

Efficient, Aerobic, Ruthenium-Catalyzed Oxidation of Alcohols into Aldehydes and Ketones

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The oxidation of alcohols into aldehydes and ketones is of paramount importance in synthetic organic chemistry.¹ The plethora of reagents that have been developed to accomplish this reaction is testimony to its importance.² Unfortunately, one or more equivalents of these, often hazardous or toxic, oxidizing agents are usually required. From an economical and environmental viewpoint, catalytic oxidation processes are thus extremely valuable and those employing molecular oxygen or air are particularly attractive.³ However, few efficient, catalytic, aerobic oxidations are known that proceed under mild conditions and are amenable to the preparation of fine chemicals.⁴

We have recently reported a copper-catalyzed oxidation system which employs molecular oxygen or air as the ultimate, stoichiometric oxidant.⁵ Using this method, alcohols are smoothly converted into carbonyl compounds in good yields and water is released as the only byproduct. During optimization of this procedure, we decided to investigate the ability of other metallic species to catalyze the aerobic oxidation of alcohols into ketones and aldehydes. Our preliminary studies focused on the use of various ruthenium salts (Figure 1).

The propensity of ruthenium complexes to transform alcohols into carbonyl derivatives has been well documented.^{6–10} In

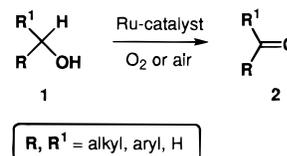


Figure 1.

many cases, the stoichiometric oxidant used in these processes is either an amine *N*-oxide, an iodosobenzene derivative, a peroxide, or a combination of oxygen and an aldehyde. In this latter case, 1 equiv of a carboxylic acid is also produced.¹¹ Few ruthenium-catalyzed oxidations of alcohols into carbonyl derivatives are known that employ molecular oxygen as the ultimate oxidant.

In 1978, Tang and co-workers reported that hydrated RuCl₃ catalyzed the aerobic oxidation of secondary alcohols into ketones, albeit in modest yields.¹² Subsequently, Matsumoto has revealed that RuO₂·H₂O is an effective catalyst for the transformation of allylic alcohols into enals and enones.¹³ More efficient catalysis can be achieved by the use of trinuclear ruthenium complexes. These organometallics have been shown by Drago to oxidize a variety of simple alcohols into aldehydes and ketones under a 40 psi of O₂.¹⁴ Finally, the elegant work of Bäckvall, which uses a combination of cobalt and ruthenium catalysts for the oxidation of some allylic and benzylic alcohols, is also a notable contribution to this area of research.¹⁵

The eagerness of Cu(I) salts to react with O₂ and generate bis-copper peroxides¹⁶ coupled with the ability of Ru(VII) complexes to smoothly oxidize a range of alcohols prompted us to investigate this bimetallic combination. For our initial experiments, we selected *p*-chlorobenzyl alcohol **3** as the test substrate and reacted it in toluene, under a stream of oxygen, with catalytic quantities of ruthenium salts, in the presence of copper(I) ions and base. The results of these studies are collected in Table 1.

When commercially available tetrapropylammonium perruthenate (TPAP; 5 mol %) was added to a suspension of CuCl·Phen (5 mol %), K₂CO₃ (200 mol %), and 1,2-bis(ethoxycarbonyl)hydrazine (DEADH₂; 25 mol %) in toluene, and the oxidation was performed as described previously,⁵ an 80% conversion of **3** into **4** was realized within 2.5 h (entry 1). This success prompted us to investigate the need for all of the components of this mixture for the oxidation process. Omission of DEADH₂ led to an improvement in catalyst activity and complete conversion of the alcohol took place within the same reac-

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Table 1. Aerobic, Ruthenium-Catalyzed Oxidation of *p*-Chlorobenzyl Alcohol

Entry	[Ru]	Additives	Conversion ^(a)	Time
1	Pr ₄ N ⁺ RuO ₄ ⁻	CuCl·Phen (5 mol %) DBADH ₂ (25 mol %) K ₂ CO ₃ (200 mol %)	80%	2.5 h
2	Pr ₄ N ⁺ RuO ₄ ⁻	CuCl·Phen (5 mol %) K ₂ CO ₃ (200 mol %)	100%	2.5 h
3	Pr ₄ N ⁺ RuO ₄ ⁻	K ₂ CO ₃ (200 mol %)	100%	1 h
4	Pr ₄ N ⁺ RuO ₄ ⁻	4 Å MS	100%	30 min

^a The conversion was measured by ¹H NMR spectroscopy and by capillary GC analysis.

tion time (entry 2). Removing the CuCl·Phen complex significantly enhanced the rate of oxidation of **3** into **4** without affecting the conversion to aldehyde **4** (entry 3). Thus, in contrast to our earlier assumption (*vide supra*), the presence of the copper complex has a retarding effect on the oxidation process. Finally, we achieved a quantitative transformation of **3** into **4**, in less than half an hour, using TPAP in the presence of O₂ and 4 Å MS (entry 4).¹⁷ This remarkably simple procedure was then applied to a range of representative alcohols (Table 2).

As can be seen from Table 2, benzylic, allylic, and secondary alcohols undergo smooth oxidation into the corresponding aldehydes and ketones (entries 1–3, 5–6, and 10). Whereas geraniol affords geranial without isomerization of the conjugated C–C double bond, nerol gives neral with minor erosion of the geometric integrity of the alkene (entries 5 and 6). It is noteworthy that these reactions proceed faster and with improved yields in 1,2-dichloroethane as compared to those in toluene.¹⁸ Remarkably, the catalyst is compatible with a range of heteroatoms, including sulfur heterocycles (entry 9).¹⁹ The oxidation of α-ketols produces 1,2-diketones with no overoxidation in the case of benzoin (entry 7). Some cleavage could be observed for the dibutyl derivative (entry 8). Primary aliphatic alcohols are smoothly converted into the corresponding aldehydes in good yields (entry 4). However, the reaction has to be performed in the absence of the 4 Å MS. The reason for this behavior is not clear at present.

It is noteworthy that smaller amounts of TPAP could be used in this process, though the reaction becomes more sluggish. For example, whereas the oxidation of **3** to aldehyde **4** is complete within 30 min under standard conditions (5 mol % TPAP), about 18 h are required to afford the same yield of **4** if only 1 mol % TPAP is employed.²⁰ Quite remarkably, the catalyst remains active even after this extended period of time.

In summary, we have discovered that TPAP can be used as an effective catalyst for the aerobic oxidation of alcohols to

(17) Other ruthenium salts, e.g., RuCl₃, RuCl₂(PPh₃)₂, KRuO₄, and Bu₄N⁺RuO₄⁻, were also tested and proved to be less efficient than TPAP.

(18) The nature of the solvent appears to be critical to the success of these aerobic oxidations. While CH₂Cl₂ or CH₃CN are commonly used for the TPAP/NMO protocol, rapid catalyst deactivation occurs under our aerobic procedure if CH₂Cl₂ or CH₃CN is employed as the solvent. Toluene and fluorobenzene proved to be the solvents of choice, though 1,2-dichloroethane could be superior at times.

(19) In addition to entry 9, pyridine-3-methanol is smoothly converted into pyridine-3-carboxaldehyde. Attempted ruthenium-catalyzed oxidations of triphenylphosphine, *N*-methylmorpholine, and thioanisole to the corresponding oxides resulted in quantitative recovery of the starting materials. This observation suggests that the aerobic oxidation proceeds probably by a dehydrogenation mechanism rather than an oxygen transfer process. The reaction also tolerates a range of protecting groups, such as benzyl and silyl ethers.

Table 2. Ruthenium-Catalyzed Aerobic Oxidation of Alcohols

Entry	Substrates	Products	Yields ^(a)
1			81% ^(b)
2			70% ^(b)
3			88% ^(b)
4			73% ^(c)
5			80% ^(d)
6			74% ^(e)
7			89% ^(b)
8			56% ^(f)
9			64% ^(b)
10			58% ^(g)

^a All yields are for pure, isolated products. ^b The conversion is quantitative. ^c The reaction was performed without molecular sieves, in refluxing toluene, and proceeded with a 94% conversion. ^d The reaction was performed in 1,2-dichloroethane, at reflux, without molecular sieves. The conversion was quantitative, and no double bond isomerization occurred. ^e The reaction was carried out in 1,2-dichloroethane, at reflux, and proceeded in 88% conversion. Some geranial was also detected (~5%). ^f Pentanoic acid could also be isolated in low yield (<10%). ^g A 73% conversion was realized under the standard conditions. The recovered starting material amounted to 20%.

aldehydes and ketones.²¹ To the best of our knowledge, this novel procedure superseeds any previously reported aerobic, catalytic oxidations of alcohols by virtue of its simplicity, efficiency, and versatility. Although much work still remains, mild and ecologically benign aerobic oxidations of alcohols now appear to be within reach.

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(20) While this process proved rather insensitive to changes in concentration, a small increase in temperature resulted in a dramatic improvement in the reaction rate and the conversions (**3** into **4**, 20 °C, 55% conversion, 2.5 h; 50 °C, >98% conversion, 2.5 h).

(21) Typical experimental procedure, preparation of *p*-chlorobenzaldehyde: A suspension of TPAP (48 mg, 6.125 mmol, 0.05 equiv) and powdered, activated 4 Å MS (200 mg) in toluene (12 mL) was stirred for 2–3 min. *p*-Chlorobenzyl alcohol (0.27 g, 2.5 mmol) was added, and a gentle current of oxygen was passed through the dark suspension *via* a glass-inlet tube. The reaction mixture was heated at 60–70 °C. After 30 min, TLC (SiO₂; EtOAc/petrol = 1:4; R_f(**3**) = 0.48, R_f(**4**) = 0.80) indicated the complete disappearance of the starting material and the mixture was cooled to room temperature. The suspension was filtered through a pad of Celite, and the pad was further washed with CH₂Cl₂/hexane (1:1). The combined filtrates were carefully evaporated under reduced pressure, and the product was further purified by column chromatography on silica gel, using CH₂Cl₂/hexane (1:1) as eluent, to give the title compound (0.23 g, 81% yield). ¹H NMR (CDCl₃, 300 MHz): δ_H 9.98 (1H, s), 7.82 (2H, d, J = 8.4 Hz), 7.50 (2H, d, J = 8.4 Hz). ¹³C NMR (CDCl₃, 75.5 MHz): δ_C 191.3, 141.5, 135.4, 131.5, 130.0.