OTf}$ + 2 **NaDTBP** with O_2 in 30 mmolar acetonitrile solutions including addition of **NaDTBP**/**Q** after 15 s. The reaction mixtures were worked up after 13 min (yields are given in percent and refer to converted **NaDTBP**).

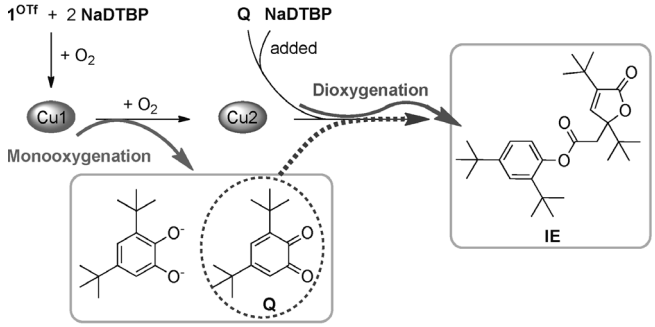
Entry	Addition	IE	C	Q	BP	IA	DTBP
1	–	53	33	–	14	–	–
2	0.4 **Q**	64	34	9	12	1	–
3	1 **NaDTBP**, 1 **Q**	104	42	10	42	–	2

2 **NaDTBP** were set to 100% substrate, so that the data can be compared more easily with the normal reaction of $\mathbf{1}^{OTf}$ and 2 **NaDTBP** (hence, in the reaction of $\mathbf{1}^{OTf}$ with 2 **NaDTBP** + 0.4 **Q** the overall amount of substrate available is 120%). It becomes clear that after an initial phase **Q** is indeed converted, presumably to **IE**.

In a further experiment, again $\mathbf{1}^{OTf}$ and 2 **NaDTBP** were treated with O_2, and after 15 s a mixture of 1 **NaDTBP** and 1 **Q** was added (within 45 s). In this case the yield of **IE** could be raised to 104% after 13 min (Table 3, entry 3). Only 2% of the employed **NaDTBP** was left in the reaction mixture, which is remarkable, since accordingly three equivalents per copper center were converted under these conditions, whereas in the absence of **Q** only two equivalents can be converted. This means that the copper species responsible for **IE** formation relies on the presence of **Q**. That **Q** and **NaDTBP** react even

without copper on O_2 addition to give mainly **IE** was excluded by another independent experiment (see Supporting Information). However, the increase in the yield of **BP** on going from entry 2 to 3 of Table 3 can be rationalized, because the mixture of **NaDTBP** and **Q** added after a 15 s delay itself forms **BP** (see above and Supporting Information).

Taken together our findings reveal the scenario depicted in Scheme 4. Initially, a copper species responsible for monooxygenation is formed (Cu1 in Scheme 4), and we assume that this corresponds to a dinuclear Cu_2O_2 intermediate. After α-oxygenation the formation of a copper species responsible for dioxygenation (Cu2 in Scheme 4) follows, which subsequently uses **Q** as substrate.



Scheme 4. Illustration of the complex process of the reaction of $\mathbf{1}^{OTf}$, 2 **NaDTBP**, and added **Q**/**NaDTBP** with O_2.

As mentioned in the introduction, flavonol-2,4-dioxygenase is the only copper protein known to also show dioxygenase activity, albeit only for one substrate, namely, flavonol. It is mononuclear and activates the substrate by electron abstraction ($S \rightarrow Cu^{II}$) forming a Cu^{I} complex of the substrate radical. Given this information, it is certainly conceivable that the copper species Cu2 is mononuclear. A change from a dinuclear to a mononuclear complex after monooxygenation would open additional coordination sites for binding further equivalents of **NaDTBP**, **Q**, or even weakly coordinating anions (OTf^- should coordinate better than PF_6^-). This may also explain the anion-dependent reactivity of complexes **1**–**3**, which in particular concerns the formation of intradiol products.

It is difficult to determine the influence of the ligands, the complexes of which all behave quite similarly despite steric (**L1** versus **L2**) and electronic (**L3**) differences. One common and perhaps relevant feature is the fact that only two of the three N-donor units coordinate to one Cu^{I} center, while the third one binds to a second Cu ion in the solid state and presumably remains dangling/hemilabile in the monomers on dissolution. The same was found for corresponding Cu^{II} complexes.[8] Hence, the coordination sphere is more open (on demand) than in other complexes. However, we believe that our ligands are not unique in promoting dioxygenation. Other known complexes may also mediate this reaction if adequate conditions are chosen.

Conclusion

As mainly $\mathbf{1}^{OTf}$ was investigated the conclusions also focus on this compound, although many of these also hold for $\mathbf{2}^{OTf}$ and $\mathbf{3}^{PF6}$. Compound $\mathbf{1}^{OTf}$ binds two equivalents of **NaDTBP**, which can be converted with O_2 to give the characteristic products of tyrosinase and intradiol-cleaving catechol dioxygenase, a reactivity which so far has been observed rather rarely. Initially, a copper species responsible for the monooxygenation must form (Cu1 in Scheme 4), followed by the formation of an active copper species responsible for dioxygenation (Cu2 in Scheme 4), which subsequently uses **Q** as substrate.

A further equivalent of **NaDTBP** cannot be converted, but on addition of an excess of **DTBP** catalytic formation of **Q** is observed. Product yields sensitively depend on the reaction conditions, such as concentration, equivalents of **NaDTBP** provided, and astonishingly also on the counteranions. The highest yield of the cleavage product **IE** is obtained in concentrated solutions with added **Q** and **NaDTBP**. Future work will aim at revealing the nature of the intermediate promoting dioxygenation and assessing the similarities/differences of our system in comparison with flavonol-2,4-dioxygenase.

Experimental Section

General

All manipulations were carried out in a glovebox or else by Schlenk-type techniques under a dry and O_2-free argon atmosphere. The ^1H and ^{13}C NMR spectra were recorded on a Bruker AV 400 NMR spectrometer with CD_3CN or $CDCl_3$ as solvent at 20 °C.The ^1H NMR spectra were calibrated against the residual proton signals, and the ^{13}C NMR spectra against natural-abundance ^{13}C resonances of the deuterated solvents. Solvents were purified by employing an MBraun Solvent Purification System SPS. Microanalyses were performed on a HEKAtech Euro EA 3000 elemental analyzer. IR spectra were recorded on a Shimadzu FTIR 8400S in the region 4000–400 cm^{-1} by using solid samples prepared as KBr pellets. Variable-temperature UV/Vis spectra were obtained at on an Agilent 8453 UV-Visible Spectrophotometer equipped with a Unisoku USP-203A cryostat. Mass spectra (ESI) were recorded on an Agilent Technologies 6210 Time-of-Flight-LC-MS instrument. Resonance raman spectra were acquired by using a Bruker RAM II FT-Raman Module.

Materials

L1,[8] **L3**,[9] $\mathbf{1}^{OTf}$,[8] $\mathbf{1}^{PF6}$,[8] and **I**[16] were synthesized as described in the literature.

Synthesis of L2

1-(2-Pyridylcarbonyl)-2-benzimidazolylphenol (II): 2-(2-Pyridylcarbonyl)benzoic acid **I** (6.7 g, 0.0295 mol) and *o*-phenylenediamine (3.2 g, 0.0296 mol) were treated with HCl (24 mL, 5 M) and heated to reflux for 6 h. After cooling to RT the mixture was neutralized with $NaHCO_3$ solution. A black solid was formed, which was washed three times with H_2O (5 mL). Subsequently, dichloromethane (30 mL) was added and the solvent was removed in vacuum to give **II** as a gray solid (5.3 g, 0.0176 mol, 60%). ^1H NMR (400 MHz, [D_6]DMSO): $\delta = 7.00$ (m, 1H, B-Im CH), 7.10 (m, 1H, B-Im

CH), 7.26 (m, 2H, B-Im CH), 7.41 (m, 1H, Py CH-5), 7.58 (m, 1H, Py CH-3), 7.64 (m, 1H, Ph CH), 7.72 (m, 1H, Ph CH-2), 7.84 (m, 1H, Py CH-4), 7.98 (m, 1H, Ph CH), 8.07 (m, 1H, Ph CH), 8.15 (m, 1H, Py CH-6), 12.85 ppm (s, 1H, B-Im NH).

1-(2-Pyridylcarbonyl)-2-(2-methyl)benzimidazolylphenol (III): Compound **II** (6.3 g, 0.0176 mol) was suspended in THF (15 mL) and treated with NaH (760 mg, 32 mmol). This mixture was stirred for 40 min, and afterwards MeI (2.0 mL, 32 mmol) was added. Then, ethanol/2-propanol (2/1, 2 mL) and H_2O (200 mL) were added. After 3 min a white solid had formed, which was collected by filtration, dissolved in dichloromethane (5 mL), and dried with $MgSO_4$. After layering the product solution with hexane, **III** was isolated as a white solid (2.9 g, 0.0092 mol, 52%). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 3.76$ (s, 3H, B-Im CH_3), 6.93 (m, 1H, B-Im CH), 7.11 (m, 1H, B-Im CH), 7.17 (d, 2H, $^3J_{H,H} = 4.0$ Hz, B-Im CH), 7.44–7.51 (m, 2H, Py CH-5 and CH-3), 7.59 (d, 1H, $^3J_{H,H} = 8.4$ Hz, Ph CH), 7.66 (m, 2H, Ph CH and Py CH-5), 7.85 (d, 1H, $^3J_{H,H} = 8.0$ Hz Ph CH), 7.92 (m, 1H, Ph CH), 8.17 ppm (d, 1H, $^3J_{H,H} = 4.0$ Hz Py CH-6); ^{13}C NMR ($CDCl_3$): $\delta = 31.1$ (NCH_3), 109.1 (B-Im CH), 119.5 (B-Im CH), 121.9 (B-Im CH), 122.6 (B-Im CH), 123.3 (Ph CH), 125.2 (Py CH-5), 129.3 (Ph CH), 129.7 (Py CH-3/4), 130.5 (Ph C_q), 130.7 (Ph CH), 130.7 (Py CH-3/4), 135.6 (Ph CH), 136.2 (B-im C_q-9), 139.6 (Ph C_q), 142.6 (B-Im C_q-4), 147.0 (Py CH-6), 152.4 (B-Im C_q-2), 154.5 (Py C_q-2), 195.6 ppm (C=O).

Alcohol precursor of L2, IV: *n*BuLi (2.5 M in hexane, 3.6 mL) was added at −78 °C to a solution of *N*-methylimidazole (0.72 mL) in THF (10 mL). After stirring at this temperature for 1.5 h, the reaction mixture was transferred to a solution of **III** (2.9 g) in THF (15 mL). The mixture became dark green. It was warmed to RT, neutralized with HCl (2 M), and treated with a saturated NaCl solution (10 mL). The organic layer was separated and the aqueous layer extracted twice with dichloromethane (3 mL). The combined organic layers were dried with $MgSO_4$, and the solvent was removed in vacuum. 1.05 g of **IV** could be obtained. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 3.55$ (s, 3H, OCH_3), 3.62 (s, 3H, Im CH_3), 6.45 (s, 1H, B-Im CH_3), 6.62 (m, 2H, Im CH, 7.03 (m, 1H, B-Im CH), 7.21 (m, 3H, B-Im CH), 7.39 (m, 4H, Ph CH), 7.57 (m, 2H, Py CH-*5* and CH-3), 7.68 (m, 1H, Ph CH), 8.41 ppm (d, 1H, $^3J_{H,H} = 4.0$ Hz, Py CH-6).

Ligand L2: Compound **IV** (1.05 g, 2.7 mmol) and NaH (64 mg, 2.7 mmol) were heated to reflux in THF (15 mL) for 5 h and then stirred overnight at RT Afterwards MeI (0.17 mL, 2.7 mmol) was added, and after 3 h the solvent was removed in vacuum. The obtained light brown solid was treated with a mixture of dichloromethane (10 mL) and H_2O (10 mL). The aqueous layer was extracted three times with dichloromethane (5 mL). The combined organic layers were dried with $MgSO_4$ and the solvent was removed in vacuum. The oil obtained was purified by column chromatography with a mixture of acetonitrile, methyl *tert*-butyl ether, and NEt_3 in a ratio of 9:3:1. **L2** could be isolated in 10% yield (110 mg, 0.27 mmol). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.92$ (s, 3H, OCH_3), 3.23 (s, 3H, Im CH_3), 3.42 (s, 3H, B-Im CH_3), 6.85 (s, 1H, Im CH-4), 6.91 (s, 1H, Im CH-5), 7.09 (m, 1H, Py CH-5), 7.24–7.30 (m, 4H, B-Im CH), 7.40 (m, 1H, Ph CH), 7.53 (m, 3H, Py CH-4/3 and Ph CH), 7.70 (m, 1H, Ph CH), 7.79 (m, 1H, Ph CH), 8.55 ppm (d, 1H, $^3J_{H,H} = 2.5$ Hz, Py CH-6); ^{13}C NMR (400 MHz, $CDCl_3$): $\delta = 30.6$ (B-Im CH_3), 34.8 (Im CH_3), 52.9 (OCH_3), 109.0 (C_q), 119.3 (Py CH-5), 121.7 (Im CH-5), 122.0 (Py CH-5), 123.1 (Im CH-4), 123.3 (Im CH-4), 123.4 (C_q), 126.2 (Im CH-5), 127.3 (Ph CH), 128.8 (2C, Ph C_q), 129.2 (Ph-Im Cq), 130.2 (Ph CH), 131.8 (Ph C_q), 134.9 (2C, B-Im C_q-4 and B-Im C_q-9), 135.5 (Py CH-4), 142.2 (B-Im C_q-2), 146.5 (Im C_q-2), 148.4 (Py CH-6), 159.4 ppm (Py C_q); elemental analysis calcd (%) for $C_{25}H_{23}N_5O$ (409.48 g mol^{-1}): C 73.33, H 5.66, N 17.10; found: C 73.29, H 5.82, N 16.12.

Synthesis of Cu complexes

[(L2)Cu]OTf (2^{OTf}): The reaction of **L2** (50 mg, 0.122 mmol) and $[Cu(MeCN)_4]OTf$ (46 mg, 0.122 mmol) in THF (2 mL) led to the precipitation of a light yellow solid, which was isolated by filtration and washed with THF (2 mL) and diethyl ether (2 mL). After drying, $\mathbf{2}^{OTf}$ (72 mg, 0.116 mmol, 95%) was isolated. ^{1}H NMR (400 MHz, CD_3CN): $\delta = 3.10$ (s, 3H, OCH_3), 3.65 (s, 6H, Ph-Im NCH_3, Im NCH_3), 6.73 (br m, 2H, Im CH-5), 7.21 (m, 1H), 7.33 (m, 3H, Ph CH), 7.44 (m, 4H), 7.61 (m, 2H), 7.96 ppm (m, 2H); IR (KBr): 3130 (w), 3067 (w), 2962 (m), 2907 (w), 1591 (m), 1480 (m), 1473 (m), 1462 (m), 1450 (m), 1434 (m), 1409 (m), 1263 (vs), 1225 (m), 1165 (m), 1155 (m), 1111 (m), 1086 (m), 1059 (m), 1030 (vs), 983 (m), 929 (w), 819 (m), 787 (m), 754 (m), 638 (s), 618 (m), 573 (w), 517 cm^{-1} (m); ESI-MS (+ve, MeCN): $m/z = 472.1079$ (calcd for $[LCu]^+$: 472.1199); elemental analysis calcd (%) for $C_{26}H_{23}CuF_3N_5O_4S$ (622.10 g mol^{-1}): C 50.20, H 3.73, N 11.26, S 5.15; found: C 50.35, H 3.68, N 11.32, S 3.75.

[(L2)Cu]PF_6 (2^{PF6}): The reaction of **L2** (80 mg, 0.195 mmol) and $[Cu(MeCN)_4]OTf$ (73 mg, 0.195 mmol) in THF (6 mL) led to the precipitation of a light yellow solid, which was isolated by filtration and washed with THF (2 mL) and diethyl ether (2 mL). After drying, $\mathbf{2}^{PF6}$ (111 mg, 0.180 mmol, 92%) was isolated. Crystals suitable for single-crystal X-ray diffraction studies could be obtained by layering an acetonitrile solution of $\mathbf{2}^{PF6}$ with diethyl ether. ^{1}H NMR (400 MHz, CD_3CN): $\delta = 3.10$ (s, 3H, OCH_3), 3.65 (s, 6H, Ph-Im NCH_3, Im NCH_3), 6.73 (br m, 2H, Im CH-5), 7.21 (m, 1H), 7.33 (m, 3H, Ph CH), 7.44 (m, 4H), 7.61 (m, 2H), 7.96 ppm (m, 2H); IR (KBr): 3133 (w), 2960 (w), 2841 (w), 1593 (m), 1481 (m), 1476 (m), 1463 (m), 1452 (m), 1432 (m), 1403 (m), 1284 (w), 1227 (w), 1163 (m), 1112 (m), 1087 (m), 1059 (m), 1005 (w), 982 (w), 929 (w), 877 (m), 840 (vs), 787 (m), 760 (m), 749 (s), 728 (w), 558 (s), 531 cm^{-1} (m); ESI-MS (+ve, MeCN): $m/z = 472.1081$ (calcd for $[LCu]^+$: 472.1199); elemental analysis calcd (%) for $C_{25}H_{23}CuF_6N_5OP$ (617.99 g mol^{-1}): C 48.59, H 3.75, N 11.33; found: C 48.69, H 3.77, N 11.60.

[(L3)Cu]OTf (3^{OTf}): The reaction of **L3** (100 mg, 0.295 mmol) and $Cu(MeCN)_4OTf$ (111 mg, 0.295 mmol) in THF (4 mL) led to the precipitation of a white solid, which was isolated by filtration and washed with THF (2 mL) and diethyl ether (2 mL). After drying, $\mathbf{3}^{OTf}$ (148 mg, 0.268 mmol, 91%) was isolated. ^{1}H NMR (400 MHz, CD_3CN): $\delta = 1.30$ (s, 9H, Pz $C(CH_3)_3$), 3.09 (s, 3H, OCH_3), 3.23 (s, 3H, Im NCH_3), 3.96 (s, 3H, Pz NCH_3), 6.09 (s, 1H, Pz CH-4), 6.89 (s, 1H, Im CH-4), 7.07 (s, 1H, Im CH-5), 7.27 (m, 1H, Py CH-5), 7.88 (m, 1H, Py CH-4), 7.99 (d, 1H, $^3J_{H,H} = 8.0$ Hz, Py CH-3), 8.36 ppm (1H, d, $^3J_{H,H} = 4.4$ Hz, Py CH-6); ^{13}C NMR (CD_3CN): $\delta = 29.4$ (Pz $C(CH_3)_3$), 32.0 (Pz $C(CH_3)_3$), 35.0 (Im NCH_3), 39.8 (Pz NCH_3), 53.1 (OCH_3), 81.8 (C_q OCH_3), 104.8 (Pz CH-4), 121.1 (Py CH-3), 124.0 (Py CH-5), 124.9 (Im CH-5), 127.2 (Im CH-4), 138.4 (Py CH-4), 146.1 (Im C_q-2), 149.8 (Py CH-6), 150.4 (Pz C_q-3), 153.9 (Pz C_q-5), 162.1 ppm (Py CH-2); IR (KBr): 3141 (m), 3110 (m), 2965 (m), 2933 (m), 2911 (m), 2880 (w), 2835 (w), 1602 (w), 1570 (w), 1536 (m), 1492 (m), 1476 (m), 1426 (m), 1419 (m), 1379 (m), 1369 (m), 1282 (vs), 1259 (vs), 1224 (m), 1161 (m), 1141 (s), 1106 (m), 1068 (m), 1049 (m), 1031 (s), 973 (m), 908 (m), 892 (m), 803 (m), 769 (s), 752 (m), 709 (w), 702 (w), 636 (s), 572 (m), 517 cm^{-1} (m); ESI-MS (+ve, MeCN): $m/z = 402.1399$ (calcd for $[LCu]^+$: 402.1355); elemental analysis calcd (%) for $C_{20}H_{25}CuF_3N_5O_4S$ (552.05 g mol^{-1}): C 43.51, H 4.56, N 12.69, S 5.81; found: C 43.60, H 4.41, N 12.67, S 5.59.

[(L3)Cu]PF_6 (3^{PF6}): The reaction of **L3** (136 mg, 0.401 mmol) and $Cu(MeCN)_4PF_6$ (149 mg, 0.400 mmol) in THF (4 mL) led to the precipitation of a white solid, which was isolated by filtration and washed with THF (2 mL) and diethyl ether (2 mL). After drying, $\mathbf{3}^{PF6}$ (205 mg, 0.374 mmol, 93%) was isolated. Crystals suitable for

single-crystal X-ray diffraction studies could be obtained by layering an acetonitrile solution of $\mathbf{3}^{PF6}$ with diethyl ether. ^{1}H NMR (400 MHz, CD_3CN): $\delta = 1.30$ (s, 9H, Pz C(CH_3)$_3$), 3.09 (s, 3H, OCH_3), 3.23 (s, 3H, Im NCH_3), 3.96 (s, 3H, Pz NCH_3), 6.09 (s, 1H, Pz CH-4), 6.89 (s, 1H, Im CH-4), 7.07 (s, 1H, Im CH-5), 7.27 (m, 1H, Py CH-5), 7.88 (m, 1H, Py CH-4), 7.99 (d, 1H, $^3J_{H,H} = 8.0$ Hz, Py CH-3), 8.36 ppm (1H, d, $^3J_{H,H} = 4.4$ Hz, Py CH-6); ^{13}C NMR (CD_3CN): $\delta = 29.4$ (Pz C(CH_3)$_3$), 32.0 (Pz *C*(CH_3)$_3$), 35.0 (Im NCH_3), 39.8 (Pz NCH_3), 53.1 (OCH_3), 81.8 (C_q OCH_3), 104.8 (Pz CH-4), 121.1 (Py CH-3), 124.0 (Py CH-5), 125.0 (Im CH-5), 127.2 (Im CH-4), 138.5 (Py CH-4), 146.0 (Im C_q-2), 149.8 (Py CH-6), 150.4 (Pz C_q-3), 154.0 (Pz C_q-5), 162.1 (Py CH-2); IR (KBr): 3152 (w), 3120 (w), 2965 (m), 2830 (w), 1599 (m), 1600 (w), 1537 (m), 1493 (m), 1474 (m), 1438 (m), 1380 (m), 1368 (m), 1286 (w), 1249 (m), 1217 (w), 1159 (w), 1110 (m), 1081 (m), 1049 (m), 980 (w), 896 (m), 839 (vs), 769 (s), 708 (w), 557 (s), 448 cm^{-1} (w); ESI-MS (+ve, MeCN): $m/z = 402.1409$ (calcd for $[LCu]^+$: 402.1355); elemental analysis calcd (%) for $C_{19}H_{25}CuF_6N_5OP$ (547.93 g mol^{-1}): C 41.65, H 4.60, N 12.78; found: C 41.97, H 4.61, N 12.78.

$[(L^B)Cu(OH)_2Cu(L^B)](OTf)_2$ (4): Complex $\mathbf{2}^{OTf}$ (12 mg, 0.019 mmol) was diluted in acetonitrile (1 mL). Afterwards the argon atmosphere in the Schlenk tube was replaced by O_2. Within 2 min the solution turned blue. After layering this product solution with diethyl ether (4 mL), **4** (9 mg, 0.007 mmol, 73%) was isolated after 5 d as blue crystals, which were washed with diethyl ether and dried in vacuum. IR (KBr): 3568 (m), 3130 (w), 3067 (w), 2962 (m), 2907 (w), 1591 (m), 1480 (m), 1473 (m), 1462 (m), 1450 (m), 1434 (m), 1409 (m), 1263 (vs), 1225 (m), 1165 (m), 1155 (m), 1111 (m), 1086 (m), 1059 (m), 1030 (vs), 983 (m), 929 (w), 819 (m), 787 (m), 754 (m), 638 (s), 618 (m), 573 (w), 517 cm^{-1} (m); ESI-MS (+ve, MeCN): $m/z =$ 472.1079 (calcd for $[LCu]^+$: 472.1199); elemental analysis calcd (%) for $C_{52}H_{48}Cu_2F_6N_{10}O_{10}S_2$ (1278.21 g mol^{-1}): C 48.86, H 3.79, N 10.96, S 5.02; found C 49.42, H 3.61, N 11.07, S 4.89.

Oxygenation reactions

In a typical reaction of $\mathbf{1}^{OTf}$ (7.5 mmolar), 1 **NaDTBP**, and O_2, $\mathbf{1}^{OTf}$ (20 mg, 0.03 mmol) and **NaDTBP** (7 mg, 0.03 mmol) were dissolved in acetonitrile (4 mL) under the inert argon atmosphere of a glovebox, and the reaction mixture was stirred for 10 min. Subsequently, an excess of O_2 was added and the mixture was stirred for further 40 min under the O_2 atmosphere. The reaction was quenched by the addition of HCl (2 mL, 4 M). Then, the resulting mixture was extracted with dichloromethane (3×5 mL). The combined organic phases were filtered through silica gel, dried over $MgSO_4$, and all volatile components were then removed under vacuum. The residue was analyzed by ^{1}H NMR spectroscopy by adding 1,3,5-tribromobenzene to the solution as an internal standard. The average standard deviation was 1–3% depending on the product and stoichiometric relation between starting materials.

Catalytic reactions

Copper complex, 2 **NaDTBP**, and 70 **DTBP** were dissolved in acetonitrile (7.5 mmolar solutions with respect to copper complex) under the inert argon atmosphere of a glovebox, and the reaction mixture was stirred for 10 min. Subsequently, an excess of O_2 was added and the mixture was stirred for a further 20 h under the O_2 atmosphere. The mixture was then worked up as described above. The TONs for the formation of **Q** were 22 for $\mathbf{1}^{OTf}$, 19 for $\mathbf{2}^{OTf}$, and 20 for $\mathbf{3}^{PF6}$. Additionally, **BP** was formed with TONs of 32 for $\mathbf{1}^{OTf}$, 16 for $\mathbf{2}^{OTf}$ and 34 for $\mathbf{3}^{PF6}$. Reactions with different precursor ratios, different concentrations and with copper complexes $\mathbf{2}^{OTf}$ and $\mathbf{3}^{PF6}$ were performed in analogy to the described procedure.

Data for IE

^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.04$ (s, 9H, Lact C-4-CCH_3), 1.23 (s, 9H, Lact C2-CCH_3), 1.28 (s, 9H, Phen C-4-CCH_3), 1.32 (s, 9H, Phen C-2-CCH_3), 3.13 (m, 2H, CH_2), 6.74 (d, 1H, Phen CH-5), 7.09 (s, 1H, Lact CH), 7.16 (m, 1H, Phen CH-6), 7.35 ppm (d, 1H, Phen CH-3). ^{13}C NMR (400 MHz, $CDCl_3$): $\delta = 25.5$ (Lact C-4-*C*CH_3), 28.1 (Lact C-2-*C*CH_3), 30.3 (Phen C-2-*C*CH_3), 31.8 (Phen C-4-*C*CH_3), 32.0 (Lact C-2-*C*CH_3), 34.6 (Phen C-2-*C*CH_3), 34.7 (Phen C-4-*C*CH_3), 38.2 (Lact C-4-*C*CH_3), 38.5 (CH_2), 88.6 (Lact C_q-4), 123.0 (Phen CH-5), 123.8 (Phen CH-6), 124.1 (Phen CH-3), 139.7 (Phen CH-2), 143.8 (Lact C_q-2), 146.4 (Phen C_q-1), 146.5 (Lact CH), 148.3 (Phen C_q-4), 168.2 (Lact COO), 171.3 ppm (Est COO); IR (KBr): 3482 (m), 2961 (s), 2909 (m), 2878 (m), 1757 (vs), 1507 (w), 1496 (m), 1482 (m), 1463 (m), 1400 (w), 1364 (m), 1246 (w), 1192 (m), 1155 (m), 1122 (w), 1084 (m), 1040 (m), 1019 (w), 998 (m), 925 (w), 886 (m), 836 (w), 791 (w), 648 (w), 498 (w); ESI-MS (+ve, MeCN): $m/z = 443.3161$ (calcd for H**IE**$^+$: 443.3317).

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[15] In fact, $\mathbf{1}^{\mathbf{OTf}}$ reacts with **Q**: addition of **Q** to a solution of $\mathbf{1}^{\mathbf{OTf}}$ in acetonitrile followed by treatment with HCl yields after workup a mixture of **C** and **Q** in the ratio 43:57. This suggests the formation of a semiquinone complex as the initial product, which then disproportionates.

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