

The Ruthenium/TEMPO-Catalysed Aerobic Oxidation of Alcohols

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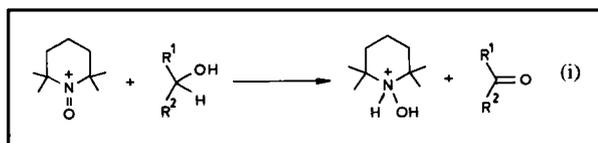
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*The combination of $\text{RuCl}_2(\text{PPh}_3)_3$ and 2,2',6,6'-tetramethylpiperidine *N*-oxyl (TEMPO) affords an efficient catalytic system for the aerobic oxidation of a variety of primary and secondary alcohols, giving the corresponding aldehydes and ketones, in > 99 per cent selectivity in all cases. This interesting catalytic system is probably based on a hydridometal mechanism, involving a ' $\text{RuH}_2(\text{PPh}_3)_3$ '-species as the active catalyst. TEMPO acts as a hydrogen transfer mediator and is regenerated by oxygen.*

The catalytic conversion of primary alcohols into aldehydes and of secondary alcohols into ketones is essential for the preparation of many key synthetic intermediates in organic chemistry (1). Traditional methods for performing such transformations generally involve the use of stoichiometric quantities of inorganic oxidants, notably chromium(VI) reagents (2), and generate copious quantities of inorganic waste. Hence, the quest for effective catalytic systems that use clean inexpensive oxidants such as oxygen and hydrogen peroxide – a 'green method' – to convert alcohols to carbonyl products on an industrial scale remains an important challenge.

Most examples of aerobic oxidation of alcohols, both homogeneous and heterogeneous, involve the use of Group VIII metal complexes as catalysts (3). In particular, ruthenium compounds, which are widely used as catalysts in organic synthesis have been thoroughly investigated (4). For example, tetrapropylammonium perruthenate (TPAP), either as such (5), or supported on an ion exchange resin (6) or MCM-41 (a mesoporous molecular sieve) (7), and ruthenium hydrotalcites (8) are capable of aerobically oxidising a variety of alcohols to carbonyl compounds. However, all the reported metal systems require relatively large quantities of catalyst (5–10 mol%) and/or additives, that is cocatalyst (10–20 mol%) and drying agent (2 equiv.), to achieve their activity.

In addition to metal complexes, stable nitroxyl radicals, such as 2,2',6,6'-tetramethylpiperidine *N*-oxyl (TEMPO), have been used as catalysts for the oxidation of alcohols to aldehydes, ketones and carboxylic acids (9). Typically, these transformations employ 1 mol% of the nitroxyl radical and a stoichiometric amount of a terminal oxidant, such as sodium hypochlorite (10), trichloroisocyanuric acid (11), *m*-chloroperbenzoic acid (12), sodium bromite (13), sodium chlorite (14) and Oxone® (15). In these systems, an oxoammonium cation is generated and acts as the active oxidant, see Reaction (i).



Alternatively, the use of TEMPO in combination with copper salts and oxygen as the primary oxidant was reported by Semmelhack (16). However, this system was effective only with easily oxidised benzylic and allylic alcohols.

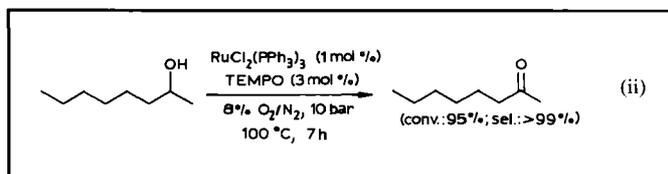
Ruthenium/TEMPO Catalyst System

Based on the catalytic 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

Ruthenium/TEMPO-Catalysed Aerobic Oxidation of Various Alcohols ^a					
Entry	Substrate	Product	Substrate/Catalyst ratio	Time, h	Conversion, ^b %
1	octan-2-ol	octan-2-one	100	7	98 (90)
2 ^c	octan-1-ol	octanal	50	7	85
3	benzylalcohol	benzaldehyde	200	2.5	> 99 (90)
4	<i>p</i> -nitrobenzylalcohol	<i>p</i> -nitrobenzaldehyde	200	6	97
5	1-phenylethanol	acetophenone	100	4	> 99 (93)
6 ^c	geraniol	geranial	67	7	91
7 ^c	3-methyl-2-butene-1-ol	3-methyl-2-butenal	67	7	96
8	cyclooctanol	cyclooctanone	100	7	92
9 ^c	octan-2-ol/octan-1-ol	octan-2-one/octanal	50	7	10/80
10	benzylalcohol/1-phenylethanol	benzaldehyde/acetophenone	200	3	90/5

^a Reaction conditions: 15 mmol substrate, ratio of RuCl₂(PPh₃)₃:TEMPO = 1:3, 30 ml chlorobenzene, 10 ml min⁻¹ O₂:N₂ (8:92; v/v), *p* (total pressure) = 10 bar, *T* = 100°C. ^b Conversions based on GC results (selectivity > 99% in all cases) using *n*-hexadecane as internal standard. The numbers in parenthesis are isolated yields (21). ^c O₂ atmosphere

as a test substrate and allowed it to react in chlorobenzene with catalytic quantities of a ruthenium complex in the presence of TEMPO and oxygen. The best results were obtained when using 1.0 mol% of RuCl₂(PPh₃)₃ (17) and 3.0 mol% of TEMPO (18), see Reaction (ii). In this case, the



turnover frequency (TOF) was 14 h⁻¹, which is superior to the most active aerobic ruthenium system described in the literature, that is TPAP (5), which in our hands gave a TOF of 5.5 h⁻¹ for octan-2-ol (19).

The use of RuCl₂(PPh₃)₃/TEMPO as catalyst for the aerobic oxidation of alcohols was then applied to a range of representative alcohols. As can be seen from the Table, 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 (19). 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 hour. The ability to suppress over-oxidation is due to the well known anti-oxidant activity of TEMPO. This stable nitroxyl radical efficiently scavenges free radical intermediates during autoxidation and thereby terminates free radical chains.

Allylic alcohols were selectively converted into the corresponding unsaturated aldehydes in high yields without intramolecular hydrogen transfer (Entries 5 and 6). Some ruthenium(II) phosphine complexes are known to catalyse intramolecular hydrogen transfer reactions of allylic alcohols to saturated ketones (20), which obviously is not occurring in the present system. Besides aliphatic and allylic alcohols, cyclic and benzylic alcohols were also smoothly oxidised into the corresponding ketones and aldehydes (Entries 3, 4 and 7). In these cases lower catalyst loadings were required (substrate/catalyst > 100).

A problem in the present aerobic Ru/TEMPO catalysed oxidation of alcohols is the deactivation of both ruthenium and TEMPO during catalysis. Attempts to use heterogeneous TEMPO systems, such as PIPO (polymer immobilised TEMPO) (22) or MCM-41 and silica-supported TEMPO (23), lead to inactive systems (24). This is probably due to coordination of ruthenium to the amine moiety in PIPO and absorption of ruthenium on the MCM-41 and silica surfaces. The latter was

proven by performing the Ru/TEMPO catalysed aerobic oxidation of octan-2-ol in the presence of silica. In this case, only minor formation of octan-2-one was observed as well as a brightening of the reaction mixture from dark brown to slightly orange. Because of the results with heterogeneous TEMPO systems and the fact that ruthenium is much more expensive than TEMPO, we refocused our aim and are currently working on the heterogenisation of ruthenium.

Mechanistic Aspects

Although in separate experiments secondary alcohols are oxidised faster than primary ones, in competitive experiments, the Ru/TEMPO system displayed a preference for primary versus secondary alcohols (Entries 8 and 9). Since these reactions are generally believed to involve the intermediate formation of an alkoxy-ruthenium complex (25), we interpret this result as an indication that the ruthenium preferentially complexes with primary alcohols, leading to selective oxidation of the latter even though the rate-determining dehydrogenation step is faster with secondary alcohols.

When the effect of the TEMPO concentration on the oxidation rate was investigated, an almost linear increase was observed, with respect to the TEMPO concentration in the range 0–4 mol%, for the oxidation of octan-2-ol, see Figure 1. Above 4 mol% the increase starts to level out, and further addition of TEMPO led to only a minor increase in the yield obtained after 1 hour. The same ‘mediator’ dependency was observed with a ruthenium/benzoquinone/MnO₂ system, reported by Bäckvall and coworkers (26), and we propose a similar mechanism, see Figure 2. The result can be explained in terms of a change in the rate-limiting step. At low concentrations of TEMPO, reoxidation of the ‘ruthenium hydride’-species may be the slowest step, whereas at high concentrations of TEMPO, dehydrogenation is probably rate limiting.

Under an inert atmosphere, no regeneration of TEMPOH should take place and RuCl₂(PPh₃)₃ catalyses the stoichiometric reaction of TEMPO and octan-2-ol.

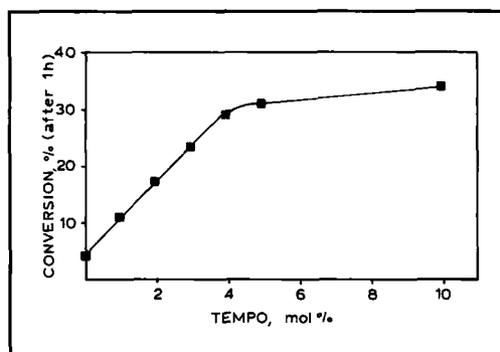


Fig. 1 The conversion of octan-2-ol in chlorobenzene at 100°C after 1 hour, using aerobic oxidation catalysed by the RuCl₂(PPh₃)₃/TEMPO system. A range of TEMPO concentrations have been employed

We performed this experiment and found octan-2-one and TEMPH as products in the ratio of 3:2, see Reaction (iii). Most likely, TEMPH is formed by a degradation reaction of the extremely unstable TEMPOH, see Reaction (iv). Attempts to prepare TEMPOH (27) under an inert atmosphere always resulted in the formation of TEMPH. On the other hand, in the presence of oxygen TEMPOH is very rapidly converted back to TEMPO. These results support the mechanism shown in Figure 2 and indicate that TEMPO acts as a hydrogen transfer mediator.

Most probably, the active ruthenium dihydride species is RuH₂(PPh₃)₃, as in the RuCl₂(PPh₃)₃-catalysed hydrogen-transfer reactions (28). In the ruthenium/TEMPO-catalysed aerobic oxidation of octan-2-ol, RuH₂(PPh₃)₄ was as active as RuCl₂(PPh₃)₃, that is, octan-2-ol was quantitatively converted to octan-2-one within 9 hours using 1.5 mol% of either catalyst and 4.5 mol% of TEMPO. The stoichiometric reaction of TEMPO with

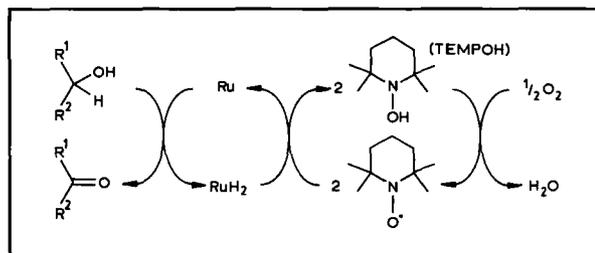
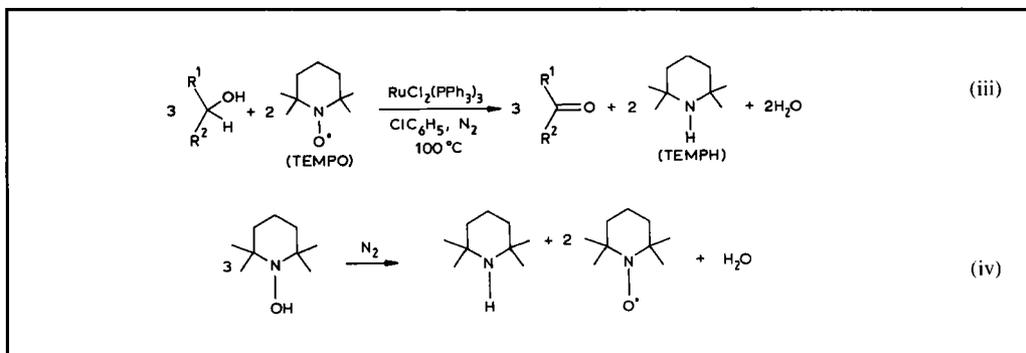


Fig. 2 Schematic mechanism of the Ru/TEMPO-catalysed aerobic oxidation of alcohols



$\text{RuH}_2(\text{PPh}_3)_4$ in chlorobenzene, under an inert atmosphere, also resulted in the formation of TEMPH.

Based on the results presented above, we propose the following catalytic cycle to explain the aerobic $\text{RuCl}_2(\text{PPh}_3)_3$ /TEMPO-catalysed aerobic oxidation of alcohols, see Figure 3. The reaction of ' $\text{RuH}_2(\text{PPh}_3)_3$ ' with TEMPO, followed by the insertion of an alcohol to form a ruthenium alkoxide species, is currently under investigation (using *in situ* IR spectroscopy and electron-spray mass

spectrometry) and probably proceeds via complex (a). The formed ruthenium alkoxide species (b) undergoes normal β -hydrogen elimination to produce the ketone/aldehyde and the active ruthenium dihydride species.

Concluding Remarks

We have discovered that the combination of catalytic amounts of $\text{RuCl}_2(\text{PPh}_3)_3$ (< 2 mol%) and TEMPO (< 5 mol%) affords an efficient catalytic system for the aerobic oxidation of a broad range

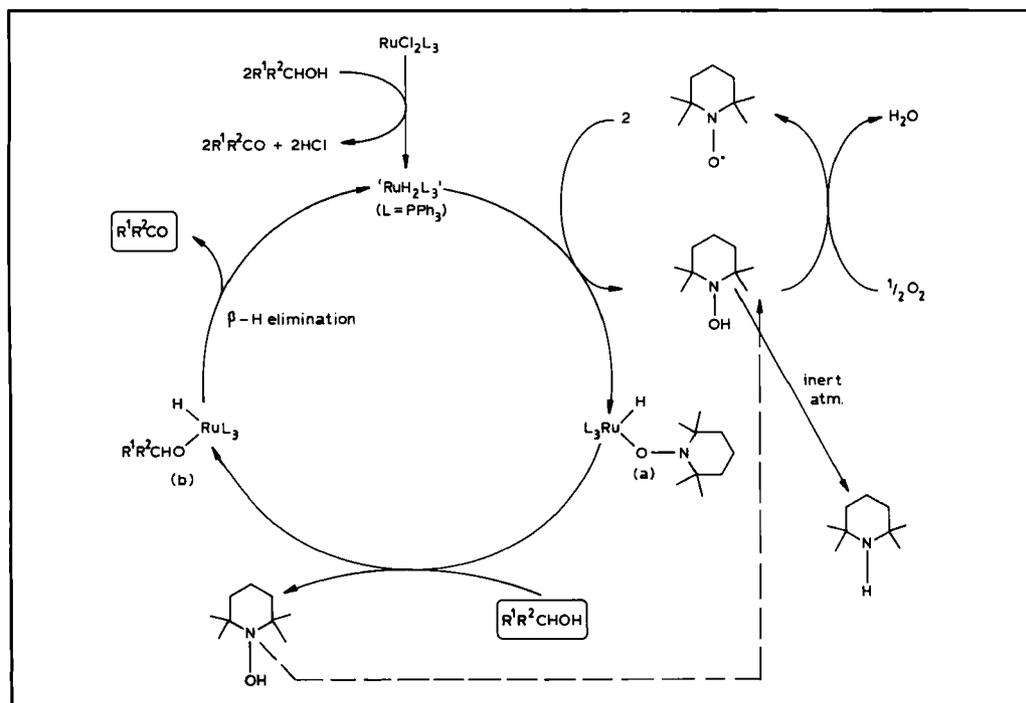


Fig. 3 Proposed mechanism for the Ru/TEMPO-catalysed aerobic oxidation of alcohols

of primary and secondary alcohols, giving the corresponding aldehydes and ketones, in > 99 per cent selectivity in all cases. Most probably, this interesting catalytic system is based on a hydridometal mechanism, involving a $\text{RuH}_2(\text{PPh}_3)_3$ -intermediate. TEMPO acts as a hydrogen transfer mediator and is easily regenerated by oxygen. We are presently investigating methods for heterogenising the ruthenium catalyst.

Acknowledgement

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References

- R. A. Sheldon and J. K. Kochi, "Metal Catalysed Oxidations of Organic Compounds", Academic Press, New York, 1981; S. V. Ley, J. Norman, W. P. Griffith and S. P. Marsden, *Synthesis*, 1994, 639; M. Hudlicky, "Oxidations in Organic Chemistry", ACS, Washington, DC, 1990 and references cited therein
- G. Cainelli and G. Cardillo, "Chromium Oxidations in Organic Chemistry", Springer, Berlin, 1984
- R. A. Sheldon, I. W. C. E. Arends and A. Dijkstra, *Catal. Today*, 2000, 57, 157
- T. Noata, H. Takaya and S.-I. Murahashi, *Chem. Rev.*, 1998, 98, 2599
- I. E. Marko, P. R. Giles, M. Tsukazaki, I. Chellé-Regnaut, C. J. Urch and S. M. Brown, *J. Am. Chem. Soc.*, 1997, 119, 12661
- B. Hinzen, R. Lenz and S. V. Ley, *Synthesis*, 1998, 977
- A. Bleloch, B. F. G. Johnson, S. V. Ley, A. J. Price, D. S. Shephard and A. W. Thomas, *Chem. Commun.*, 1999, 1907
- T. Matsushita, K. Ebitani and K. Kaneda, *Chem. Commun.*, 1999, 265; K. Kaneda, T. Yamashita, T. Matsushita and K. Ebitani, *J. Org. Chem.*, 1998, 63, 1750
- A. E. J. de Nooy, A. C. Besemer and H. van Bekkum, *Synthesis*, 1999, 1153 and references cited therein; J. M. Bobbitt and M. C. L. Flores, *Heterocycles*, 1988, 27, 509
- P. L. Anelli, C. Biffi, F. Montari and S. Quici, *J. Org. Chem.*, 1987, 52, 2559; A. Dijkstra, I. W. C. E. Arends and R. A. Sheldon, *Chem. Commun.*, 2000, 271
- C.-J. Jenny, B. Lohri and M. Schlageter, *European Appl.* 775,684; 1997
- J. A. Cella, J. A. Kelley and E. F. Kenchan, *J. Org. Chem.*, 1975, 40, 1860; S. D. Ryckovsky and R. Vaidyanathan, *J. Org. Chem.*, 1999, 64, 310
- T. Inokuchi, S. Matsumoto, T. Nishiyama and S. Torii, *J. Org. Chem.*, 1990, 55, 462
- M. Zhao, J. Li, E. Mano, Z. Song, D. M. Tschaen, E. J. J. Grabowski and P. J. Reider, *J. Org. Chem.*, 1999, 64, 2564
- C. Bolm, A. S. Magnus and J. P. Hildebrand, *Org. Lett.*, 2000, 2, 1173
- M. F. Semmelhack, C. R. Schmid, D. A. Cortés and C. S. Chou, *J. Am. Chem. Soc.*, 1984, 106, 3374
- $\text{RuCl}_2(\text{PPh}_3)_3$ was prepared according to: R. Holm, *Inorg. Synth.*, 1970, 12, 238
- Typical procedure for the aerobic oxidation of octan-2-ol: octan-2-ol (15.0 mmol; 1.96 g), *n*-hexadecane (internal standard; 3.0 mmol; 0.69 g), $\text{RuCl}_2(\text{PPh}_3)_3$ (0.225 mmol; 216 mg) and TEMPO (0.675 mmol; 106 mg) were dissolved in 30 ml of chlorobenzene, heated in a high-pressure reactor (10 bar) to 100°C under a continuous stream (10 ml min^{-1}) of an oxygen-nitrogen mixture (8:92, v/v) and stirred for 7 hours. Octan-2-ol conversion and octan-2-one selectivity were determined using GC-analysis (50 m \times 0.53 mm CP-Wax 52 CB column).
- A. Dijkstra, I. W. C. E. Arends and R. A. Sheldon, *Chem. Commun.*, 1999, 1591
- J.-E. Bäckvall and U. Andreasson, *Tetrahedron Lett.*, 1993, 34, 5459; B. M. Trost and R. J. Kulawiec, *Tetrahedron Lett.*, 1991, 32, 3039
- Typical procedure for isolating the product: the reaction mixture was diluted with *n*-hexane (to remove ruthenium) and dried over MgSO_4 . The resulting mixture was filtered and the solvent removed in vacuo. The product was separated from chlorobenzene using Kugelrohr distillation.
- A. Dijkstra, I. W. C. E. Arends and R. A. Sheldon, *Chem. Commun.*, 2000, 271
- M. J. Verhoef, J. A. Peters and H. van Bekkum, *Stud. Surf. Sci. Catal.*, 1999, 125, 465; C. Bolm and T. Fey, *Chem. Commun.*, 1999, 1795; D. Brunel, P. Lentz, P. Sutra, B. Deroide, F. Fajula and J. B. Nagy, *Stud. Surf. Sci. Catal.*, 1999, 125, 237
- A. Dijkstra, I. W. C. E. Arends and R. A. Sheldon, submitted to *Synlett*
- A. Hanyu, E. Takezawa, S. Sakaguchi and Y. Ishii, *Tetrahedron Lett.*, 1998, 39, 5557; K. B. Sharpless, K. Akashi and K. Oshima, *Tetrahedron Lett.*, 1976, 29, 2503; Y. Sasson and J. Blum, *Tetrahedron Lett.*, 1971, 24, 2167; S.-I. Murahashi, T. Noata, K. Ito, Y. Maeda and H. Taki, *J. Org. Chem.*, 1987, 52, 4319
- U. Karlson, G.-Z. Wang and J.-E. Bäckvall, *J. Org. Chem.*, 1994, 59, 1196
- C. M. Paleos and P. Dais, *J. Chem. Soc. Chem. Commun.*, 1977, 345
- A. Aranyos, G. Csornyik, K. J. Szabó and J.-E. Bäckvall, *Chem. Commun.*, 1999, 351

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