Ru-based oxidation catalysis

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Ranging from the oxidative conversion of water to O_2 to the elegant hydroxylation of olefins and to oxidative dehydrogenation of alcohols Ru-mediated oxidations are finding increasing application due to the unique properties of this extremely versatile transition metal, whose oxidation state can vary from $-II$ to $+VIII$. Covering recent developments in both homogeneously and heterogeneously catalysed oxidations (in liquid-phase as well as in novel reaction media), this *tutorial review* aims to provide investigators with a general picture of the chemical and structural origins of the excellent performance of many ruthenium catalysts and to promote further advancement that, it is envisaged, will soon benefit society at large.

Introduction

Whether applied to the selective oxidation of alkanes, olefins or alcohols with dioxygen, hydrogen peroxide or other easily accessible and environmentally friendly oxidants, or to the oxidative generation of O_2 from water, Ru-based oxidation catalysis is a powerful and extremely *versatile* synthetic tool to afford selectively oxygenate products both in homogeneous and in heterogeneous conversions.[1]

Numerous Ru complexes can selectively catalyse a large variety of oxidative transformations including the generation of dioxygen from water, the dihydroxylation of olefins, the oxidative dehydrogenation of alcohols to carbonyls and the asymmetric epoxidation of alkenes, thus opening the way to

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Sandro Campestrini

Sandro Campestrini was born in Trento, Italy. In 1989 he received his PhD in chemistry at the University of Padua where he worked with Professor Fulvio Di Furia on peroxo-complexes of Mo(VI). He later moved to work with Professor Bernard Meunier at Toulouse's CNRS and continued his studies on bioinorganic chemistry with Professor Cynthia J. Burrows at New York University at Stony Brook. He is currently Associate Professor at the Department of Chemical Sciences of Padua's University. His research interests focus on the development of catalytic oxidation systems using "green" primary oxidants as well on reactions in non-conventional solvents such as supercritical CO_2 and ionic liquids. He is author of more than 40 scientific papers and 7 international patents.

Mario Pagliaro

Mario Pagliaro obtained his PhD in 1998 from Italy's Ministry of Research with a thesis on carbohydrate oxidation reporting work carried out in Jerusalem with Professor David Avnir at the Hebrew Univesity and in the Netherlands with Dr Arjan de Nooy at Zeist's TNO Institute. He then moved to France at Grenoble's CNRS and in late 2000 was appointed full time research chemist at the Institute of Chemistry of Italy's Research Council (the Cnr) based in Palermo, where in early 1999 he had also established a management school named "Quality College del Cnr". His research interests are in the field of catalysis, conversion of renewables, photo- and electrochemistry. In 2005 he was "Maître de conférences associé" at the Ecole Nationale Superieure de Chimie de Montpellier (France).

Rosaria Ciriminna

Rosaria Ciriminna obtained her Laurea in chemistry from the University of Palermo in 1995. She started her scientific career in 1990 with a Cnr's fellowship to study the chemistry of Mediterranean natural products (terpenes) with Professor Franco Piozzi. She has worked at the Universities of Reading (UK) and Padua and later at Montpellier's ENCSM. In 2001 she was asked to present her results with the aerobic catalysts developed at the 4th World Congress on Oxidation Catalysis (Berlin); and in the same year she was appointed research chemist at Palermo's Cnr Institute of nanostructured materials. Her current research interests include sol–gel hybrid materials applied to environmentally benign syntheses and sensing.

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the conversion of petroleum products to valuable oxygenate chemicals as well as, potentially, to the extraction of energy from renewable sources.

Due to its central position in the Periodic Table, situated in the middle of the second row of the transition-metal series, ruthenium shows properties that are common to both early- and late-transition-metals resulting in "a confluence of desirable properties optimal for catalysis, such as the high reactivity of elements to its left and the less oxophilic and Lewis acidic nature of those to its right".[2] Ru complexes display the *widest range* of oxidation states of all the elements: From Ru(VIII) (corresponding to d^0) as in ruthenium tetroxide and Ru(VII) as in perruthenates to Ru(−II), (corresponding to d^{10}).

In the words of the pioneers in the field: "Oxoruthenates are ideally suited as oxidant in organic syntheses since the strongly donating oxo (O^{2-}) ligand stabilises high oxidation states".[3] Hence, RuO_4, a tetrahedral d^0 species, is a powerful and non-selective oxidant that, being soluble in organic solvents, was the first Ru species to find use in organic chemistry (in 1953) when Djerassi first described its use as stoichiometric oxidant to cleave double bonds.[4]

The same species, can be efficiently used in the chemical, low-temperature *oxidative destruction of dioxins* and other organochlorine substances such as hexachlorobenzene, polychlorinated biphenyls, and organochlorine pesticides with complete oxidation to carbonate and chloride. The overall conversion (named the Sydox process)[5] breaks down apparently intractable wastes in moderate conditions rather than "using the sledge-hammer approach of a high temperature incinerator" with oxygen as terminal oxidant, reoxidising the ruthenium catalyst at the anode with a small applied voltage in an electrocatalytic process.

$$RuO_4 \xrightarrow{1.00\ V} RuO_4^- \xrightarrow{0.59\ V} RuO_4^{2-} \xrightarrow{0.2\ V} RuO_2\ (aq.)\quad (1)$$

RuO_4^- is also a strong and poorly selective oxidant (the redox potentials in aqueous alkaline solutions are given in eqn 1), and yet by the mid 1980s Ley and Griffith discovered that its salts with large organic cations such as Pr_4N^+, Ph_4P^+ were soluble in organic solvent and showed a remarkable selective activity in the oxidation of alcohols in combination with *N*-methylmorpholine *N*-oxide (NMO) as primary oxidant.[3] Due to unprecedented selectivity in the presence of a vast variety of different oxidisable groups (double bonds, epoxide, acetals, esters, amines, lactones, amides *etc.*), tetra-*n*-propyl ammonium perruthenate (TPAP) rapidly became a commercial chemical.

During the same period, Ru-porphyrins emerged as catalysts for both the aerobic epoxidation of olefins and, especially, for the oxidation of alkanes (often with enhanced performance in the presence of visible or UV light).[6] High-valent metal–oxo complexes such as Ru–porphyrins, in fact, are analogues to monooxygenase enzymes such as cytochrome P450, and like the latter species are capable of promoting the oxidation of light alkanes with O_2 as they catalyze C–H bond activation by oxygen insertion, and thus methane hydroxylation: *i.e.* the main objective of today's research in catalysis and one of the "Holy Grails" of chemistry.[7]
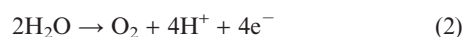
A central idea concerning oxidation catalysis with oxoruthenates is that: *i)* "by varying the oxidation state and also the nature of the co-ligands the oxidising power of the complex can be fine tuned".[3] In addition, *ii)* once the oxidation mechanism has been identified, one can modify the reaction conditions in order to accelerate the desired conversion and thereby enhance the process selectivity. Finally, *iii)* instead of varying the structural properties of the Ru complex, one can modify those of the material entrapping the catalytic complex, for example those of a sol–gel (surface hydrophilic–lipophilic balance, textural properties *etc.*) and achieve oxidative conversions that are not possible with classical solution chemistry.

Thus, for example, detailed mechanistic investigations of Ru-catalysed processes recently led to the control of the regioselective oxidation of *vic*-diols with RuO_4[8] and to the use of H_2O_2 as primary oxidant in the oxidation of carbinols with encapsulated TPAP.[9]

Reviewing recent developments of Ru-based oxidation processes, we show how these concepts were put into action, concluding with some open problems whose solution, it is envisaged, will eventually benefit our global society besides the valued applications of Ru-based reduction catalysis largely employed by today's fine chemicals industry.

Oxidation of water to O_2

The recent discovery of a new Ru complex capable of turning H_2O into O_2 at an unprecedented rate opens the way to the efficient replication of the photosynthetic reaction performed by green plants (the terminal reaction, or photosystem II, eqn 2)[10] of enormous interest for developing renewable energy sources.

$$2H_2O \rightarrow O_2 + 4H^+ + 4e^- \quad\quad (2)$$

Aiming to model this natural oxidation which occurs *via* a manganese tetramer, Llobet and co-workers have synthesized the dinuclear bis(aqua) ruthenium complex $[Ru_2^{II}(bpp)(trpy)_2(H_2O)_2]^{3+}$ (bpp = 2,2'-bipyridine; trpy = 2,2':6',2''-terpyridine).

In aqueous acidic solution the acetate-bridged precursor $[Ru_2^{II}(\mu\text{-OAc})(bpp)(trpy)_2]^{2+}$ (Fig. 1) rapidly turns into the aqua complex and it is this molecule that upon fast oxidation to its Ru^{IV}–Ru^{IV} state with Ce(IV), catalytically oxidises water
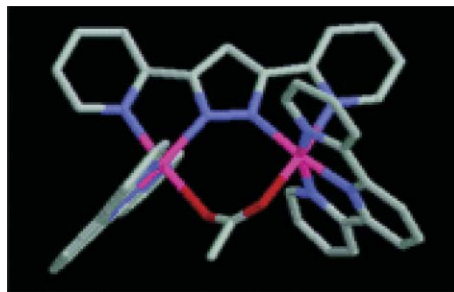

Fig. 1 The acetate-bridged precursor of the new Ru-complex capable of turning water into O_2 at an unprecedented rate is dinuclear (pink = ruthenium, red = oxygen, purple = nitrogen, and gray = carbon).
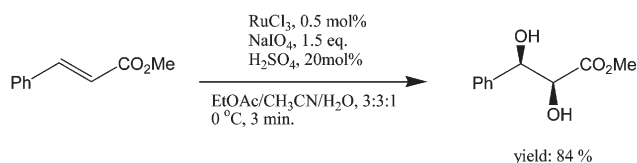
to oxygen in a slower pseudo-first-order process involving the coupling of the oxo groups to form O_2, with a rate constant of $1.4 \times 10^{-2} \ s^{-1}$.

In practice, the system 0.914 mM **1**/93.0 mM Ce(IV) in 0.1 M triflic acid up to a total volume of 2 mL rapidly generates molecular oxygen, giving an overall yield of 34 µmol of O_2 (18.6 metal cycles) after 48 h with an efficiency of 73.0% (with regard to the oxidant) and 3 times faster than previously reported for Ru–O–Ru type catalysts (containing rotating Ru–O–Ru groups). On the other hand, in this novel complex two Ru metal nuclei have been deliberately placed in *close proximity* and in an adequate orientation (using the dinucleating Hbpp and the meridional trpy ligands) to form strategically oriented Ru=O groups, which are crucial in affording high catalytic activity.
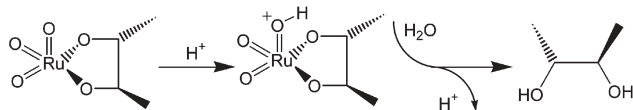
Hydroxylation of olefins

Aiming at replacing expensive and toxic osmium, in the mid 1990s Shing reported that RuO_4—the oxide isoelectronic to OsO_4 prepared *in situ* with $NaIO_4$ from inexpensive $RuCl_3$—is a fast, but rather unselective and difficult to control, dihydroxylation catalyst.[11] Recently, however, Plietker discovered that the addition of mineral acid significantly improves the process selectivity opening the way to easy preparation of a large variety of racemic glycols from readily available olefins.[8]
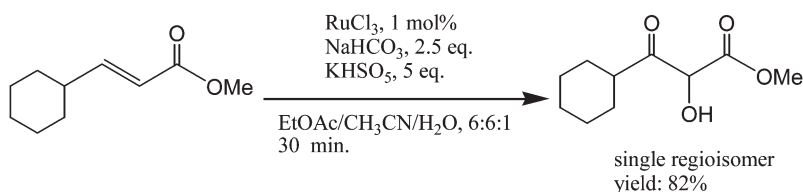
Thus by simply using a low catalytic amount of RuO_4 (0.5 mol%) in the presence of 20 mol% protic acid a large variety of olefins are rapidly and selectively dihydroxylated carrying out the reaction at 0–4 °C in an opimal solvent combination of ethyl acetate, acetonitrile and water in a ratio of 3:3:1 (Scheme 1).[8]
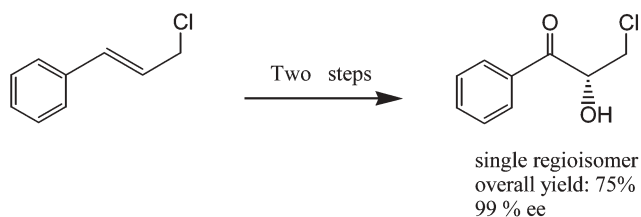
Scheme 1 Optimised conditions for the RuO_4-mediated dihydroxylation of olefins.

Scheme 2 Postulated proton activation of the intermediate ruthenate.

Scheme 4 Two-step RuO_4-catalysed oxidation of olefin to α-hydroxy ketone.

Protons accelerate the rate of the dihydroxylation by enhancing the rate of hydrolysis of the intermediated ester likely formed in the catalytic cycle (Scheme 2).
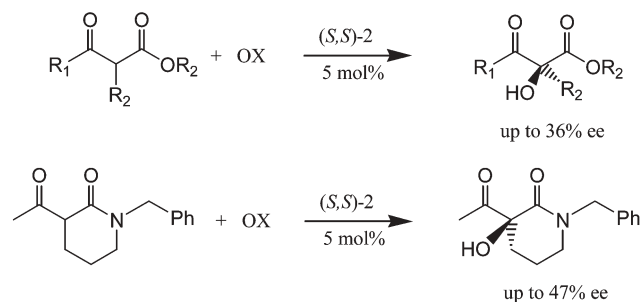
Initial protonation takes place on an oxo centre as shown in Scheme 2, but the critical intermediate is likely be the minor tautomeric form where the proton is transferred to one of the diolate oxygens leading to ring opening, after which the second diolate oxygen is much more labile in acid. Overall, since the dihydroxylation reaction competes with the C=C cleavage reaction by RuO_4 itself and by $NaIO_4$, rapid quenching of the reaction mixture with thiosulfate affords high yields of diols for a broad class of mono and 1,2-disubstituted olefins.[8]

Moreover, replacing the acid with a bicarbonate buffer and $NaIO_4$ with ®Oxone—a commercial oxidant whose active ingredient is potassium peroxymonosulfate—Plietker also introduced another mild method for the direct RuO_4-catalyzed ketohydroxylation of olefins to α-hydroxy ketones (Scheme 3);[12] and for the mono oxidation of *vic*-diols in a two-step sequence of asymmetric dihydroxylation and regioselective monooxidation for the synthesis of a broad scope of enantiopure acyloins and α-hydroxy ketones (Scheme 4).
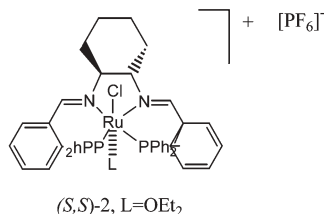
The method is based on the concept of a *nucleophilic reoxidant*. Two different functional groups are introduced in one step and the Kishi rules, known from OsO_4-catalyzed dihydroxylations, were found to be valid also for the RuO_4-catalyzed ketohydroxylation leading to moderate to good diastereomeric ratios in the oxidation of olefins possessing an allylic stereogenic center. Furthermore, the reactivity profile emerging from competitive experiments between different substituted olefins allows the prediction of which is the most reactive of different C=C double bonds present in a molecule.[12]

Another sophisticated reaction mediated by Ru is the enantioselective formation of a quaternary stereogenic center by direct hydroxylation of various β-ketoesters with H_2O_2 and the Ru(II) complex [RuCl(OE₂)((*S,S*)-PNNP)]PF₆ (Scheme 5).[13]

Interestingly, comparing oxidants in Scheme 5 it may be noted that a much larger excess of H_2O_2 is needed than CHP due to the fact that when hydrogen peroxide is used as oxidant

Scheme 3 RuO_4-catalysed ketohydroxylation of olefins.

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Scheme 5 The enantioselective hydroxylation of β-ketoesters and acyl lactames with hydrogen peroxide is catalyzed by the Ru complex (below).
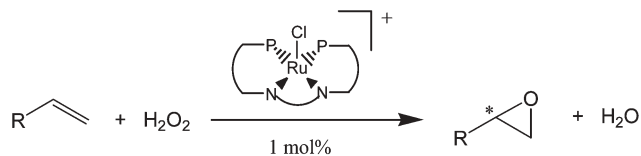
(which is clearly second only to air/oxygen in desirability) more decomposition tends to occur than with other oxidants, owing to the particular redox chemistry of H_2O_2 and consequent catalytic decomposition cycle (an effect at times called "catalase activity", see below for the same decomposition tendency as exemplified by the effect of H_2O_2 addition rate).

A necessary condition for Ru to catalyze the hydroxylation is for the ketoester to show a very substantial extent of enolization under reaction conditions since the mechanism involves the enantioselective epoxidation of a free enol by oxene transfer from an oxo complex. Indeed, the catalytic Ru(II) complexes with these chiral tetradentate P_2N_2 ligands [RuCl((S,S)-PNNP)]+ and [RuCl(OEt2)((S,S)-PNNP)]+ had been previously developed to catalyze the asymmetric epoxidation of olefins with H_2O_2 as oxidant (Scheme 6).[14]

Enantiomeric excesses up to 42% were obtained in the enantioselective epoxidation of styrene and of other unfunctionalized olefins. The reaction is highly stereospecific, as the epoxidation of (Z)-2-methylstyrene gives a *cis* : *trans* ratio of 99 : 1.

Ru porphyrins: Hydroxylation of alkanes and epoxidations of alkenes

Several ruthenium complexes are capable of catalyzing the oxidation of alkanes.[15] In a seminal recent work, comparing a ruthenium–oxo catalyst with its iron–oxo analogue toward

Scheme 6 Asymmetric epoxidation of olefins is mediated by Ru(II) complexed by tetradentate ligands.

methane hydroxylation by Cpd I(Ru) (a Ru(V) complex with porphine as the macrocycle, and thiolate as the sixth ligand) by density functional theoretical calculations, Shaik and cowokers derived the fundamental factors of catalytic activity.[16] They concluded that ruthenium–oxo catalysts are expected to lead to *more stereoselective* hydroxylations and *larger turnover numbers*, due both to lesser production of "suicidal" side-products that destroy the catalyst and to the fact that the ruthenium complex is more electrophilic than its iron analogue, having lower hydrogen abstraction barriers.
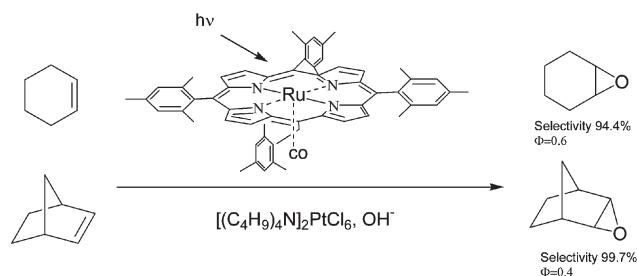
These reactivity features of the ruthenium–oxo system originate from a key fundamental factor: the strong 4d(Ru)–2p(O,N) overlaps, which produce high-lying π*(Ru–O), σ*(Ru–O), and σ*(Ru–N) orbitals and thereby lead to *a preference of ruthenium for higher-valent oxidation states* with higher electrophilicity, for the effectively concerted low-spin (LS) hydroxylation mechanism, and for less "suicidal" complexes (and thus, ruthenium–oxo species are predicted to be more robust catalysts than their iron–oxo analogues).

Showing such large potential for practical applications, the first photochemical epoxidation enhanced by visible light with *water as both electron and oxygen donor* was reported in which visible light irradiation of a reaction mixture of carbonyl-coordinated tetra(2,4,6-trimethyl)phenylporphyrinatoruthenium(II) (Ru(II)TMP(CO)) as a photosensitizer, hexachloroplatinate(IV) as an electron acceptor, and an alkene in alkaline aqueous acetonitrile induces selective epoxidation of the alkene with high quantum yield ($\Phi = 0.6$, selectivity = 94.4% for cyclohexene and $\Phi = 0.4$, selectivity = 99.7% for norbornene) (Scheme 7).[17]
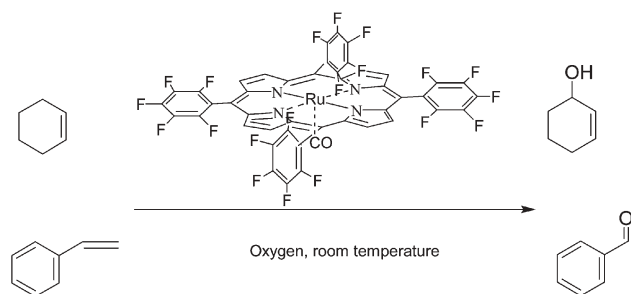
The reaction mechanism involves an electron transfer from the excited triplet state of Ru(II)TMP(CO) to hexachloro-platinate(IV) and subsequent formation of OH(−)-coordinated Ru(III) species, leading to an oxo–ruthenium complex as the key intermediate of the photochemical epoxidation.

Not surprisingly, therefore, Ru–porphyrin complexes are also capable of catalyzing the *aerobic* oxidation of olefins under mild conditions. The first example was reported by Groves in 1986 with dioxo(tetramesitylporphyrinato)-ruthenium(VI) [Ru(TMP)(O2)] catalyzing the aerobic epoxidation of olefins at ambient temperature and pressure.[18]

More recently Labinger found that a highly electron-deficient perhalogenated porphyrin ruthenium complex (TFPPCl8)Ru(CO) [TFPPCl8 = octachlorotetrakis(pentafluorophenyl)porphyrin] catalyzes the aerobic oxidation of olefins with O2 at room temperature with cyclohexene being oxidized primarily at the allylic position, and styrene primarily

Scheme 7 Photochemical Ru-porphyrin-mediated epoxidations.

Scheme 8 Aerobic epoxidation of olefins at room temperature is mediated by TFPPCl$_8$: A highly electron-deficient perhalogenated porphyrin ruthenium (the eight chloro substituents are not shown).
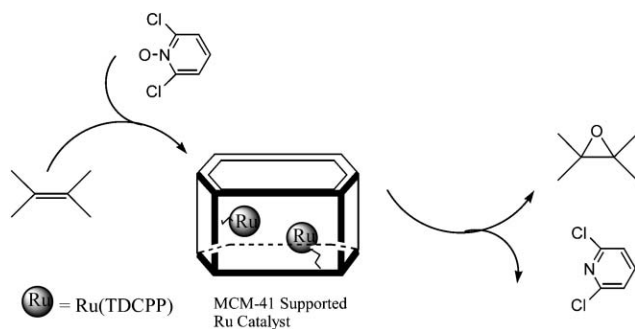
to *benzaldehyde* (due to a radical autoxidation mechanism, Scheme 8).[19]

Aiming at simple catalyst recovery and selectivity gain, Ru–porphyrins have been heterogenized in solid matrices. For example, *meso*-tetrakis(2,6-dichlorophenyl)porphyrin, [Ru^{II}(TDCPP)(CO)(EtOH)] was anchored *via* axial nitrogen ligands to the inner surface of mesoporous MCM-41 molecular sieves modified with 3-aminopropyltriethoxysilane.[20]

Despite limited stability (used repeatedly in 3 runs the catalyst retained 67% of its initial activity due to catalyst leaching or deactivation), the resulting material was a selective epoxidation catalyst (with 2,6-dichloropyridine *N*-oxide as terminal oxidant) capable of converting aromatic and aliphatic alkenes to their epoxides in good yields and selectivities and, stereospecifically, *cis*-alkenes such as *cis*-stilbene, *cis*-β-methyl-styrene, and *cis*-β-deuteriostyrene; showing also the size selectivity typical of a molecular sieve (Scheme 9).

Remarkably, an analogous surface control of oxidation by an adsorbed Ru–oxo complex was reported by Gallagher and Meyer also in the case of hydrocarbon oxidation.[21] Indeed, adsorption of the Ru aqua complex [Ru^{II}(tpy)(bpy(PO$_3$H$_2$)$_2$)-(OH$_2$)]$^{2+}$ (bpy(PO$_3$H$_2$)$_2$ is 2,2′-bipyridyl-4,4′-diphosphonic acid; tpy is 2,2′:6′,2″-terpyridine) to the external surface of transparent, thin films of TiO$_2$ nanoparticles grown on glass leads to control over the oxidation reaction by the tethered Ru^{IV}–oxo complex whereas cyclohexene in solution is oxidized to the ketone, the surface-bound complex yields primarily the alcohol.

In solution, in fact, two-electron oxidation forms Ru^{IV}, but this species reacts rapidly with Ru^{II} to produce Ru^{III}.

Scheme 9 Heterogeneous epoxidation of alkenes mediated by Ru–porphyrin complex entrapped in MCM-41 silicate.

However, when tethered to the TiO$_2$ surface, the disproportionation reaction is slowed, and the Ru^{II} species can be detected by UV-visible spectroscopy. Hence, kinetic studies on the oxidations of cyclohexene, benzyl alcohol, phenol, and *trans*-stilbene by surface-bound Ru^{IV}=O^{2+} reveal evidence for initial 2-electron steps to give Ru^{II} intermediates in all four cases.

Oxidation of alcohols

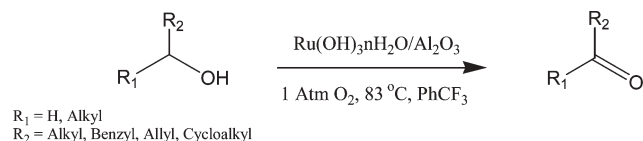"In the field of alcohol (as well as of ether and amide oxidation) ruthenium-based catalysts belong to the state of the art in their field and bear great potential for application in fine chemical synthesis".[1] Mizuno and coworkers, for instance, recently described a Ru(III)/Al$_2$O$_3$ catalyst capable of oxidizing alcohols, diols and amines under aerobic conditions (Scheme 10; but replacing oxygen with safer air does not affect either conversions or selectivities).[22]

Used in 2.5–10 mol% Ru/Al$_2$O$_3$ is extremely active in mediating the aerial oxidation of an impressive variety of alcohols, ranging from substituted benzyl to alkyl, allyl, and cycloalkyl alcohols. With reaction times varying from 1 to 10 hours, conversions are generally higher than 80% with selectivities to carbonyl in most cases better than 99%. Furthermore, unlike monomeric complexes of Ru and Pd, Ru/Al$_2$O$_3$ successfully catalysed the oxidation of primary alcohols containing heteroatoms such as oxygen, sulfur and nitrogen to the corresponding aldehydes in high yields. Moreover, the catalyst can be efficiently re-used: the oxidation of benzyl alcohols was repeated seven times and benzaldehyde was quantitatively produced at the same rate as in the first run with a TON of ~300 which is the highest (thus far) for a Ru-based aerobic catalyst.
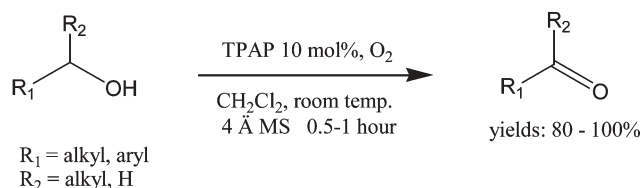
Besides ruthenium hydrotalcites,[23] another efficient bicatalytic system uses a combination of RuCl$_2$(PPh$_3$)$_3$ (1 mol%) and 2,2′,6,6′-tetramethylpiperidine *N*-oxyl (TEMPO, 3 mol%) to afford an efficient catalytic system for the aerobic oxidation of a variety of primary and secondary alcohols at 100 °C with 10 bar of O$_2$/N$_2$ (8/92, v/v), giving the corresponding aldehydes and ketones, in >99% selectivity in all cases.[24] The catalytic system is probably based on a hydridometal mechanism, involving a 'RuH$_2$(PPh$_3$)$_3$'-species as the active catalyst in which TEMPO acts as a hydrogen transfer mediator (and is regenerated by oxygen).

As mentioned above, however, crystalline, non-volatile and air stable material TPAP prepared from RuO$_4$ and (n-Pr$_4$N)OH in basic solutions is the commercial catalytic oxidant of choice due to its ease of use, excellent performance and versatility.[3]

Working with various organic solvents (the authors were attempting to develop a selective oxidant for alcohols insoluble in water), as stoichiometric reagent TPAP behaves as an

R$_1$ = H, Alkyl
R$_2$ = Alkyl, Benzyl, Allyl, Cycloalkyl

Scheme 10

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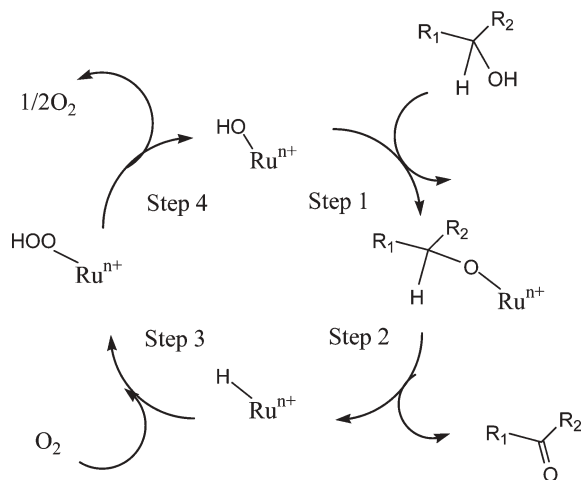*Chem. Soc. Rev.*, 2005, **34**, 837–845 | 841

Scheme 11

overall three-electron oxidant for a wide range of multi-functional species; but its full potential was revealed when its catalytic behaviour with *N*-methylmorpholine *N*-oxide (NMO) as terminal oxidant was uncovered by its inventors.

In general, the reactions are carried out in mixtures of dichloromethane–acetonitrile at room temperature utilizing 5–10 mol% TPAP and reach completion rapidly, typically in a few hours. The maximum turnover numbers (TON) obtained under these conditions do not exceed *ca.* 250 and at the end of the reaction a black precipitate of inactive RuO_2 is isolated.

In 1997, however, Markò[25] (and Ley himself)[26] showed that O_2 at low pressure (1 bar) is an optimal primary oxidant for TPAP-mediated alcohol oxidation at 80 °C opening the route to the commercial oxidation of alcohols to carbonyl compounds (a process of paramount importance in manufacturing commodities and fine chemicals) with the cleanest (and cheapest) oxidant (Scheme 11).

Hence, whereas this chemical transformation is still carried out at industrial level with stoichiometric amounts of toxic and hazardous chromium(VI) and manganese(VI) reagents, benzyl and allyl alcohols can now be smoothly and quantitatively transformed into the corresponding aldehydes in less than 40 min, while non-activated primary alcohols react somewhat more slowly. In the case of 1-octanol, for instance, after 1 hour 80% alcohol conversion was obtained with a 100% selectivity for the corresponding aldehyde.

Based on a large body of evidence—*i.e.* oxidation of radical clock substrates, Hammett ρ plots, and a kinetic analysis of the reactive system—Mizuno recently proposed the reaction mechanism depicted in Scheme 12,[22] which could be confirmed also for aerobic oxidations mediated by perruthenate.

The faster oxidation of primary over secondary alcohols supports the formation of a ruthenium alcoholate species by the ligand exchange of ruthenium hydroxide derivatives with alcohols (step 1), as the formation of a metal alcoholate is a well recognized requirement for the selective oxidation of the primary hydroxyl.
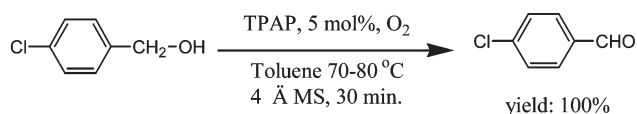
The rate determining step is the β-hydride elimination in the alcoholate species affording the carbonyl product and a Ru-hydride species in step 2 (as shown by a primary kinetic isotope effect (k_H/k_D) of 4.2–5.0 at 373–333 K and by the Hammett constant ρ of −0.46). The reoxidation of Ru-hydride (step 3) proceeds smoothly and is not rate determining (as shown by the zero-order dependence of reaction rates on the oxygen pressure). Finally, a rapid decomposition of the ruthenium hydroperoxide regenerates the catalyst (step 4).

The TPAP–O_2 oxidizing system meets several principles of Green Chemistry[27] and raises the prospect for industrial oxidations because of: *i*) its applicability to a wide range of alcohols, diols and amines, *ii*) the use of air as terminal oxidant, *iii*) simple products/catalyst separation and *iv*) the catalyst re-usability. In all cases, however, the maximum TON observed was *ca.* 20 and the reason for catalyst deactivation seems to be due to the formation of inactive, colloidal RuO_2. Markò[25] showed that catalyst deactivation is solvent dependent and that reaction temperatures around 80 °C are required. Hence, under optimised conditions, only 1 mol% of TPAP could be used for the complete conversion of *p*-chlorobenzyl alcohol into the corresponding aldehyde (Scheme 13).
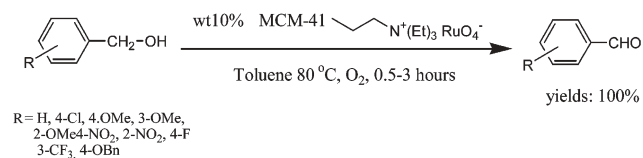
In order therefore to recover and re-use precious catalytic TPAP, perruthenates were soon heterogenized in a variety of organic and inorganic matrixes.

Besides a polystyrene-bound version consisting of perruthenate (PSP) ionically tethered to an Amberlyst anion exchange resin which was soon reported to be "unstable towards leaching"[29] a remarkably more efficient and sophisticated catalyst was obtained by tethering RuO_4^- to the inner pores of mesoporous silicate MCM-41 derivatised with quaternary ammonium –Si–$(CH_2)_3$–$N^+(CH_3CH_2)_3$ anchors.[28] The resulting heterogeneous catalyst is highly active for the preparation of a wide range of benzyl aldehydes (Scheme 14).
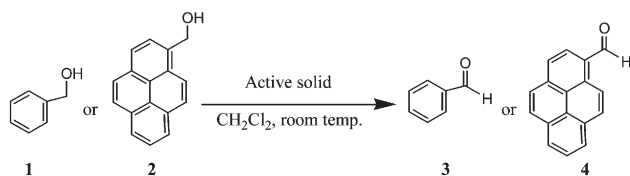
Interestingly, heterogenisation resulted in a major activity improvement with respect to homogeneous TPAP itself, as the 10% wt of catalyst employed corresponds to 0.3% wt of Ru,

Scheme 13

R = H, 4-Cl, 4-OMe, 3-OMe, 2-OMe4-NO_2, 2-NO_2, 4-F 3-CF_3, 4-OBn

Scheme 14

Scheme 12

Scheme 15

and thus to a turnover number of *several hundreds*, pointing to a catalyst deactivation process which is somehow *inhibited* by effective heterogenization of perruthenate at the solid's surface.

Using a zeolite to embed perruthenate using a similar approach the selectivity of the reaction can be extended also on a shape–molecule base. Hence, a FAU zeolite embedding perruthenate (Ru–FAU) cannot mediate the aerial oxidation of 1-pyrenecarbinol (too large to enter pores of zeolite) to 1-pyrenecarboxaldehyde while it easily converts benzyl alcohol to benzaldehyde (Scheme 15).[29]
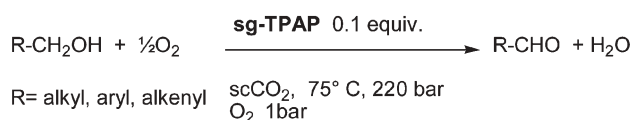
Using sol–gel technology for encapsulating TPAP within the vast internal porosity of amorphous organically modified silicates (ORMOSIL), we prepared a series of "off-the shelf" solid aerobic catalysts capable of meeting the requirements of different reaction media and of terminal oxidants.

In particular, the (controllable) ratio between methyltrimethoxysilane (MeTMS) and tetramethyl orthosilicate (TMOS) affects the material's textural properties and hydrophilicity–lipophilicity balance (HLB) which dictate the catalytic performance. Hence, carrying out the aerobic oxidations in the hydrophobic solvent toluene, the HLB of the catalyst surface is the main factor in determining the performance as catalyst, with 75% and 100% of methyl-modified xerogels exhibiting the best activities in spite of their lower porosity.[30]

In supercritical carbon dioxide (scCO$_2$)—a fluid where diffusion of the solute reactants to the catalyst's solid surface is greatly enhanced—the 50% methylated ORMOSIL gel with larger porosity was best.[31] (Scheme 16).

In both cases, comparison between the doped organosilicas reactivity with that of unsupported TPAP clearly showed that sol–gel encapsulation largely *enhances* the perruthenate activity. Interpretation of the structure–activity relationship observed provided guidelines for the development of even more efficient heterogeneous catalysts for oxidative dehydrogenations specifically designed for operating in scCO$_2$, *i.e.* a hybrid organic–inorganic 10% fluorinated silica glass doped with TPAP.[32]

In this case, affinity of both scCO$_2$ and O$_2$ for fluorinated hydrocarbons enhances diffusivity of the dissolved substrate and product molecules through the vast accessible porosity (0.53 cm^3 g^{-1}) facilitating their transfer to and from the inner catalyst's pore surface; moderate (10%) silica fluorination by a short-chain fluoroalkyl-containing monomer affords the best

Scheme 16

performing catalyst by ensuring prevention of TPAP burying in the material's bulk.

The potential of sol–gel catalysts in opening the route to conversions that are *not* possible *via* classical solution chemistry is shown by the use of H$_2$O$_2$ in alcohols oxidation catalysed by sol–gel entrapped TPAP.[9] Hence, whereas anhydrous hydrogen peroxide (in ethyl ether) added to a TPAP suspension is rapidly decomposed, *slow* addition by means of a syringe-pump to a suspension of sol–gel silica-entrapped TPAP containing an alcohol results in almost quantitative conversions of the alcohol substrate (Fig. 2).

In this case, the polar nature of hydrogen peroxide, requires the use of unmodified silica glass while hydrophobized glasses limit its diffusion to the material's surface, and thus the reaction rate. Simple addition of 3Å molecular sieves ensures water removal (to suppress over-oxidation of the aldehydes to carboxylic acid), resulting in a practical selective catalytic process since, unlike dioxygen, H$_2$O$_2$ does *not* require high temperatures to react while, like the latter species, it is a clean and atom-efficient primary oxidant

ORMOSIL being living materials, the catalytic activity of hybrid glasses doped with TPAP—no matter whether employed in scCO$_2$ or in organic solvent—substantially increases with time several months after the xerogels' preparation (Fig. 3).[33]

This surprising result is due to progressive *migration* of the active perruthenate ion pair from the aggregates at the surface of the ORMOSIL's sol–gel cages where it is partly buried to the new internal accessible porosity of the xerogel which forms upon further hydrolysis and condensation of the unreacted –Si(OR) groups. As a result, a low catalytic amount (0.5 mol%) of entrapped TPAP can now be used to afford still high yield of aldehyde, yielding a turnover number of 140 (one of the highest for a Ru aerobic catalyst).

Washing the solid catalyst with various organic solvents between consecutive reaction runs in scCO$_2$ cause a fast TPAP degradation (Fig. 4).[27]

Catalyst degradation rate depends on the nature of the solvent. In DCM, which is a good solvent for unsupported
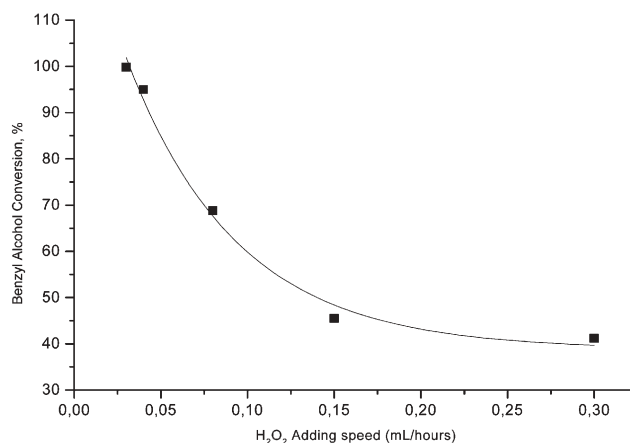

Fig. 2 Benzyl alcohol conversion (0.05 mmol in 3.0 mL ether) as function of the velocity of H$_2$O$_2$ addition (3.0 mL of H$_2$O$_2$ 4.7 × 10^{-2} M in ether) in the presence of TPAP-doped ormosils (0.005 mmol) at 25 °C.

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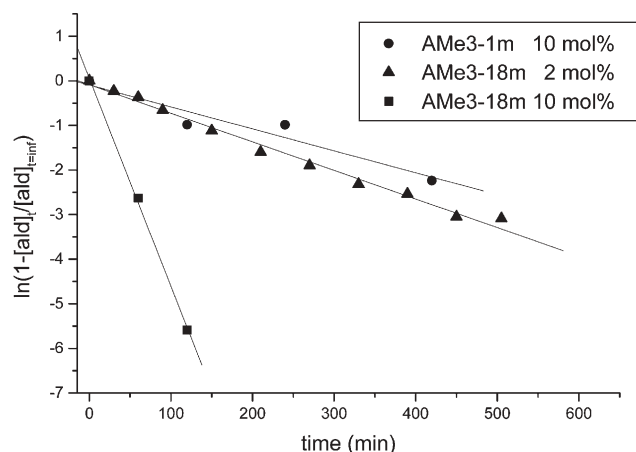*Chem. Soc. Rev.*, 2005, **34**, 837–845 | 843

Fig. 3 Aerobic oxidation of benzyl alcohol to benzaldehyde in scCO$_2$ over TPAP entrapped in aged (■, ▲) and fresh (●) 75% methyl-modified silica matrix.
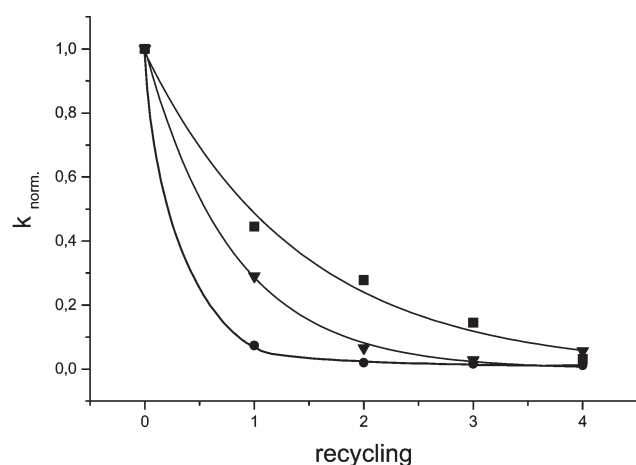

Fig. 4 Dependence of normalized rate constants for benzyl alcohol (4.83 × 10^{-2} mmol) oxidation with O$_2$ (1 atm) catalysed by Me3A(NoNaF)-TPAP (5.0 × 10^{-3} mmol) in scCO$_2$ at 22 MPa and 75 °C, as a function of catalyst recycling and washing solvent (■: ethyl ether; ▼: n-hexane; ●: dichlomethane).

TPAP, the inactivation is quick and already after the first recycle the catalyst is almost inactive, whereas in Et$_2$O and even more in hexane (where TPAP does not dissolve) the decay in efficiency is noticeably slower.

These observations seem to corroborate the hypothesis of a TPAP inactivation caused by *self-aggregation of Ru derivatives*, even though a chemical interaction with the solvent cannot be ruled out. Indeed Kozhevnikov and co-workers have shown the presence of various (minor) by-products pointing to TPAP degradation;[34] while the time course typical of TPAP catalysed aerobic oxidations—a faster stage up to 40–50% substrate conversion followed by a slower one—indicates a complex reaction mechanism[35] in which the homogeneous oxidation mediated by perruthenate is subsequently heterogeneously catalysed by colloidal RuO$_2$.

These results reinforce the option of using scCO$_2$ as reaction medium with the TPAP ion pairs physically segregated as happens in the organosilica sol–gel cages, where both

intermolecular and solvent-dependent degradation are *intrinsically* prevented.

An alternative method for TPAP catalyst recovering from reaction mixtures, uses 10 mol% homogeneous TPAP for alcohol oxidations with NMO in the presence of a ionic liquid achieving a TON of *ca.* 10. Addition of ether at the end of the reaction ensures sequestration of the catalyst as a black-green suspension while the insoluble ionic liquid results in separation of clear supernatant liquid containing the oxidation products. While the recovered catalyst can be re-used five times without significant loss of catalytic activity in benzyl alcohol oxidation, in the case of cinnamyl alcohol a significant slowing of the reaction was observed in the fourth recycling.[36]

The fact that RuO$_2$ can, under certain conditions, act as aerobic catalyst was recently shown by White and co-workers who described the preparation and use of a zeolite-confined nanometer-sized RuO$_2$ (RuO$_2$–FAU), by a one-step hydrothermal method.[37] The spatial constraints of the rigid zeolitic framework ensure incorporation of RuO$_2$ nanoparticles (1.3 nm) into the supercages of faujasite zeolite that are structurally similar to highly hydrous RuO$_2$. These RuO$_2$ nanoclusters—which cannot diffuse out of the relatively narrow channels pores of the zeolite during the catalytic process, making the catalyst stable and re-usable—at 80 °C exhibit selective activity in the aerobic oxidation of alcohols with air at ambient pressure (TONs from 2 to 28, depending on the substrate).

Finally, all the above mentioned leach-proof Ru-doped silicates (Fig. 5), being highly selective and versatile, show great potential for applications to micro-reactions.[38]

In fact, in contrast to a batch reactor where the catalyst is in large excess over the reactants, this is not the case in micro-reactors contributing to higher turnover while no removal of the catalyst from the reaction mixture is required as the solid catalyst is immobilized, as recently demonstrated for several other reactions with similar functionalized silica gels packed in a capillary.[39]

Fig. 5 Tiny particles of leach-proof and versatile catalytic ORMOSIL-entrapped perruthenate such as this 150 μm catalyst particle are ideally suited for being packed in capillaries and used in micro-reactions.

Conclusions and outlook

Ru-based oxidation catalysis is being rapidly developed as it affords fundamental products for today's society, from both economic and environmental viewpoints. Ranging from powerful detoxification oxidations with RuO_4 applied to the chemical destruction of dioxins to sophisticated ketohydroxylations and to the direct oxidation of methane, research on Ru-based oxidations is flourishing; and recently it resulted even in the most efficient water splitting catalysts for the generation of oxygen known. Increasing concerns over the high price and limited availability of petroleum, will eventually push our society to find a more rational use of hydrocarbons— for instance as chemical oxygenate feedstocks—and a move towards renewable energy sources. And in both these cases, Ru-based oxidation catalysis is envisaged to play a major role.

A number of scientific problems, however, remain to be solved in order to help the widespread industrial use of Ru-mediated oxidations. For instance, the stability of oxo–ruthenium porphyrin, PorRuO, linked to a cysteinate ligand, needs to be largely improved if these molecules are to find any practical applications since functionalized porphyrins, particularly with thiolate coordination, have difficulty in surviving the harsh conditions of inserting Ru in place of Fe.[16]

Similarly, in the case of water oxidation to dioxygen with dinuclear complex **1**, there is a need to limit deactivation caused by ligand oxidation due to intermolecular interactions and thus stabilise high activity. Elucidating some of the basic concepts of oxidations mediated by this fascinating metal, this tutorial review aims to contribute to further advancements in one of the most exciting fields of current chemical research.

Acknowledgements

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