# Ruthenium-Catalyzed Oxidation of Nonactivated Alcohols by $MnO_2$

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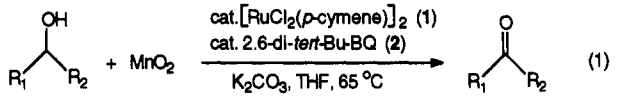
Nonactivated alcohols are oxidized to ketones by $MnO_2$ in the presence of a catalytic system consisting of $[RuCl_2(p\text{-cymene})]_2$ (1) and 2,6-di-*tert*-butylbenzoquinone (2). The reaction proceeds via a ruthenium-catalyzed dehydrogenation of the alcohol and subsequent hydrogen transfer to 2,6-di-*tert*-butylbenzoquinone (2). The hydroquinone formed is reoxidized to quinone by $MnO_2$.

The oxidation of alcohols to ketones is an important transformation in organic synthesis.[1] Although many useful methods are known there is still a need to develop milder procedures which employ oxidants with oxidation potentials as low as possible. The use of a transition-metal catalyst is an attractive way to meet this requirement. A number of transition-metal-based procedures have been developed, and in particular, ruthenium-catalyzed oxidations of alcohols have attracted considerable attention.[2-7]

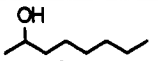
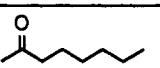
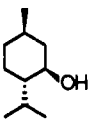
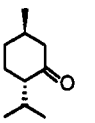
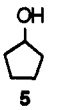
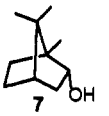
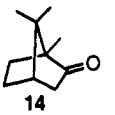
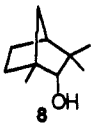
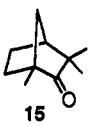
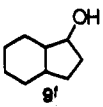
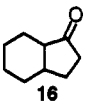
We recently developed mild procedures for oxidation of alcohols involving a ruthenium-catalyzed dehydrogenation and subsequent hydrogen transfer.[5,6a] We have now developed a ruthenium-catalyzed (1) oxidation of nonactivated secondary alcohols employing $MnO_2$ as the oxidant (eq 1). In this process, a quinone (2) is employed as hydrogen transfer mediator.



(1)

The present procedure is based on a ruthenium-catalyzed dehydrogenation of the alcohol in the presence of base ($K_2CO_3$).[6,8] Because of the reaction conditions (presence of $K_2CO_3$), it was necessary to employ the more resistant 2,6-di-*tert*-butyl-1,4-benzoquinone (2). Attempts to use less substituted 1,4-benzoquinones such as *p*-benzoquinone failed because of undesired side reactions of the quinone.[9,10]

**Table 1. Ruthenium-Catalyzed Oxidation of Secondary Alcohols to Ketones by $MnO_2$[a]**

| entry | alcohol | time (h) | product | yield[b] (%) |
|---|---|---|---|---|
| 1[c] |  3 | 17 |  10 | 85 (80)[d] |
| 2[c] |  4 | 32 |  11 | 66 |
| 3 |  5 | 20 |  12 | 70 |
| 4[c] |  6 | 31 |  13 | 70 |
| 5 |  7 | 18 |  14 | 87 |
| 6 |  8 | 24 |  15 | 40 |
| 7[e] |  9[f] | 28 |  16 | 80 (66)[d] |

[a] Unless otherwise noted the reaction was performed on a 1.0 mmol scale in refluxing THF (2.5 mL) with 1.2 mol % of ($(RuCl_2(p\text{-cymene}))_2$ (1), 20 mol % of 2,6-di-*tert*-butylbenzoquinone (2), 2.2 mol % of $K_2CO_3$, and 110 mol % of $MnO_2$. [b] Unless otherwise noted the yield was determined by gas chromatography. The selectivity for ketones was >98%. [c] 2.5 mol % of 1 was used. [d] Isolated yield. [e] 5 mmol scale. [f] Mixture of endo and exo alcohol.

A number of different ruthenium catalysts with quinone 2 as hydrogen acceptor were tested for the oxidation of secondary alcohols in the presence of $K_2CO_3$. Of those tried we found the following reactivity order, $RuCl_2(PPh_3)_3 \sim Ru(COD)Cl_2$ + dppe[11] < $RuCl_2(benzene)PPh_3$[12] << $[RuCl_2(p\text{-cymene})]_2$ (1).[12] The *p*-cymene catalyst 1 was

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(1) (a) Larock, R. C. *Comprehensive Organic Transformations*, VCH Publishers, Inc.: New York, 1989; pp 604–614. (b) *Comprehensive Organic Synthesis*, Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 7. Ley, S. V.; Malin, A. *Ibid.* pp 251–289. Lee, T. V. *Ibid.* pp 291–303. Proctor, G. *Ibid.* pp 305–327.

(2) Bäckvall, J.-E.; Chowdhury, R. L.; Karlsson, U.; Wang, G. Z. In *Perspectives in Coordination Chemistry*; Williams, A. F., Floriani, C., Merbach, A. E., Eds.; Verlag Helvetica Chimica Acta: Basel, 1992; p 463.

(3) (a) Bilgrien, C.; Davis, S.; Drago, R. S. *J. Am. Chem. Soc.* **1987**, *109*, 3786. (b) Sharpless, K. B.; Akashi, K., Oshima, K. *Tetrahedron Lett.* **1976**, 2503.

(4) Kanemoto, S.; Matsubara, S.; Takai, K.; Oshima, K.; Utimoto, K.; Nozaki, H. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 3607.

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(7) Griffith, W. P.; Ley, S. V.; Whitcombe, G. P.; White, A. D. *J. Chem. Soc., Chem. Commun.* **1987**, 1625.

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(9) Becker, H. D. In *The Chemistry of Quinoid Compounds*; Patai, S., Ed.; Wiley: New York, 1974; pp 335–423.

(10) Ulrich, H.; Richter, R. In *Methoden der Organische Chemie/(Houben-Weyl)*; Müller, E., Ed.; Bd. VII/3a, Thieme: Stuttgart, 1977; pp 720–723.

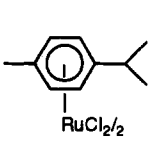
(11) Dppe = 1,2-bis(diphenylphosphino)ethane.

(12) Bennett, M. A.; Smith, A. K. *J. Chem. Soc., Dalton Trans.* **1974**, 233.

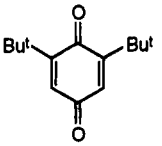
(13) The quality of the $MnO_2$ is not critical. Any type of commercially available quality can be employed and it does not have to be activated.

0022-3263/94/1959-1196$04.50/0 

the catalyst of choice and was found to be approximately 20 times faster than $RuCl_2$(benzene)$PPh_3$.



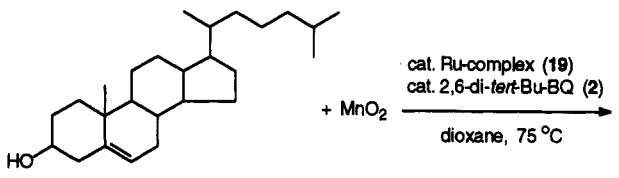

1



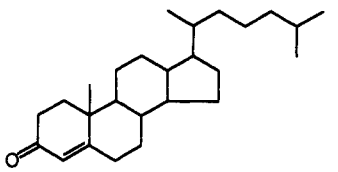

2

Oxidation of 2-octanol (3) by $MnO_2$ (1.1 equiv)[13] in THF at 65 °C, employing the catalytic system consisting of ruthenium complex 1 and quinone 2, afforded 2-octanone (10) in 85% yield (Table 1, entry 1). A number of other alcohols were oxidized by $MnO_2$ employing this catalytic system. In the absence of catalyst, only benzylic and allylic alcohols can be oxidized by $MnO_2$,[14] and nonactivated alcohols are not oxidized. However, with the present catalytic system (eq 1), a number of nonactivated secondary alcohols were oxidized to ketones under mild conditions (Table 1). In the case of borneol (7, entry 5), there was a very slow and not synthetically feasible oxidation by $MnO_2$ without the catalyst. For the other alcohols given in Table 1 there was no detectable oxidation by $MnO_2$ in the absence of the ruthenium catalyst.

Cholesterol (17) has previously been reported to be unreactive[3b] or to decompose[15] in ruthenium-catalyzed oxidations. In accordance with these observations the catalytic system of eq 1 (i.e., 1 and 2) gave <5% of ketone 18. However, when the temperature was increased and 1 was replaced by the more resistant ruthenium complex 19,[16] a reasonable conversion was obtained, and 4-cholesten-3-one (18) was isolated in 40% yield (eq 2).

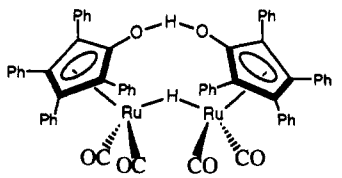



17




18 (40%)

(2)




19

The amount of $MnO_2$ did not affect the rate, but variation of the 2,6-di-*tert*-butyl-1,4-benzoquinone (2) concentration did. An almost linear increase in oxidation rate was observed with respect to the quinone concentration in the range 0–10 mol % in the oxidation of cyclohexanol (Figure 1). Above 20 mol % the increase starts to level out, and further addition of quinone led to a moderate increase of the rate. This result can be explained in terms of a change in the rate-limiting step. When a low concentration of quinone is used its reaction with ruthenium hydride might become the slowest step, whereas at high concentration of the quinone, the dehydrogenation is probably rate limiting (Scheme 1).

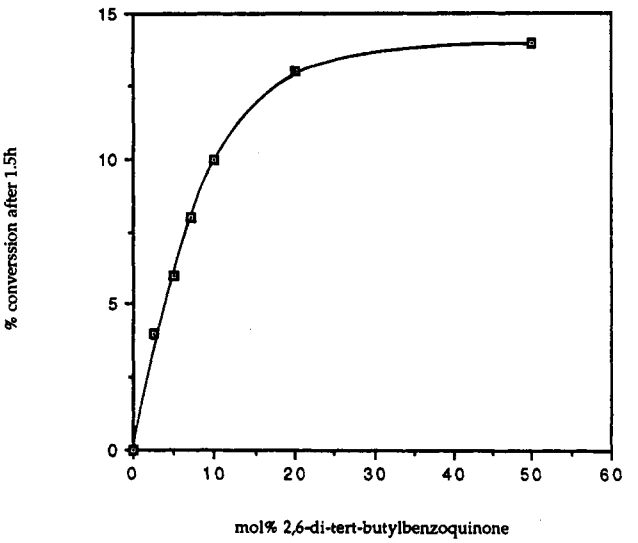
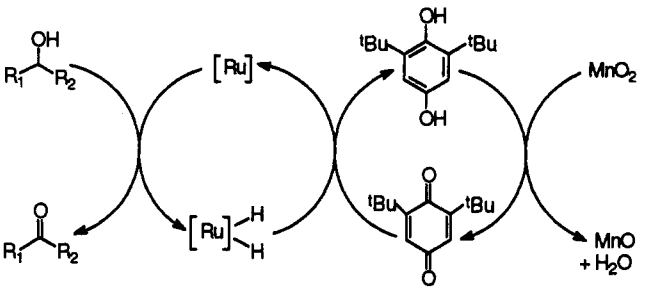



**Figure 1.** Conversion after 1.5 h in ruthenium-catalyzed $MnO_2$ oxidation of cyclohexanol (6) in THF at 65 °C with 1 at different concentrations of quinone 2.

**Scheme 1**




The oxidation of alcohols to ketones probably involves formation of a ruthenium alkoxide, which undergoes $\beta$-elimination to produce the ketone and ruthenium hydride (Scheme I).[2,4] The ruthenium hydride would then react with the quinone to give a hydroquinone, and in this process the active ruthenium species is regenerated. The hydroquinone formed is readily reoxidized by manganese dioxide.[17]

In summary, we have developed a mild ruthenium-catalyzed oxidation of nonactivated secondary alcohols by $MnO_2$[13] which is cocatalyzed by 2,6-*di*-tert-butylbenzoquinone (2).[18]

## Experimental Section

NMR spectra were measured in $CDCl_3$ solutions with a Varian Unity 400 spectrometer, $^1H$ at 400 MHz and $^{13}C$ at 100.6 MHz, with tetramethylsilane ($\delta$ 0.0, $^1H$) or chloroform-$d_1$ ($\delta$ 77.0, $^{13}C$)

(14) Pratt, E. F.; Van de Castle, J. F. *J. Org. Chem.* **1961**, *26*, 2973. Kimura, T.; Fujita, M.; Sohmiya, H.; Ando, T. *Bull. Chem. Soc. Jpn.* **1992**, *65*, 1149.
(15) Müller, P.; Godoy, J. *Tetrahedron Lett.* **1981**, *22*, 2361.
(16) Menashe, N.; Shvo, Y. *Organometallics* **1991**, *10*, 3885.
(17) A similar reoxidation of hydroquinone by $MnO_2$ in a palladium-catalyzed reaction has been described: Bäckvall, J.-E.; Byström, S. E.; Nordberg, R. E. *J. Org. Chem.* **1984**, *49*, 4619.
(18) The procedure does not work well with primary alcohols due to disproportionation of the aldehyde product.[16]

as internal standard. IR spectra were recorded on a Perkin-Elmer 1600 FT-IR spectrometer. GC analyses were performed with a Varian 3400 gas chromatograph with a 30-mDB-5 J&M fused silica column. THF was distilled under nitrogen from sodium benzophenone. Ruthenium complexes **1**[12] and **19**[16] were prepared according to literature procedures. 2,6-Di-*tert*-butyl-1,4-benzoquinone (**2**) was purchased from Aldrich and sublimated before use. $MnO_2$ was obtained from Merck and was used without prior activation. All starting materials were purchased from Aldrich except hexahydroindan-1-ol which was prepared by hydrogenation of 1-indenol using a 5% rhodium–alumina catalyst.[19]

**General Procedure for Ruthenium-Catalyzed Oxidation of Alcohols by $MnO_2$.[20] Hexahydroindan-1-one (16).** $(RuCl_2(p\text{-cymene}))_2$ (**1**) (7.3 mg, 0.012 mmol) was dissolved in THF (2.5 mL) under nitrogen. Hexahydroindan-1-ol (**9**) (140 mg, 1.0 mmol) was added to the solution followed by addition of 2,6-di-*tert*-butyl-1,4-benzoquinone (**2**) (44 mg, 0.20 mmol), $K_2CO_3$ (3 mg, 0.022 mmol), and $MnO_2$ (96 mg, 1.1 mmol). The reaction mixture was stirred for 28 h at 65 °C and then cooled to room temperature. (GC showed 80% conversion of the alcohol to the ketone.) Pentane/ether (1:1, 15 mL) was added, and the mixture was filtered through a Celite plug. The residue was washed with aqueous 2 M NaOH (3 × 2.5 mL) and dried ($MgSO_4$). The crude product was purified by flash chromatography (pentane/ether = 75/25) affording 92 mg (66%) of hexahydroindan-1-one:[21] $^1H$ NMR δ 2.24 (m, 1 H), 2.19 (dd, $J$ = 10, 5.7 Hz, 3 H), 1.95 (m, 1 H), 1.88 (m, 1 H), 1.64 (m, 2 H), 1.55 (m, 1 H), 1.41 (m, 2 H), 1.18 (m, 1 H), 0.6–1.1 (m, 2 H); $^{13}C$ NMR δ 220.0, 49.58, 36.17, 34.87, 28.18, 25,61, 24.0, 22.88, 22.54; IR (KBr) 2930, 2853, 1737, 1447, 1167 $cm^{-1}$.

**2-Octanone (10) (5 mmol scale), (–)-menthone (11), cyclopentanone (12), cyclohexanone (13), (–)-camphor (14), and (–)-fenchone (15)** were prepared from the corresponding alcohols employing the general procedure described for **16** and were characterized by comparison with authentic samples.[22] In the preparation of **10**, **11**, and **13** 2.5 mol % of catalyst **1** was used.

**4-Cholesten-3-one (18).** To a solution of cholesterol (389 mg, 1 mmol) in dioxane (2.5 mL) was added ruthenium complex **19** (9.6 mg, 0.01 mmol), quinone **2** (44 mg, 0.20 mmol), and $MnO_2$ (110 mg, 1.3 mmol). The mixture was stirred for 20 h at 75 °C and then cooled to room temperature. Ether (15 mL) was added, and the reaction mixture was filtered through Celite. The crude product was purified by flash chromatography (pentane/ether = 50/50) to afford 153 mg (40%) of **18**. The product was characterized by comparison with an authentic sample of **18**.[22] $^1H$ NMR δ 5.75 (s, 1 H, CH=C), 2.22–2.48 (m, 4 H), 2.02 (m, 2 H), 1.84 (m, 2 H), 1.55–1.75 (m, 2 H), 1.22–1.74 (m, 10 H), 1.2 (s, 3H), 0.94–1.18 (m, 8 H), 0.91 (d, J = 6 Hz, 3 H), 0.86 (dd, $J$ = 9, 3 Hz, 6 H), 0.71 (s, 3 H).

**Acknowledgment.** We are grateful to the Swedish Research Council for Engineering Science and the Swedish Natural Science Research Council for financial support.

(19) McKlein, G. W.; Smith, V. F., Jr. *J. Org. Chem.* **1970**, *35*, 52.
(20) Dodecane (40 μL) was added to the reactions, except when the ketones were isolated, and used as an internal standard.
(21) McMurry, J. E.; Miller, D. D. *J. Am. Chem. Soc.* **1983**, *105*, 1660.
(22) Commercially available from Aldrich.