Efficient ruthenium–TEMPO-catalysed aerobic oxidation of aliphatic alcohols into aldehydes and ketones

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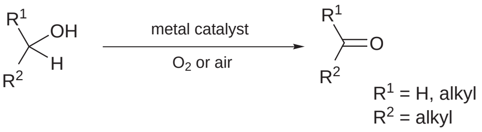
The combination of $RuCl_2(PPh_3)_3$ and TEMPO affords an efficient catalytic system for the aerobic oxidation of a broad range of primary and secondary (aliphatic) alcohols at 100 °C, giving the corresponding aldehydes and ketones, respectively, in $>99\%$ selectivity in all cases.

The oxidation of primary and secondary alcohols into their corresponding aldehydes and ketones, respectively, plays a central role in organic synthesis.[1] Traditionally, such transformations have been performed with stoichiometric quantities of inorganic oxidants, such as chromium(VI) compounds.[2] The quest for effective catalytic systems that use clean, inexpensive primary oxidants, such as molecular oxygen or hydrogen peroxide, *i.e.* a 'green method' for converting alcohols to carbonyl compounds on an industrial scale, remains an important challenge.[3]

Ruthenium compounds have been extensively investigated[4] as catalysts for alcohol oxidations using a variety of primary oxidants, *e.g.* iodosobenzene,[5] *N*-methylmorpholine *N*-oxide,[6] *tert*-butyl hydroperoxide,[7] hypochlorite,[8] bromate[9] or a combination of oxygen and an aldehyde.[10] Ruthenium compounds, *e.g.* $RuCl_2(PPh_3)_3$,[11a] trinuclear ruthenium complexes[11b] and Ru-hydrotalcite,[11c] have also been shown to catalyse the oxidation of alcohols using oxygen as the sole oxidant, but the scope was generally limited to activated alcohols, *i.e.* allylic and benzylic alcohols.

A few ruthenium-based systems for the catalytic aerobic oxidation of non-activated aliphatic alcohols (Scheme 1) are known.[12] For example, ruthenium complexes in combination with hydroquinone as cocatalyst,[12b,c] and tetrapropylammonium perruthenate (TPAP), either as such[12d] or supported on an ion exchange resin,[12e] catalyse the reaction in Scheme 1. Two heterogeneous ruthenium catalysts, the improved Ru/Co-hydrotalcite[12f] and Ru/CeO_2,[12g] have also been described. Besides ruthenium, a few other metals, *e.g.* palladium,[13] cobalt[14] and copper,[3,15] have also been shown to catalyse the reaction in Scheme 1. However, all reported systems require relatively large quantities of catalyst (5–10 mol%) and/or additives, *i.e.* cocatalyst (10–20 mol%) and drying agents (2 equiv.), to achieve their activity.

The stable free radical 2,2′,6,6′-tetramethylpiperidine *N*-oxyl (TEMPO) catalyses the oxidation of alcohols by positive halogen compounds, *e.g.* hypochlorite, hypobromite and trichloroisocyanuric acid.[16,17] In this reaction, the corresponding oxoammonium salt is the active oxidant. The hydroxylamine, which is formed, is reoxidised by the positive halogen compound. Alternatively, the use of TEMPO in combination with copper salts and oxygen as primary oxidant was reported by Semmelhack.[18] However, this system was effective only with easily oxidised benzylic and allylic alcohols, simple primary and secondary alcohols being largely unreactive.



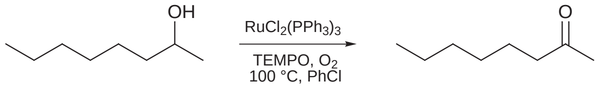
Scheme 1

Based on the various systems described above, we reasoned that the combination of ruthenium and TEMPO would likely lead to an efficient catalytic system for the aerobic oxidation of alcohols. For our initial experiments, we selected octan-2-ol as the test substrate and allowed it to react in PhCl with catalytic quantities of $RuCl_2(PPh_3)_3$ in the presence of TEMPO and oxygen. The results of these studies are collected in Table 1.

A typical reaction was carried out as follows: octan-2-ol (15.0 mmol; 1.96 g), *n*-hexadecane (internal standard; 3.0 mmol; 0.69 g), $RuCl_2(PPh_3)_3$[19] (0.225 mmol; 215.7 mg) and TEMPO[20] (0.675 mmol; 105.5 mg) were dissolved in 30 ml of PhCl and heated in a high-pressure reactor (10 bar) under a nitrogen atmosphere to 100 °C. The nitrogen atmosphere was replaced by a continuous stream (10 ml min^{-1}) of an oxygen–nitrogen mixture (8 : 92; v/v) and the mixture was stirred for 7 h. Octan-2-ol conversion and octan-2-one selectivity were determined using GC-analysis (50 m × 0.53 mm CP-WAX 52 CB column).

As can be seen from Table 2, $RuCl_2(PPh_3)_3$ alone is a poor catalyst for the oxidation of octan-2-ol to octan-2-one (entry 1). On the other hand, addition of TEMPO, which itself is not active as catalyst, to $RuCl_2(PPh_3)_3$ leads to a substantial increase in activity (entry 2). The use of PhCl as solvent is not essential and was chosen merely to simplify the GC analysis. Toluene can also be employed and even better results were obtained in neat octan-2-ol (entry 4). In this case, the same absolute conversion (15 mmol) was achieved within 1 h compared to the 9–16 h needed in PhCl (entries 2 and 3). Other ruthenium compounds were also tested. $RuCl_3$ gave lower rates and $RuCl_2(bipy)_2$ and $RuCl_2(DMSO)_4$ were completely unreactive. The turnover frequency (TOF) of our system in the oxidation of octan-2-ol is 9 h^{-1} and is superior to the most active ruthenium system

Table 1 Aerobic ruthenium–TEMPO catalysed oxidation of octan-2-ol[a]



Entry	Substrate : catalyst ratio	t/h	Conversion (%)[b]	Selectivity (%)[b]
1[c]	67	7	10	>99
2	67	7	95	>99
		9	100 (90)[e]	>99
3	100	7	78	>99
		16	100 (91)[e]	>99
4[d]	625	1	8.5	>99
		5	17	>99
		22	38	>99

[a] *Reaction conditions:* 15 mmol substrate, Ru : TEMPO = 1 : 3, 30 ml PhCl, 10 ml min^{-1} O_2–N_2 (8 : 92; v/v), P = 10 bar, T = 100 °C; [b] Conversions and selectivities based on GC results using *n*-hexadecane as internal standard. [c] No TEMPO. [d] Neat octan-2-ol as solvent, [e] Isolated yield after distillation under reduced pressure.

Table 2 Ruthenium–TEMPO-catalysed aerobic oxidation of several alcohols[a]

Entry	Substrate	Product	t/h	Conversion (%)[b]
1	Octan-2-ol	octan-2-one	7	95
2[c]	Octan-1-ol	octanal	7	85
3	Octan-3-ol	octan-3-one	7	85
4[d]	Adamantan-2-ol	adamantan-2-one	7	92
5	Cyclooctanol	cyclooctanone	7	85
6[e]	$Me_2C{=}CHCH_2OH$	$Me_2C{=}CHCHO$	7	96
7[e]	Geraniol	geranial	7	91
8[d]	PhMeCHOH	PhAc	7	91
9[d]	BnOH	PhCHO	5	100
10[d]	$3\text{-}MeOC_6H_4CH_2OH$	$3\text{-}MeOC_6H_4CHO$	4	100
11[d]	$4\text{-}MeOC_6H_4CH_2OH$	$4\text{-}MeOC_6H_4CHO$	3	100
12[d]	$4\text{-}MeC_6H_4CH_2OH$	$4\text{-}MeC_6H_4CHO$	4	100
13[d]	$4\text{-}O_2NC_6H_4CH_2OH$	$4\text{-}O_2NC_6H_4CHO$	7	68

[a] *Reaction conditions:* 15 mmol substrate, 1.5 mol% $RuCl_2(PPh_3)_3$, 4.5 mol% TEMPO, 30 ml PhCl, 10 ml min^{-1} O_2–N_2 (8:92; v/v), P = 10 bar, T = 100 °C. [b] Conversions based on GC results (selectivity $>99\%$ in all cases) using *n*-hexadecane as internal standard. [c] 2 mol% $RuCl_2(PPh_3)_3$, 5 mol% TEMPO and O_2 atmosphere. [d] 1 mol% $RuCl_2(PPh_3)_3$ and 3 mol% TEMPO. [e] O_2 atmosphere.

described in the literature, *i.e.* TPAP,[12d] which in our hands gave a TOF of 5.5 h^{-1} for octan-2-ol.

The use of $RuCl_2(PPh_3)_3$–TEMPO as catalyst for the aerobic oxidation of alcohols was then applied to a range of representative alcohols. As can be seen from Table 2, octan-1-ol is oxidised selectively into octanal (entry 2). TEMPO not only accelerates the oxidation of octan-1-ol, but also completely suppresses the over-oxidation of octanal to octanoic acid. Attempted oxidation of octanal under the same reaction conditions, in the presence of TEMPO, gave no reaction in one week. On the other hand, without TEMPO octanal was converted completely to octanoic acid within 1 h. Besides primary alcohols, secondary, cyclic, allylic and benzylic alcohols also undergo smooth oxidation (selectivity in all cases $>99\%$) into the corresponding ketones and aldehydes (entries 3–13).

In competition experiments, the Ru–TEMPO system displayed a selectivity for primary *versus* secondary alcohols. When an equimolar mixture of octan-1-ol and octan-2-ol was used, 80% of the octan-1-ol was converted, in 7 h, to octanal, whereas only 10% of the octan-2-ol was oxidised to octan-2-one. For an equimolar mixture of BnOH and PhMeCHOH, after 3 h, respectively 90 and 5% conversion was obtained. The preference for primary alcohols is analogous to results obtained with other ruthenium systems, which involve an oxidative dehydrogenation mechanism.

In summary, we have discovered that $RuCl_2(PPh_3)_3$–TEMPO is an effective catalyst for the aerobic oxidation of non-activated aliphatic alcohols and a broad range of other alcohols to aldehydes and ketones, thus providing an environmentally benign method for these synthetically important transformations. To the best of our knowledge this is one of the most reactive catalysts reported to date for the aerobic oxidation of (aliphatic) alcohols. We are currently investigating the mechanistic details of this interesting catalytic system.

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