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Ortho-Hydroxylation of Phenol by Tyrosinase Model Compounds

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Abstract: A series of tyrosinase model ligands and complexes containing polyimidazoles were prepared. 2, 4-Di-*tert*-butyl-phenol was *ortho*-hydroxylated by the binuclear copper (I) complex $[Cu_2(\mathbf{6a})(CH_3CN)_2](ClO_4)_2$ **8a** and molecular dioxygen under mild conditions with up to 80.4% yield, 91.4% selectivity and 92.0% conversion.

Keywords: Tyrosinase model compound, mimic enzyme catalysis, *ortho*-hydroxylation of phenol, polyimidazole, binuclear copper (I) complex.

Tyrosinase (Tyr) is a copper monooxygenase that catalyzes oxygenation of phenols to catechols (phenolase activity) and the subsequent two-electron oxidation of catechols to the corresponding *O*-quinones (catecholase activity). Chemical and spectroscopic studies indicate that the enzyme belong to the family of type 3 copper proteins containing a binuclear copper active site coordinated by six histidines which is involved in a variety of biological functions[1, 2]. Mimic enzyme catalysis is a new challenging project in bioorganic chemistry. Attempt to duplicate peculiar monophenolase activity of Tyr in model systems can be dated from mid-1950s, there have been also a number of reports that demonstrated the catechol and /or o-quinone formation from phenol derivatives in the reaction with a copper complex under aerobic conditions[3-6]. Casella and co-workers have recently reported the first synthetic complex (**Scheme 1**) that can react with exogenous phenolic compounds to yield the corresponding catechols[7]. With respect to the intermolecular reactions between phenols and the peroxo intermediate, however, most of reactions so far reported afford a C-C coupling dimer as a major product, moreover, the yield of the catechol is not satisfactory. Itoh *et al*. reported that efficient conversion of phenol derivatives to the corresponding catechols was achieved by intermolecular reactions of a (μ-η^2 : η^2-peroxo) binuclear copper (Ⅱ) complex derived from $[Cu^{I}(L^{PY2Bz})](PF_6)$ (**Scheme 2**), with lithium salts of phenols at -94℃[8]. However, to our knowledge, the binuclear three-coordinate copper (I) complexes derived from the polyimidazole ligands exhibiting tyrosinase-like activity on exogenous phenols under mild conditions have not been reported.

Our interest has been focused on the synthesis and application of imidazole, imidazolium and their derivatives[9-15]. We previously reported the synthesis of novel

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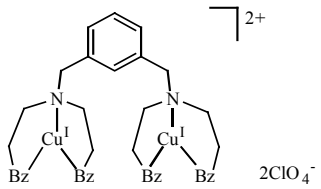
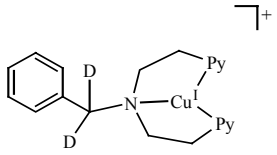
Scheme 1

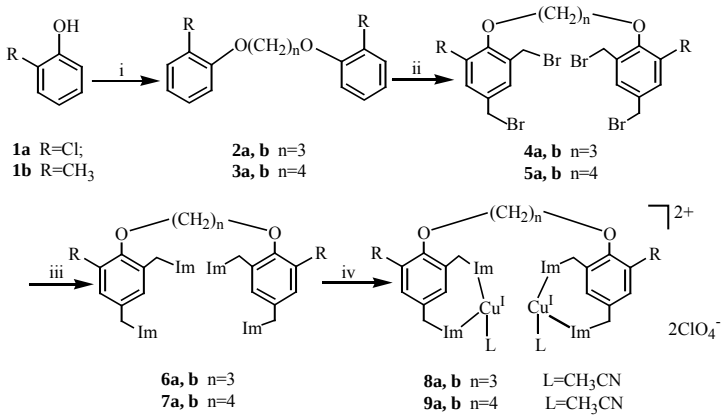


Bz =1-methyl-benzimidazole

Scheme 2



Scheme 3 Synthesis of ligands and complexes



1a R=Cl; **1b** R=CH_3 **2a, b** n=3 **3a, b** n=4 **4a, b** n=3 **5a, b** n=4

6a, b n=3 **7a, b** n=4 **8a, b** n=3 L=CH_3CN **9a, b** n=4 L=CH_3CN

Reaction conditions: (i) $Br(CH_2)_nBr$ (n=3, 4), K_2CO_3, DMF; (ii) HBr/HCHO, CH_3COOH; (iii)3-(N-imidazolyl) propanenitrile, NaOH, dioxane; (iv) $Cu(MeCN)_4ClO_4$, CH_3OH/THF

binuclear copper protein models and their applications in catalytic oxidation of benzoin[10] and catalytic hydrolysis of carboxylates and phosphates[11]. Here we report an efficient synthetic method of these model complexes (**Scheme 3**) and their application in ortho-hydroxylation of phenol.

Reaction of 2-substituted phenols **1** with $Br(CH_2)_nBr$ in the presence of K_2CO_3 gave phenol ethers **2** and **3** which were bromomethylated in bromine hydride and formaldehyde affording compounds **4** and **5**. The model ligands **6** and **7** were obtained by treatment **4, 5** with 3-(N-imidazolyl)propanenitrile followed by Hoffmann-type elimination in the presence of NaOH[14]. Then a series of binuclear copper (I) complexes **8** and **9** were prepared according to the literature[10]. The structures of all the ligands and their complexes were confirmed by ^{1}HNMR, MS and Elemental analysis *etc*. For example, the characteristic data of compound **6a** are listed below: mp: 164-165℃; IR (KBr, ν cm^{-1}): 1630, 1572, 741, 661; ^{1}HNMR (300MHz, $CDCl_3$) δ ppm: 2.28 (m, 2H, -CH_2-), 4.07 (t, 4H, J=6.3Hz, -OCH_2-), 5.15 (d, 8H, J=14.4Hz, $PhCH_2$-), 6.73 (d, 2H, J=2.0Hz, Ph-H), 6.91(s, 4H, ImH-2), 7.11 (d, 4H, J=5.3Hz, ImH-4, 5), 7.14 (d, 2H, J=2.0Hz, Ph-H), 7.62 (d, 4H, J=9.7Hz, ImH-4, 5); MS (*m*/*z*): 618.2 $(M+H)^+$; Anal. Calcd. for $C_{31}H_{30}Cl_2N_8O_2$: C, 60.29; H, 4.86; N, 18.15. Found C, 60.34; H, 4.83; N, 18.20.

The model complexes were applied to the *ortho*-hydroxylation of exogenous phenols (**Scheme 4**). The binuclear copper (I) complexes, reaction solvent, temperature,

the amount of base and the additional activated copper powder, which are the important factors affecting the *ortho*-hydroxylation, were examined. We took the reaction of 2,4-di-*tert*-butyl phenol (DTBP) **1** with complex **8a** in the presence of dioxygen as a typical example. The results were summarized in **Table 1**.

It was shown that the mixed solvent (CH_3CN/CH_2Cl_2) and low temperature facilitated the formation of catechols **2** while the coupling dimer **3** was the major product in CH_3CN or CH_2Cl_2 (entries 1, 4). The appropriate amount of K_2CO_3 was important for the reaction, since further increasing or decreasing the amount of base led to the lower yield and selectivity of **2** (entries7, 8, and 9). We also found that the additional activated copper powder of the system was necessary for minimizing other side reactions, which may bring to some complicated products. By varying binuclear copper (I) complexes and their amounts, we found that different substituted groups and bridge linkers obviously affected the *ortho*-hydroxylation of **1** and complex **8a** exhibited better results: the yield and selectivity of **2** up to 80.4%, 91.4% respectively at conversion of **1** up to 92.0% (entries10, 14, 15 and 16).

Scheme 4 *Ortho*-hydroxylation of DTBP catalyzed by the binuclear copper (I) complexes

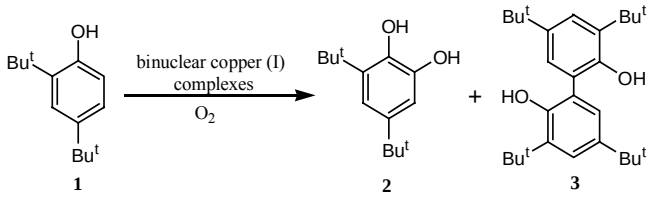


Table 1 The results of *ortho*-hydroxylation of DTBP[a]

Entry	CH_3CN / CH_2Cl_2 (mL/mL)	Catalyst (equiv.)	K_2CO_3 (equiv.)	Reaction Temp. / Time (h)		Isolated Yield (%)		Conv. (%)	Select. (%)
				0(℃)	20±2(℃)	**2**	**3**		
1	15:0	0.05	1.5	7	17	17.3	71.4	89.0	20.0
2	10:2	0.05	1.5	7	17	22.7	45.5	68.7	33.3
3	10:5	0.05	1.5	7	17	59.0	27.3	86.3	68.4
4	0:15	0.05	1.5	7	17	trace	74.0	80.0	-
5	10:5	0.05	1.5	7	11	30.8	41.2	72.0	42.8
6	10:5	0.05	1.5	4	17	50.7	29.0	82.6	63.6
7	10:5	0.05	1.0	7	13	67.0	24.9	91.9	72.9
8	10:5	0.05	2.0	7	13	55.9	34.0	90.4	62.2
9	10:5	0.05	1.5	7	13	72.7	13.6	88.9	84.2
10	10:5	0.05	1.5	10	13	80.4	7.6	92.0	91.4
11	10:5	0.10	1.5	10	13	50.0	31.8	82.0	61.1
12	10:5	0.075	1.5	10	13	54.7	30.4	85.1	64.3
13	10:5	0.03	1.5	10	13	48.2	28.6	76.8	62.8
14b	10:5	0.05	1.5	10	13	40.9	36.4	77.5	52.9
15c	10:5	0.05	1.5	10	13	31.8	40.9	73.1	43.7
16d	10:5	0.05	1.5	10	13	24.3	35.8	60.4	40.4

a: Reaction conditions catalyst **8a**; substrate (DTBP) 1 mmol; activated coppe powder (1.5 equiv.); 3Å molecular sieve 1 g;

b, c, d: catalyzed by **8b**, **9a**, **9b** respectively. The other reaction conditions were identical with a.

In conclusion, we successfully prepared a series of tyrosinase model ligands and complexes containing polyimidazoles. All the complexes are able to mediate the *ortho*-hydroxylation of exogenous phenols in the presence of dioxygen under mild conditions, which exhibits tyrosinase-like activity, and complex **8a** exhibits better results. The further study on the selective oxidation of other substrates with model complexes is in progress.

Acknowledgments

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References and Notes

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16. General procedure for *ortho*-hydroxylation: A mixture of DTBP (1 mmol), anhydrous potassium carbonate (1.5 mmol), active copper powder (1.5 mmol), 3Å molecular sieve 1 g and the catalytic amount of **8a** (0.05 mmol) was placed in a 50 mL glass flask followed by injecting degassed CH_3CN and CH_2Cl_2 (10/5 mL/mL). The reaction mixture was stirred at 0℃ for 7 h by bubbling dioxygen directly into reaction vessel, and then was stirred at room temperature for additional 13 h. The initial faint yellow solution was present dark brown at the end of reaction. The mixture was diluted with 10 mL diethyl ether and 50 mL saturation sodium chloride solution. The aqueous layer was extracted with diethyl ether (2×10 mL) and the combined organic extracts were dried over anhydrous $MgSO_4$. Removal of the solvent under reduced pressure afforded a residue that was purified through silica gel column (petrol ether / dichloromethane, 10/1).

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