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Selective copper(II)-mediated oxidative coupling of a nucleophilic reagent to the *para*-methyl group of 2,4,6-trimethylphenol†‡

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A copper(II) neocuproine system has been developed for the efficient and very selective 1,6-addition of a nucleophile to the *para*-methyl group of 2,4,6-trimethylphenol. Crystallographic and spectroscopic data point towards the involvement of a μ-methoxo–μ-phenoxo-bridged copper species which appears to generate a highly reactive quinone methide intermediate that can be attacked by a nucleophilic reagent.

Introduction

Copper-mediated oxidation reactions are of interest both in terms of industrial applications,[1,2] and in terms of understanding the mechanism of action of copper-containing enzymes.[3,4] Thus, copper-catalyzed oxygenations of phenols[5] have been investigated in detail,[6] and they usually require the use of biomimetic copper(I) species for initial dioxygen activation.[7–9] Moreover, the best model compounds reported so far involve dinuclear μ-η^2:η^2-peroxo copper(II) adducts.[10] In contrast, the copper(II)-catalyzed oxidation of phenols generally results in oxidative coupling reactions between substrate molecules.[11]

2,4,6-Trimethylphenol derivatives functionalized at the 4-position are very important organic compounds, for industrial purposes,[12,13] as well as for fundamental research studies.[14,15] Very often, their preparation requires a multistep reaction,[16] or involves a low-yielding procedure.[17] A straightforward synthetic pathway to produce 4-substituted 2,4,6-trimethylphenols involve a benzoquinone methide intermediate (Fig. 1). 1,4-Benzoquinone methides (**I**) are indeed highly reactive species, which can be justified by a resonance structure (**II**) with a dipolar character giving an electrophilic property to the methine carbon atom (Fig. 1).

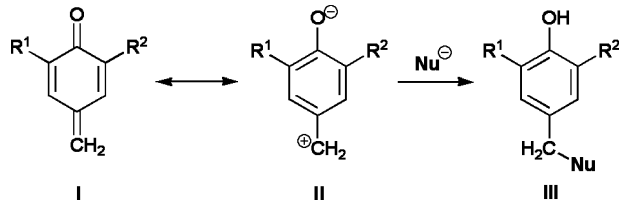

Fig. 1 Benzoquinone methide (**I**), its resonance form (**II**) and the *para*-substituted product (**III**).

Therefore, this particular character has been exploited in 1,6-additions with nucleophiles.[18,19] However, *para*-benzoquinone methides only exist transitorily in dilute solution, and this limited stability restricts their potential use with a wide variety of nucleophiles.[20] Furthermore, only a few methodologies have been developed so far to generate 2,6-dialkylquinone methide from the corresponding 2,6-dialkyl-4-methylphenol, by reaction with over-stoichiometric amounts of Ag_2O[21] or PbO_2.[22] Recently, we have reported an environmentally friendly bio-inspired Cu^{II}/neocuproine system able to perform the mild and selective *para*-formylation of 2,4,6-trimethylphenol.[23] The formation of 4-hydroxy-3,5-dimethylbenzaldehyde, an important pharmaceutical synthetic precursor,[24] is believed to result from the nucleophilic attack of methoxide to a quinone methide, leading to a ketal which is subsequently hydrolyzed to the carbonyl derivative.[23]

In the present paper, mechanistic investigations on this copper(II)-mediated 1,6-addition are reported together with the effective utilization of different nucleophilic reagents, showing the possible creation of a C–O, a C–N, or a C–C bond.

Results and discussion

Copper-mediated oxidative coupling

Four equivalents of the copper system [$CuCl_2$–(neocuproine)$_2$–NaOMe] are capable of selectively oxidizing one equivalent of 2,4,6-trimethylphenol (**IV**) to the corresponding 4-hydroxy-3,5-dimethylbenzaldehyde at room temperature in methanol (Table 1, entry 2).[23] This is in full agreement with the fact that the formation of **VIb** is a four-electron process and that copper(II) is a monoelectronic oxidant. On the basis of the active site found in type-3 copper proteins, a dinuclear copper species bridged by a phenolate and a methoxide is proposed as the key intermediate of the reaction (species **1**, Fig. 2). Thus, the *para*-benzylic proton is activated *via* the coordination of the bridging phenolate to the copper centres, leading to the formation of **1**. Each Cu^{II} ion in **1** is reduced to Cu^{I} by the phenolate bridge. This $2e^-$ transfer induces the polarization of the benzylic C–H bond, resulting in a rearrangement of the aromatic ring to a highly reactive quinone methide (**V**, Fig. 2) and two equivalents of bis-neocuproine copper(I) chloride. The nucleophilic addition of methanol to the quinone methide leads to the formation of the *para*-methoxymethyl derivative **VIa** (Fig. 2, Nu = CH_3O). A second [$2e^-$ oxidation/MeOH] step yields a ketal compound (**VIII**, Fig. 3), through the attack of a

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‡ Electronic supplementary information (ESI) available: I. UV-vis studies, II. EPR studies, III. Cyclovoltammetry, IV. NMR spectra of compounds **VIc–h**. See http://dx.doi.org/10.1039/b507199b

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Table 1 Cu^{II}-mediated 1,6-addition of nucleophiles to 2,4,6-trimethylphenol[a]

Entry	Reactant	Reaction time	Product[b]	Yield (%)
1	Methanol	1 h	**VIa**	69
2	Methanol	45 min	**VIb**	85
3	Ethane-1,2-diol	2 h	**VIc**	55
4	Ethane-1,2-diol	2 h	**VId**	15
5	2,2′-Dipyridylamine	1 h	**VIe**	30
6	2,4-Pentanedione	2 h	**VIf**	30
7	Potassium phthalimidate	2 h	**VIg**	34
8	AcOH–HCl	Overnight	**VIh**	80

[a] See Experimental section. [b] See Fig. 4.

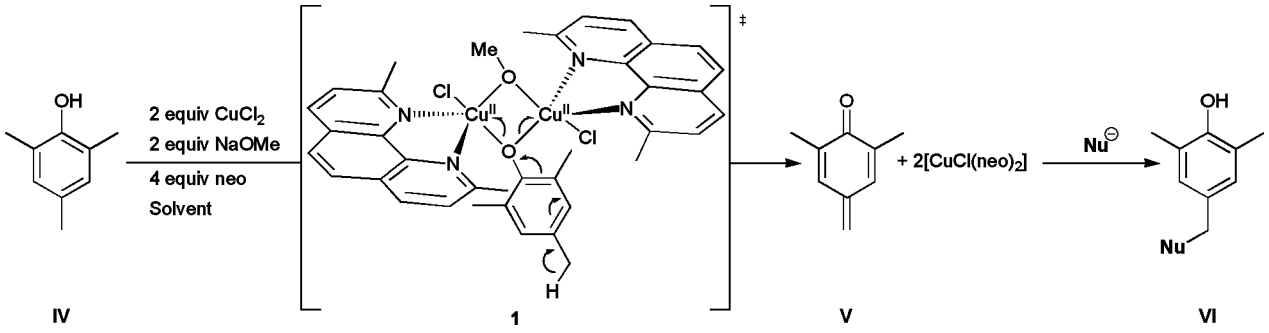

Fig. 2 Proposed mechanism for the *para*-nucleophilic addition.

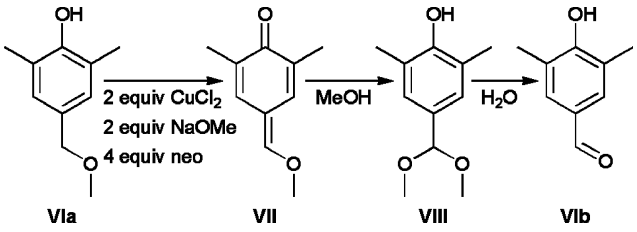

Fig. 3 Formation of 4-hydroxy-3,5-dimethylbenzaldehyde (**VIb**).

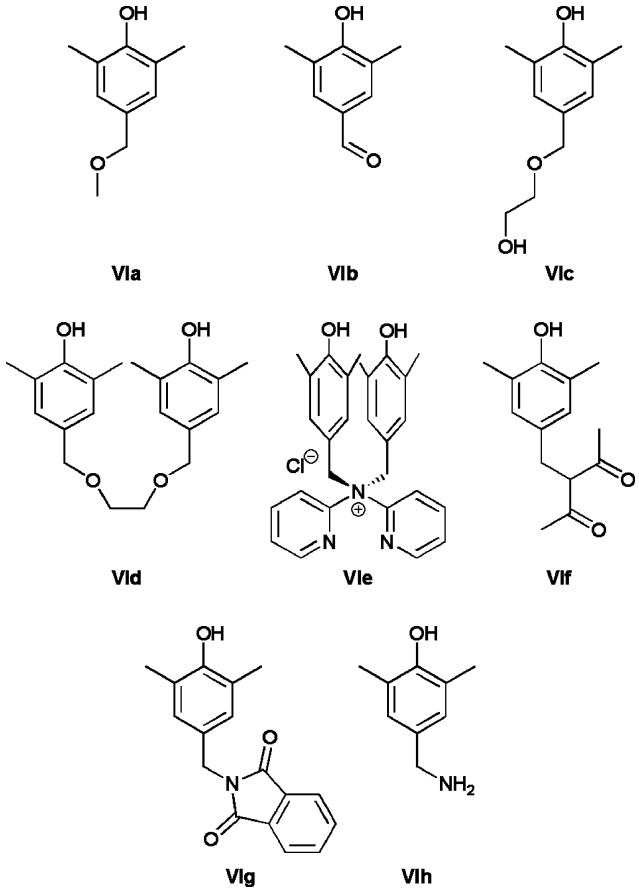

Fig. 4 Phenol derivatives obtained by copper-mediated 1,6-addition.

methoxide to a second quinone methide moiety, *i.e.* **VII**. The ketal **VIII** has been detected by proton NMR in the crude reaction mixture after evaporation of the solvent. Hydrolysis of **VIII** during the work-up gives the aldehyde **VIb** in 85% isolated yield. The intermediate *para*-methoxy derivative **VIa** arising from a two-electron oxidation could be isolated when only two equivalents of [$CuCl_2$–(neocuproine)$_2$–NaOMe] were treated with **IV** (Table 1, entry 1). Other nucleophiles have been used in DMF as the non-nucleophilic solvent and with sodium hydride as base to deprotonate **IV**, and products of type **VI** (Fig. 2) have been obtained, confirming the presence of a 1,4-benzoquinone methide intermediate of type **V** (Fig. 2). The use of one equivalent of ethane-1,2-diol as nucleophile with one equivalent of 2,4,6-trimethylphenol yields 4-((2-hydroxyethoxy)methyl)-2,6-dimethylphenol (**VIc**) in 55% yield. Compound **VId**, resulting from the double nucleophilic addition of ethane-1,2-diol to two 2,4,6-trimethylphenol substrates, is also produced as a minor product (Table 1, entries 3 and 4). Interestingly, the reaction of 2,2′-dipyridylamine with 2 equivalents of 2,4,6-trimethylphenol in the presence of [$CuCl_2$–(neocuproine)$_2$–NaH] leads to the quaternary ammonium chloride product **VIe** (Fig. 4) with a yield of 30% (Table 1, entry 5). **VIe** which results from a second oxidative coupling between the tertiary amine generated by a first 1,6-addition and 2,4,6-trimethylphenol, is an interesting molecule. Indeed, **VIe** may act both as a N_2O_2 ligand, and as a phase transfer reagent. C–C bond formation is also possible as illustrated by the reaction of the sodium salt of 2,4-pentanedione with one equivalent of 2,4,6-trimethylphenol and [$CuCl_2$(neo)$_2$] (Table 1, entry 6). Finally, the [$CuCl_2$–(neo)$_2$]-mediated oxidative coupling between potassium phthalimidate and 2,4,6-trimethylphenol gives 34% of product **VIg**, which is subsequently hydrolyzed to the amino derivative **VIh** in an excellent yield, under acidic conditions (Table 1, entries 7 and 8).

Neocuproine (neo = 2,9-dimethylphenanthroline) is essential for the oxidative coupling reaction to proceed, since no oxidation products are observed in its absence. Neo, most likely increases

Table 2 Selected bond lengths (Å) and angles (°) for $[Cu_2Cl_2(bipy)_2(\mu\text{-}Cl)(\mu\text{-}CH_3O)]$ (**2**) and $[Cu_2Cl_2(neo)_2(\mu\text{-}C_6F_5O)(\mu\text{-}CH_3O)]$ (**3**)

$[Cu_2Cl_2(bipy)_2(\mu\text{-}Cl)(\mu\text{-}CH_3O)]$ (**2**)			
Cu(1)–O(4)	1.9103(13)	Cu(1)–N(6)	2.052(3)
Cu(1)–N(17)	2.006(2)	Cu(1)–Cl(2)	2.2917(8)
Cu(1)–Cl(3)	2.5498(8)	Cu(1)–Cu(1a)[a]	3.278(6)
N(6)–Cu(1)–N(17)	79.71(10)	N(17)–Cu(1)–Cl(2)	92.24(7)
Cl(2)–Cu(1)–O(4)	92.66(3)	O(4)–Cu(1)–N(6)	94.30(7)
Cu(1)–O(4)–Cu(1a)[a]	118.21(12)	Cu(1)–Cl(3)–Cu(1a)	80.01(3)
$[Cu_2Cl_2(neo)_2(\mu\text{-}C_6F_5O)(\mu\text{-}CH_3O)]$			
Cu(1)–O(1)	2.066(7)	Cu(1)–O(10)	1.950(6)
Cu(1)–Cl(1)	2.276(3)	Cu(1)–N(20)	2.025(8)
Cu(1)–N(29)	2.270(9)	Cu(2)–O(1)	1.947(6)
Cu(2)–O(10)	1.966(7)	Cu(2)–Cl(2)	2.265(3)
Cu(2)–N(40)	2.043(8)	Cu(2)–N(49)	2.256(8)
Cu(1)–Cu(2)	3.137(8)		
N(20)–Cu(1)–Cl(1)	91.8(3)	Cl(1)–Cu(1)–O(10)	98.6(2)
O(10)–Cu(1)–O(1)	74.2(3)	O(1)–Cu(1)–N(20)	92.9(3)
N(40)–Cu(2)–Cl(2)	94.1(2)	Cl(2)–Cu(2)–O(1)	94.9(2)
O(1)–Cu(2)–O(10)	76.6(3)	O(10)–Cu(2)–N(40)	92.2(3)
Cu(1)–O(1)–Cu(2)	102.8(3)	Cu(1)–O(10)–Cu(2)	106.4(3)

[a] $-x, y, 2-z$.

the redox potential of the Cu^{II}/Cu^{I} couple.¶ Indeed, the ligand neo is a highly specific didentate ligand for Cu^{I} species, while its affinity towards Cu^{II} species is known to be depleted.[25,26] The $[Cu^{I}(neo)_2]^+$ cation is particularly stable due to the presence of *ortho*-methyl groups, which strongly stabilize the tetrahedral geometry of Cu^{I} ions, thereby precluding their reoxidation to Cu^{II} entities. The driving force of the 1,6-addition is therefore the easier reduction of copper(II) ions due to the strong affinity of neo for copper(I) species. This is corroborated by the fact that if neo is substituted by the sterically less hindered 2,2′-bipyridine, the resulting copper(II) complex does not show any activity within a reaction time of 24 h. In order to further investigate the reaction mechanism and detect the proposed active species **1** (Fig. 2), attempts to crystallize a key copper intermediate have been carried out.

Molecular structures

The solid-state structures of $[Cu_2Cl_2(bipy)_2(\mu\text{-}Cl)(\mu\text{-}CH_3O)]$ (**2**) and $[Cu_2Cl_2(neo)_2(\mu\text{-}C_6F_5O)(\mu\text{-}CH_3O)]$ (**3**) are depicted in Figs 5 and 6, with selected geometrical parameters and crystallographic data contained in Tables 2 and 3, respectively.

$[Cu_2Cl_2(bipy)_2(\mu\text{-}Cl)(\mu\text{-}CH_3O)]$. Since the use of 2,2′-bipyridine with copper(II) chloride has resulted in the lack of reactivity regarding the 1,6-addition, the first synthetic efforts have been performed using this ligand, with the aim of obtaining a stable species of type **1** (Fig. 2). Thus, reaction of one equivalent of $CuCl_2$ in DMF with half an equivalent of sodium 2,4,6-trimethylphenoxide in DMF–MeOH (5 : 1), one equivalent of 2,2′-bipyridine in DMF, and half an equivalent of sodium methoxide, followed by the addition of acetonitrile yields green block-shaped crystals of **2** (Fig. 5). The dinuclear unit consists of two symmetry related pentacoordinated copper(II) ions. Cu(1) and Cu(1a) are in a coordination environment between square pyramidal and trigonal bipyramidal ($\tau = 0.54$)[27] with a bridging Cl(3) anion and the bridging oxygen atom O(4) from a methoxide (Table 2). The other three positions are occupied

¶ The redox potentials of the Cu^{II}/Cu^{I} couple in the presence of each ligand, *i.e.* 2,2′-bipyridine or neocuproine, have been determined in DMF at a scan rate of 100 mV s^{-1}; $E = 0.18$ V (*vs.* Ag/Ag^+) for 2,2′-bipyridine; $E = 0.37$ V (*vs.* Ag/Ag^+) for neocuproine. See ESI‡ for the cyclic voltammograms (Fig. S11).

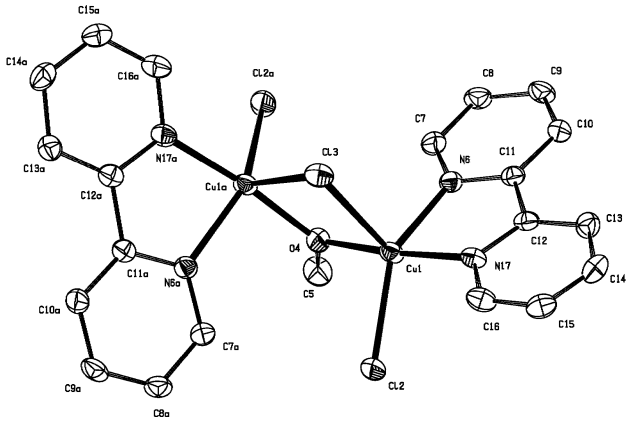

Fig. 5 Displacement ellipsoid plots of $[Cu_2Cl_2(bipy)_2(\mu\text{-}Cl)(\mu\text{-}CH_3O)]$ (**2**) at the 50% probability level. Hydrogen atoms not shown. Atoms with an additional letter "a" in the atom label are at equivalent position ($-x$, y, $1/2 - z$).

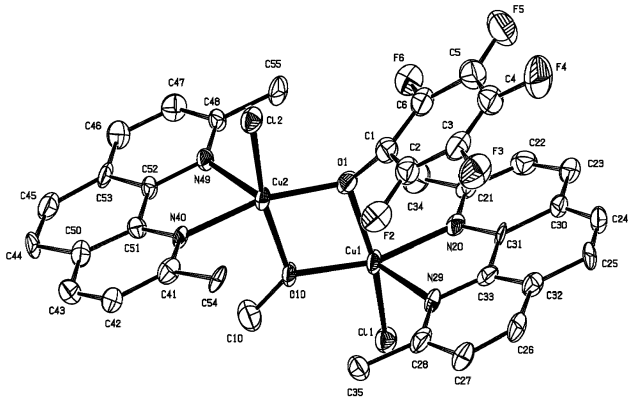

Fig. 6 Displacement ellipsoid plots of $[Cu_2Cl_2(neo)_2(\mu\text{-}C_6F_5O)(\mu\text{-}CH_3O)]$ (**3**) at the 50% probability level. Hydrogen atoms and lattice acetonitrile molecule not shown.

by two N-coordinating pyridyl moieties from a 2,2′-bipyridine (bipy) ligand with normal Cu–N distances and a coordinated chloride anion Cl(2) at an usual distance (Table 2). The angles around Cu(1) can be considered as normal (Table 2). The metal centres Cu(1) and Cu(1a) are separated by a distance of 3.278(6) Å. Unfortunately, the expected μ-methoxo–μ-phenoxo-bridged dinuclear copper coordination compound has not been obtained. This can be explained by the fact that 4-hydroxy-3,5-dimethylbenzaldehyde and 4-hydroxy-3,5-dimethylbenzoic acid are detected by proton NMR in the mother-solution of crystallization. This product indeed indicates that a very slow oxidation reaction catalyzed by the $[CuCl_2(bipy)_2]$ complex is actually taking place during the seven-day crystallization process, which excludes a possible coordination of a phenolate ligand to the copper ions. This oxidation reaction is currently under investigation.

$[Cu_2Cl_2(neo)_2(\mu\text{-}C_6F_5O)(\mu\text{-}CH_3O)]$. An alternative crystallization strategy was then followed using neocuproine as the ligand and a completely unreactive phenolic substrate, namely pentafluorophenol. Reaction of a DMF–MeOH (9 : 1) solution of one equivalent of sodium pentafluorophenoxide and two equivalents of neocuproine, with a DMF–MeOH (9 : 1) solution of two equivalents of $CuCl_2$ and 1.2 equivalents of sodium methoxide yields diamond-shaped green crystals of **3** upon addition of acetonitrile to the reaction mixture (Fig. 6). The asymmetric unit contains a dicopper complex with a partially occupied acetonitrile of crystallisation. The two copper(II) ions are in square pyramidal environments ($\tau = 0.01$ for Cu(1) and $\tau = 0.04$ for Cu(2)).[27] The basal plane around Cu(1) is constituted of two oxygen atoms, O(1) from a bridging phenoxide and

Table 3 Crystallographic data for $[Cu_2Cl_2(bipy)_2(\mu\text{-}Cl)(\mu\text{-}CH_3O)]$ (**2**) and $[Cu_2Cl_2(neo)_2(\mu\text{-}C_6F_5O)(\mu\text{-}CH_3O)]$ (**3**)

Compound	**2**	**3**·0.8CH_3CN
Formula	$C_{21}H_{19}Cl_3Cu_2N_4O$	$C_{35}H_{27}Cl_2Cu_2F_5N_4O_2$ $(C_2H_3N)_{0.8}$
M_r/g mol^{-1}	576.83	861.43
Crystal system	Monoclinic	Triclinic
Space group	$C2/c$	$P1$ (no. 1)
a/Å	16.4463(10)	9.1219(3)
b/Å	7.7606(10)	9.5962(3)
c/Å	18.5145(9)	11.4690(5)
α/°	90	77.4552(14)
β/°	114.620(3)	66.6665(16)
γ/°	90	70.856(2)
V/Å^3	2148.2(3)	866.44(6)
Z	4	1
μ/mm^{-1}	2.376	1.451
Total reflections	28223	20015
Independent reflections	2462	6029
Final R indices $[I > 2\sigma(I)]$	0.0328	0.0508
0.0814	0.1332	
R (all data)	0.0476	0.0759

$\lambda = 0.71073$ Å; $T = 150(2)$ K.

O(10) from a bridging methoxide, and one coordinated chloride anion Cl(1) at common distances. The remaining position is occupied by one of the nitrogen atoms, N(20), belonging to a neo ligand. The second neo nitrogen atom, N(29) is located at the axial position, at a longer distance. The angles around Cu(1) in the basal plane vary from 74.2(3) to 98.6(2)° (Table 2). Furthermore, the pentafluorophenoxide bridging ligand is π-stacked to the central aromatic ring of a neo molecule (centroid–centroid distance of 3.630(5) Å), giving rise to an asymmetric dinuclear moiety, unlike the coordination compound **2**. Cu(2) is also in a square pyramidal arrangement. The basal plane around Cu(2) is constituted of the oxygen atoms O(1) and O(10) from the bridging alkoxides, the chloride anion Cl(2) and the nitrogen atom N(40) from the second neo ligand. The Cu–O distances are in the usual range, as well as the Cu–N and the Cu–Cl bond distances. The axial position is occupied by the nitrogen atom N(49) from the didentate ligand, at a somewhat longer distance (Table 2). The angles around Cu(2) in the basal plane vary from 76.6(3) to 94.9(2)°. The distance between the two copper ions is 3.137(8) Å. To the best of our knowledge, this coordination compound **3** represents the first crystallographic evidence of a self-assembled μ-phenoxo–μ-methoxo-bridged dinuclear copper species with a mononucleating non-bridging ligand, namely neocuproine. Indeed, a search of the Cambridge database[28] (Conquest 1.7, version 5.26) found no other structures of this type. This expected copper compound is in full agreement with the proposed active species **1** (Fig. 2) for the reaction herein reported.

UV-Vis and EPR studies

Sequential addition of copper(II) chloride to a solution of 2,4,6-trimethylphenol–NaOMe. 4 mL of a 75 mM methanolic solution of 2,4,6-trimethylphenol (0.30 mmol) and 0.6 mL of a 0.5 M NaOMe (0.30 mmol) solution in MeOH–DMF were successively added to 68 mL DMF. The sequential addition of $CuCl_2$ (0.5 M in methanol) up to 2 equivalents per 2,4,6-trimethylphenol/NaOMe was then monitored by UV-vis. After each 0.06 mL addition of the copper solution (corresponding to 0.1 equivalent per 2,4,6-trimethylphenol/NaOMe), the reaction mixture was stirred for 5 min before recording the UV-vis spectrum (see ESI,‡ Figs S1–S3). The addition of $CuCl_2$ gives rise to the emergence of an absorption band at 650 nm (ε = 100 M^{-1} cm^{-1}) assigned to d–d transitions of a bis(phenolate)copper(II) complex. Indeed, the maximum absorption is achieved when half an equivalent copper(II) chloride is added. From 0.6 equivalent copper(II) salt added up to 2 equivalents, this band decreases with concomitant increase of a signal at about 900 nm, attributed to free $CuCl_2$ in solution.

Sequential addition of sodium methoxide to a solution of 2,4,6-trimethylphenol–NaOMe–$(CuCl_2)_2$. 2 mL of a 75 mM methanolic solution of 2,4,6-trimethylphenol (0.15 mmol), 0.3 mL of a 0.5 M MeOH–DMF solution of NaOMe (0.15 mmol) and 0.6 mL of a 0.5 M methanolic solution of $CuCl_2$ (0.30 mmol) are consecutively added to 68 mL DMF. The sequential addition of a 0.5 M methanolic solution of NaOMe (0.03 mL which corresponds to 0.1 equivalent) is subsequently followed by UV-vis. After each addition, the reaction mixture is stirred for 20 min before the UV-vis spectrum is recorded (see ESI,‡ Figs S4–S6). The initial spectrum illustrates the presence of an excess of free $CuCl_2$ in solution (absorption band at 900 nm), probably in equilibrium with [Cu(phenolate)$_n$] species (ESI,‡ Fig. S4). Upon addition of sodium methoxide, the free copper(II) band decreases to completely disappear when about 0.8 equivalent of sodium methoxide is added. Simultaneously, two bands at 420 nm (ε = 340 M^{-1} cm^{-1}) and 450 nm (ε = 400 M^{-1} cm^{-1}) are observed (ESI,‡ Fig. S5). These absorptions are typical for a μ-methoxo and a μ-phenoxo bridge, and are respectively attributed to the methanolate oxygen to Cu^{II} and the phenolate oxygen to Cu^{II} charge-transfer transitions.[29,30] Upon addition of more than 1.6 equivalents of NaOMe, this dinuclear mixed bis(μ-alkoxo)copper(II) compound appears to form other species, most likely mononuclear (ESI,‡ Fig. S6).

Sequential addition of sodium methoxide to a solution of 2,4,6-trimethylphenol–NaOMe–$(CuCl_2)_2$/(2,2′-bipyridine)$_2$. 2 mL of a 75 mM methanolic solution of 2,4,6-trimethylphenol (0.15 mmol), 0.3 mL of a 0.5 M MeOH/DMF solution of NaOMe (0.15 mmol), 0.6 mL of a 0.5 M methanolic solution of $CuCl_2$ (0.30 mmol) and 46.9 mg of 2,2′-bipyridine (0.30 mmol) are successively added to 68 mL DMF. The sequential addition of a 0.5 M methanolic solution of sodium methoxide was followed by UV-vis (0.03 mL which corresponds to 0.1 equivalent). After each addition the reaction mixture is stirred for 20 min, before recording the UV-vis spectrum (see ESI,‡ Figs. S7–S9). The initial spectrum is characteristic of a [Cu^{II}(2,2′-bipyridine)$_n$] coordination compound with an absorption at 720 nm, which is assigned to d–d transitions (ESI,‡ Fig. S7). As shown above, the electronic spectrum is modified through the addition of base (ESI,‡ Fig. S8). Thus, the band at 720 nm decreases and the two absorptions at 420 and 450 nm rise, suggesting the formation of the anticipated μ-methoxo–μ-phenoxo-bridged species. The

shoulder at 540 nm is attributed to d–d transitions (ESI,‡ Figs. S8 and S9). Once again, this dinuclear complex is most likely converted to mononuclear alkoxo-species when more than 1.2 equivalents of sodium methoxide are added to the reaction mixture (ESI,‡ Fig. S9).

Addition of various amounts of sodium methoxide to a solution of 2,4,6-trimethylphenol–NaOMe–($CuCl_2$)$_2$. 0.2 mL of a 75 mM methanolic solution of 2,4,6-trimethylphenol (0.015 mmol), 0.03 mL of a 0.5 M MeOH–DMF solution of sodium methoxide (0.015 mmol) and 0.06 mL of a 0.5 M methanolic solution of $CuCl_2$ (0.030 mmol) have been consecutively added to 6.8 mL DMF. From this reaction mixture, five 1 mL samples have been collected and their EPR spectrum recorded after addition of 0, 0.010, 0.020, 0.030 and 0.045 mL of a 0.07 M MeOH–DMF solution of sodium methoxide (0, 0.33, 0.66, 1 and 1.5 equivalents of NaOMe per 2,4,6-trimethylphenol, respectively). The initial X-band EPR spectrum is typical of a mononuclear Cu(II) complex possessing a ($d_x2_{-y}2$) or (d_{xy})^1 ground state ($S = 1/2$), with $g_\parallel > g_\perp$, with values of 2.405 and 2.090, respectively (see ESI,‡ Fig. S10).[31] The EPR spectrum displays hyperfine coupling resulting from the interaction of the unpaired electron with the nuclear spin of ^{63,65}Cu ($I = 3/2$), leading to an $A_\parallel$ of 110 G. This EPR signal characteristic for CuO_n chromophores[32] decreases upon addition of sodium methoxide to give EPR silent species when an amount of extra base corresponding to 1.5 equivalents is reached (ESI,‡ Fig. S10). This indicates the probable formation of μ-methoxo–μ-phenoxo-briged dinuclear copper species, as detected during the UV-vis studies described above (ESI,‡ Figs S4–S6).

Concluding remarks

In conclusion, a bio-inspired [$CuCl_2$–neocuproine–NaOMe] reactant has been developed for the copper-mediated oxidative coupling of various nucleophiles to the *para* C_{sp^3}–H of 2,4,6-trimethylphenol. This 1,6-addition reaction is believed to occur *via* the *in situ* formation of an unstable and thus very reactive quinone methide intermediate. Indeed, a key reaction active species has been isolated and structurally characterised which proved to be the first example of a self-assembled doubly μ-methoxo–μ-phenoxo-bridged dinuclear copper complex involving a non-dinucleating ligand, *i.e.* neocuproine. This dicopper molecule, which has also been detected by UV-vis and EPR studies, suggests the participation of bimetallic species which induce the activation of 2,4,6-trimethylphenol through the creation of a 1,4-benzoquinone methide, followed by the attack of the nucleophilic reagent to the bridged complex. The use of other phenolic substrates with a number of nucleophiles to generate new compounds by means of N–C, O–C or C–C bond formation is currently under investigation, since this copper-mediated reaction represents a potential alternative to the 2,6-dialkylquinone methide 1,6-additions reported in the literature.

Experimental

General considerations

Chemical reagents were used as received from commercial suppliers. All experiments were performed in air. UV-Vis spectra were recorded at room temperature in the 200–1100 nm range with a Cary 50 Varian spectrometer using an Helma optical fiber probe. Elemental analyses were performed at the Microanalytical Laboratory of Leiden University, The Netherlands. X-Band EPR spectra were recorded on a JEOL electron spin resonance spectrometer equipped with an Esprit 330 data system at room temperature and at 77 K, with dpph as an internal reference ($g = 2.0036$). Electrospray ionization mass spectra (ESI-MS) were recorded on a Thermo Finnigan AQA apparatus. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DPX300 spectrometer. Chemical shifts (δ) were referenced to residual proton in deuterated chloroform.

Synthesis‡

4-(Methoxymethyl)-2,6-dimethylphenol (VIa). Sodium methoxide (0.187 g, 3.30 mmol) was added to a solution of 2,4,6-trimethylphenol (**IV**) and $CuCl_2{\cdot}2H_2O$ (0.750 g, 4.40 mmol) in 35 mL of methanol. After 10 min of stirring, the nucleophilic addition was initiated *via* the addition of neocuproine (0.957 g, 4.40 mmol). After 1 h, the reaction mixture was evaporated under reduced pressure. The crude mixture was analysed by ^{1}H NMR which showed 82% conversion of 2,4,6-trimethylphenol to **VIa**. The solid residue was dissolved in 100 mL of dichloromethane. The organic phase was washed with 100 mL of 3.5% aqueous HCl. The acidic aqueous layer was further extracted with dichloromethane (2 × 50 mL). The pooled organic phases were dried over sodium sulfate and then reduced to about 10 mL. The dichloromethane solution was poured onto 100 mL diethyl ether under strong stirring and the precipitate was removed by filtration. The filtrate was evaporated under reduced pressure and the crude product was purified by column chromatography using toluene–diethyl ether (95 : 5) as the eluent. 251 mg of pure **VIa** were obtained as a colorless oil. Yield = 69%; $M = 166.22$ g mol^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.96 (s, 2H, H_{arom}), 4.60 (br s, 1H, OH), 4.32 (s, 2H, CH_2O), 3.36 (s, 3H, CH_3O), 2.24 (s, 6H, CH_3) ppm.

4-Hydroxy-3,5-dimethylbenzaldehyde (VIb). Sodium methoxide (0.500 g, 8.81 mmol) was added to a solution of 2,4,6-trimethylphenol (0.300 g, 2.20 mmol) and $CuCl_2{\cdot}2H_2O$ (1.50 g, 8.81 mmol) in 80 mL methanol. After 10 min of stirring, the oxidation reaction was started by the addition of a first portion of neocuproine (1.920 g, 8.81 mmol). A second portion of neocuproine (1.920 g, 8.81 mmol) was added after 15 min. After a reaction time of 45 min, a sample was analysed by ^{1}H NMR which showed the total conversion of 2,4,6-trimethylphenol to the corresponding aldehyde. The reaction was thus stopped and the solvent evaporated under reduced pressure. The solid residue was dissolved in 100 mL dichloromethane, and the organic phase was washed with 100 mL of 3.5% aqueous HCl. The acidic aqueous phase was further extracted with 2 × 50 mL of dichloromethane. The pooled organic layers were dried over sodium sulfate and concentrated to about 10 mL. The dichloromethane solution was poured onto 100 mL of diethyl ether under vigorous stirring and filtered. The filtrate was evaporated under reduced pressure and purified by column chromatography with diethyl ether as the eluent. 280 mg of pure 4-hydroxy-3,5-dimethylbenzaldehyde were obtained. Yield = 85%; $M = 150.17$ g mol^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.79 (s, 1H, CHO), 7.54 (s, 2H, H_{arom}), 5.66 (br s, 1H, OH), 2.31 (s, 6H, CH_3) ppm.

4-((2-Hydroxyethoxy)methyl)-2,6-dimethylphenol (VIc). 2,4,6-Trimethylphenol (0.510 g, 3.75 mmol) and $CuCl_2{\cdot}2H_2O$ (1.280 g, 7.50 mmol) were dissolved in 10 mL ethane-1,2-diol. Sodium hydride 60% (0.220 g, 5.62 mmol) was added and the 1,6-addition was started upon addition of neocuproine (1.630 g, 7.50 mmol). After 2 h of stirring, 50 mL distilled water were added and the aqueous mixture was extracted with dichloromethane (3 × 50 mL). The pooled organic phases were dried over sodium sulfate, concentrated to 10 mL, and poured onto 50 mL diethyl ether under vigorous stirring. The residue obtained after evaporation of the filtrate was purified by column chromatography on silica gel, with dichloromethane–diethyl ether (3 : 1) as the eluent. 406 mg of pure **VIc** were obtained as a colorless oil. Yield = 55%; $M = 196.24$ g mol^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.95 (s, 2H, H_{arom}), 5.05 (br s, 1H, OH), 4.41 (s, 2H, CH_2O), 3.76–3.56 (m, 4H, CH_2CH_2), 2.22 (s, 6H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 151.98, 129.21, 128.66, 123.21, 73.19, 71.06, 61.83, 15.89; MS (ESI$^+$): m/z (%): 135.5 (100) $[M + H - C_2H_6O_2]^+$, 219.5 (50) $[M + Na]^+$. The product resulting from the coupling of two 2,4,6-trimethylphenol molecules with ethane-1,2-diol was also isolated after column

chromatography as a minor compound. Thus, 90 mg of 1,2-bis(4-oxymethyl-2,6-dimethylphenol)ethane (**VId**) were obtained as a colorless powder. Yield = 15%; M = 330.42 g mol^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.96 (s, 4H, H_{arom}), 4.79 (br s, 2H, OH), 4.43 (s, 4H, CH_2O), 3.64 (s, 4H, CH_2CH_2), 2.22 (s, 12H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 151.76, 129.52, 128.62, 122.95, 73.13, 69.15, 15.86; MS (ESI$^+$): m/z (%): 135.5 (50) $[M + H - C_{11}H_{16}O_3]^+$, 353.0 (100) $[M + Na]^+$.

Bis(4-hydroxy-3,5-dimethylbenzyl)dipyridin-2-yl ammonium chloride (VIe). Sodium hydride (0.220 g, 5.62 mmol) was added to a solution of 2,4,6-trimethylphenol (0.510 g, 3.75 mmol) in DMF (25 mL). After 10 min, $CuCl_2{\cdot}2H_2O$ (1.280 g, 7.50 mmol) and 2,2′-dipyridylamine (0.321 g, 1.87 mmol) were successively added. The reaction was then started upon addition of neocuproine (3.250 g, 15.00 mmol). After 1 h, the reaction mixture was poured onto diethyl ether (100 mL) under vigorous stirring. The precipitate was collected, washed with diethyl ether (2 × 20 mL) and then re-dissolved in 50 mL dichloromethane. The dichloromethane solution was cooled to −20 °C (freezer) overnight. The precipitate was isolated and purified over a short silica gel column chromatography (filtration) with dichloromethane–methanol (9 : 1)) as the eluent. The pure product **VIe** was obtained as a white powder (0.270 g, yield = 30%; M = 476.01 g mol^{-1}). ^{1}H NMR (300 MHz, methanol-d_4): δ 8.22 (m, 2H, py-H), 7.78 (m, 2H, py-H), 7.11 (m, 2H, py-H), 6.90 (m, 2H, py-H), 6.74 (s, 4H, H_{arom}), 5.27 (s, 4H, CH_2N), 2.06 (s, 12H, CH_3); ^{13}C NMR (75 MHz, methanol-d_4): δ 157.29, 154.60, 143.72, 142.49, 129.27, 127.41, 126.09, 117.40, 114.86, 57.22, 16.62; MS (ESI$^+$): m/z (%): 439.8 (100) $[M^+]$. Calc. (%) for $C_{28}H_{30}N_3O_2Cl{\cdot}H_2O$: C, 68.07; H, 6.53; N, 8.51. Found: C, 67.95; H, 6.51; N, 8.43.

3-(4-Hydroxy-3,5-dimethylbenzyl)pentane-2,4-dione (VIf). Sodium hydride 60% (0.450 g, 11.23 mmol) was added to a solution of 2,4,6-trimethylphenol (0.510 g, 3.75 mmol) in 25 mL DMF. After 10 min stirring, $CuCl_2{\cdot}2H_2O$ (1.280 g, 7.50 mmol) and 2,4-pentanedione (0.77 mL, 7.50 mmol) were successively added. The coupling reaction was then initiated by the addition of neocuproine hydrate (1.630 g, 7.50 mmol). After 2 h, 10 mL of a 1 M HCl aqueous solution were added, and the precipitate was filtered off. The precipitate was washed with 50 mL diethyl ether. The organic phase was washed with 100 mL de-ionized water and the aqueous layer was extracted twice with 50 mL diethyl ether. The pooled organic phases were dried over sodium sulfate and the solvent was removed under reduced pressure. The solid residue was purified by column chromatography on silica gel using dichloromethane–diethyl ether (98 : 2) as the eluent. 260 mg of pure product **VIf** were obtained as a yellow oil. Yield = 30%; M = 234.29 g mol^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) of **VIe** and its enolic form: δ 6.76 (s, 1.16H, H_{arom}), 6.73 (s, 0.84H, H_{arom}), 4.53 (s, 0.42H, Ar–OH), 4.52 (s, 0.58H, Ar–OH), 3.96 (t, ^3J(H,H) = 7.52 Hz, 0.58H, CH–C(O)), 3.53 (s, 0.84H, Ar–CH_2), 3.02 (d, 1.16H, Ar–CH_2), 2.23–2.08 (m, 12H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 204.19, 191.96, 150.96, 150.63, 130.73, 129.06, 128.57, 127.30, 123.33, 108.69, 70.20, 33.43, 31.85, 29.69, 23.21, 15.98, 15.86; MS (ESI$^+$): m/z (%): 135.5 (20) $[M + H - C_5H_8O_2]^+$, 235.1 (100) $[M + H]^+$, 257.1 (30) $[M + Na]^+$.

2-(4-Hydroxy-3,5-dimethylbenzyl)isoindoline-1,3-dione (VIg). Sodium hydride 60% (0.220 g, 5.62 mmol) was added to a solution of 2,4,6-trimethylphenol (0.510 g, 3.75 mmol) in 25 mL DMF. After 10 min, $CuCl_2{\cdot}2H_2O$ (1.280 g, 7.50 mmol) and potassium phthalimidate (0.760 g, 4.13 mmol) were successively added. The 1,6-addition was then started by addition of neocuproine hydrate (1.630 g, 7.50 mmol). After 2 h stirring, 10 mL of 1 M HCl were added and the reaction mixture was filtered. The precipitate was washed with 50 mL diethyl ether. The filtrate was washed with de-ionized water (100 mL). The aqueous phase was further extracted with diethyl ether (2 × 50 mL) and the joint organic phases were dried over sodium sulfate and evaporated under reduced pressure. The solid residue was purified by column chromatography (SiO_2, dichloromethane–diethyl ether (9 : 1)). 357 mg of pure product **VIg** were obtained as a white powder. Yield = 34%; M = 281.31 g mol^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.83 (dd, ^3J(H,H) = 5.40, ^3J(H,H) = 3.09 Hz, 2H, H_{arom}), 7.69 (dd, ^3J(H,H) = 5.40, 3.09 Hz, 2H, H_{arom}), 7.07 (s, 2H, H_{arom}), 4.71 (s, 2H, CH_2), 4.64 (s, 1H, OH), 2.20 (s, 6H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.16, 151.82, 133.89, 132.16, 129.12, 128.06, 123.26, 123.10, 41.10, 15.84; MS (ESI$^+$): m/z (%): 282 $[M + H]^+$. Calc. (%) for $C_{17}H_{15}NO_3$: C, 72.58; H, 5.37; N, 4.98. Found: C, 72.00; H, 5.45; N 4.89.

4-(Aminomethyl)-2,6-dimethylphenol (VIh). A solution of **VIg** (0.220 g, 0.78 mmol) in 4 mL of AcOH–6 M HCl (1 : 1) was refluxed overnight. The solvent was evaporated under reduced pressure and the solid residue was purified by column chromatography on silica gel using the solvent mixture dichloromethane–MeOH–NH_3 (32 wt%)(aq) (84 : 15 : 1) providing the pure product **VIh** as a colourless oil (0.094 g, yield = 80%; M = 151.21 g mol^{-1}). ^{1}H NMR (300 MHz, methanol-d_4): δ 6.87 (s, 2H H_{arom}), 3.62 (s, 2H, CH_2), 2.19 (s, 6H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 153.48, 133.68, 128.72, 125.72, 46.05, 16.68; MS (ESI$^+$): m/z (%): 135.3 (100) $[M + H - NH_3]^+$, 152.5 (25) $[M + H]^+$.

$[Cu_2Cl_2(C_{10}H_8N_2)_2(CH_3O)(Cl)]$ (2). 2,4,6-Trimethylphenol (0.200 g, 1.47 mmol) was added to a suspension of NaH 60% (0.058 g, 1.47 mmol) in 12 mL of DMF–MeOH (5 : 1). A solution of $CuCl_2{\cdot}2H_2O$ (0.501 g, 2.94 mmol) in 6 mL DMF was added to the reaction mixture, followed by a suspension of 2,2′-bipyridine (0.459 g, 2.94 mmol) in 4 mL DMF. 128 mL of DMF were then added. Finally, a solution of NaH 60% (0.071 mg, 1.76 mmol) in 2 mL MeOH was added. Green block crystals were obtained after seven days by acetonitrile diffusion into the DMF–MeOH solution of reactants. Single crystals, suitable for X-ray structure determination were isolated by filtration. Yield = 62%. Calc. (%) for $Cu_2Cl_2(bipy)_2(\mu\text{-}CH_3O)(\mu\text{-}Cl)$: C, 43.72; H, 3.32; N, 9.71. Found: C, 43.65; H, 3.51; N, 9.46. EPR silent.

$[Cu_2Cl_2(C_{14}H_{12}N_2)_2(CH_3O)(C_6F_5O)]{\cdot}0.8CH_3CN{\cdot}H_2O$ (3). A mixture of NaOMe (11.4 mg, 0.20 mmol), pentafluorophenol (37 mg, 0.2 mmol) and neocuproine (87 mg, 0.40 mmol) was dissolved in 35 mL of DMF–MeOH (9 : 1) and stirred during 5 min. A solution of $CuCl_2{\cdot}2H_2O$ (68 mg, 0.40 mmol) in 3 mL DMF–MeOH (9 : 1) was added and the reaction mixture was stirred 5 min before adding a second portion of NaOMe (13.6 mg, 0.24 mmol). 20 mL of acetonitrile were added to the dark green solution and after three days, green crystals, suitable for X-ray crystallography, were collected by filtration. Yield = 47%. Calc. (%) for $Cu_2Cl_2(neo)_2(\mu\text{-}CH_3O)(\mu\text{-}C_6F_5O){\cdot}0.8CH_3CN{\cdot}H_2O$: C, 49.98; H, 3.60; N, 7.64. Found: C, 50.09; H, 3.53; N, 7.69. EPR silent.

X-Ray crystallography

Crystallographic data were collected on a Nonius KappaCCD[33] diffractometer with graphite-monochromated Mo-Kα radiation with a frame time of 60 s per degree and a detector distance of 40 mm. A suitable crystal was mounted on the tip of a 0.1 mm diameter glass capillary. Crystal, data collection, and refinement parameters are given in Table 3. The structures were solved using SHELXS86[34] and DIRDIF.[35] All non-hydrogen atoms were refined with anisotropic displacements parameters. All hydrogen atoms were placed in ideal positions and refined as riding atoms with relative isotropic displacement parameters.

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See http://dx.doi.org/10.1039/b507199b for crystallographic data in CIF or other electronic format.

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