Selective benzylic C–C coupling catalyzed by a bioinspired dicopper complex†

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A highly preorganized bioinspired dicopper complex with imidazole ligation catalyzes the selective benzylic *para*-C–H activation of 2,4,6-trimethylphenol under aerobic conditions, yielding either the stilbenequinone or 4-methoxymethyl-2,6-dimethylphenol depending on the solvent used.

Biological type 3 dicopper sites are fascinating models for the synthetic chemist and may serve as blueprints for the development of new bioinspired synthetic copper catalysts for selective oxidation or oxygenation chemistry.[1] Prominent examples of those metalloenzymes are tyrosinase (Tyr) and catechol oxidase (CO), which mediate the *ortho*-hydroxylation of phenolic substrates to catechols (Tyr)[2] and the subsequent oxidation of catechols to *ortho*-quinones (Tyr and CO).[3] In order to emulate such synergetic metal ion reactivity in a preorganized bimetallic system, we have recently prepared a new pyrazole-based ligand with imidazole-containing side arms that can host two copper ions at a distance of around 4 Å (**1**, Fig. 1).[4] Although not strictly analogous to the biological sites where the proximate copper ions are ligated by three N-bound histidine residues, **1** was anticipated to enable cooperative substrate transformations in a bioinspired approach. Its labile MeOH···OMe bridge allows rapid binding and activation of substrates within the bimetallic pocket.[5] Here we show that **1** catalyzes the selective oxidative functionalization of 2,4,6-trimethylphenol (TMP) at the *para* methyl group, in particular the benzylic C–C coupling to give stilbenequinones, and we provide some first mechanistic insights.

TMP derivatives functionalized at the 4-position are important organic compounds, both for industrial purposes and fundamental research studies.[6] Copper-mediated oxidations of TMP with dioxygen usually lead to oxygenated products such as 4-hydroxy-3,5-dimethylbenzaldehyde,[7] and just recently a catalytic version has been reported for this benzylic C–H activation with a binuclear dicopper species suggested as a key intermediate.[8] Bimetallic mechanisms are also being discussed for a related copper-catalyzed reaction, the oxidative C–O coupling of 2,6-dimethylphenol (DMP) to give poly-

(phenylene)ether (PPE), an important engineering thermoplastic.[9]

Some pyrazolate-based dinuclear copper complexes similar to **1** are highly active catalysts for this polymerization, with activities depending on the particular ligand systems employed.[10] In contrast, the bioinspired complex **1**, when reacted with DMP, was found to selectively yield the alternative C–C coupled product 3,3′,5,5′-tetramethyl-4,4′-diphenoquinone (DPQ). In order to rationalize that particular selectivity, we employed the *para*-alkylated derivative TMP as a potential substrate. When catalyst **1** is treated with an excess of TMP in MeCN–CH$_2$Cl$_2$ at ambient conditions, the fully oxidized C–C coupled product 3,3′,5,5′-tetramethylstilbene-4,4′-quinone (TMSQ) is obtained as the major product with yields up to 65% after 24 h (Scheme 1). Oxidative coupling at the benzylic position of alkylated phenols such as TMP is quite delicate and usually requires a large amount of strong oxidant.[11] Few systems are hitherto known to selectively catalyze that transformation, and mechanistic insight is scarce.[12]

Turn over numbers (TON) for the present reaction increase linearly with TMP concentration (see ESI†), and a 5 : 1 (TMP : **1**) ratio has been used for further mechanistic studies. Since the methanolate bridge in **1** serves as an internal base, no addition of co-catalyst is required. When left standing in air without stirring, TMSQ forms as dark red crystals from the reaction mixture.[13] In the presence of methanol, 4-methoxymethyl-2,6-dimethylphenol (MDP) is obtained as the main product (Scheme 1).

In order to get a first insight into the mechanism of this catalytic process, the reaction was followed by means of UV-Vis, NMR and EPR spectroscopy. The electronic spectrum of **1** in MeCN–CH$_2$Cl$_2$ shows a band at 989 nm (ε = 269 L mol^{-1} cm^{-1}) with a shoulder at 724 nm, corresponding to d–d transitions of Cu^{II} ions in a trigonal bipyramidal ligand environment. Within the first few minutes after addition of TMP, the reaction mixture becomes red and a relatively
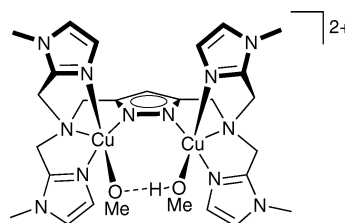
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† Electronic supplementary information (ESI) available: Experimental section including EPR studies. Crystal data for **2′**. See DOI: 10.1039/b718162k
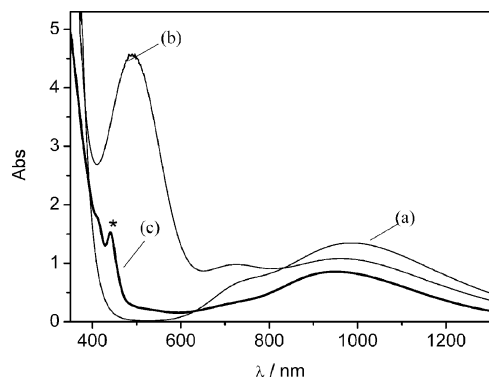

Fig. 1 Schematic representation of catalyst **1**.
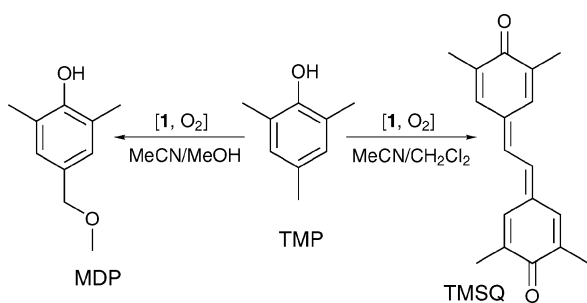
Scheme 1 Oxidative C–C coupling of TMP and 1,6-nucleophilic addition of MeOH catalyzed by **1**.

Scheme 2 Key intermediate **2** and initial benzylic C–C coupling of TMP to give TMBB and the mixed-valent Cu^ICu^{II} intermediate **3**.

intense band appears at λ_{max} = 495 nm ($\varepsilon \approx 1500$ L mol^{-1} cm^{-1}), while the ligand field band shifts to 960 nm (Fig. 2). These spectral changes are attributed to coordination of TMP within the bimetallic pocket of **1** to give the key intermediate **2** (Scheme 2).

Assignment of the red color to a phenolate → Cu^{II} LMCT transition is corroborated by the trend in λ_{max} for differently substituted phenols: adducts between **1** and the less electron rich substrates DMP and 4-*tert*-butylphenol give rise to LMCT bands that are shifted hypsochromically with λ_{max} = 472 nm and 455 nm, respectively. The assignment is further confirmed by Raman spectroscopy, which has proven particularly useful for elucidating the structural and electronic properties of copper-phenolate complexes.[14,15] Excitation into the LMCT band of **2** results in a spectrum that is very similar to those of other Cu^{II}-phenolate systems (Fig. 3), with characteristic resonance-enhanced modes at, *inter alia*, 1237 cm^{-1} (ν_{7a}, C–O stretching) and 1607 cm^{-1} (ν_{8a}, C_{ortho}–C_{meta} ring stretching).[15]

Structural information about the proposed key intermediate **2** comes from the crystallographic characterization of a model complex **2′** that was obtained from the reaction of **1** with pentafluorophenol (PFP)—a phenol that is not prone to oxidation (Fig. 4).‡ As anticipated, the PFP anion is bound to only one of the two Cu^{II} ions (Cu1) and forms a strong intramolecular H-bond to the MeOH molecule that is coordinated to the adjacent Cu2 within the bimetallic pocket

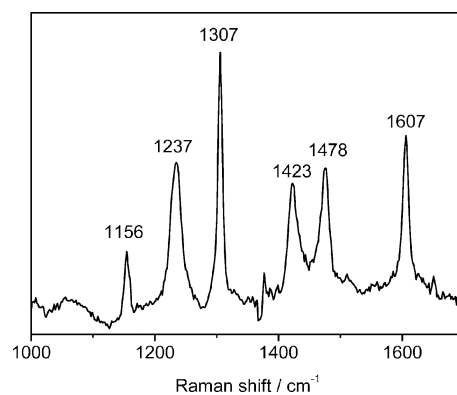(d (O1···O2) = 2.583(6) Å). The exchange of methanolate in **1** for a PFP anion in **2′** causes only slight changes in the coordination spheres of the five-coordinate Cu ions (τCu = 0.80/0.73 in **2′** *versus* 0.88 in **1**[4]), but the PFP adduct appears to be stabilized by π–π stacking between the C_6F_5-ring and one imidazole unit of the ligand side arms (interplane distance 3.88 Å, angle 4.5°, with the imidazole ring containing N11 and N12).

Formation of TMSQ from the solution of the red intermediate **2** begins after a relatively long initiation period (1.5 h), at which point the absorption band of the product occurs at 440 nm ($\varepsilon \approx 96\,000$ L mol^{-1} cm^{-1}). When the reaction of **1** and TMP is performed under anaerobic conditions in a glove box, the initially observed intense LMCT band again gradually disappears within several hours to give a yellow-green solution. Only traces (less than 0.1%) of TMSQ are observed under these conditions (Fig. 2, spectrum (c)). Work-up of the reaction mixture reveals that the C–C coupled but non-oxidized 4,4′-dihydroxy-3,3′,5,5′-tetramethylbibenzyl (TMBB) is formed as the sole product (Scheme 2; see ESI for complete characterization†). Formation of TMBB represents a 1e$^-$ oxidation per TMP substrate. Since the yield of TMBB formed under anaerobic conditions is consistent with a stoichiometric 1 : 1 reaction between **1** and TMP, the dicopper complex **1** should thereby be semi-reduced to its mixed-valent Cu^ICu^{II} state (**3**). This is consistent with the decrease in intensity of the Cu^{II} d–d transition upon formation of TMBB (Fig. 2, spectra (a) and (c)). Further evidence comes from X-band EPR

Fig. 2 UV-Vis spectra of the reaction mixture (initial concentrations of **1**: 0.005 mol L^{-1}; TMP: 0.025 mol L^{-1}; solvent: MeCN–CH$_2$Cl$_2$ 4 : 6 v/v): (a) solution of **1**; (b) few minutes after addition of TMP (red solution of **2**); (c) 48 h after addition of TMP under anaerobic conditions (yellow-green solution; the asterisk denotes traces of TMSQ; see text for explanation).
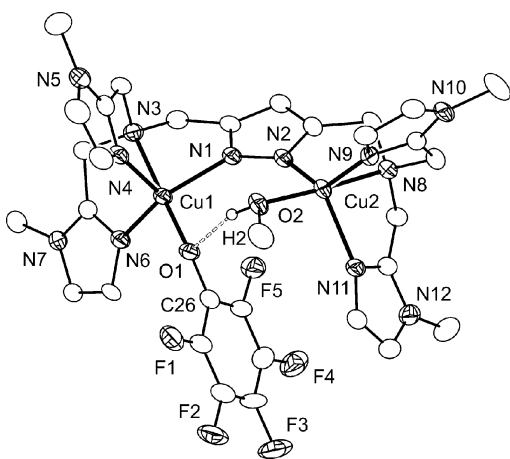

Fig. 3 Resonance Raman spectrum of the red solution of key intermediate **2** in MeCN (RT, λ_{ex} = 488 nm, solvent signals are subtracted).

Fig. 4 ORTEP plot (30% probability thermal ellipsoids) of the structure of **2′**. For the sake of clarity all hydrogen atoms except H2 have been omitted. Cu1···Cu2 4.309(1) Å; see ESI† for other atom distances and angles.

spectroscopy (see ESI†): **1** is EPR silent at 15 K but at 50 K shows a broad absorption around 3000 G with a weak half-field signal, characteristic of an exchange-coupled antiferromagnetic dicopper(II) system ($J = -35.3$ cm^{-1} was derived from SQUID data[4]). In contrast, the spectrum of the frozen yellow-green solution containing **3** recorded at 15 K shows a typical axial EPR spectrum for a single Cu^{II}, suggesting that **3** is a valence-localized Cu^{I}Cu^{II} species on the EPR time scale. Furthermore, spectral parameters for **3** are very similar to those of a Cu^{I}Cu^{II} compound prepared independently from the pyrazolate/imidazole-based ligand and each one equivalent of a Cu^{I} and Cu^{II} salt ($g_{\text{II}} = 2.25$, $g_{\perp} = 2.06$, $|A_{\text{II}}| = 157$ G, $|A_{\perp}| = 20$ G).

Obviously, molecular oxygen is not involved in the initial C–C coupling, but only in subsequent re-oxidation of the semi-reduced dicopper complex and transformation of TMBB to the final product TMSQ. Control experiments show that TMBB itself is not oxidized to TMSQ in air, but it is rapidly oxidized upon exposure to air in the presence of catalyst **1**.

In conclusion, a highly preorganized dicopper complex has allowed the development of a new catalytic procedure for the *para* C–H activation of TMP with aerial dioxygen as the oxidant. Selective formation of either TMSQ or MDP is achieved depending on the solvent used. The reaction proceeds through initial coordination of TMP to the dicopper site, followed by benzylic C–C coupling that leads to TMBB as the first product. The resulting semi-reduced Cu^{I}Cu^{II} species is then re-oxidized by dioxygen to revive catalyst **1**. A model complex for the first key intermediate, featuring a coordinated and strongly hydrogen-bonded phenolate within the bimetallic pocket, has been isolated and structurally characterized. Whereas the benzylic C–C coupling of TMP to give TMBB may suggest a radical-based process and involvement of a

(possibly short-lived) Cu^{I}-phenoxide radical species in the key step, spectroscopic data support a Cu^{II}-phenolate ground state description for the red intermediate **2**. While mechanistically distinct from the type 3 dicopper sites (which shuttle between the Cu^{II}Cu^{II} and Cu^{I}Cu^{I} states without involvement of 1e^{-} radical chemistry), some new cooperative two-centre reactivity has resulted from the present bioinspired approach. Cu-mediated formation of MDP from TMP in the presence of methanol has previously been suggested to proceed *via* 1,6-nucleophilic addition of methanol to a quinone methide intermediate,[8] which would require an initial 2e^{-} transfer that is not observed here. Further studies are now directed at elucidating details of the electronic structure of **2**, the activation of dioxygen by the mixed-valent species **3** with the possible generation and involvement of superoxide, and finally a full mechanistic understanding of the various reaction steps.

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