

Aerobic Oxidation of Secondary Alcohols *via* Ruthenium-catalysed Hydrogen Transfer Involving a New Triple Catalytic System

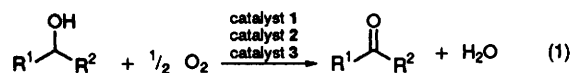
Guo-Zhi Wang, Ulrika Andreasson and Jan-E. Bäckvall*

Department of Organic Chemistry, University of Uppsala, Box 531 S-751 21 Uppsala, Sweden

Aerobic oxidation of secondary alcohols was performed employing a new triple catalytic system (Ru-catalyst **1**, 2,6-di-*tert*-butylbenzoquinone **2**, and Co-macrocycle **3**) under a low concentration of molecular oxygen (air : nitrogen is between 1 : 3 and 1 : 20) at ambient pressure.

Recently mild and selective processes for aerobic oxidation of organic compounds have been developed.^{1,2} These new processes are based on a principle for electron transfer similar to that occurring in biological systems. Thus, a stepwise electron transfer *via* coupled redox systems leads to low energy barriers and mild reaction conditions.

In one of these processes primary benzylic and allylic alcohols are oxidised to aldehydes by molecular oxygen under mild conditions.² This oxidation involves a ruthenium-catalysed dehydrogenation of the alcohol with subsequent transfer of the hydrogen.³⁻⁷ Extension to secondary alcohols is not straightforward because of the more difficult dehydrogenation of secondary alcohols by ruthenium. We have now designed a ruthenium catalyst **1** and special redox systems, **2** and **3**, which are compatible with the reaction conditions required for secondary alcohols. With this new catalytic system secondary alcohols can for the first time be oxidised to ketones by air in an efficient and selective manner [eqn. (1)].



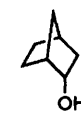
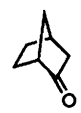
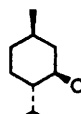
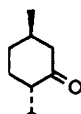
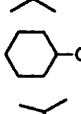
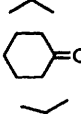
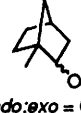
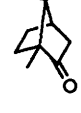


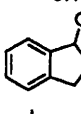
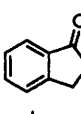
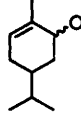
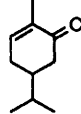
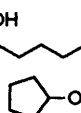
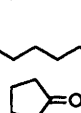
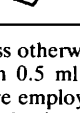
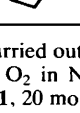
Aerobic oxidation of secondary alcohols to ketones was carried out in toluene (100 °C) or THF (65 °C) employing the triple catalytic system consisting of ruthenium complex **1**, quinone **2** and cobalt macrocycle **3** (the latter complex serves as an oxygen activating component). Cyclic alcohols were oxidised in toluene in good to high yields (Table 1, entries 1–6). The reaction works well with sterically hindered alcohols such as menthol, borneol and fenchol (entries 2, 4 and 5 respectively). The aerobic oxidation can also successfully be carried out in THF at 65 °C (Table 1, entries 7–9). For some alcohols such as carveol (entry 7) this procedure was superior since the reaction in toluene gave side products. In the oxidation of carveol and cyclopentanol (entries 7 and 9) the ketone product was isolated in good yield in each case.

The oxidation requires the sterically hindered quinone **2** and attempts to use *p*-benzoquinone gave poor results. It was also demonstrated that the process requires the presence of all three components of the catalytic system, and the exclusion of any of them stopped the reaction. It is interesting to note that the reaction does not require a high pressure of molecular

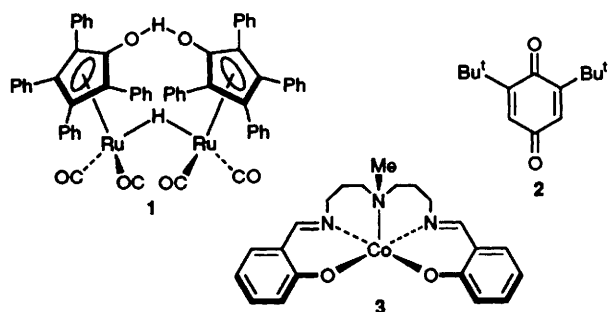
oxygen. In fact, it can be run at ambient pressure employing air and nitrogen in mixtures between 1 : 3 and 1 : 20. This is an important aspect of the reaction and a great advantage from a safety handling point of view.

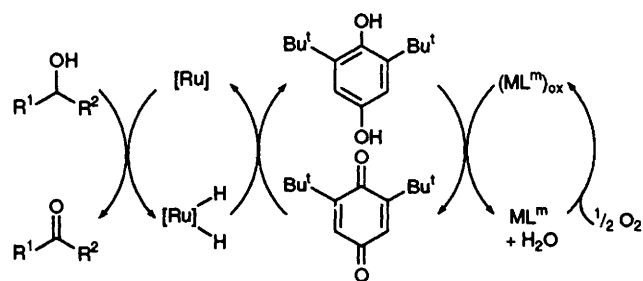
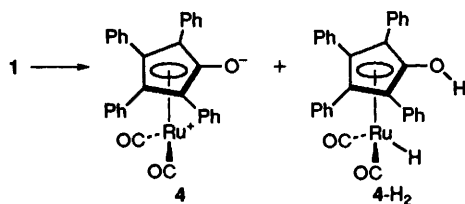
A low concentration of molecular oxygen in the reaction atmosphere was found to be essential for a successful result. A higher concentration of molecular oxygen increased the initial rate slightly, but the total number of turnovers of the ruthenium catalyst decreased. This is because the ruthenium catalyst **1** is sensitive towards molecular oxygen and at a higher O₂ concentration it undergoes decomposition.^{7c} In this respect

Table 1 Ruthenium-catalysed aerobic oxidation of *sec*-alcohols co-catalysed by quinone **2** and cobalt complex **3**.^a

Entry	Substrate	Conditions ^b	t/h	Product	Yield (%) ^c
1		A	36		87
2		A	48		88
3		A	48		89
4	 <i>endo:exo</i> = 60:40	A	36		75
5		A	36		96
6		A	36		92
7		B ^d	24		96(86) ^e
8		B	40		97
9		B ^d	36		99(89) ^e

^a Unless otherwise noted the reactions were carried out on a 1 mmol scale in 0.5 ml of solvent with 0.6–1.5% of O₂ in N₂ at ambient pressure employing 0.5 mol% of Ru-complex **1**, 20 mol% of **2** and 2 mol% of **3**. ^b A: toluene, 100 °C; B: THF, 65 °C. Temperatures given here are bath temperatures. ^c Unless otherwise noted yields were determined by GC with *n*-dodecane as internal standard. ^d Performed on a 4 mmol scale in 1 ml of THF. ^e Isolated yields after distillation under reduced pressure.



Scheme 1 (ML^m = cobalt macrocycle 3)

the cobalt macrocycle plays an important role in that it scavenges the liquid reaction phase from molecular oxygen and hence protects catalyst **1** towards decomposition. It is interesting to note that the present system does not seem to suffer from the production of water.[†]

The triple catalytic system can be described according to Scheme 1. Formally the catalytic system can be divided into two parts. The first part involves a ruthenium-catalysed hydrogen transfer from the alcohol to quinone **2**,⁸ via a dehydrogenation of the alcohol. Ruthenium catalyst **1** has previously been used in related dehydrogenation reactions.^{2d,7b,8} The second part of the catalytic system involves reoxidation of 2,6-di-*tert*-butylhydroquinone to quinone **2** by molecular oxygen/**3**.

It is likely that catalyst **1** divides into two parts which would represent the hydrogen acceptor **4** and hydrogen donor (**4**-H₂) parts of Scheme 1. Catalyst **4** would also have the ability to abstract a proton from the alcohol and act as base. We have previously reported that the presence of a catalytic amount of base leads to a dramatic rate acceleration of ruthenium-catalysed hydrogen transfer reactions involving secondary alcohols.³

A number of transition metal-catalysed oxidations of alcohols have been described,^{9–11} but only a few of these are based on molecular oxygen as oxidant.^{1a,12,13} The present procedure, which is based on a new triple catalytic system, leads to a selective and efficient aerobic oxidation of alcohols to ketones. It works at an O₂-concentration which is low enough to allow the reaction to be performed cheaply and safely.

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Footnote

[†] Formation of hydrate from the ketone products and subsequent dehydrogenation does not seem to be a problem.

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