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Letter

Multidentate *N*-heterocyclic podand ligand. Efficient oxygenation of phenols catalyzed by novel cobalt complex

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Abstract

An efficient catalytic system for oxygenation of phenols to the *p*- or *o*-quinones with molecular oxygen was achieved by utilization of a complex catalyst consisting of $Co(OAc)_2$ and the multidentate *N*-heterocyclic podand ligand, *N,N'*-bis{2-(2-pyridyl)ethyl}-2,6-pyridinedicarboxamide.

Keywords: Acetate ligand; Cobalt; *N*-Heterocyclic ligand ; Multidentate podand ligand; Oxygenation; Phenols; Quinones

1. Introduction

Selective oxygenation of various organic compounds with molecular oxygen is of importance from synthetic and biological viewpoints. Smooth electron transfer based on reversible redox of transition metal complexes is required for an efficient catalytic cycle. Since ligand coordination greatly contributes to controlling its process, good ligand design is essential to construct a versatile catalytic system. In a previous paper [1], it has been demonstrated that the coordination interaction between $FeCl_2$ and the flexible multidentate podand ligand, *N,N'*-bis{2-(4-imidazolyl)ethyl}-2,6-pyridinedicarboxamide (BIPA), ingeniously enhances the epoxidation reaction with molecular oxygen. This method does not require the coexistence of a reductant, being in contrast to P-450 and its model systems. The requisite complex is considered to be formed for the efficient epoxidation. This finding prompted us to investigate an oxygenation system based on flexible podand ligands.

Tyrosinase is a typical monooxygenase. A variety of tyrosinase models have been investigated so far to address its mechanism [2] and a more efficient oxygenation system [3]. Since chelate Co(II) complexes are known to catalyze the oxygenation of phenols to *p*-benzoquinones, extensive studies have been focused on the complexes of Schiff bases [4], porphyrins [5], and so on [6]. However, these catalysts are not always synthetically useful, partly due to the instability of these ligands. Herein we report a selective and efficient oxygenation of phenols with molecular oxygen induced by a complex catalyst consisting of $Co(OAc)_2$ and a multidentate *N*-heterocyclic podand ligand.

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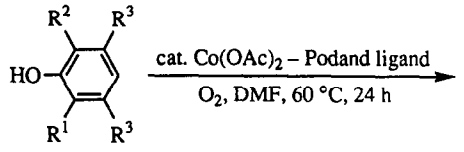
2. Results and discussion

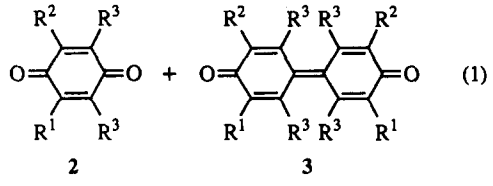
Treatment of 2,6-di-*t*-butylphenol (**1a**) with 5 mol% of $Co(OAc)_2$ and 2-BPEPA, *N,N'*-bis{2-(2-pyridyl)ethyl}-2,6-pyridinedicarboxamide, in DMF under an atmospheric pressure of molecular oxygen resulted in the selective formation of the corresponding *p*-benzoquinone **2a** in a good yield with a small amount of the dehydrogenative coupling product **3a** (Eq. 1). DMF was superior to *N,N*-dimethylacetamide and 1-methyl-2-pyrrolidinone as a solvent (Table 1). $Cu(OAc)_2$ [2a,d,3] did not induce the oxygenation reaction only giving the diphenoquinone **3a** even in the presence of 2-BPEPA.

It should be noted that the oxygenation depends on the podand ligands. Use of BIPA bearing the 4-imidazolyl group, which is effective in the $FeCl_2$- or $Co(OAc)_2$-catalyzed epoxidation reaction with molecular oxygen [1], drastically decreased the conversion to **2a** with the predominant formation of **3a**. A combination of 2-BPEPA and $Co(OAc)_2$ gives a poor result in the epoxidation [1]. Taking them into consideration, the 4-imidazolyl and 2-pyridyl groups are considered to play a respective important role in each oxygenation possibly due to the difference of the coordination interaction. It is consistent with the observation that BPHEPA bearing the phenyl group instead was no more efficient ligand for the present oxygenation.

The complexation of $Co(OAc)_2$ with 2-BPEPA was verified by the following observations. Cyclic voltammetry of $Co(OAc)_2$ with an equimolar amount of 2-BPEPA in methanol gave the new cobalt reduction wave at −0.07 V. A new absorption at 317 nm also appeared in the UV–Vis. spectrum of $Co(OAc)_2$ and 2-BPEPA in DMF. The cobalt complex was isolated by treatment of $Co(OAc)_2$ with an equimolar amount of 2-BPEPA in methanol. The spectral data showed the substitution of cobalt with two amide moieties and the different coordination sites of two podand 2-pyridyl groups. One of them is assumed to serve as an intramolecular axial ligand as proposed in

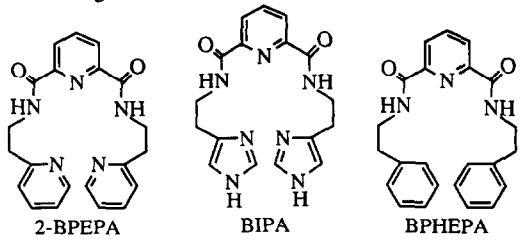


1a : R^1=R^2=Bu-*t*, R^3=H
b : R^1=R^2=Me, R^3=H
c : R^1=R^3=Me, R^2=H



2 **3** (1)

Podand ligand :

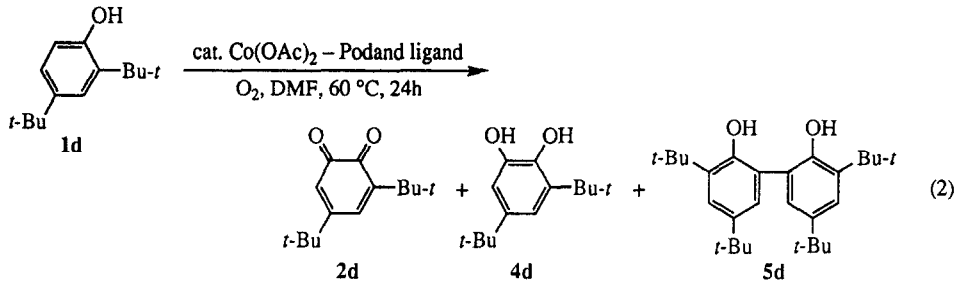


2-BPEPA BIPA BPHEPA

Table 1
Catalytic oxidation of phenols [a]

1	Ligand	Solvent	Yield (%) [b]	
			2	3
a	2-BPEPA	DMF	86, 82[c]	9
	2-BPEPA[d]	DMF	92	6
	BIPA	DMF	10	41
	BPHEPA	DMF	0	38
	–	DMF	0	45
	2-BPEPA	DMAC[e]	54	10
	2-BPEPA	NMP[f]	76	7
b	2-BPEPA	DMF	77, 71[c]	1
	BIPA	DMF	1	0
	BPHEPA	DMF	0	0
	–	DMF	0	0
c	2-BPEPA	DMF	70	0
	BIPA	DMF	0	0
	BPHEPA	DMF	0	0
	–	DMF	0	0

[a] Metal salt, 0.01 mmol; ligand, 0.01mmol; **1**, 0.20 mmol.
[b] GLC yields based on **1**.
[c] Isolated yield.
[d] Use of the isolated complex.
[e] DMAC = *N,N*-dimethylacetamide.
[f] NMP = 1-methyl-2-pyrrolidinone



Podand ligand :	2-BPEPA	72, 69[a] %	5 %	trace
	BIPA	0	0	9 %
	BPHEPA	0	0	0
	—	0	0	0

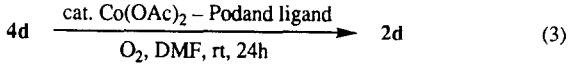
[a]Isolated yield

the Fe(II)–BIPA complex [1]. This coordination mode is likely to contribute the efficiency of the catalyst. The higher catalytic activity was attained by use of thus isolated complex in the oxygenation of **1a** to **2a** (Table 1).

A substituent on a phenol ring is known to markedly influence the rate of oxidation due to redox potential. More distinct efficiency of the podand ligand 2-BPEPA was observed in the oxygenation of 2,6-dimethylphenol (**1b**) to the quinone **2b**. Furthermore, the $Co(OAc)_2$-catalyzed oxygenation of 2,3,5-trimethylphenol (**1c**) to **2c** was almost quantitatively accomplished by 2-BPEPA. A combination of $Co(OAc)_2$ and 2-BPEPA is only effective. In contrast, with BIPA or BPHEPA, the oxygenation reaction did not proceed under the conditions employed here.

The phenol **1d** blocked at the *para* position underwent the selective catalytic oxygenation to the *o*-benzoquinone **2d** in the presence of $Co(OAc)_2$ and 2-BPEPA. The activity difference of the podand ligands was huge only giving poor results with BIPA and BPHEPA as shown in Eq. 2.

Facile dehydrogenation of 3,5-di-*t*-butylcatechol (**4d**) to **2d** was achieved by the catalytic system consisting of $Co(OAc)_2$ and 2-BPEPA or BIPA under the milder conditions (Eq. 3). This finding suggests that the introduction of the hydroxyl group is the rate determining step in the oxygenation reaction of **1d**.



Podand ligand :	2-BPEPA	96 %	BPHEPA	33 %
	BIPA	93	—	34

Multidentate coordination of flexible *N*-heterocyclic podand ligands is considered to a key factor for the construction of efficient oxygenation systems.

3. Experimental section

BIPA, 2-BPEPA, and BPHEPA were prepared according to the method reported in a previous paper [7].

3.1. General procedure for the oxygenation of phenols

To a mixture of the phenol **1** (0.20 mmol) and the ligand (0.01 mmol) was added $Co(OAc)_2$ (0.01 mmol) in DMF (0.2 ml), and the resulting mixture was stirred under an atmospheric pressure of oxygen at 60°C for 24 h. The mixture was diluted with ether (30 ml), washed with 1.5 M HCl solution and brine, and dried over $MgSO_4$. GLC analysis (1.0 m, 10% SE-30 column, 50–250°C) of the concentrated residue showed the formation of **2–5** (Table 1 and Eq. 2). The quinone **2** was isolated by chromatography on a silica gel column. Melting point (mp) and spectral data for all products were identical with those of authentic samples [4a,6].

2,6-Di-*t*-butyl-1,4-benzoquinone (**2a**): mp 65–66°C (uncorrected); R_f=0.40 (hexane–chloroform v/v 1:1); IR (KBr) 1654 (C=O) cm^{-1}; ^1H NMR (600 MHz, $(CD_3)_2CO$) δ 6.49 (s, 2H), 1.29 (s, 18H); MS (EI) *m/z* 220 (M^+) [4a].

3,3′,5,5′-Tetra-*t*-butyldiphenoquinone (**3a**): mp 242–243°C (uncorrected); R_f=0.55 (hexane–chloroform v/v 1:1); IR (KBr) 1608 (C=O) cm^{-1}; ^1H NMR (600 MHz, $(CD_3)_2CO$) δ 7.87 (s, 4H), 1.34 (s, 36H); MS (EI) *m/z* 408 (M^+) [4a].

2,6-Dimethyl-1,4-benzoquinone (**2b**): mp 70–72°C (uncorrected); R_f=0.25 (hexane–chloroform v/v 1:4); IR (KBr) 1656 (C=O) cm^{-1}; ^1H NMR (600 MHz, $(CD_3)_2CO$) δ 6.59 (s, 2H), 2.02 (s, 6H); MS (EI) *m/z* 136 (M^+) [4a].

3,3′,5,5′-Tetramethyldiphenoquinone (**3b**): mp 208–210°C (uncorrected); R_f=0.10 (hexane–chloroform v/v 1:4); IR (KBr) 1594 (C=O) cm^{-1}; ^1H NMR (600 MHz, $(CD_3)_2CO$) δ 8.09 (s, 4H), 2.08 (s, 12H); MS (EI) *m/z* 240 (M^+) [4a].

2,3,5-Trimethyl-1,4-benzoquinone (**2c**): mp 29–30°C (uncorrected); R_f=0.40 (chloroform); IR (KBr) 1650 (C=O) cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 6.56 (s, 1H), 2.04 (s, 3H), 2.03 (s, 3H), 2.01 (s, 3H); MS (EI) *m/z* 150 (M^+) [4a].

3,5-Di-*t*-butyl-1,2-benzoquinone (**2d**): mp 113–114°C (uncorrected); R_f=0.35 (chloroform); IR (KBr) 1656 (C=O) cm^{-1}; ^1H NMR (600 MHz, $(CD_3)_2CO$) δ 7.10 (d, J=2.3 Hz, 1H), 6.14 (d, J=2.3 Hz, 1H), 1.27 (s, 9H), 1.25 (s, 9H); MS (EI) *m/z* 222 (M^+ +2) [6].

3,3′,5,5′-Tetra-*t*-butyl-2,2′-dihydroxybiphenyl (**5d**): mp 188–190°C (uncorrected); R_f=0.75 (chloroform); IR (KBr) 3540 (OH) cm^{-1}; ^1H NMR (600 MHz, $(CD_3)_2CO$) δ 7.38 (d, J=2.4 Hz, 2H), 7.09 (d, J=2.4 Hz, 2H), 1.46 (s, 18H), 1.32 (s, 18H); MS (EI) *m/z* 410 (M^+) [6].

3.2. *Dehydrogenation of 3,5-di-t-butylcatechol (4d)*

To a mixture of the 3,5-di-*t*-butylcatechol (**4d**, 0.20 mmol) and the ligand (0.01 mmol) was added $Co(OAc)_2$ (0.01 mmol) in DMF (0.2 ml), and the resulting mixture was stirred under an atmospheric pressure of molecular oxygen at room temperature for 24 h. The mixture was diluted with ether (30 ml), washed with 1.5 M HCl solution and brine, and dried over $MgSO_4$. GLC analysis (1.0 m, 10% SE-30 column, 50–250°C) of the concentrated residue showed the formation of **2d** (Eq 3). The quinone **2d** was isolated by chromatography on a silica gel column.

3.3. *Isolation of Co–2-BPEPA complex*

A mixture of 2-BPEPA (0.10 mmol) and $Co(OAc)_2$ (0.10 mmol) in methanol (1.0 ml) was stirred under nitrogen at room temperature for 24 h. After evaporation of the methanol solution in vacuo, the complex was separated by chromatography on a silica gel column. Co–2-BPEPA Complex: mp 205–207°C (uncorrected); R_f=0.08 (chloroform–methanol v/v 1:1); IR (KBr) 1594 (C=O) cm^{-1}; ^1H NMR (600 MHz, CD_3OD) δ 9.57 (dd, 1H, J=5.9, 1.5 Hz), 8.33 (t, 1H, J=7.8 Hz), 8.15 (dd, 1H, J=7.8, 0.9 Hz), 8.11 (dt, 1H, J=7.7, 1.5 Hz), 8.01 (dd, 1H, J=5.9, 1.5 Hz), 7.90 (dd, 1H, J=7.8, 0.9 Hz), 7.72 (ddd, 1H, J=7.7, 5.9, 0.9 Hz), 7.71 (dt, 1H, J=7.7, 1.5 Hz), 7.56 (dd, 1H, J=7.7, 0.9 Hz), 7.25 (dd, 1H, J=7.7, 0.9 Hz), 7.14 (ddd, 1H, J=7.7, 5.9, 0.9 Hz), 4.2–4.1 (m, 2H), 4.07 (dd, 1H, J=13.1, 9.0 Hz), 3.27 (dt, 1H, J=14.3, 2.6 Hz), 3.16 (dt, 1H, J=14.3, 2.6 Hz), 3.00 (dd, 1H, J=15.0, 6.4 Hz), 2.47 (ddd, 1H, J=15.0, 11.9, 9.0 Hz), 2.18 (dt, 1H, J=14.3, 4.0 Hz); ^{13}C NMR (150 MHz, CD_3OD) δ 172.0, 171.7, 165.1, 163.1, 158.2, 157.0, 151.7, 142.0, 141.5, 141.1, 128.9, 127.2, 125.4, 125.2, 125.0, 124.5, 41.5, 40.5, 37.4, 36.7; MS (FAB) *m/z* 433; UV–Vis. 317 nm ([Co–2-BPEPA complex] = 4.0×10^{-4} M, solvent DMF, under nitrogen); Cyclic voltammetry E_{pc} = −0.07 V vs. SCE ([Co–2-BPEPA complex] = 2.0×10^{-3} M, [Bu_4NClO_4] = 0.1 M, solvent MeOH, scan rate = 50 mV/s, glassy carbon working electrode).

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