DOI: 10.1002/adsc.200900347

Synthesis of 2,5-Diaminoquinones by One-Pot Copper-Catalyzed Aerobic Oxidation of Hydroquinones and Addition Reaction of Amines

Sungjin Kim,[a] Daehwan Kim,[a] and Jaiwook Park[a,*]

[a] Department of Chemistry, Pohang University of Science and Technology (POSTECH), San 31 Hyojadong, Pohang, Kyeongbuk 790-784, Republic of Korea
Fax: (+82)-54-279-3399; e-mail: pjw@postech.ac.kr

Received: May 19, 2009; Revised: September 3, 2009; Published online: October 28, 2009

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.200900347.

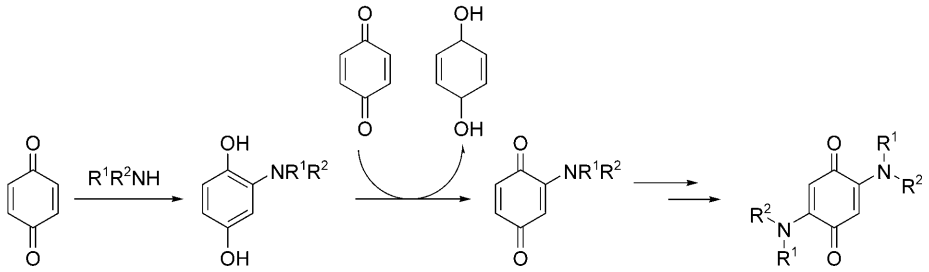
Abstract: The aerobic oxidation of various hydroquinones was achieved by using copper nanoparticles entrapped in aluminum oxyhydroxide [Cu/AlO(OH)] at room temperature. Furthermore, 2,5-diamino-1,4-benzoquinones were synthesized directly from hydroquinone and amines by a one-pot procedure consisting of the copper-catalyzed aerobic oxidation of hydroquinones and the double addition of amines to the resulting quinones.

Keywords: aerobic oxidation; 2,5-diaminobenzoquinones; catalysis; conjugate addition; copper

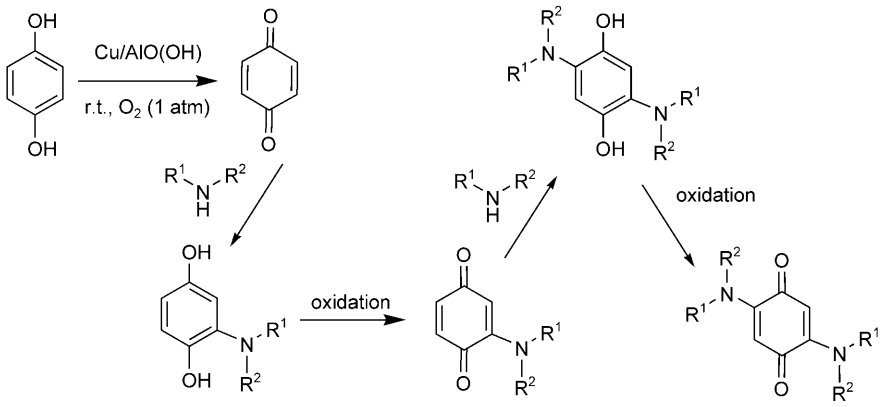
Quinones are valuable and versatile compounds in nature and in organic synthesis.[1] In particular, aminoquinones have been studied for pigments and pharmaceuticals.[2,3] Recently, 2,5-diamino-1,4-benzoquinones were reported as potent drug candidates for Alzheimer's disease.[4]

The addition of amines to *p*-benzoquinone is a usual procedure for the preparation of 2,5-diamino-1,4-benzoquinones.[5] However, the yields are generally low due to the consumption of two-thirds of the *p*-benzoquinone for the oxidation of intermediate hydroquinones (Scheme 1).[6] Therefore, a stoichiometric amount of oxidants such as copper salts is used to improve the yields.[6b] This method, however, still suffers from low reactivity of primary amines, and requires six equivalents of amines to complete the addition reactions. Recently, a direct synthesis of diaminoquinones from hydroquinone, which accompany the oxidation of hydroquinone by electrochemical reactions,[7] or enzymatic reactions,[8] has been reported. However, the direct synthetic methods require restricted reaction conditions, including reaction temperature, solvent, electrolytes, and pH. Besides, more than five equivalents of amines are used for the direct synthesis.

There are several catalyst systems for the aerobic oxidation of hydroquinone derivatives: $CuSO_4$/Al_2O_3,[9] Fe(III)-EDTA,[10] dinuclear copper complex,[11] platinum complex,[12] NPV_6Mo_6/C,[13] and polymer-incarcerated gold nanoparticles (PI Au).[14] However, they often suffer from high reaction temperature, low recyclability, and limited substrate scope. Recently, Kobayashi and co-workers have reported a notable catalyst system consisting of polymer-incarcerated platinum nanoparticles (PI Pt),[15] which can oxidize even electron-difficient hydroqui-



Scheme 1. Synthesis of 2,5-diamino-1,4-benzoquinones from 1,4-benzoquinone and amines.



Scheme 2. Direct synthesis of 2,5-diamino-1,4-benzoquinones using **1** under an oxygen atmosphere.

nones at room temperature. Meanwhile, we have developed a heterogeneous copper catalyst [Cu/AlO(OH), **1**] that is prepared from readily available reagents through a simple procedure and shows a high activity in the (3+2) Huisgen cycloaddition of alkynes and azides.[16,17] Herein, we report that the copper catalyst **1** is highly active and recyclable for the aerobic oxidation of a wide range of hydroquinones. Furthermore, our catalyst is effective for the direct synthesis of 2,5-diamino-1,4-benzoquinones from amines and hydroquinones under ambient conditions (Scheme 2).

The activity of **1** was compared with those of commercial copper catalysts in the aerobic oxidation of hydroquinone (Table 1). Remarkably, our catalyst **1** (3 mol% of Cu) showed a distinct activity to give *p*-benzoquinone in almost quantitative yield in 3 h at room temperature under an oxygen atmosphere (1 atm),[18] while commercial copper catalysts such as CuO, CuO nanopowder, CuO/Al_2O_3, Cu_2O, $CuCl_2 \cdot 2H_2O$, and CuCl were not active under these conditions. The oxidation did not proceed in the absence of **1** (Table 1, entry 8). To check the leaching-out of catalytic species during the oxidation,[19] the filtrate of the reaction mixture under the conditions of entry 1 after 1 h was monitored for 24 h and analyzed by ICP-MS. Further oxidation was not observed in the filtrate, although a tiny amount of copper species was present.[20]

Table 1. Activities of Cu/AlO(OH) (**1**) and commercial Cu catalysts for the aerobic oxidation of hydroquinone.[a]

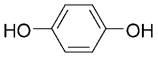
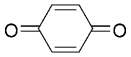
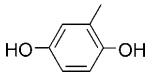
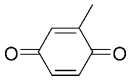
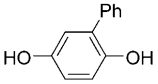
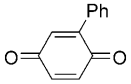
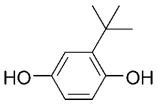
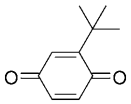
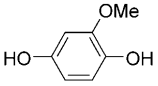
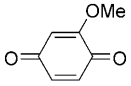
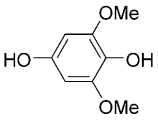
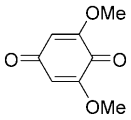
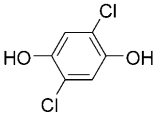
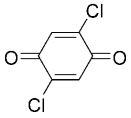
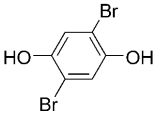
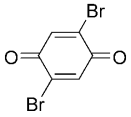
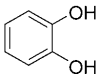
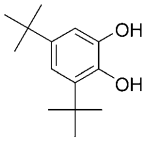
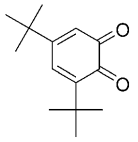
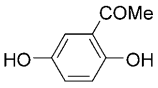
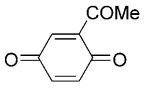
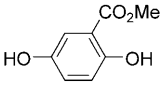
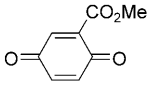
Entry	Catalyst [mol% of Cu]	Time [h]	Yield[b] [%]
1	**1** [3]	3	96
2	CuO [100]	3	0
3	CuO nanopowder [100]	3	<1
4	CuO/Al_2O_3 [6]	3	<1
5	Cu_2O [100]	3	0
6	$CuCl_2 \cdot 2H_2O$ [100]	3	<1
7	CuCl [100]	3	0
8	none	24	0

[a] The reaction was performed on 0.50 mmol of hydroquinone in 3.0 mL of toluene with a copper catalyst at 25 °C under O_2 (1 atm).
[b] Determined by GC with an internal standard.

The scope of our catalyst system was investigated under the conditions of the entry 1 of Table 1 (Table 2). Mono- and disubstituted hydroquinones were transformed successfully into the corresponding quinones in high yields in 1–4 h (Table 2, entries 1–8), except those having carbonyl groups (Table 2, entries 11 and 12). Methoxy-substituted hydroquinones were oxidized faster than halide-substituted ones (Table 2, entries 5–8). The oxidation of pyrocatechol was not possible with our catalyst (Table 2, entry 9). However, 3,5-di-*tert*-butylcatechol was transformed into 3,5-di-*tert*-butyl-1,2-benzoquinone in quantitative yield although the reaction rate was much slower than that of hydroquinone (Table 2, entry 10). We tested the recyclability of **1** in the oxidation of methylhydroquinone (Table 3). The solid catalyst was recovered by decanting the product solution. Although initial rates decreased slightly in reuse,[21] the oxidation using 3 mol% of Cu was completed within 2 h even in the fifth use.

Then, we investigated the activity of **1** for the synthesis of 2,5-diamino-1,4-benzoquinones from hydroquinone and amines by a one-pot procedure, which requires continuous oxidation of the intermediate hydroquinones formed from the reaction of quinones with amines (Scheme 2). 2,5-Diamino-1,4-benzoquinones were obtained as the major products in high yields in the reaction of hydroquinone with various amines (Table 4).[22] Primary amines (Table 4, entries 1–4) as well as secondary amines (Table 4, entries 5–7) were reacted successfully with hydroquinone. In all cases, only two equivalents of amines were enough to complete the reaction, except for the case of benzylamine. Under the conditions of the oxidation, benzylamine was consumed in side reactions, and the corresponding diaminobenzoquinone was ob-

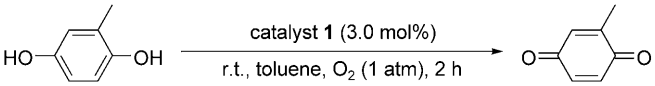
Table 2. Oxidation of hydroquinones and catechols using **1**.[a]

Entry	Substrate	Product	Time [h]	Yield[b] [%]
1			3	96
2			2	99
3			4	99[c]
4			2	99
5			2	95[c]
6			1	94[c]
7			3	99
8			3	98[c]
9			24[d]	0
10			24[d]	99[c]
11			24[d]	0
12			24[d]	0

[a] The reaction was performed on 0.50 mmol of substrate in 3.0 mL of toluene with **1** (3.0 mol% of Cu) at 25 °C under O_2 (1 atm).
[b] Determined by GC with an internal standard.
[c] Isolation yield.
[d] 5.0 mol% of Cu was used.

tained only in 72% yield by using four equivalents of benzylamine (Table 4, entry 2). Notably, 2-methylaziridine did not suffer from ring-opening or polymerization during the coupling reaction (Table 4, entry 7). It is also notable that memoquin, a potent drug candidate for Alzheimer's disease, was obtained in 71% isolated yield by our catalytic method. In a conventional synthesis employing 1,4-benzoquinone and N^1-ethyl-N^1-(2-methoxybenzyl)hexane-1,6-diamine, the

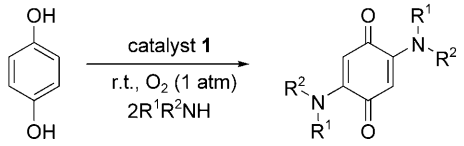
Table 3. Recycling test for **1**.[a]

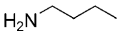
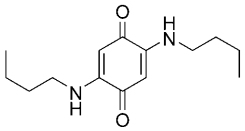
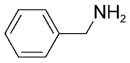
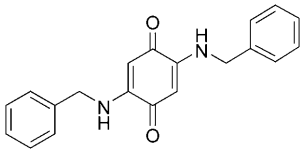
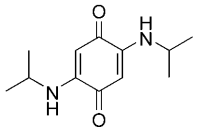
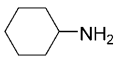
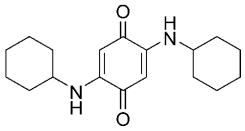
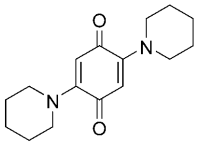
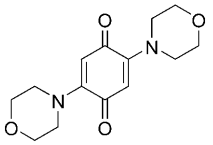
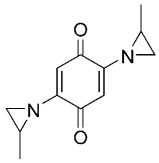
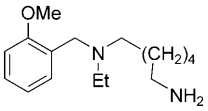
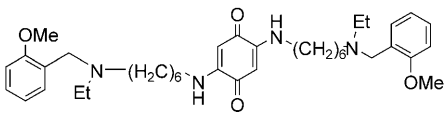


Reuse	1	2	3	4	5
Yield[b] [%]	>99	>99	>99	>99	>99

[a] After washing the catalyst with toluene (3.0 mL) three times, methylhydroquinone was added for reuse.
[b] Determined by GC.

Table 4. Direct coupling between hydroquinone and various amines using **1**.[a]



Entry	Substrate	Time [h]	Product	Yield[b] [%]
1		14		88
2[c]		24		72
3		6		90
4		6		83
5		6		96 (92)[d]
6		6		85
7		6		89
8		24		71

[a] The reaction was performed on 1.0 mmol of hydroquinone and 2.0 mmol of amine dissolved in 3.0 mL of ethyl acetate with **1** (3.0 mol% of Cu) at 25 °C under O_2 (1 atm).
[b] Isolation yield.
[c] Two equivalents of benzylamine were added after 12 h.
[d] The number in parenthesis is the yield in the third use.

yield is only 17% (Table 4, entry 8).[4a] The recyclability of our catalyst **1** was also tested in the coupling reaction of piperidine; the catalyst can be reused at least three times without significant loss of activity (Table 4, entry 5).

In conclusion, we have demonstrated an efficient aerobic oxidation of various hydroquinones at room temperature, which is catalyzed by a recyclable copper catalyst. Furthermore, the copper catalyst has been applied successfully for the synthesis of 2,5-di-

amino-1,4-benzoquinones directly from hydroquinones and two equivalents of amines in a one-pot procedure.

Experimental Section

Synthetic Procedure for Catalyst 1 [Cu/AlO(OH)]

$CuCl_2 \cdot 2H_2O$ (400 mg, 2.3 mmol), Pluronic P123 (4.0 g) [$EO_{20}PO_{70}EO_{20}$ (EO = ethylene oxide, PO = propylene oxide], Al(O-*sec*-Bu)$_3$ (9.1 g, 37 mmol) and absolute ethanol (8.0 g) were placed in a 100-mL flask equipped with a condenser. The reaction mixture was heated at 160 °C for 3 h. To the resulting suspension, water (3 mL) was added slowly to form a bluish gel. After cooling to room temperature, the bluish gel was filtered, washed with acetone, and dried at 120 °C for 2 h to give **1** as greenish powder; yield: 3.7 g (4.0 wt% of Cu). The copper content was estimated by ICP analysis.

Aerobic Oxidation of Hydroquinone at Room Temperature

Catalyst **1** (22 mg, 3.0 mol% of Cu) was added to a mixture of hydroquinone (55 mg, 0.50 mmol) and toluene (3 mL), and the reaction mixture was stirred at room temperature for 3 h under an O_2 balloon. The yield of 1,4-benzoquinone was determined by GC using acetophenone as an internal standard.

Recycling Test for 1

Catalyst **1** (22 mg, 3.0 mol% of Cu) was added to a mixture of methylhydroquinone (62 mg, 0.50 mmol) and toluene (3 mL), and the reaction mixture was stirred at room temperature for 2 h under an O_2 balloon. The solution containing the product was decanted and the solid catalyst was washed with toluene three times. The reaction was repeated by adding toluene (3 mL) and methylhydroquinone (62 mg, 0.50 mmol).

Coupling Reaction between Hydroquinone and Amines

The reaction of hydroquinone with piperidine is typical. To a solution of hydroquinone (110 mg, 1.0 mmol) and piperidine (170 mg, 2.0 mmol) in ethyl acetate (3 mL) was added **1** (44 mg, 3.0 mol% of Cu), and the reaction mixture was stirred at room temperature for 6 h under an O_2 balloon. The catalyst was separated by filtration, and the filtrate was purified by column chromatography to give 2,5-dipiperidino-1,4-benzoquinone; yield: 260 mg (96%).

Synthesis of Memoquin (Table 4, entry 8)

N^1-Ethyl-N^1-(2-methoxybenzyl)hexane-1,6-diamine was prepared according to the literature prodecure.[4a] To a flask containing the amine (530 mg, 2.0 mmol), hydroquinone (110 mg, 1.0 mmol), and **1** (44 mg, 3.0 mol% of Cu) were added ethyl acetate (3 mL), and the reaction mixture was stirred at room temperature for 24 h under an O_2 balloon. The catalyst was separated by filtration, and the filtrate was purified by column chromatography to give memoquin; yield: 450 mg (71%).

Acknowledgements

We are grateful for the financial supports from Korea Research Foundation (KRF-2008-314-C00203), and the Korean Ministry of Education through the BK21 project for our graduate program.

References

[1] a) J. S. Swenton, in: *The Chemistry of the Quinonoid Compounds*, Vol. 2, (Eds.: S. Patai, Z. Rappoport), Academic Press, New York, **1988**; b) S. Yamamura, in: *The Chemistry of Phenols*, Part 2, (Ed.: Z. Rappoport), Wiley, Chicester, **2003**; c) M. Balci, M. S. Gültekin, M. Celik, in: *Science of Synthesis*, Vol. 28, (Ed.: A. G. Griesbeck), Georg Thieme Verlag, Stuttgart, **2006**.

[2] a) P. Spiteller, N. Arnold, M. Spiteller, W. Steglich, *J. Nat. Prod.* **2003**, *66*, 1402–1403; b) P. Spiteller, W. Steglich, *J. Nat. Prod.* **2002**, *65*, 725–727.

[3] a) M.-L. Kndracki, M. Guyot, *Tetrahedron Lett.* **1987**, *28*, 5815–5818; b) A. E. Mathew, R. K. Y. Zee-Chang, C.-C. Cheng, *J. Med. Chem.* **1986**, *29*, 1729–1795; c) K.-Y. Zee-Chang, C.-C. Cheng, *J. Med. Chem.* **1970**, *13*, 264–268; d) R. E. Lutz, T. A. Martin, J. F. Codington, T. M. Amacker, R. K. Allison, N. H. Leake, R. J. Rowlett, J. D. Smith, J. W. Willson, *J. Org. Chem.* **1949**, *14*, 982–1000.

[4] a) A. Cavalli, M. L. Bolognesi, S. Capsoni, V. Andrisano, M. Bartolini, E. Margotti, A. Cattaneo, M. Recanatini, C. Melchiorre, *Angew. Chem.* **2007**, *119*, 3763–3766; *Angew. Chem. Int. Ed.* **2007**, *46*, 3689–3692; b) M. L. Bolognesi, R. Banzi, M. Bartolini, A. Cavalli, A. Tarozzi, V. Andrisano, A. Minarini, M. Rosini, V. Tumiatti, C. Bergamini, R. Fato, G. Lenaz, P. Hreli, A. Cattaneo, M. Recanatini, C. Melchiorre, *J. Med. Chem.* **2007**, *50*, 4882–4897.

[5] a) W. K. Anslow, H. Raistrick, *J. Chem. Soc.* **1939**, 1446–1457; b) J. V. Schurman, E. I. Becker, *J. Org. Chem.* **1953**, *18*, 211–217; c) P. Ballesteros, R. M. Claramunt, C. Escolático, M. D. S. Maria, *J. Org. Chem.* **1992**, *57*, 1873–1876.

[6] a) R. Baltzly, E. Lorz, *J. Am. Chem. Soc.* **1948**, *70*, 861–862; b) A. H. Crosby, R. E. Lutz, *J. Am. Chem. Soc.* **1956**, *78*, 1233–1235.

[7] S. M. Golabi, F. Nourmohammadi, A. Saadnia, *J. Electroanal. Chem.* **2003**, *548*, 41–47.

[8] a) T. H. J. Niedermeyer, M. Lalk, *J. Mol. Catal. B* **2007**, *45*, 113–117; b) T. H. J. Niedermeyer, A. Mikolasch, M. Lalk, *J. Org. Chem.* **2005**, *70*, 2002–2008.

[9] T. Sakamoto, H. Yonehara, C. Pac, *J. Org. Chem.* **1997**, *62*, 3194–3199.

[10] B. Sain, P. S. Murthy, T. V. Rao, *Tetrahedron Lett.* **1994**, *35*, 5083–5084.

[11] H. Zhou, Z. Q. Pan, Q. H. Luo, G. Q. Mei, D. L. Long, J. T. Chen, *Chin. J. Chem.* **2005**, *23*, 835–842.

[12] K. Sakai, T. Tsubomura, K. Matsumoto, *Inorg. Chim. Acta* **1995**, *234*, 157–161.
[13] S. Fujibayashi, K. Nakayama, Y. Nishiyama, Y. Ishii, *Chem. Lett.* **1994**, *23*, 1345–1348.
[14] H. Miyamura, M. Shiramizu, R. Matsubara, S. Kobayashi, *Chem. Lett.* **2008**, *37*, 360–361.
[15] H. Miyamura, M. Shiramizu, R. Matsubara, S. Kobayashi, *Angew. Chem.* **2008**, *120*, 8213–8215; *Angew. Chem. Int. Ed.* **2008**, *47*, 8093–8095.
[16] I.-S. Park, M.-S. Kwon, Y. Kim, J.-S. Lee, J. Park, *Org. Lett.* **2008**, *10*, 497–500.
[17] a) M.-S. Kwon, D. Kim, C.-M. Park, J.-S. Lee, K.-Y. Kang, J. Park, *Org. Lett.* **2005**, *7*, 1077–1079; b) W.-H. Kim, I.-S. Park, J. Park, *Org. Lett.* **2006**, *8*, 2543–2545; c) I.-S. Park, M.-S. Kwon, N. Kim, J.-S. Lee, K.-Y. Kang, J. Park, *Chem. Commun.* **2005**, 5667–5669; d) I.-S. Park, M.-S. Kwon, K.-Y. Kang, J.-S. Lee, J. Park, *Adv. Synth. Catal.* **2007**, *349*, 2039–2047; e) S. Kim, S. W. Bae, J.-S. Lee, J. Park, *Tetrahedron* **2009**, *65*, 1461–1466; f) M.-S. Kwon, S. Kim, S. Park, W. Bosco, R. K. Chidrala, J. Park, *J. Org. Chem.* **2009**, *74*, 2877–2879.
[18] The reaction was tested in ethyl acetate, acetone, chloroform, and acetonitrile in the presence of **1** (3.0 mol% of Cu) for 3 h at 25 °C under an O_2 (1 atm) to give *p*-benzoquinone in 56%, 54%, 10%, and 0% yields, respectively.
[19] R. A. Sheldon, M. Wallau, I. W. C. E. Arends, W. Schuchardt, *Acc. Chem. Res.* **1998**, *31*, 485–493.
[20] About 0.087% of the copper in **1** was leached out.
[21] See Supporting Information.
[22] The oxidation of hydroquinone was faster in toluene than in ethyl acetate, but the coupling reactions of hydroquinone with amines were faster in ethyl acetate.

