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Click. Coordinate. Catalyze. Using CuAAC Click Ligands in Small-Molecule Model Chemistry of Tyrosinase

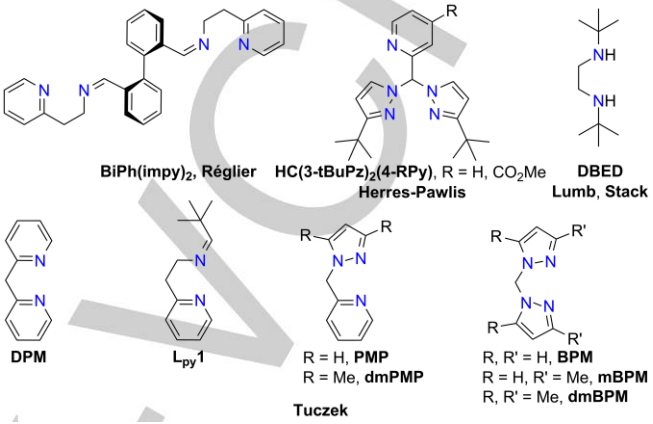
Benjamin Herzigkeit,[a] Benedikt M. Flöser,[a] Nadja E. Meißner,[a] Tobias A. Engesser,[a] Felix Tuczek*[a]

Abstract: Three triazolylmethylpyridine ligands are synthesized using the copper-catalyzed azide-alkyne cycloaddition (CuAAC). The corresponding copper(I) complexes are investigated as catalysts for the oxygenation of several monophenols, in analogy to the enzyme tyrosinase. Importantly, they show a higher catalytic activity than previously investigated systems. This is ascribed to the lower charge donation of the electron-poor triazole heterocycle, supporting the hydroxylation of phenolic substrates by an electrophilic substitution mechanism.

Type-3 copper proteins are metalloproteins sharing similar active sites. They contain two copper atoms (CuA and CuB) which are each coordinated by three histidines and bind dioxygen as peroxide in a side-on (μ-η^2:η^2) coordination.[1,2] Even though their active sites are almost identical, their reactivities differ greatly.[3] Hemocyanin (Hc) is involved in oxygen transport in molluscs and arthropods. Tyrosinase (TY) catalyzes the conversion of L-tyrosine to L-DOPAquinone and therefore plays a central role in, e.g., melanogenesis of mammals and birds.[4] Catechol oxidase (CO), on the other hand, is only able to convert L-DOPA to L-DOPAquinone. The first X-ray crystallographic characterization of a tyrosinase from the bacterium *Streptomyces castaneoglobisporus* was presented by Matoba *et al.*[5] In the meantime, many more crystal structures of copper-containing polyphenol oxidases (PPOs) have appeared, allowing to relate their structural differences to the functional discrimination between TY and CO activity.[6-8] Nevertheless, details of the molecular mechanism of tyrosinase are still unclear or under discussion.[6-8]

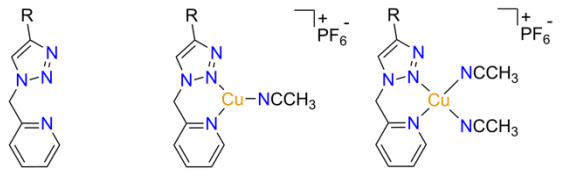
Important information regarding the reactivity of tyrosinase may be obtained from small-molecule model systems. Many research groups followed this line of research; correspondingly, the number of functional models of tyrosinase has steadily increased over the years (Scheme 1).[1,2,9,10] The first catalytically active system was developed by Réglier *et al.*, being able to convert 2,4-di-*tert*-butylphenol (DTBP-H) to 3,5-di-*tert*-butylquinone (DTBQ) with a turnover number (TON) of 16 after 1 h.[11] Further systems were devised by Casella *et al.*[12], Stack *et al.*[13], Lumb *et al.*[14], Herres-Pawlis *et al.*,[15] and others.[1,2,9,16]

Our group´s first catalytic model system was the imino-pyridine **L_{py}1**, derived from Réglier´s Cu_2**BiPh(impy)$_2$** system (Scheme 1).[11, 17] It was capable of converting DTBP-H to DTBQ with a turnover number (TON) of 22. By changing the heterocyclic and the imine *N* donor of our parent bidentate ligand we were able to create further catalytic model systems achieving TONs of up to 31.[18] Thereby we observed a higher catalytic efficiency in case of benzimidazole/imine, pyrazole/imine or pyrazol/pyrazol containing systems (Scheme 1) whereas a decrease of catalytic activity was found for imidazole/oxazoline systems.[18,19] In general, the use of comparatively electron-poor pyrazole groups in the ligand framework led to more active catalysts.[20]



Scheme 1. Mono- and binucleating ligands used in model complexes for the oxygenation of various substrates in a tyrosinase-like fashion.[2,11,15,20]

Another electron-poor *N*-donor ligand which to date has not been utilized in studies regarding the oxygenation of external substrates is 1,2,3-triazole. Triazoles are employed in various fields of chemistry, biochemistry, drug discovery, polymer and material science for their unique properties and their easy accessibility.[21] Application of the prominent CuAAC click reaction, which was first introduced by Sharpless *et al.*, enables the use of a highly efficient, stereospecific and easy to purify method to synthesize a wide array of organic products.[21,22] With respect to coordination chemistry, exploiting the methodology of “clicking” two modular units together allows to effectively tune the properties of ligands.[23,24]



Scheme 2. Triazolylmethylpyridine ligands (**1a-c**) and their heteroleptic Cu(I) complexes (**2a-c**) used in this study.

Herein, we report the synthesis of three novel copper(I) complexes (Scheme 2) supported by triazolylmethylpyridine ligands and their catalytic activity regarding the monooxygenation of

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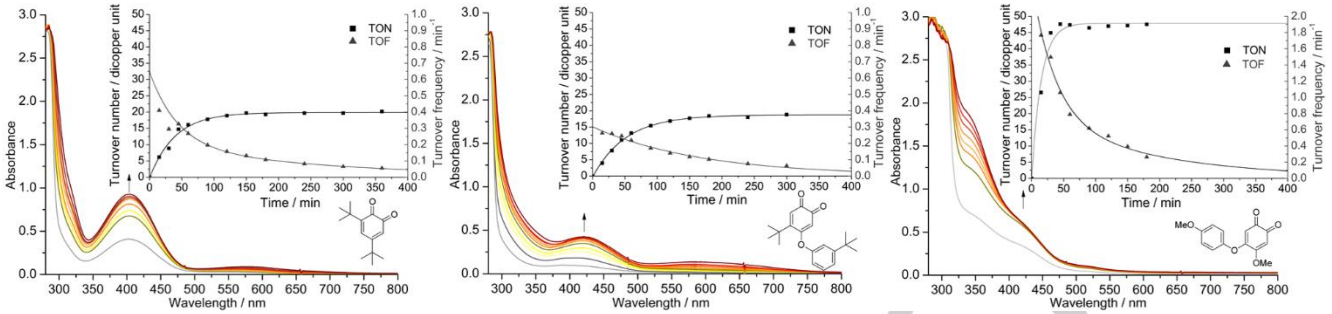
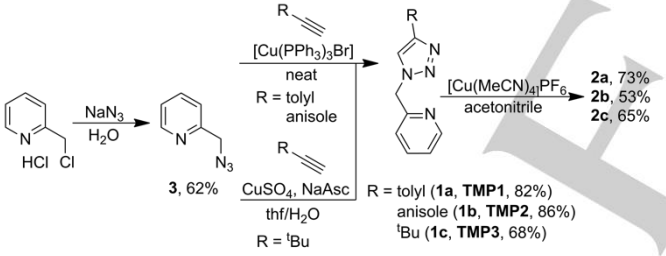


Figure 1. Catalytic oxygenation of a 500 µm solution of [Cu(MeCN)**TMP1**]PF_6 (**2a**) in the presence of DTBP-H (left) , [Cu(MeCN)**TMP2**]PF_6 (**2b**) in the presence of TBP-H (middle) and [Cu(MeCN)$_2$**TMP3**]PF_6 (**2c**) in the presence of MeOP-H (right) under Bulkowski/Réglier conditions (50 equiv. substrate, 100 equiv. triethylamine) in dichloromethane at room temperature; quartz cell length l =1 mm; inset: Turnover number per dicopper unit (black squares) and turnover frequency per minute (gray triangles) as a function of time.

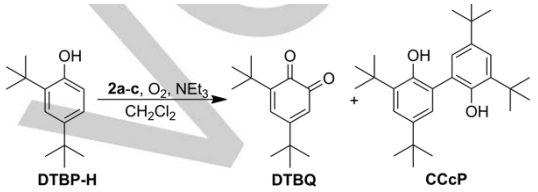
the substrates DTBP-H, 3-*tert*-butylphenol (TBP-H) and 4-methoxyphenol (MeOP-H). The results are compared with those obtained from previously synthesized systems, and the influence of different substituents (tolyl, anisole and *t*-butyl) at the triazole moiety on the catalytic activity of the derived copper complex is discussed.

The two ligands **TMP1** (**1a**) and **TMP2** (**1b**) were synthesized according to a procedure developed by Košmrlj *et al.* (Scheme 3).[25] The synthesis of **TMP3** (**1c**) applying the same protocol, however, resulted in low yields. Using the synthetic pathway of Bertani *et al*. gave better results.[26] Employing the ligands (**1a**-**c**) and tetrakis(acetonitrile)copper(I) hexafluorophosphate (**CuP**) in a ratio of 1 to 1 the mono-ligated copper(I) complexes **2a**-**c** could be obtained (for details see SI).



Scheme 3. Syntheses of the ligands (**1a**-**c**) and the heteroleptic copper(I) complexes (**2a**, **2b**).

The catalytic tyrosinase activity of the heteroleptic copper(I) complexes **2a**-**c** was investigated regarding the three monophenolic substrates DTBP-H, TBP-H and MeOP-H which exhibit different structural and electronic properties. Whereas DTBP-H is converted to the *ortho*-quinone DTBQ as well as the C-C coupling product 3,3',5,5'-tetra-*tert*-butyl-2,2'-biphenol (CCcP), the less sterically demanding monophenols TBP-H and MeOP-H form secondary products after monooxygenation (Scheme 4, 5). All catalytic reactions were carried out under Bulkowski/Réglier conditions.[27] To this end, oxygen was bubbled into a 500 µM solution of copper(I) complex in dichloromethane with 50 equivalents of substrate and 100 equivalents triethylamine under anaerobic conditions at room temperature. Progress of the reactions was monitored by *in situ* UV/vis spectroscopy based on the absorption bands of the characteristic products (407 nm, ε = 1830 L mol^{-1} cm^{-1} for DTBQ[11,18]; 425 nm, ε = 898 L mol^{-1} cm^{-1} for the coupled quinone cpQ of TBP-H;[19] and 418 nm, ε = 524 L mol^{-1} cm^{-1} for the coupled quinone cpMeOQ, formed from MeOP-H) [19].



Scheme 4. Catalytic reaction of the phenolic substrate DTBP-H to DTBQ and CCcP.

Upon oxygenation of DTBP-H with **2a-c**, the color of the reaction mixture immediately changed from colorless to yellow, rapidly turning brown. For copper complex **2a** a TON of 20 was determined after 6 hours (cf. Figure 1, left). Similar results were observed for complex **2b** and **2c** with TONs of 22 and 24, respectively, after 5 hours (Figure S1, S2). Within the first hour the oxygenation of the substrate occurred with a moderate turnover frequency (TOF) for all three complexes (Figure 1, S1, S2, insets). Formation of DTBQ was further examined by NMR. To this end, an aliquot was removed from the reaction mixture after one hour, diluted to a 100 µM solution and quenched with 6 M hydrochloride acid to remove any copper species. After work-up the residue was investigated by ^{1}H- and ^{13}C-NMR spectroscopy (Figure S3-S8). The resulting spectra revealed the formation of DTBQ, the C-C coupling product CCcP as well as starting material DTBP-H (Tab. S1).

As a second substrate we investigated TBP-H (Scheme 5). In contrast to DTBP-H, there is no *tert*-butyl group in *ortho*-position to the hydroxyl group, which should decrease the steric interaction between the ligand and the substrate and possibly lead to a higher TON. Due to the lack of the *tert*-butyl group, however, the initially formed 4-*tert*-butylquinone (4-TBQ) undergoes an oxidative coupling with TBP-H and reacts to the coupled quinone 4-(*tert*-butyl)-5-(3-(*tert*-butyl)-phenoxy)-cyclohexa-3,5-dien-1,2-dione (cpQ, Scheme 5). Oxygenation of the reaction mixture with complexes **2a**, **2b** and **2c** resulted in TONs of 20 (Figure S9), 19 (Figure 1, middle) and 24 (Figure S10), respectively.

As evident from Figure 1 (middle), the prominent absorption band at ~395 nm shifts to 425 nm in the course of oxygenation, reflecting the transformation of the intermediate product 4-TBQ to the coupled quinone (cpQ). After quenching and work-up of an aliquot of the reaction mixtures the NMRs showed the product cpQ and starting material TBP-H (Table S1, Figure S11-S16).

Table 1. Overview of the tyrosinase-like activity for the conversion (TON) of several substrates for systems supported by bidentate ligands.

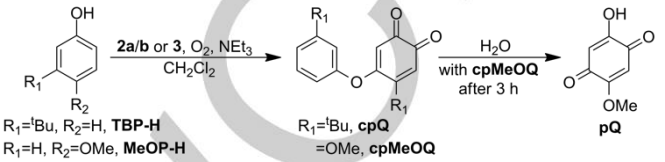
System	DPM [17]	BPM [19]	dmBPM [19]	LIMZ [19]	BIMZ [19]	PMP [20]	dmPMP [20]	TMP1 *this work*	TMP2 *this work*	TMP3 *this work*
DTBP-H	0	21	11	16	9	14	11	20	22	24
TBP-H	-	22	12	20	6	25	13	20	19	24
MeOP-H	-	35	15	34	6	34	33	42	45	48

Finally, the monooxygenation of MeOP-H with complexes **2a**-**c** was studied (Scheme 5). This reaction initially leads to 4-methoxyquinone (4-MeOQ), which then reacts to the coupled *ortho*-quinone 4-methoxy-5-(4-methoxyphenoxy)cyclohexa-3,5-diene-1,2-dione (cpMeOQ). Both of these reactions are rapid due to the strong mesomeric (+M) effect of the *para*-methoxy substituent and the lack of a *tert*-butyl residue in *ortho*-position to the hydroxy group. After one hour cpMeOQ is converted to 2-hydroxy-5-methoxy-[1,4]-benzoquinone (pQ) due to the presence of water formed in the previous reaction steps (Scheme 5). Notably, all catalysts mediate the conversion of MeOP-H to the coupled quinone cpMeOQ within the first hour (Figure 1, right, S17, S18, insets). Oxygenation with complex **2a** results in a TON of 42 (Figure S17) whereas with complex **2b** a slightly higher TON (45) is achieved (Figure S18). Both complexes are topped by **2c** exhibiting a TON of 48 (Figure 1, right). The reaction mixture was quenched after one and three hours, respectively (Table S1, Figure S19-S30).

Evidently the three new complexes are able to mediate a tyrosinase-like monooxygenation of all three substrates. Moreover, TONs for the new catalysts are high compared to the other model systems (Table 1). Thereby complex **2c** is the most active, achieving a TON of 24 with DTBP-H and TBP-H. Regarding these two substrates the new systems **2a**-**c** are roughly comparable to the bispyrazolylmethane systems (**BPM**),[19] though with respect to the substrate MeOP-H they exceed the previously achieved TONs significantly with complex **2c** taking the lead (TON = 48). This demonstrates the overall high versatility of the new catalysts.

A salient difference to the systems investigated earlier is the fact that a high steric interaction with the substrates, as found in systems like **dmBPM** and **dmPMP** (cf Scheme 1), is absent for the triazole coordinated catalysts **2a**-**c**. This is evident from the observation that the substituent at the C4 position of the triazole moiety exhibits only a small influence on the catalytic activity (Table 1). Regarding the reaction mechanism we propose that it proceeds in the same manner as in our other bidentate model systems.[2,17] We detected a μ-η^2:η^2-peroxo complex for the catalysts at low temperatures (-90 °C) in acetone, albeit with small intensity (see Figure S31-33 for experimentally and theoretically obtained UV/vis-spectra). Generally, a stable peroxo intermediate is more difficult to detect if the corresponding copper complex has a high catalytic activity.[17,19]

Controlling the influence of ligands on the electronic structure of transition-metal centers is mandatory for a rational design of corresponding catalysts. Regarding tyrosinase model systems, we systematically explored the impact of heterocyclic groups by exchanging the pyridine donors in the $\mathbf{L_{py}1}$ and **DPM** ligands with imidazole, benzimidazole or pyrazole moieties (cf Scheme 1). Herein, we showed that introduction of triazoles, being the most



Scheme 5. Catalytic reaction of the substrate TBP-H to cpQ and MeOP-H to cpMeOQ and pQ.

electron-poor moieties in this series, leads to the highest turnover numbers. Supposedly, the negative inductive effect of the additional nitrogen atom leads to a lower charge donation of the heterocycle *via* coordinating N atom to the metal center, thus rendering the reactive copper peroxo species more electrophilic. Based on the S_E mechanism evidenced for the aromatic hydroxylation reaction in these systems the catalytic activity regarding the monooxygenation of phenolic substrates is correspondingly enhanced.[28]

In summary we have presented three new small molecule models for a tyrosinase-like oxygenation of three different monophenols. Importantly, the TONs with the substrates DTBP-H (24) and MeOP-H (48) were found to be higher than in previously investigated model systems containing exclusively heterocyclic *N*-donors whereas the TON with TBP-H (24) was not increased. Overall, triazole donors generate a higher catalytic conversion than pyrazole or pyridine donors. On the other hand, a steric influence at the C4-position of the triazole *N*-donor plays a less important role for the conversion of monophenols to *ortho*-quinones, as the most reactive system **2c** does contain a *tert*-butyl group and still shows the highest TON. This indicates that the electronic properties of the ligands are of utmost importance for the reactivity of these systems. In the future, expansion of the ligand library with more clickable triazoles, whose electronic influence can easily be changed by, e.g., an electron withdrawing carboxylic ester group, should help to further improve the catalytic activity and the mechanistic understanding of functional tyrosinase models.

Keywords: tyrosinase • triazoles • oxygenation • homogeneous catalysis • ligand design

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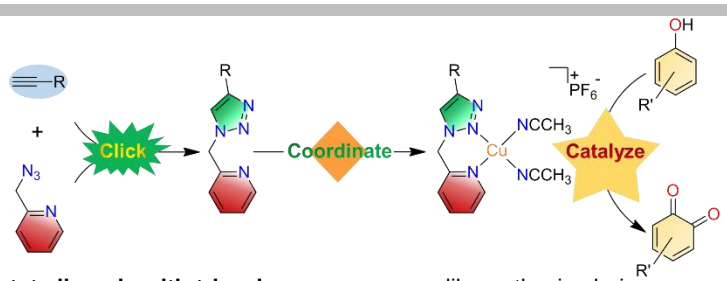

Bidentate ligands with triazole groups are readily synthesized *via* a copper catalyzed azide-alkyne cycloaddition. Their copper complexes turn out to be highly active catalysts for the oxygenation of various monophenols, in analogy to the enzyme tyrosinase.

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