C–H Activation

Copper-Mediated Selective Oxidation of a C–H Bond**

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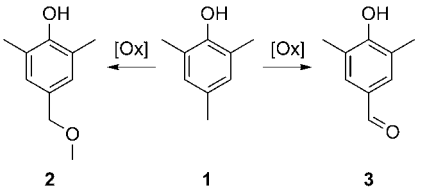
Substituted hydroxybenzaldehydes are important feedstock materials for the pharmaceutical and perfume industries.[1,2] These compounds are commonly made by the selective oxidation of aromatic methyl groups. However, this chemical reaction is difficult and often proceeds to the carboxylic acid derivative. Thus, 4-hydroxy-3,5-dimethylbenzaldehyde (HDB) is a valuable intermediate, especially for the preparation of drugs.[3–5] A number of synthetic routes to HDB starting from 2,4,6-trimethylphenol (TMP) involving stoichiometric amounts or an excess of oxidant are known.[6–10] So far, the only catalytic oxidation of TMP to HDB was achieved by Takehira and co-workers.[11–14]

Copper-containing enzymes, such as vanillyl alcohol oxidase[15] or laccase[16] can selectively produce the aromatic aldehyde functional group from a methyl group. We report here a bioinspired Cu^{II}/neocuproine system to perform the selective *para*-formylation of mesitol [Eq. (1)]. The reaction



2 1 3 (1)

of TMP (**1**) with $[CuCl_2(neo)_x]$ (neo = neocuproine = 2,9-dimethylphenanthroline) and sodium methoxide as cocatalyst in methanol at room temperature leads to the formation of 4-(methoxymethyl)-2,6-dimethylphenol (**2**, MDP) and/or HDB (**3**), depending on the experimental conditions (Table 1).

Without neocuproine no oxidation products were observed (entry 1); neo is thus necessary for the reaction to proceed, most likely to increase the oxidation potential of the

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Table 1: Results of the Cu^{II}/neocuproine-mediated oxidation of TMP (**1**) to MDP (**2**) and/or HDB (**3**) according to Equation (1).[a]

Entry	Reactant [equiv]				Product distribution [mol%][b]		
	TMP	$CuCl_2$	NaOMe	neo	TMP	MDP	HDB
1	1	2	2	0	100	–	–
2	4	2	2	4	71	29	–
3	2	2	2	4	49	51	–
4	1	2	2	4	–	60	20
5	0.5	2	2	4	–	–	100[c]
6	1	2	1.5	2	18	82[d]	–
7[e]	1	0.14	0.3	0.105	–	–	100[f]
8[e]	1	0.14	0.3	0.035	11	80[g]	9

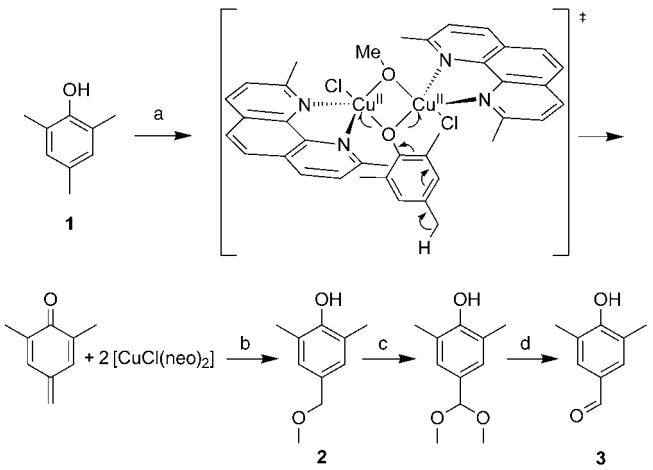
[a] [Ox] = [$CuCl_2$(neo)$_x$] + NaOMe; see the Supporting Information for the experimental procedure. [b] The yields (±5%) were determined by ^{1}H NMR spectroscopy after a reaction time of 30 min. [c] No products of over-oxidation could be detected; HDB was isolated in 85% yield. [d] Isolated in 69% yield. [e] Optimized catalytic reactions performed at 65°C under argon with H_2O_2. The yields (±5%) were determined by ^{1}H NMR spectroscopy using 1,2,4,5-tetrabromobenzene as an internal standard. [f] After a reaction time of 6 h. [g] After a reaction time of 12 h.

Cu^{II}/Cu^{I} pair. The neo ligand is indeed a highly specific bidentate ligand for Cu^{I} species, while its affinity towards Cu^{II} species is known to be low.[17,18] The bis-neocuproine copper(I) complex $[Cu(neo)_2]^+$ is extremely stable due to the presence of *ortho*-methyl groups, which strongly stabilize the tetrahedral geometry of Cu^{I} ions, thereby preventing their reoxidation to Cu^{II}. The driving force of the reaction is thus the more facile reduction of copper(II) ions owing to the affinity of neo for copper(I) species (see the Supporting Information). This is confirmed when neo is replaced by the sterically far less crowded 2,2′-bipyridine, as the resulting copper complex is inactive.

The amount of TMP used in the reaction was then varied. When 2 or 1 equiv of TMP per Cu^{II}/neo were used, total conversion of the substrate could not be achieved (Table 1, entries 2 and 3). The oxidation reactions exclusively led to the formation of MDP in 29% and 51% yield, respectively. These results are in accordance with the fact that the formation of MDP is a two-electron process. If 0.5 equiv of TMP is allowed to react with 1 equiv of Cu^{II}/neo, both MDP and HDB are produced (entry 4). The quantitative formation of the benzaldehyde derivative HDB was achieved with a TMP/Cu ratio of 0.25 (four-electron oxidation; entry 5). A series of experiments was subsequently carried out to improve the selectivity towards the methoxymethyl derivative. This study showed that very good selectivities in MDP could only be reached when moderate amounts of the basic cocatalyst were used along with one equivalent of neo per copper ion. For instance, the *para*-methoxymethyl compound could be produced in 82% yield in the presence of 0.75 equiv of NaOMe instead of 1 equiv (entry 6).

Based on the active site found in enzymes containing the type-3 copper site, a dinuclear copper species bridged by a phenolate and a methoxide is proposed as the key intermediate of the reaction (Scheme 1). The *para*-benzylic proton is activated through the coordination of the phenolate to the metal ions. Deprotonated TMP reduces each Cu^{II} to Cu^{I}. This $2e^-$ transfer induces the polarization of the benzylic C–H bond, which results in a rearrangement of the aromatic ring to a quinone methide. The nucleophilic addition of methanol to the quinone methide leads to the formation of the *para*-methoxymethyl derivative MDP. A second step ($2e^-$ oxidation/MeOH) yields a ketal compound, which has been detected by ^{1}H NMR spectroscopy in the crude mixture after evaporation of the solvent. Hydrolysis during the work-up affords HDB. The same result was observed when argon was used in place of air, suggesting that molecular oxygen is not involved in the C–O bond formation.

To further study the reaction mechanism and detect the proposed active species, attempts were made to crystallize a key intermediate. Reaction of a DMF/MeOH (9:1) solution of sodium pentafluorophenoxide (1 equiv)—a phenolate that is inactive towards oxidation—and neo (2 equiv) with $CuCl_2$ (2 equiv), NaOMe (1.2 equiv), and acetonitrile yields diamond-shaped green crystals suitable for X-ray diffraction (see the Supporting Information). A PLATON[19] representation of the molecular structure of this compound is depicted in Figure 1. As previously postulated by several authors, [20] a dinuclear copper(II) species bridged by both a methoxide and a pentafluorophenoxide is obtained. To the best of our knowledge, this is the first crystallographic evidence of a self-assembled, mixed μ-methoxo-μ-phenoxo-bridged dinuclear copper complex with a mononucleating nonbridging ligand, namely, neocuproine. This structure is in total agreement with the proposed active species for the reaction described above.



Scheme 1. Proposed reaction mechanism for the stoichiometric formation of MDP (**2**) and HDB (**3**) from TMP (**1**). a) NaOMe (2 equiv), $CuCl_2$ (2 equiv), neo (4 equiv), MeOH; b) MeOH; c) $2e^-$ oxidation: NaOMe (2 equiv), $CuCl_2$ (2 equiv), neo (4 equiv), MeOH; d) H_2O.

The investigation was then focused on performing this oxidation with catalytic amounts of the Cu^{II}/neo complex. This would provide an environmentally friendly and economically favorable system for industrial application. This mech-

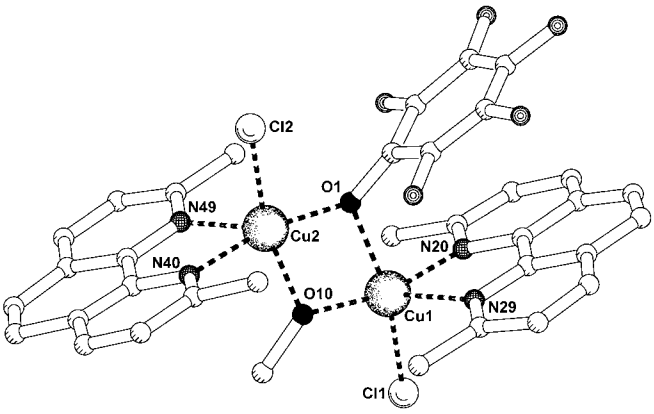


Figure 1. Molecular structure of $[Cu_2Cl_2(neo)_2(\mu\text{-}CH_3O)(\mu\text{-}C_6F_5O)]$. Selected bond lengths [Å] and angles [°]: Cu1–O1 2.066(7), Cu1–O10 1.950(6), Cu1–Cl1 2.276(3), Cu1–N20 2.025(8), Cu1–N29 2.270(9), Cu1–Cu2 3.137(8), Cu2–O1 1.947(6), Cu2–O10 1.966(7), Cu2–Cl2 2.265(3), Cu2–N40 2.043(8), Cu2–N49 2.256(8); Cu1-O1-Cu2 102.8(3), Cu1-O10-Cu2 106.4(3). See also the Supporting Information.

anism would imply the reoxidation of the Cu^{I} species, which a priori seems to be unlikely due to the very high stability of the $[Cu(neo)_2]^+$ cation. For this purpose, only 1 equiv of neo was used per Cu^{II} ion, as we anticipated a more facile reoxidation of the resulting Cu^{I} complex $[Cu(neo)]^+$. The first logical procedure was to perform the catalytic reaction in air, or in pure dioxygen, and heat the reaction mixture to promote the Cu^{I} oxidation. Only one catalytic cycle can be completed under these experimental conditions, suggesting that molecular oxygen is not strong enough to achieve the Cu^{I} reoxidation. To overcome this difficulty, hydrogen peroxide, an activated form of dioxygen, was successfully used as oxidant, and the experimental conditions were optimized. Thus, 0.14 equiv of $[CuCl_2(neo)]$, in the presence of 2 equiv of H_2O_2 and 0.3 equiv of NaOMe as basic cocatalyst, could catalyze the quantitative formylation of 1 equiv of TMP after 6 h (Table 1, entry 7). The selective oxidation was performed under argon and refluxing methanol. The controlled production of MDP could be carried out using a smaller amount of neo (0.035 equiv instead of 0.105 equiv; entries 7 and 8). Most likely, the presence of less ligand leads to the formation of different active species, allowing the isolation of the intermediate product **2**. No effective catalytic method for preparing MDP has yet been reported. Therefore, the synthetic procedure described here is the first effective catalytic preparation of MDP.

In conclusion, a new environmentally friendly, high-yielding procedure has been developed for the *para* C_{sp^3}-H oxidation of TMP. This compound can be selectively oxidized to form either MDP or HDB, two valuable industrial compounds. A key reaction intermediate, a self-assembled μ-methoxo-μ-phenoxo-bridged dinuclear copper complex involving a mononucleating ligand, was isolated and structurally characterized. This dicopper complex suggests the participation of bimetallic active species in the catalytic cycle as well as the nucleophilic attack of a methanolate anion to the bis-alkoxo-bridged complex. The substrate scope for this catalytic oxidation reaction is currently being investigated.

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