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Catalytic oxidation of hindered phenols by a copper(I) complex and dioxygen†

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Abstract

The dioxygen reaction product of a binuclear copper(I) complex of a new *m*-xylyl-based ligand has proven to be a catalyst in the promotion of oxidative carbon–carbon coupling of hindered phenols, which leads to bisphenol and diphenoquinones.

Keywords: *m*-xylyl-based dinucleating ligand; binuclear copper complexes; phenol oxidation.

The activation and processing of dioxygen by copper play a crucial role in biological systems[1] and are of interest in oxidative synthetic reactions.[2] Tyrosinase is a dinuclear copper-containing monooxygenase, which hydroxylates monophenols (tyrosine) and further oxidizes the *o*-diphenol to an *o*-quinone.[1,2] For the construction of biomimetic systems exhibiting tyrosinase-like activity, *m*-xylyl-based dinucleating ligands have proven very useful.[3–8] However, a major drawback of such systems, with the exception of the benzimidazole system of Casella and co-workers,[9] is the rapid hydroxylation of the C–H bond of the 2-position and hence they are not suitable for catalytic oxidation of externally introduced substrates. As a first step toward achieving such a goal we have modified our original ligands L^1/L^2,[4,5] which exhibit aromatic ring hydroxylation (C–H→C–OH), by a C–F bond containing ligand L^3 (Scheme 1).‡ We provide here a general straightforward route to bring about oxidative carbon–carbon coupling of hindered phenols leading to bisphenol and diphenoquinones.

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† Dedicated to Professor M. V. George on the occasion of his 73rd birthday.

‡ The structural characterization of the phenoxo- and hydroxo-bridged dicopper(II) product **4** unequivocally demonstrated the oxygenation of the ligand L^1.[4]

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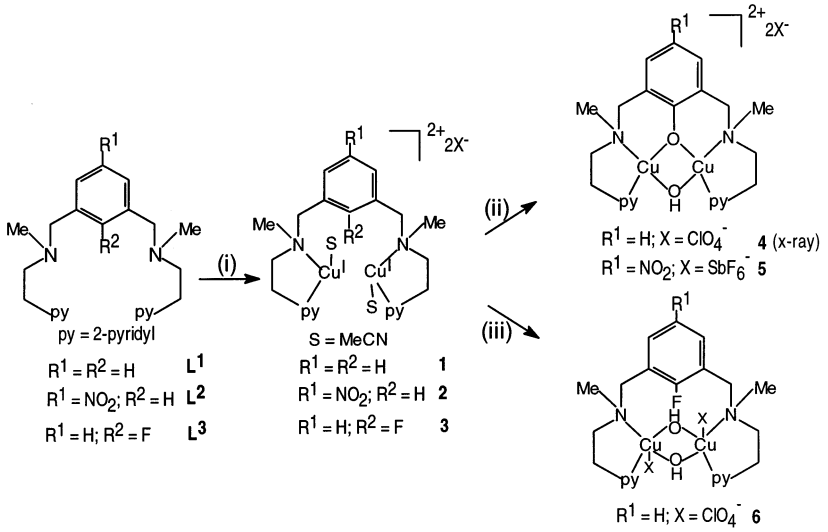


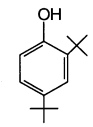
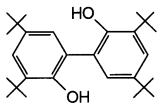
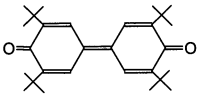
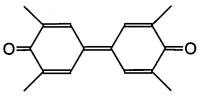
Scheme 1. Reaction conditions: (i) $[Cu(MeCN)_4]X$ ($X = ClO_4^-$ or SbF_6^-), CH_2Cl_2, N_2; (ii) and (iii), O_2

The new ligand α,α′-bis[(*N*-methyl-2-pyridyl)ethylamino]-2-fluoro-*m*-xylene (L^3) was prepared by condensation of 2,6-bis-(bromomethyl)fluorobenzene[10] (1.77 mmol) and 2-(2-methylaminoethyl)pyridine (3.54 mmol) in the presence of Et_3N (3.54 mmol) in THF (25 ml) for 24 h at 298 K. Subsequent filtration, followed by removal of solvent yielded a thick yellow oil of L^3 in 90% yield.[§] The yellowish copper(I) complex $[(L^3)Cu^I_2(MeCN)_2][ClO_4]_2$ **3** was generated by adding the ligand L^3 (0.255 mmol), dissolved in CH_2Cl_2 (10 ml), to the appropriate amount of $[Cu(MeCN)_4](ClO_4)$[4] under strictly anaerobic conditions. Subsequent reaction with dry O_2 at −50°C instantaneously leads to a green solution, which on warming to room temperature, afforded a blue solid of composition '$(L^3)Cu^{II}_2(OH)_2(ClO_4)_2$' **6** in 80% yield (Scheme 1).[¶]

[§] Elemental analysis: calcd for $C_{24}H_{29}N_4F$: C, 73.47%, H, 7.40%; N, 14.29%. Found: C, 73.88%; H, 7.81%; N, 14.54%. ^1H NMR data: (δ/ppm vs TMS) in $CDCl_3$: 2.35 (s, 6H, NMe), 2.92 (t, 4H, -CH_2-), 3.07 (t, 4H, -CH_2-), 3.71 (s, 4H, PhCH_2N), 7.02–7.62 (m, 9H, Ar-H) and 8.49 (d, 2H, pyridyl-6H). Mass analysis: m/z calcd for $C_{24}H_{29}N_4F$: 392. Found: 392.

[¶] **Caution**: The perchlorate salt is potentially explosive and should be handled with care. Elemental analysis: calcd for $Cu_2C_{24}H_{31}N_4Cl_2FO_{10}$: C, 38.29%; H, 4.12%; N, 7.45%. Found: C, 38.91%; H, 4.29%; N, 7.68%. Mass (FAB) analysis: m/z calcd for $Cu_2C_{24}H_{31}N_4Cl_2FO_{10}$: 752. Found: 755 (M+3H$^+$). IR (Nujol, cm^{-1}), ν(OH) 3480; $\nu(ClO_4^-)$ (coordinated perchlorate) 1120, 1100, 1070, 620 (cf. Gupta, R.; Mukherjee, S.; Mukherjee, R. *J. Chem. Soc., Dalton Trans.* **1999**, 4025–4030). UV–Vis (MeCN) λ_{max}/nm (ε/M^{-1} cm^{-1}): 640 (180), 375 sh (400), 295 sh (4100) and 262 (13 500). Isolation of a similar dihydroxy-bridged compound with tridentate arms (but with Cl in the place of F) has been reported: Nasir, M. S.; Cohen, B. I.; Karlin, K. D. *Inorg. Chim. Acta* **1990**, *176*, 185–186.

Table 1
Catalytic oxidation of hindered phenols by dicopper(I) complex **3** and dioxygen[a–c]

substrate	product	yield (%)	Reaction time (hrs.)	Turnover number
		91	6	5
		85 (nil)[d]	6 (60)	5 (50)
		86 (96)[e]	6 (9)	10 (50)

[a] Reaction conditions for mushroom tyrosinase catalysis: phosphate buffer (pH 6.8); diphenoquinones were exclusive products when the catalytic reaction was performed in only phosphate buffer; however, when MeCN was used as co-solvent 4,4′-bisphenols were also isolated, though in poorer yields than diphenoquinones. [b] Yield reported in this paper is defined as: (product formed/substrate used) x 100. Turnover number is defined as the number of moles of substrate/number of moles of copper(I) complex **3**. [c] Yields and turnover numbers in parentheses are for the enzyme tyrosinase . [d] MeCN as co-solvent, yield: 40%. [e] MeCN as co-solvent, yield: 70%.

Reaction of 2,4-di-*tert*-butylphenol, 2,6-di-*tert*-butylphenol or 2,6-dimethylphenol with CH_2Cl_2 solutions of **3** resulted in the formation of phenoxyl radical derived coupling products.[‖] It should be mentioned here that the synthetic accessibility of oxidative carbon–carbon coupling of hindered phenols leading to diphenoquinones and bisphenols is, however, rather complicated.[11,12] To get an idea of the potential of our system relative to that of natural systems we

[‖] *Experimental conditions for phenol oxidation*: Typically, the substrate was added to a CH_2Cl_2 solution (10 ml) of **3** at 25°C, under strictly anaerobic conditions and then the mixture was exposed to dioxygen, contained in a balloon, for ~10 s and immediately excess O_2 was pumped off and the reaction mixture was allowed to stir. After 6 h solvent was removed and the crude material was treated with 0.1N HCl and the organic product was extracted into CH_2Cl_2 and characterized by mass and ^1H NMR spectra. 0.128 mmol of dicopper(I) complex **3** converts 5 equivalents of 2,4-di-*tert*-butylphenol and 2,6-di-*tert*-butylphenol to the corresponding C–C coupling product. An equimolar amount converts 10 equivalents of 2,6-dimethylphenol to the corresponding diphenoquinone. Characterization data: (a) 3,3′,5,5′-tetra-*tert*-butyl-2,2′-dihydroxybiphenyl ^1H NMR: (δ/ppm vs TMS) in $CDCl_3$: 1.35 (s, 18H, CMe_3), 1.43 (s, 18H, CMe_3), 6.75 (d, 2H, Ar-H), 7.04 (d, 2H, Ar-H). Mass spectrum (solid) 410 [3,3′,5,5′-tetra-*tert*-butyl-2,2′-droxybiphenyl, M] (90%), 411 (M+H$^+$) (56%), 396 {(M−Me)+H$^+$} (58%), 395 (M−Me) (94%). (b) 3,3′,5,5′-tetra-*t*-butyl-4,4′-diphenoquinone ^1H NMR: (δ/ppm vs TMS) in $CDCl_3$: 1.40 (s, 36H, CMe_3), 7.80 (s, 4H, Ar-H). Mass spectrum (solid) 410 [3,3′,5,5′-tetra-*t*-butyl-4,4′-diphenoquinone, M+2H$^+$] (60%), 396 {(M−Me)+H$^+$} (31%), 395 (M−Me) (66%). (c) 3,3′,5,5′-tetramethyl-4,4′-diphenoquinone ^1H NMR: (δ/ppm vs TMS) in $CDCl_3$: 2.3 (s, 12H, Me) and 8.7 (s, 4H, Ar-H). Mass spectrum (solid) 242 [3,3′,5,5′-tetramethyl-4,4′-diphenoquinone, M+2H$^+$] (100%) and 240 (M) (30%).

have compared our results with the activity of mushroom tyrosinase[13] (Table 1) and two observations emerge: (i) for 2,6-di-*tert*-butylphenol the dioxygenated product of complex **3** provides a better isolated yield of the diphenoquinone than that obtained with tyrosinase. For 2,6-dimethylphenol the yields obtained with tyrosinase and our system are comparable. (ii) Compared to tyrosinase the turnover numbers obtained with the present system are not impressive. However, it is beyond doubt that the product obtained from our binuclear complex **3** and dioxygen is a catalyst in promoting the oxidation of hindered phenols and the yields of the diphenoquinones are good. It is worth noting here that well-characterized copper(II)-peroxo complexes also show similar reactivity behavior.[14,15]

In summary, we have demonstrated that under suitable reaction conditions, CH_2Cl_2 solutions of a dicopper(I) complex catalytically convert 2,4-di-*tert*-butylphenol to a C–C coupled bisphenol product and 2,6-dimethylphenol or 2,6-di-*tert*-butylphenol to diphenoquinones. This is the first time that a *m*-xylyl-based open-chain ligand system, providing only two nitrogens coordinated to each copper center, that exhibits aromatic ring hydroxylation (C–H to C–OH transformation) has been modified by replacement of the C–H bond activating site by a C–F bond, exhibits exogenous substrate reactivity. In essence, replacement of the *m*-xylyl C–H bond by C–F inhibits the endogenous ligand hydroxylation and this is a necessary condition to perform the present catalytic oxidations.** In this work hindered phenols have been used as the substrates and a comparison has been made regarding the efficiency of this model system to that of a naturally occurring *tyrosinase*. Structural characterization of the irreversibly oxidized dihydroxy-bridged copper(II) compound **6** is currently underway and will be published elsewhere.

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** It should be noted here that although Karlin et al.[10] synthesized a closely similar ligand with tridentate arms containing bis[(2-pyridyl)ethyl]amine units, the use of such a system for externally added substrate oxidation studies has so far not been reported.

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