A Rapid and Efficient Synthesis of Quinone Derivatives: Ru(II)- or Ir(I)-Catalyzed Hydrogen Peroxide Oxidation of Phenols and Methoxyarenes

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Abstract: Hydroquinone and methoxybenzene derivatives were catalytically oxidized promptly to the corresponding quinones in up to 99% yield. With a catalyst loading of 0.01 mol %, a maximum TON of 8.4×10^3 was attained in the case of Ru(II)-complex. Ru(II)(pybox-*dh*)(pydic) is able to enhance the hydrogen peroxide oxidation of substituted hydroquinones as well as methoxybenzenes, but Ir[(coe)$_2$Cl]$_2$ and Ir[(cod)Cl]$_2$ were found to be effective catalysts only for the former substrates under similar oxidation conditions.

Keywords: homogeneous catalysis; hydrogen peroxide; hydroquinones; N ligands; oxidation; ruthenium

Quinones are an interesting and important class of compounds because they and their derivatives play a vital role in biosynthetic routes. These compounds are found as structural units in antibiotics, pigments, and compounds having antihemorrhagic activity (e.g., the vitamin K group).[1] Furthermore, they are useful intermediates for fine organic synthesis, i.e., in the production of vitamin E.[2] In the laboratory, substituted quinones are used as oxidizing agents,[3] and as starting materials for the synthesis of polycyclic compounds by virtue of their dienophelic reactivity in the Diels–Alder reaction.[4] The redox properties of quinones are important to the functioning of living cells, where compounds called ubiquinones (coenzymes Q) act as biochemical oxidizing agents to mediate the electron-transfer processes involved in energy production. In plant tissues the plastoquinones perform a similar function in photosynthesis.

The oxidation of 1,2- or 1,4-dihydroxybenzenes to the corresponding quinones has been achieved by a variety of oxidants such as silver oxide or silver carbonate,[5] dipotassium nitrosodisulfonate(Fremy's salt),[6] Jones' reagent,[7] hypervalent iodine,[8] ceric ammonium nitrate (CAN),[9] etc. However, these systems have some drawbacks due to their toxicity, high reaction temperatures and acidic or basic conditions. More convenient oxidants, such as molecular oxygen and hydrogen peroxide, have therefore attracted considerable attention; they were generally used in the presence of metal-complex catalysts with moderate to good selectivity. The role of hydrogen peroxide in organic synthesis has grown steadily over the years. The use of it as an oxygen donor is particularly attractive, both for its high oxygen contents and the formation of water as a side product. Also, aqueous hydrogen peroxide is a stable reagent, provided it is handled and stored in the proper manner.[10] During the last decade, many catalytic methods of oxidation have been developed to oxidize phenols or methoxybenzenes to the corresponding quinones using H_2O_2 as an oxidant with diphenyl diselenide,[11] methylrhenium trioxide (MTO),[12] polymer-supported MTO,[13] I_2 or the HI-H_2SO_4 system,[14] a Cu(II)-resin system,[15] and TiO_2-SiO_2 mixed oxides.[16]

We now report a new and highly selective synthesis of quinones from dihydroxybenzene and methoxybenzene derivatives with the involvement of H_2O_2 as the oxidant and Ru(II)(pybox-*dh*)(pydic) or Ir[(coe)$_2$Cl]$_2$ or Ir[(cod)Cl]$_2$ as catalyst. Encouraged by our previously reported oxidation system which included Ru(II)- and Ir(I)-complexes as catalyst,[17] we applied that oxidation system to quinone synthesis from dihydroxybenzene and methoxybenzene derivatives. First, we applied this catalytic hydrogen peroxide oxidation system to 2,3,5-trimethylhydroquinone (Scheme 1). Table 1 shows the yields of the reaction of hydrogen peroxide oxidation of 2,3,5-trimethylhydroquinone in different solvent systems. Uniquely, 2,3,5-trimethylbenzoquinone has been formed very rapidly with a high yield in THF rather than in other solvents with both Ru(II)- and Ir(I)-catalytic systems (Table 1, entries 1 and 2). Other solvents

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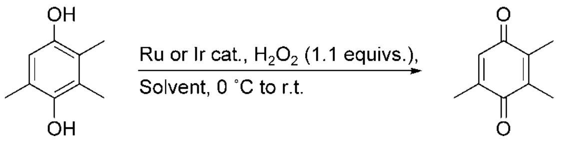
Table 1. Solvent effects on the Ru(II)- and Ir(I)-catalyzed hydrogen peroxide oxidation of 2,3,5-trimethylhydroquinone.

Entry	cat[a] [mol %]	Solvent [1 mL]	Time	Yield [%]	TON[b]	TOF[c]
1	A (0.1)	THF	30 min	95	950	1900
2	B (1.0)	THF	30 min	>99	99	198
3	A (0.1)	1,4-dioxane	35 min	89	890	1526
4	B (1.0)	1,4-dioxane	85 min	>99	99	70
5	A (0.1)	CH_2Cl_2	50 min	87	870	1044
6	B (1.0)	CH_2Cl_2	100 min	>99	99	59
7	A (0.1)	CH_3OH	4 h	89	890	222
8	B (1.0)	CH_3OH	80 min	95	95	71
9	A (0.1)	DMF	4 h	82	820	205
10	B (1.0)	DMF	2 h	99	99	50
11	A (0.1)	H_2O	40 min	80	800	1200
12	B (1.0)	H_2O	4 h	44	44	11

[a] A: Ru(II)(pybox-dh)(pydic)(0.1 mol %); B: $[Ir(coe)_2Cl]_2$ (1 mol %).
[b] Turnover number.
[c] Turnover frequency.



Scheme 1.

like 1,4-dioxane, CH_2Cl_2, CH_3OH and DMF can also be used in this oxidation system (Table 1, entries 3–10). Even H_2O is a considerably effective solvent for the Ru(II)-catalytic system (Table 1, entry 11). The reaction time as well as the yields of the quinones varied with different catalytic systems in various solvent media.

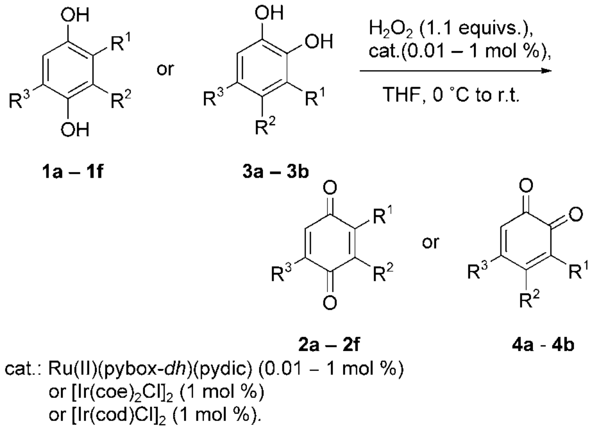
We have also investigated the H_2O_2 oxidation of various dihydroxybenzene derivatives using Ru(pybox-dh)(pydic), $[Ir(coe)_2Cl]_2$ and $[Ir(cod)Cl]_2$ as catalyst (Scheme 2) and the results are summarized in Table 2. The oxidation of hydroquinone has long been well known. This reaction occurs at a slow rate without the presence of a catalyst at room temperature and it was found that after 8 days only 3% quinone was formed (Table 2, run 1). Both 1,4- and 1,2-benzoquinones with electron-donating substituents were readily converted into the corresponding quinones with good to quantitative yields by the Ru(II)- or Ir(I)-complex-catalyzed H_2O_2 oxidation system (Table 1, runs 2–18 and 22–30). But when the substituent was a carboxyl group no quinone was formed (runs 19–21). Ru(II)(pybox-*dh*)(pydic) is more rapid and suitable than the Ir(I) complex for this type of oxidation. The catalyst loading was up to 0.01 mol % to give the corresponding quinone in 84% yield with TON [turnover number = product (mol)/catalyst (mol)] = 8400 (Table 2, run 12). Again, $Ir[(coe)_2Cl]_2$ is a much better catalyst than $Ir[(cod)Cl]_2$ for the same reason. The catalytic activity among these three catalysts in the present oxidation system seems to be Ru(II) > $Ir[(coe)_2Cl]_2$ > $Ir[(cod)Cl]_2$.

Table 2. Ru(II)- or Ir(I)-catalyzed oxidation of 1,2- and 1,4-dihydroxybenzene by 31% H_2O_2.

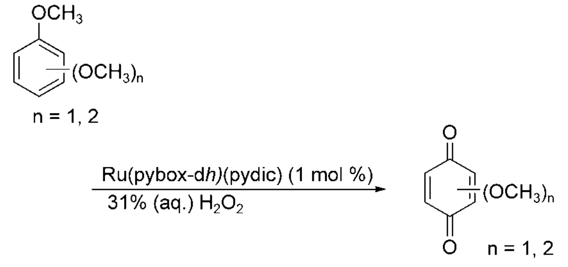
Substrate	R^1	R^2	R^3	Product	Run	Catalyst [mol %]	Time	Yield [%]
1a	*t*-Bu	H	*t*-Bu	**2a**	1	-	8 days	3
					2	A (1)	0.5 h	96
					3	A (0.1)	1.1 h	97
					4	A (0.01)	48 h	47
					5	B (1)	1 h	94
					6	C (1)	2 h	94
1b	C_6H_5	H	H	**2b**	7	A (0.1)	2 h	98
					8	A (0.01)	24 h	38
					9	B (1)	1.2 h	99
					10	C (1)	6 h	90
1c	CH_3	CH_3	CH_3	**2c**	11	A (0.1)	0.7 h	92
					12	A (0.01)	72 h	84
					13	B (1)	0.5 h	99
					14	C (1)	0.6 h	98
1d	*t*-Bu	H	H	**2d**	15	A (0.1)	2 h	92
					16	A (0.01)	72 h	70
					17	B (1)	0.5 h	84
					18	C (1)	0.5 h	70
1e	COOH	H	H	–	19	A (0.1)	19 h	-
					20	B (1)	19 h	-
					21	C (1)	19 h	-
1f	CH_3	CH_3	H	**2f**	22	A (0.1)	1.2 h	82
					23	A (0.01)	72 h	66
					24	B (1)	0.5 h	99
					25	C (1)	0.3 h	98
3a	H	*t*-Bu	H	**4a**	26	A (0.1)	0.9 h	86
3b	*t*-Bu	H	*t*-Bu	**4b**	27	A (0.1)	1.1 h	95
					28	A (0.01)	72 h	75
					29	B (1)	44 h	80
					30	C (1)	44 h	58

Catalysts: A: Ru(II)(pybox-dh)(pydic); B: $[Ir(coe)_2Cl]_2$; C: $[Ir(cod)Cl]_2$.

Oxidation of methoxybenzene derivatives to produce quinones is also very important as a synthetic route to many valuable compounds. Considerable success has been achieved by utilization of the Ru(porphyrin)-2,6-dichloropyridine *N*-oxide system.[18] But this method requires acidic conditions, elevated reaction temperature and long reaction time. In contrast to this method, here we describe a highly selective and effective method for the synthesis of quinones from methoxybenzenes by the Ru(II)(pybox-*dh*)(pydic)-31% (aqueous) H_2O_2 system (Scheme 3). The results are summarized in Table 3. Methoxybenzene derivatives were oxidized to produce mainly *p*-benzoquinones that greatly depend on the



Scheme 2.

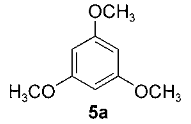
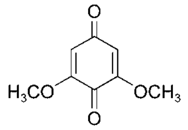
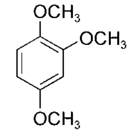
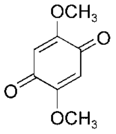
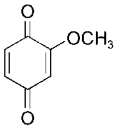
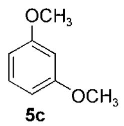
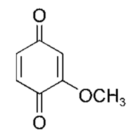
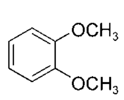
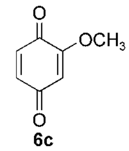


Scheme 3.

structure of the substrates as well as the solvent systems. The compound 1,3,5-trimethoxybenzene gave an excellent result in both THF and MeOH-H_2O solvent media (Table 3, runs 1 and 2). But *m*-dimethoxybenzene gave a quantitative yield in the MeOH-H_2O system rather than in THF (Table 3, run 6). The compound 1,2,4-trimethoxybenzene, with a good conversion gave a mixture of *p*-benzoquinone products. In the MeOH-H_2O solvent system 2,5-dimethoxybenzoquinone was formed as the major product (Table 3, run 4). *o*-Dimethoxybenzene (**5d**) did not respond in THF medium, but in the MeOH-H_2O system the it gave a 40% yield of **6c** (Table 3, runs 7 and 8).

In conclusion, the Ru(II)- or Ir(I)-catalyzed hydrogen peroxide oxidation system works well to convert rapidly dihydroxybenzene to quinones in good to excellent yields. Also, the Ru(II)(pybox-*dh*)(pydic)-31% (aqueous) H_2O_2 system selectively converts methoxybenzene derivatives to quinones. The mechanism of the present oxidation systems is still unclear. It requires at least 3

Table 3. Oxidation of methoxybenzene derivatives by the Ru(pybox-dh)(pydic)-31% (aqueous) H_2O_2 system.

Run	Substrate[a]	Catalyst [mol %]	Solvent	H_2O_2 [equivs.]	Time [h]	Product [isolated yield]			
1	 **5a**	1	THF[b]	3	2	 **6a**	91%		
2		1	MeOH-H_2O[c]	3	0.5		93%		
3	 **5b**	1	THF[b]	3	1	 **6b**	22%	 **6c**	30%
4		1	MeOH-H_2O[c]	3	1		57%		23%
5	 **5c**	1	THF[b]	3	24	 **6c**	33%		
6		1	MeOH-H_2O[c]	3	2		97%		
7	 **5d**	1	THF[b]	5	24	 **6c**	---		
8		1	MeOH-H_2O[c]	5	6		40%		

[a] Substrate (0.5 mmol).
[b] THF (1.0 mL).
[c] MeOH-H_2O (1.0 mL) (1:1 v/v).
[d] MeOH (1.0 mL).

equivalents of H_2O_2 to convert methoxybenzenes to quinones, whereas for hydroxybenzene oxidation, merely 1.1 equivalents of H_2O_2 are enough. More systemetic investigation of these oxidation systems is required, which is now being carried out. Meanwhile, this Ru(II)- or Ir(I)-catalyzed hydrogen peroxide oxidation system can be used for the synthesis of very useful biologically active quinones since these methods are very mild, easy and simple.

Experimental Section

General

All reactions were carried out in the normal air atmosphere. THF and MeOH were purchased as reagent grade and were used without any purification. Reactions were monitored by TLC using 250 µm Merck (Art. 5715) precoated silica gel. Flash column chromatography was performed over Merck (Art. 7734) silica gel.

Catalysts were synthesized according to the literature. All starting materials are commercially available and were used as received.

Ru(II)- or Ir(I)-Catalyzed Oxidation of 1,2- and 1,4-Dihydroxybenzenes by 31% (Aqueous) H_2O_2; Typical Procedure

Table 2, run 7: To a solution of 2-phenylhydroquinone (**1b**; 1.862 g, 10.0 mmol) in THF (20 mL) was added solid Ru(II)-(pybox-*dh*)(pydic) (4.9 mg, 0.01 mmol) at 0 °C followed by addition of hydrogen peroxide (aqueous 31%, 1.2 mL, 11.0 mmol). The resulting mixture was stirred for 2.0 h at room temperature. The organic phase was extracted with dichloromethane, and dried over Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel to give quinone **2b**; yield: 1.805 g (98% isolated).

Ru(II)-Catalyzed Oxidation of Methoxybenzenes by 31% (Aqueous) H_2O_2; Typical Procedure

Table 3, run 6: To a solution of 1,3-dimethoxybenzene (**5c**; 65 µL, 0.5 mmol) in MeOH-H_2O (1 : 1, 1.0 mL) was added solid Ru(II)(pybox-*dh*)(pydic) (2.4 mg, 0.005 mmol) at 0 °C followed by addition of hydrogen peroxide (aqueous 31%, 165 µL, 1.5 mmol). The resulting mixture was stirred for 2.0 h at room temperature. The organic phase was extracted with dichloromethane, and dried over Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel to give quinone **6c**; yield: 67.3 mg (97% isolated).

Supporting Information

Characterization data for the compounds prepared are contained in the Supporting Information.

References

[1] General reviews: a) S. Yamamura, in: *The Chemistry of Phenols*, Part 2, (Ed.: Z. Rappoport), chap. 17, Wiley, Chicester, **2003**, pp. 1153–1346; b) J. S. Swenton, in: *The Chemistry of the Quinonoid Compounds*, Vol. 2, (Eds.: S. Patai, Z. Rappoport), chap. 15, Wiley, New York, **1988**, pp. 899–962.

[2] P. Schudel, H. Mayer, O. Isler, in: *The Vitamines*, Vol. 5, (Eds.: W. H. Sebroll, R. S. Harris), Academic Press, New York, **1972**, p. 165.

[3] K. S. Feldman, S. Quideau, H. M. Appel, *J. Org. Chem.* **1996**, *61*, 6656.

[4] a) K. Mikami, M. Terada, Y. Motoyama, T. Nakai, *Tetrahedron: Asymmetry* **1991**, *2*, 643–646; b) K. Mikami, Y. Motoyama, M. Terada, *J. Am. Chem. Soc.* **1994**, *116*, 2812; c) J. D. White, Y. Choi, *Org. Lett.* **2000**, *2*, 2373; d) K. C. Nicolaou, S. A. Snyder, T. Montagnon, G. Vassilikogiannakis, *Angew. Chem. Int. Ed.* **2002**, *41*, 1668.

[5] T. Land, in: *Comprehensive Organic Chemistry*, Vol. 1, (Ed.: J. F. Stoddart), Pergamon Press, Oxford, **1979**, p. 1216.

[6] a) H. Teuber, W. Rau, *Chem. Ber.* **1953**, *86*, 1036; b) H. Zimmer, D. C. Lanken, S. W. Morgan, *Chem. Rev.* **1971**, *71*, 229; c) O. Cherkaoni, P. Nebois, M. Domard, B. Fenet, *Tetrahedron* **1996**, *52*, 9499.

[7] D. Liotta, J. Arbiser, J. W. Short, M. Saindane, *J. Org. Chem.* **1983**, *48*, 2932.

[8] a) N. Kato, T. Sugaya, T. Mimura, M. Ikuta, S. Kato, Y. Kuge, S. Tomioka, M. Kasai, *Synthesis* **1997**, 625; b) H. Tohma, H. Morioka, Y. Harayama, M. Hashizume, Y. Kita, *Tetrahedron Lett.* **2001**, *42*, 6899.

[9] M. A. Brimble, L. J. Duncalf, S. J. Phythiom, *J. Chem. Soc. Perkin Trans. 1* **1997**, 1399.

[10] M. G. Clerici, *Studies in Surface Science and Catalysis*, in: *Heterogeneous Catalysis and Fine Chemicals III*, Vol. 78, (Eds.: M. Guisnet, J. Barbier, J. Barrault, C. Bouchole, D. Duprez, G. Perot, C. Montassies), Elsevier, Amsterdam, **1993**, p. 21.

[11] D. V. Pratt, F. Ruan, P. B. Hopkins, *J. Org. Chem.* **1987**, *52*, 5053.

[12] I. R. Beattie, P. Jones, *J. Inorg. Chem.* **1979**, *18*, 2318.

[13] R. Saladino, V. Neri, E. Mincione, P. Filippone, *Tetrahedron* **2002**, *58*, 8493.

[14] F. Minisci, A. Citterio, E. Vismara, F. Fontana, S. De Bernardinis, *J .Org. Chem.* **1989**, *54*, 728.

[15] I. Owsik, B. Kolarz, *J. Mol. Catal. A: Chemical* **2002**, *178*, 63–71.

[16] O. A. Kholdecva, N. N. Trukhan, M. P. Vanina, V. N. Romannikov, V. N. Parmon, J. Mrrwiec-Bialon, A. B. Jarzebski, *Catalysis Today* **2002**, *75*, 204.

[17] a) S. Iwasa, A. Fakhruddin, Y. Tsukamoto, M. Kameyama, H. Nishiyama, *Tetrahedron Lett.* **2002**, *43*, 6159; b) S. Iwasa, K. Tajima, S. Tsushima, H. Nishiyama, *Tetrahedron Lett.* **2001**, *42*, 5897.

[18] T. Higuchi, C. Sataka, M. Hirobe, *J. Am. Chem. Soc.* **1995**, *117*, 8879.