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Green Chemistry

Catalytic Oxidation of Organic Substrates by Molecular Oxygen and Hydrogen Peroxide by Multistep Electron Transfer—A Biomimetic Approach**

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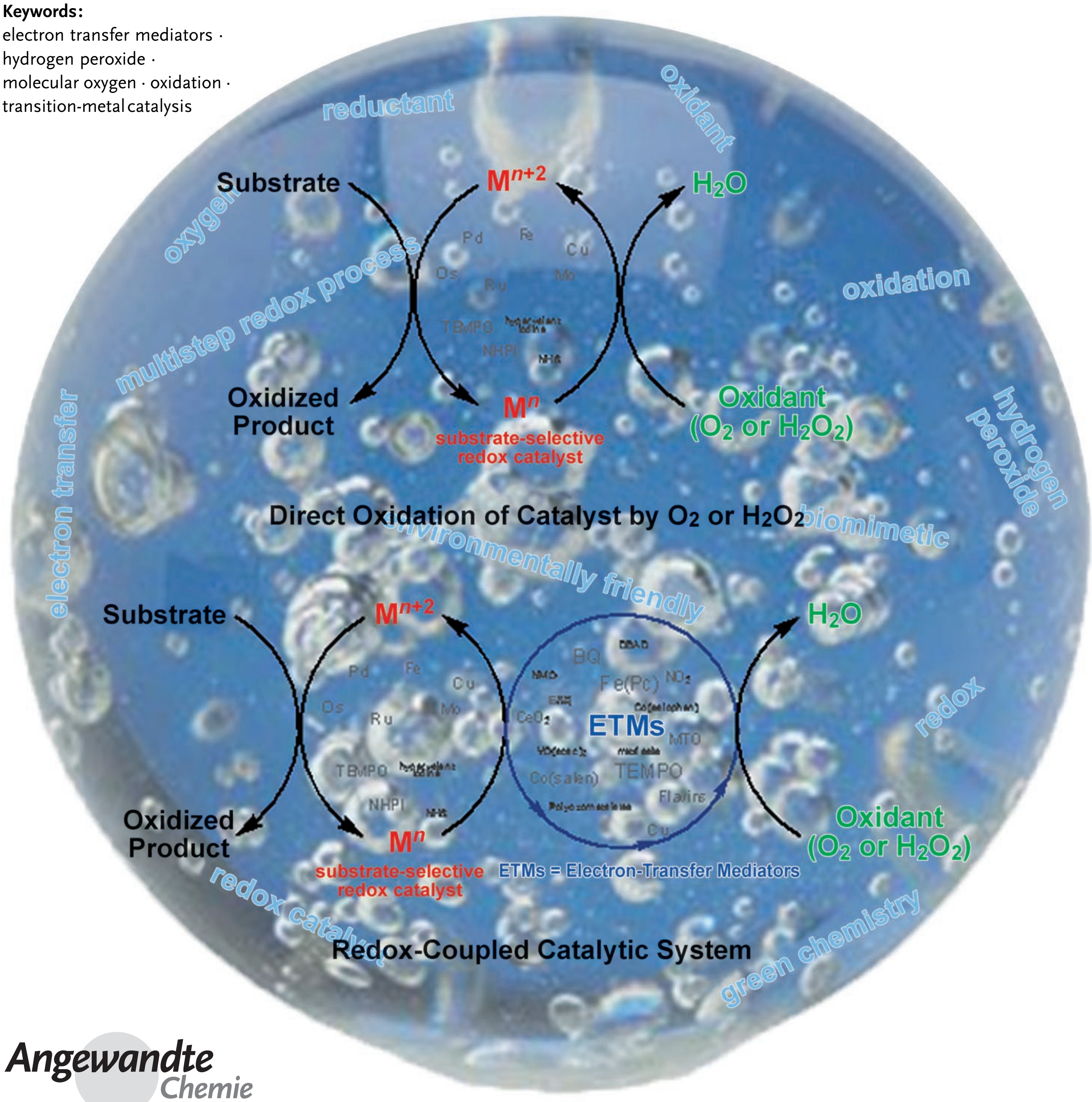
Keywords:
electron transfer mediators · hydrogen peroxide · molecular oxygen · oxidation · transition-metal catalysis



Oxidation reactions are of fundamental importance in nature, and are key transformations in organic synthesis. The development of new processes that employ transition metals as substrate-selective catalysts and stoichiometric environmentally friendly oxidants, such as molecular oxygen or hydrogen peroxide, is one of the most important goals in oxidation chemistry. Direct oxidation of the catalyst by molecular oxygen or hydrogen peroxide is often kinetically unfavored. The use of coupled catalytic systems with electron-transfer mediators (ETMs) usually facilitates the procedures by transporting the electrons from the catalyst to the oxidant along a low-energy pathway, thereby increasing the efficiency of the oxidation and thus complementing the direct oxidation reactions. As a result of the similarities with biological systems, this can be dubbed a biomimetic approach.

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1. Introduction

Oxidation reactions play an important role in organic synthesis, and there is currently a demand for more selective and efficient oxidation methods.[1] Pressure from society has placed restrictions on industrial oxidation technology, with emphasis on the need for sustainable and environmentally friendly processes. Today there is an increasing demand to use oxidants such as molecular oxygen and hydrogen peroxide, which are environmentally friendly and do not give rise to any waste products. Both of these oxidants fulfill the requirement of "green chemistry".[2]

Molecular oxygen and hydrogen peroxide have many advantages and only a few minor disadvantages. The main advantages are that both of them are environmentally friendly and show a high efficiency per weight of oxidant. Compared to hydrogen peroxide, molecular oxygen has the advantage that it is inexpensive (for example, air can often be used), but it has the disadvantage that rigorous safety handling is required for large-scale applications. One advantage of H_2O_2 over O_2 that is appreciated by industrial chemists is that it is a liquid which is miscible with water and is relatively easy to handle. On the negative side, H_2O_2 can undergo radical-induced decomposition to H_2O and $1/2\,O_2$. Impurities and traces of metallic particles can induce this process.

The direct oxidation of organic substrates by either O_2 or H_2O_2 is rare as the energy barrier for electron transfer from the organic substrate to the oxidant is usually high. For molecular oxygen, which has a triplet ground state, this high-energy barrier is nature's way of protecting organic compounds from destructive oxidation. Nature has also found methods to make controlled aerobic oxidations under highly mild conditions. The unfavorable kinetics associated with direct aerobic oxidations is circumvented in the respiratory chain, which is involved in many biological oxidations.[3]

The process is rather complicated and involves several enzyme complexes containing a variety of redox cofactors (Scheme 1). The electrons are passed in multistep redox processes from an energy-rich electron donor to oxygen. For example, an alcohol is dehydrogenated by NAD^+ and the NADH produced (energy-rich electron donor) is oxidized by molecular oxygen as the terminal oxidant. The redox couple $NAD^+/NADH + H^+$ serves, together with the dehydrogenase enzyme, as a substrate-selective catalyst in the biological oxidation. Cytochrome *c* (a small protein covalently attached to an iron porphyrin, which is the active redox part) accepts electrons from complex III and donates them to complex IV (cytochrome *c* oxidase), which carries the electrons to molecular oxygen and reduces it to water. The mobile coenzymes ubiquinone (coenzyme Q) and cytochrome *c* serve as a link for the transfer of electrons between the complexes of the respiratory chain from NADH to molecular oxygen.[4]

For a catalytic oxidation reaction, the substrate-selective catalyst, which may often be a transition metal (M^{n+2}/M^n), oxidizes the substrate to the desired product. The reduced form of the catalyst is subsequently reoxidized by the stoichiometric oxidant. From an environmental point of view, it is desirable that the oxidant is either molecular oxygen or hydrogen peroxide (Scheme 2).

There are various examples where the metal is directly reoxidized by O_2 or H_2O_2.[5–10] Although these direct reoxidations of the metal give efficient oxidations in many cases, this approach fails in other cases because the electron transfer

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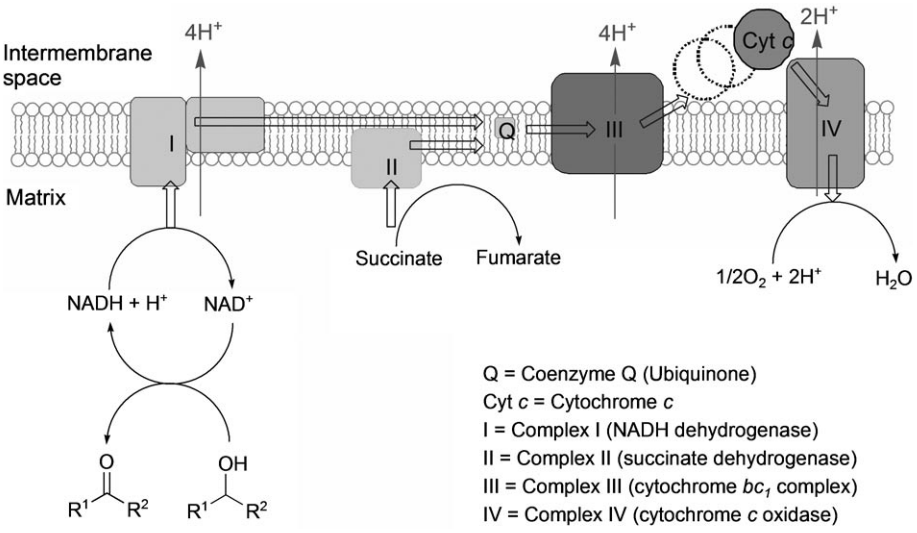
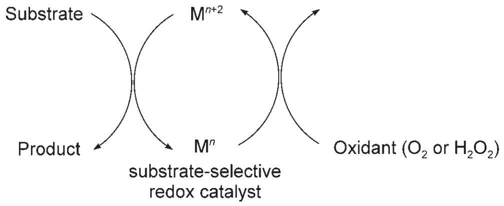
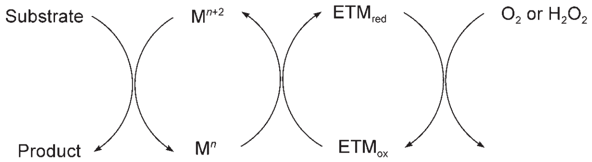


Scheme 1. Aerobic respiratory chain (electron transfer).



Scheme 2. Oxidation with a substrate-selective redox catalyst.

between M^n and O_2 or H_2O_2 is too slow compared to decomposition of the reduced metal. For example, in palladium-catalyzed aerobic oxidations, the precipitation of palladium metal (palladium black) from soluble palladium species (Pd-H, Pd^0) often competes kinetically with reoxidation by O_2.[5] To circumvent this problem one can employ ligands that stabilize Pd^0 and that are stable under oxidative conditions. Another strategy is to mimic biological oxidation systems[3] and squeeze in an electron-transfer mediator (ETM) between the substrate-selective redox catalyst and O_2 or H_2O_2 (Scheme 3). This ETM would then carry the electrons from M^n to the oxidant along a low-energy pathway which would compete kinetically with side reactions of the reduced form of the metal (precipitation, decomposition).



Scheme 3. Electron transfer facilitated by an electron-transfer mediator (ETM).

The use of coupled catalytic systems with ETMs (such as that in Scheme 3) is an important complement to the simple systems based on direct reoxidation of the metal by O_2 or H_2O_2, and significantly extends the use of oxygen and H_2O_2 as the final oxidants in metal-catalyzed reactions. In this Review we will focus on oxidation reactions where a transition metal is the substrate-selective catalyst and ETMs are used for the reoxidation of the metal by O_2 or H_2O_2. We call this a biomimetic approach because of its similarities to biological systems.

2. Palladium-Catalyzed Aerobic Oxidation with ETMs

Palladium-catalyzed oxidations have been studied extensively[11] and aerobic oxidations using palladium catalysts have, in particular, received much attention in the past decade. However, as stated above, the direct reoxidation of palladium by molecular oxygen is difficult in many cases. There are examples in palladium-catalyzed oxidations where the palladium is directly reoxidized by O_2 without electron-transfer mediators (ETMs). These examples involve the oxidation of alcohols to ketones, alkenes to carbonyl compounds, and intramolecular heterocyclizations of

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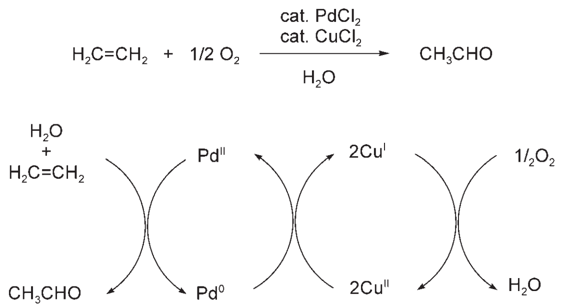
Jan-Erling Bäckvall was born in Malung, Sweden, in 1947. He received his PhD from the Royal Institute of Technology, Stockholm, in 1975 under the guidance of Prof. B. Åkermark. After postdoctoral work (1975–1976) with Prof. K. B. Sharpless at Massachusetts Institute of Technology, he joined the faculty at the Royal Institute of Technology (Kungliga Tekniska högskolan). He was appointed Professor of Organic Chemistry at Uppsala University in 1986. In 1997 he moved to Stockholm University where he is currently Professor of Organic Chemistry. He is a member of the Royal Swedish Academy of Sciences and the Finnish Academy of Science and Letters. His current research interests include transition-metal-catalyzed organic transformations, biomimetic oxidations, and enzyme chemistry.

alkenes.[5,6,10] A notable example of the direct reoxidation of palladium by molecular oxygen in the aerobic oxidation of alcohols was reported by Sheldon and co-workers,[10] where a water-soluble phenanthrolinepalladium(II) complex was used as the catalyst.

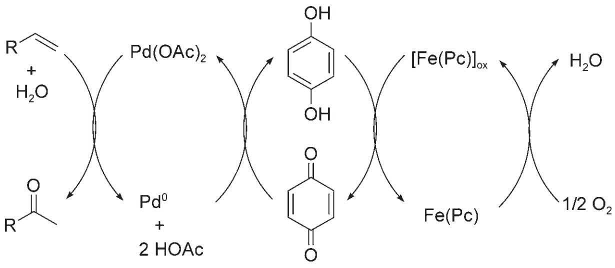
An illustrative example of the principle of using an ETM is the Wacker oxidation of ethylene to acetaldehyde (Scheme 4).[12] This is a large-scale industrial process for the oxidation of ethylene to acetaldehyde by air (O_2) which is catalyzed by $PdCl_2$ and $CuCl_2$, with the former being the substrate-selective redox catalyst.



Scheme 4. Wacker oxidation of ethylene to acetaldehyde.

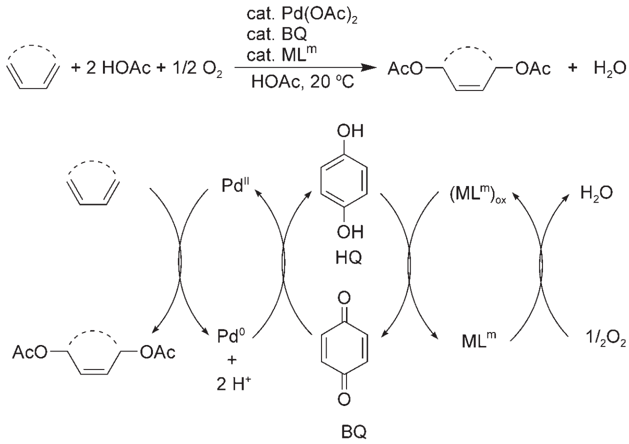
The reaction between ethylene and palladium chloride in water was first observed in 1894 by Phillips,[13] who found that it gave rise to acetaldehyde and palladium black. About 60 years later German researchers at Wacker Chemie found that $CuCl_2$/CuCl can carry the electrons from Pd^0 to molecular oxygen. The direct reoxidation of Pd^0 back to Pd^{II} by molecular oxygen in water is difficult since the energy barrier is higher than that for catalyst decomposition, that is, precipitation of Pd black.[14] The facile transfer of electrons from Pd^0 to $CuCl_2$ may be due to a close interaction between the palladium and copper,[15] and CuCl is known to be readily oxidized by air to $CuCl_2$ in aqueous solution.[16]

The Wacker process has been extended to the oxidation of a large variety of alkenes.[11,17] In these reactions, which are sometimes run in a mixture of a polar solvent and water, chloride ions are required to stabilize the system and the combination of $PdCl_2$, $CuCl_2$, and O_2 is used. However, the presence of chloride ions has a negative effect on the rate (there is an inverse square dependence on the chloride ion concentration)[18] which makes the reaction unselective and leads to the formation of chlorinated by-products.[19] The reactor also corrodes under the oxidative conditions employed. For this reason a chloride-free Wacker oxidation is highly desirable, and several methods for the reoxidation of Pd^0 in the absence of chloride ions have been developed.[20–22] For example, the use of palladium acetate together with benzoquinone and a complex with a macrocyclic ligand L^m (ML^m) as ETMs resulted in a highly efficient chloride-free Wacker oxidation of terminal alkenes. The best results were obtained when iron phthalocyanine (Fe(Pc)) was used as the oxygen-activating complex ML^m (Scheme 5).[20] It is essential that a catalytic amount of strong acid (for example, $HClO_4$) is present to keep the palladium in solution. A large-scale, chloride-free Wacker-type process with a polyoxometalate as the oxygen-activating component has been developed by Catalytica Inc. (see Scheme 8).[21]



Scheme 5. Chloride-free Wacker oxidation of alkenes.

The above-mentioned catalytic system of quinone/ML^m used for the reoxidation of Pd^0 by O_2 was also applied to the aerobic 1,4-oxidation of 1,3-dienes (Scheme 6).[20b,23] In this case, $Pd(OAc)_2$ in acetic acid serves as the substrate-selective redox catalyst for a conjugated diene, transforming it to a 1,4-diacetoxy-2-alkene.[24] The ETM, which can be a metal porphyrin, metal phthalocyanine, or a metal–salen complex, also serves as the oxygen-activating catalyst of the system. The ML^m catalyst reacts with molecular oxygen to give $M(O_2)L^m$ complexes.



Scheme 6. Aerobic 1,4-diacetoxylation of 1,3-dienes; ML^m = Co(tpp), Fe(Pc), or Co(salophene); tpp = tetraphenylporphyrin.

The selection of quinone as the oxidant for the palladium is based on the fact that quinones are well-known oxidants and electron carriers in palladium-catalyzed oxidations.[25] However, under the reaction conditions for the transformations described in Schemes 5 and 6, it is not possible to directly reoxidize the hydroquinone formed with molecular oxygen, and therefore an additional ETM is required. Since some metal complexes with macrocyclic ligands (metal macrocycles) are able to catalyze the aerobic oxidation of catechols and hydroquinones,[26] they have been used in catalytic amounts in the presence of molecular oxygen to obtain a successful catalytic system. The success of these processes is based on a stepwise low-energy electron transfer that has lower redox potentials, in analogy with that occurring in biological systems (cf. the respiratory chain). A control experiment showed that the reaction stops completely if any of the catalysts (Pd, benzoquinone (BQ), ML^m) is removed. The direct oxidation of palladium(0) by molecular oxygen in acetic acid is slow under these conditions.[27] On the other hand, the coupled system in which ETMs are utilized leads to low-energy electron transfer (Figure 1).

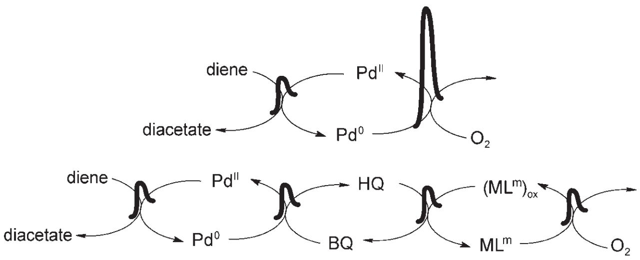
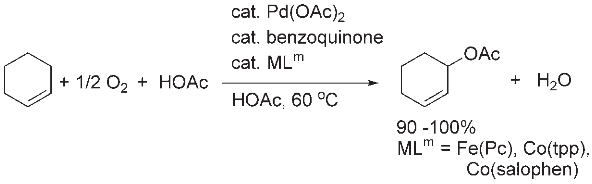


Figure 1. The influence of ETMs on the energy barrier in the Pd-catalyzed oxidation of dienes.

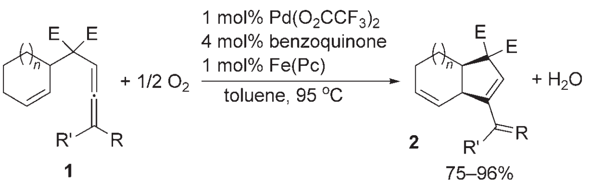
It is also important to point out that there are four oxidants with decreasing oxidation potentials[28] (O_2, $(ML^m)_{ox}$, BQ, and Pd^{II}) and four components that can be oxidized (ML^m, hydroquinone (HQ), Pd^0, and diene). Thus, there are ten thermodynamically favored redox reactions that can occur, but only four of these are kinetically favored and will occur. The high kinetic control is due to the fact that there is a coordination between those redox couples that interact; for example, O_2 coordinates to ML^m,[29] HQ binds to the metal macrocycle,[30] Pd^0 is known to coordinate to BQ,[31] and finally Pd^{II} forms a complex with the diene.[20b]

The coupled quinone/metal macrocycle system for the aerobic reoxidation of palladium(0) to palladium(II) was also applied to the allylic oxidation of olefins.[20b] The reaction is efficient and gives a high yield of the allylic acetate in the aerobic oxidation of cyclohexene [Eq. (1)].



(1)

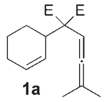
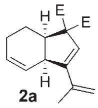
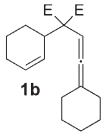
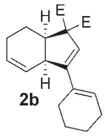
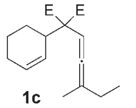
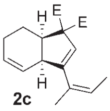
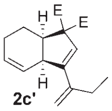
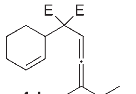
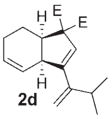
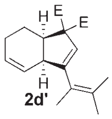
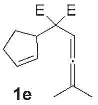
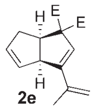
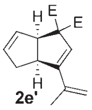
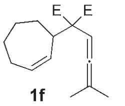
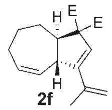
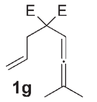
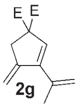
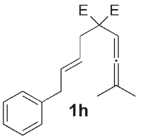
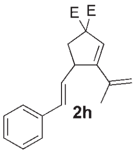
Very recently, an analogous three-component catalyst system has been applied successfully to the aerobic Pd-catalyzed oxidative carbocyclization of allene-substituted olefins [Eq. (2), E = CO_2Me].[32] The scope of the reaction was studied and different cyclic and acyclic alkenes as well as differently substituted allenes were subjected to the reaction conditions, and gave the corresponding products in high to excellent yields (Table 1).



(2)

The reaction involves a highly efficient carbon–carbon bond formation under low catalytic loading and aerobic conditions. There are not many examples of palladium-catalyzed aerobic oxidations involving C–C bond formation and, in most of them, a high catalytic loading or high oxygen pressure is required.[6c,33] Here one should also mention the work by the research groups of Larhed[34] and Jung[35] concerning the aerobic oxidative Heck reaction, where Pd^{II}-catalyzed C–C bond formation occurs under aerobic oxidative conditions in the presence of stabilizing ligands. Reaction (2) can also be carried out with the oxygen-activating catalyst [Fe(Pc)] immobilized on a resin. It was demonstrated that the immobilized catalyst can be recycled five times

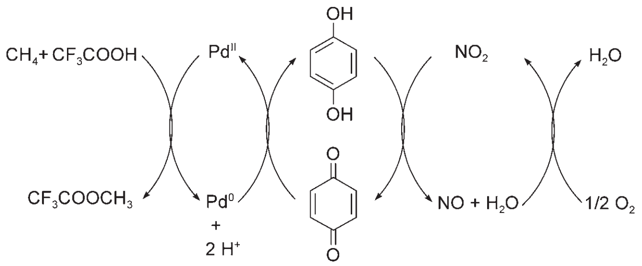
Table 1: Palladium(II)-catalyzed aerobic allylic oxidation of **1** according to Equation (2).[a]

Entry	Substrate	Product	Yield [%]
1	 **1a**	 **2a**	96
2	 **1b**	 **2b**	86[b] 96[c]
3	 **1c**	 **2c**  **2c'** E/Z = 1:2	81 **2c**:**2c'** = 1:1
4	 **1d**	 **2d**  **2d'**	83 **2d**:**2d'** = 1:1
5	 **1e**	 **2e**  **2e'**	75[b] **2e**:**2e'** = 3:1
6	 **1f**	 **2f**	90
7	 **1g**	 **2g**	90[c]
8	 **1h**	 **2h**	93[c]

[a] Reaction conditions, unless otherwise noted: 1 mol% $Pd(O_2CCF_3)_2$, 4 mol% BQ, 1 mol% Fe(Pc) in 2 mL toluene at 95 °C for 8 h under 1 atm O_2, with slow addition (6 h) of **1** (1 mmol). [b] Reaction for 14 h was required for full conversion. [c] 0.2 mmol **1**, 5 mol% $Pd(O_2CCF_3)_2$, 20 mol% BQ, 5 mol% Fe(Pc) in 2 mL toluene at 95 °C for 3 h.

without any detectable loss of activity, which increases the utility of the procedure.

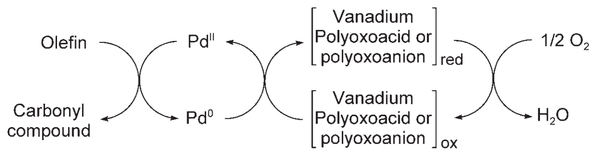
A recent application of ETMs is the aerobic oxidation of methane reported by Bao and co-workers.[36] In this reaction Pd^{II} acts as the substrate-selective catalyst and oxidizes methane to methyl trifluoroacetate, and the Pd^0 formed is reoxidized by benzoquinone. The hydroquinone formed is recycled to benzoquinone by NO_2/O_2. In this application, the redox couple $(ML^m)_{ox}/(ML^m)_{red}$ used in the above examples as the oxygen-activating catalyst is replaced by the redox couple NO₂/NO (Scheme 7).



Scheme 7. Catalytic oxidation of methane by dioxygen through an electron-transfer chain.

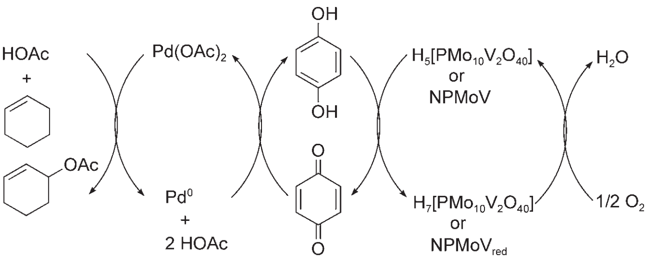
A similar catalytic system in which the ML^m was substituted for a second transition-metal acetate (Cu, Mn, or Co) was used for the allylic oxidation of cyclohexenes in which molecular oxygen was used as the terminal oxidant.[37] A control experiment in which the palladium salt ($Pd(OAc)_2$) was omitted gave no reaction. This finding shows that the second transition metal only serves as an ETM. Recently, this system was used for the allylic oxidation of limonene under aerobic conditions.[38]

Polyoxometalates constitute an interesting class of compounds that include hetero-polyacids. Some of these compounds have found use as oxidation catalysts in reactions in which the stoichiometric oxidant is either hydrogen peroxide or molecular oxygen.[39] Some transition-metal-substituted polyoxometalates have been considered to be inorganic analogues of metalloporphyrins.[40] An industrial process for the chloride-free Wacker oxidation of alkenes with a hetero-polyoxometalate as an ETM was developed by Catalytica (Scheme 8).[21] The system includes a palladium(II) catalyst as well as a polyoxo acid or polyoxo anion oxidant comprised of vanadium and dioxygen in contact with aqueous solutions of the catalyst, and is suitable for a large variety of olefins.



Scheme 8. Aerobic oxidation of olefins (Catalytica Inc.).

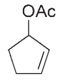
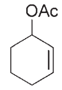
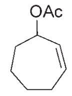
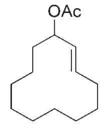
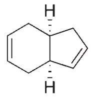
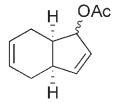
Hetero-polyacids were also used for the activation of molecular oxygen in place of the metal macrocycle in the Pd^{II}/quinone/ML^m system. This three-component catalytic electron-transfer system (Pd^{II}/quinone/hetero-polyacids) was used for the aerobic 1,4-diacetoxylation of conjugated dienes and the allylic oxidation of olefins (Scheme 9).[41,42]



Scheme 9. Aerobic allylic oxidation; $H_5PMo_{10}V_2O_{40}$ in Ref. [42], NPMoV in Ref. [43].

A related system in which a molybdovanadophosphate (NPMoV) and hydroquinone were employed as ETMs for allylic oxidation was reported independently by Ishii and co-workers (Scheme 9); some selected examples are presented in Table 2.[43] The reactivity of the multicatalyst system was dependent on the ring size of the alkenes: Cyclopentene and cyclohexene were transformed into the corresponding allylic acetates in almost quantitative yields, while higher temperatures and longer reaction times were required for larger rings to obtain the products in good yield. It is noteworthy that in the case of a cyclohexene fused with a cyclopentene ring the acetoxylation occurs only at the five-membered ring (entry 5). Omitting hydroquinone from the catalytic system led to low yields of the acetates. However, in later reports the system was applied with NPMoV as the sole ETM in a variety of

Table 2: Acetoxylation of various cycloalkenes according to Scheme 9.[a]

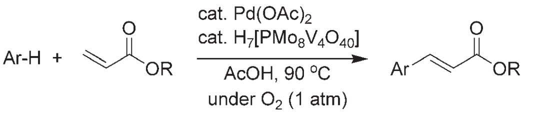
Entry	Substrate	*t* [h]	*T* [°C]	Product	Yield [%]
1	cyclopentene	4	60		98
2	cyclohexene	4	60		99
3	cycloheptene	6	70		93
4	cyclododecene	15	80		77
5		15	60		65

[a] The cycloalkene (0.2 mmol) was allowed to react in the presence of $Pd(OAc)_2$ (5 mol%), HQ (20 mol%), NPMoV (35 mg), and Na_2CO_3 (53 mg) in acetic acid (10 mL) and an oxygen atmosphere (1 atm).

reactions including the acetalization of alkenes[44] and the Wacker-type oxidation of cyclopentene,[45] terminal alkenes, and dienes.[46]

The same authors reported the oxidative carbomethoxylation of alkenes using the same catalyst system (Pd/NPMoV) in methanol and in a carbon monoxide/air atmosphere.[47] The reaction proceeds with cyclopentene to give mixtures of *cis*-1,2-cyclopentanedicarboxylate and *cis*-1,3-cyclopentanedicarboxylate in good yields. Different temperatures and CO/air pressures lead to different ratios of the two isomers. No reaction is observed with cyclohexene, and the yields are only moderate when other alkenes are employed. In a later study, the carboxylation of anisole derivatives was achieved in acetic acid under similar conditions.[48] In this case the reaction conditions affected the conversion, but the selectivity and ratio remained constant.

Another polyoxometalate used by Ishii and co-workers in palladium-catalyzed aerobic reactions is molybdovanadophosphoric acid (HPMoV). The direct aerobic oxidative arylation of acrylates and other electron-deficient olefins under mild conditions was achieved with this compound [Eq. (3)].[49] The palladium(0) generated in this oxidative Heck arylation of the acrylate is reoxidized by the hetero-polyacid/O_2 (the reaction is analogous to that shown in Scheme 8). Another related application of the same catalyst system is the oxidative cross-coupling of acrylates with vinyl carboxylates.[50]



(3)

Other three-component catalyst systems related to the Pd^{II}/quinone/hetero-polyacid system have employed $CuSO_4$ instead of the quinone, and this system was applied to the Wacker oxidation of cyclohexene. In this case, either molecular oxygen or hydrogen peroxide was used as the terminal oxidant.[51]

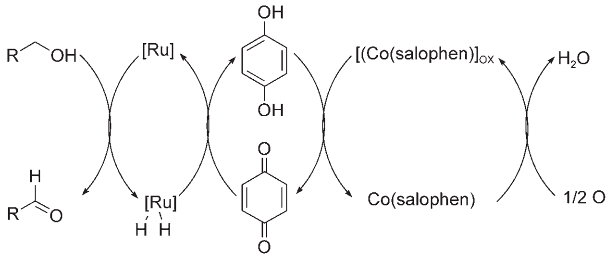
The solvent in the original Wacker process is water, which gives good results for the oxidation of ethylene to acetaldehyde under acidic conditions. However, long-chain terminal olefins show poor solubility in water, and thus results in low reaction rates, and the presence of acid favors isomerization, and leads to low selectivity toward methyl ketones.[52] Much effort has been made to solve this problem, including the use of surfactants,[53] cyclodextrins,[54] supported catalysts,[55] and nonclassical solvents such as poly(ethyleneglycol)s,[56] fluorous phases,[57] ionic liquids,[58] and supercritical carbon dioxide.[59]

The palladium acetate/benzoquinone system has also been used with hydrogen peroxide as the terminal oxidant.[60] In this way, alkenes such cyclohexene and 5-decene were converted cleanly into the corresponding allylic acetates; however, methyl ketones were obtained with terminal alkenes. The hydrogen peroxide/hydroquinone system was also used for the palladium-catalyzed 1,4-diacetoxylation of 1,3-dienes and ring closure of 1,5-dienes.[60]

3. Ruthenium-Catalyzed Aerobic Oxidation with ETMs

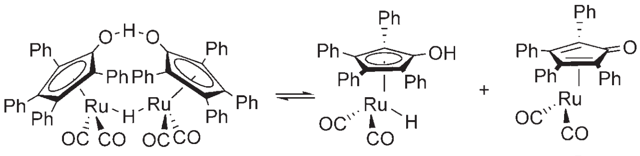
The dehydrogenation of alcohols to give aldehydes or ketones by the use of low-valent ruthenium complexes has been known for more than two decades,[61] and more recently such complexes have been applied to the dehydrogenation of amines to give imines.[62] Morton and Cole-Hamilton[61a] reported that treatment of alcohols such as butanol or isopropyl alcohol with $[RuH_2(N_2)(PPh_3)_3]$ at 150 °C in the presence of NaOH led to dehydrogenation and the production of hydrogen gas with high turnovers. Interestingly, the same ruthenium complexes had been used as hydrogenation catalysts.[63] More recently, the ruthenium-catalyzed dehydrogenation of alcohols to give H_2 and a ketone has been reported by Park and co-workers.[64,65] The ability of ruthenium complexes to act as dehydrogenation and hydrogenation catalysts is reflected by their use in hydrogen-transfer reactions.[66] The principle of these hydrogen-transfer reactions is that the ruthenium dehydrogenates the alcohol and the ruthenium hydride formed adds to a ketone or an electron-deficient olefin. One way to develop an aerobic oxidation system would be to allow the generated ruthenium hydride to add to benzoquinone. The hydroquinone thus formed could then be recycled by the ML^m/O_2 system (see Schemes 5 and 6).

It was demonstrated that benzoquinone can serve as a hydrogen acceptor for the ruthenium-catalyzed dehydrogenation of benzyl alcohol: The use of the ruthenium complex $[RuCl_2(PPh_3)_3]$ (1.2 mol %) as the substrate-selective redox catalyst in the oxidation of benzyl alcohol by benzoquinone afforded benzaldehyde in 70 % yield (turnover number (TON) = 58) at room temperature.[67] This oxidation was combined with a reoxidation system of hydroquinone (see Schemes 5 and 6) to give an aerobic process for the oxidation of the alcohol.[67] To obtain good efficiency it was necessary to employ $[RuCl(OAc)(PPh_3)_3]$ as the catalyst and to use Co(salophen) (with a PPh_3 ligand) as the oxygen-activating catalyst. The principle of this biomimetic oxidation is shown in Scheme 10. With this system, TONs up to 70 were obtained and the yield of benzaldehyde was 60 %. Other primary alcohols such as geraniol, cinnamyl alcohol, and 2-naphthylmethanol were also oxidized to their aldehydes by this system.



Scheme 10. Three-component catalyst system for the aerobic oxidation of primary alcohols.

The biomimetic catalytic system was extended to the aerobic oxidation of secondary alcohols.[68] The substrate-selective redox catalyst used for this transformation was the dimeric ruthenium catalyst **3**, which dissociates to the two halves **4** and **5**.[69] In the preliminary study, 2,6-di(*tert*-butyl)benzoquinone was used as the hydrogen acceptor since *p*-benzoquinone degraded under the reaction conditions used for the oxidation of secondary alcohols.[68a] In a subsequent study, the system was optimized with respect to the quinone.[68b] Of the various quinones tested, it was found that 2,6-dimethoxybenzoquinone (**6**) was the best quinone in the coupled biomimetic oxidation system in which air was used as the oxidant (Scheme 11). Thus, the coupled catalytic system chosen for the aerobic oxidation of secondary alcohols consists of the binuclear ruthenium complex **3**, quinone **6**, and oxygen-activating cobalt complex **7**.

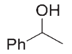
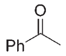
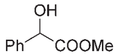
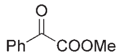
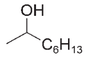
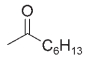
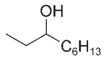
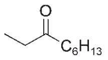
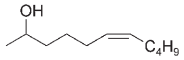
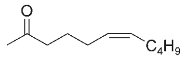
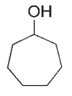
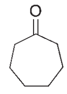
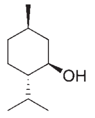
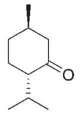


3 **4** **5**

It is interesting to note that although 2,6-dimethoxybenzoquinone (**6**) was the optimal quinone for the aerobic oxidation, chloranil (2,3,5,6-tetrachlorobenzoquinone) was faster than **6** for the reoxidation of **4** to **5**, as shown by running the oxidation with each of the two quinones as the stoichiometric oxidant without **7** and O_2. The faster reoxidation of **4** to **5** in the presence of chloranil as the oxidant compared to that with **6** is expected since the oxidation potential of chloranil is higher than that of **6**. However, in the coupled catalytic system, the reoxidation of the reduced hydroquinone also has to be fast, and this step is faster for the electron-rich 2,6-dimethoxyhydroquinone than for the electron-deficient tetrachlorohydroquinone.

A number of alcohols were oxidized to their corresponding ketones by air using the biomimetic system of Scheme 11 (some selected examples are listed in Table 3). The system was successfully applied to the oxidation of benzylic alcohols. More resistant substrates, such as linear and cyclic aliphatic alcohols, can be oxidized to the corresponding ketones with good to excellent yields and high turnover frequencies (TOFs). It is noteworthy that this catalytic system tolerates the presence of C–C double bonds, with no epoxidation of them observed. Sterically hindered alcohols were also efficiently oxidized to ketones. In most cases, the reaction was complete within 1–2 h, with TONs of 100–200 with catalyst **3**.

Table 3: Ruthenium-catalyzed biomimetic aerobic oxidation of secondary alcohols according to Scheme 11.[a]

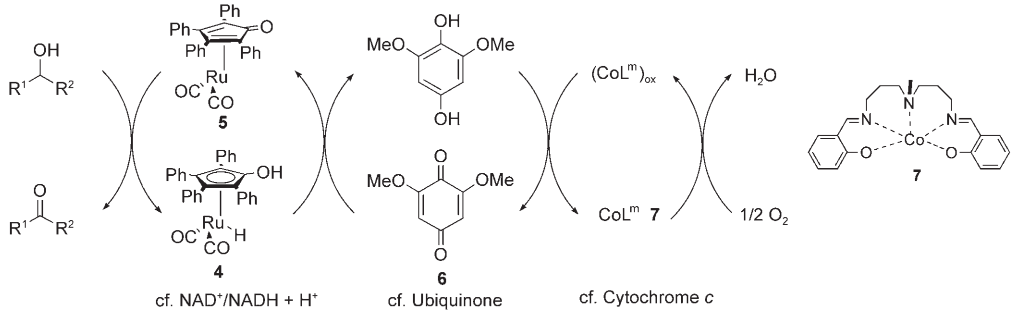
Entry	Substrate	*t* [h]	Product	Yield [%]
1		1		89
2		2		81
3		1		92
4		1		92
5		2.5		92
6		1		92
7		2		80

[a] Reaction conditions: 1 mL toluene, 100 °C, 0.5 mol% **3**, 20 mol% **6**, 2 mol% **7**.

This biomimetic aerobic oxidation of alcohols is reminiscent of biological oxidations. A comparison of the biomimetic and biological reagents is shown in Scheme 11). It is interesting to note that nature has chosen, through evolution, an electron-rich quinone (ubiquinone) to obtain a low-energy electron transfer from the corresponding hydroquinone to the heme portion of cytochrome *c*.

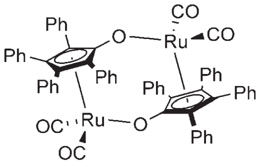
In addition to the previous work, a zeolite-encapsulated Co(salophen) catalyst was prepared and used in the three-component catalyst system for the oxidation of primary alcohols to aldehydes and of secondary alcohols to ketones.[70] The new catalyst shows some advantages over the homogeneous system, for example ease of handling and the possibility of recycling it irrespective of the solvent used.

Most of the ruthenium-catalyzed aerobic oxidations deal with the oxidation of alcohols, however, ruthenium catalyst **3** can also be used for the dehydrogenation of amines to imines.[62] The three-component catalyst system described above was successfully applied to the aerobic oxidation of



Scheme 11. Biomimetic aerobic oxidation of alcohols.

amines.[71] The active species in catalyst **3** is the 16-electron complex **5** which can also be generated from the dimeric structure **8**,[72] which was the selected catalyst for these reactions. Both ketimines and aldimines were obtained in good to excellent yields from the oxidation of the corresponding amines. Amines giving ketimines were oxidized faster than amines giving aldimines [Eq. (4)]. The combination of the biomimetic ruthenium-catalyzed oxidation of amines in the coupled catalytic system with an organocatalytic asymmetric Mannich reaction in one pot produces β-amino aldehydes in high yields, excellent chemoselectivity, and up to > 99 % *ee*.[73]



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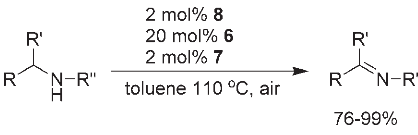


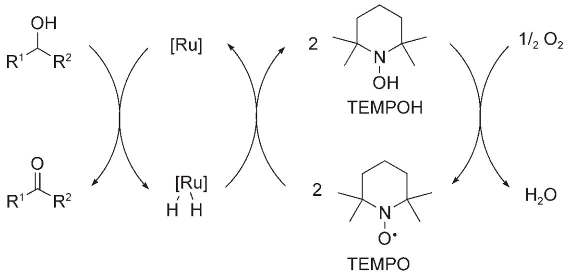
(4)

Sheldon and co-workers have reported a related aerobic oxidation of alcohols where the combination of [RuCl$_2$(PPh$_3$)$_3$] and 2,2,6,6-tetramethylpiperidine *N*-oxide (TEMPO) affords an efficient catalytic system.[74] The catalytic system was applied to a variety of representative primary and secondary alcohols, which gave the corresponding aldehydes and ketones, respectively, with greater than 99 % selectivity in all cases. Other ruthenium catalysts were tested but gave lower reaction rates or were completely inactive. Various metal chlorides (Fe^{II}/Fe^{III}, Ni^{II}, Pd^{II}, and Co^{II}/Co^{III}) were tried as possible catalysts, but showed no activity when combined with TEMPO.

Mechanistic studies are inconsistent with an oxoruthenium or oxoammonium species, which led the authors to propose a mechanism in which TEMPO acts as the ETM between the substrate-selective ruthenium catalyst and molecular oxygen.[74b] It was proposed that the ruthenium catalyst dehydrogenates the alcohol to give a ruthenium hydride ("RuH$_2$(PPh$_3$)$_3$") species that reacts with TEMPO. The reduced form of TEMPO (TEMPOH) reacts with molecular oxygen to regenerate TEMPO (Scheme 12).

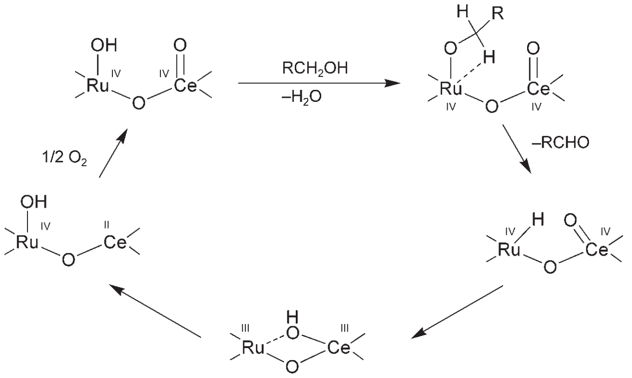
TEMPO does not only accelerate the oxidation of primary alcohols to aldehydes, it also suppresses the overoxidation to carboxylic acids by its well-documented antioxidant activity. This stable nitroxyl radical is able to scavenge radical intermediates during autoxidation, thereby terminating free-radical reactions.[75]

Ishii and co-workers reported a related coupled electron-transfer system for the oxidation of alcohols. The [RuCl$_2$(PPh$_3$)$_3$]/hydroquinone system at atmospheric oxygen pressure and in the presence of catalytic amounts of K$_2$CO$_3$ at 60 °C led to the oxidation of primary alcohols to aldehydes in high yield.[76]



Scheme 12. Ru/TEMPO catalyst system for the aerobic oxidation of alcohols.

Kaneda and co-workers developed an active trimetallic Ru/CeO$_2$/CoO(OH) system for the oxidation of alcohols in the presence of molecular oxygen.[77] The heterogeneous catalyst is effective for the oxidation of allylic, benzylic, and secondary aliphatic alcohols to give the corresponding ketones in high yield (88–99 %). Primary alcohols can be converted into carboxylic acids; linear alcohols give excellent yields, whereas branched or cyclic alcohols afford moderate yields. Ru^{IV} species immobilized on the surface of the CeO$_2$/CoO(OH) support are responsible for the oxidation of the alcohols. The reoxidation of the reduced Ru is believed to be promoted by Ce^{IV} to give Ru^{IV} and Ce^{II}. It was proposed that the electron transfer from Ru to Ce proceeds via a Ce^{III}/Ru^{III} intermediate. The Ru^{IV}/Ce^{II} species is reoxidized by molecular oxygen to regenerate the Ru^{IV}/Ce^{IV} system (Scheme 13). It was assumed that the reaction of primary alcohols furnishes aldehydes by means of the Ru/Ce system which are subsequently oxidized to carboxylic acids by Co.



Scheme 13. Proposed reoxidation of Ru by Ce under aerobic conditions.

The use of a ruthenium/cobalt catalyst with oxygen as the terminal oxidant for the oxidation of alcohols in the presence of an aldehyde was reported by Murahashi et al.[78] The aerobic oxidation is proposed to proceed through two sequential pathways: 1) formation of peracids by a cobalt-mediated radical chain reaction of the aldehydes with molecular oxygen and 2) ruthenium-catalyzed oxidation of the alcohols by the formed peracid. Ruthenium performs the main oxidation reaction of the alcohols, and the cobalt acetate serves as a co-catalyst for promoting the reaction of molecular oxygen with the aldehyde. This case is a special electron-transfer oxidation in which a stoichiometric amount of an aldehyde is consumed and oxidized to the carboxylic acid, which is a drawback of this method.

It should be mentioned that other transition metals can be used in coupled electron-transfer systems for H_2O_2- and O_2-based oxidations of alcohols (see Sections 5 and 6).

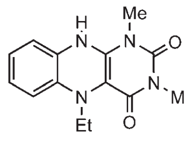
4. Osmium-Catalyzed Biomimetic Oxidation

It has been known since the beginning of the last century that OsO_4 reacts with olefins to give an osmate ester that can be hydrolyzed to a diol and $OsO_2(OH)_2$.[79] The OsO_4/OsO_3 system is an excellent substrate-selective redox catalyst for the dihydroxylation of alkenes. Recycling of Os^{VI} to Os^{VIII} by direct oxidation with H_2O_2[80] or with O_2[81] has been realized. These reoxidations lead to low selectivity for many olefins as a result of competing C–C bond cleavage and other side reactions. More recently, efficient oxidations with O_2 under irradiation of visible light or at an elevated pH value have been reported.[82,83] The latter process works quite well with a range of alkenes.

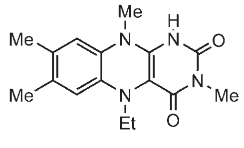
In 1976 efficient oxidants for the reoxidation of Os^{VI} to Os^{VIII} in catalytic dihydroxylations were reported for the first time.[84,85] In particular the Upjohn procedure,[85] in which *N*-methylmorpholine *N*-oxide (NMO) is employed as the oxidant, was a major breakthrough and led to the frequent use of the osmium-catalyzed dihydroxylation. The synthetic utility of the catalytic dihydroxylation was dramatically enhanced when Sharpless and co-workers introduced the enantioselective version.[86]

In the Upjohn procedure, alkenes are dihydroxylated under mild conditions, with OsO_4 acting as the substrate-selective redox catalyst (Scheme 14). This system leads to low-energy electron transfer and the use of very mild reaction conditions for the reoxidization of Os^{VI} back to Os^{VIII} by NMO. In this process, *N*-methylmorpholine (NMM) is formed as a side product.

It would be highly desirable to be able to reoxidize NMM to NMO by either molecular oxygen or hydrogen peroxide to obtain a "green" biomimetic dihydroxylation. In 1998 we reported that flavin **9** catalyzes the efficient oxidation of tertiary amines to amine oxides at room temperature.[87] Flavins constitute a part of flavoenzymes in a number of monooxygenases; flavin **9** differs from those previously employed, for example, **10**,[88] in that N-10 is unsubstituted and that there is an alkyl group at N-1. Furthermore, there are no methyl groups at C-7 and C-8. The reaction of tertiary amines with 30% aqueous H_2O_2 for one–two hours at room temperature in the presence of **9** gave quantitative yield of the amine oxide [Eq. (5)], whereas the corresponding reaction catalyzed by **10** gave less than 10% yield.



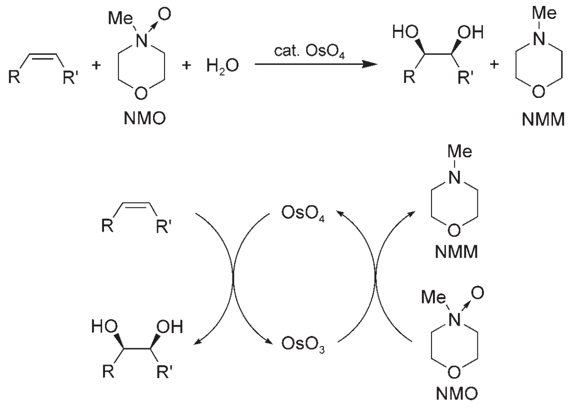
9



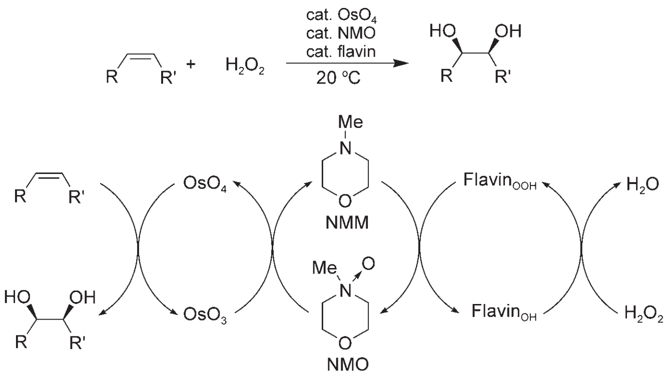
10

$$R_3N \quad + \quad H_2O_2 \quad \xrightarrow[20^{\circ}C,\ 1\text{-}2\ h]{\text{cat. } \mathbf{9}} \quad \underset{95\text{-}100\%}{R_3\overset{+}{N}\text{-}O^{-}} \quad + \quad H_2O \qquad (5)$$

The new flavin was used as a catalyst for the in situ reoxidation of NMM to NMO in the Upjohn procedure. This reaction constitutes a new biomimetic dihydroxylation of alkenes by H_2O_2, with OsO_4 acting as the substrate-selective redox catalyst, and with NMM and flavin **9** acting as ETMs.[89] This combination results in a highly environmentally friendly dihydroxylation of alkenes (Scheme 15). As in the other biomimetic oxidation systems discussed above, this system also leads to a mild kinetically controlled electron transfer from the substrate (alkene) to the terminal oxidant (hydrogen peroxide) at room temperature. The low-energy electron



Scheme 14. The Upjohn procedure for an osmium-catalyzed dihydroxylation.

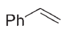
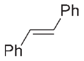
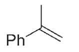
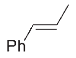
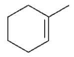


Scheme 15. Biomimetic dihydroxylation of alkenes with the Os/NMO/flavin system.

transfer with decreasing redox potentials is the key to this selectivity, similar to the biological oxidations.

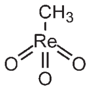
The H_2O_2-based oxidation was extended to the use of chiral ligands, such as the Sharpless ligand $(DHQD)_2PHAL$. The method allowed a range of olefins to be oxidized to the corresponding diols in high enantioselectivity (Table 4, Method A).[89b] In subsequent work, the Sharpless ligand was investigated as an ETM source as well as a source of chirality in the catalytic system.[90] The nitrogen atom of the tertiary amine of $(DHQD)_2PHAL$ was used as the oxo- and electron carrier, with the *N*-oxide formed acting as the reoxidant of Os^{VI}. The results obtained with $(DHQD)_2PHAL$ functioning as an ETM and a chiral ligand are comparable to those obtained when NMM and $(DHQD)_2PHAL$ were used together as the ETM and the chiral ligand, respectively (Table 4, Method B).

Table 4: Biomimetic asymmetric dihydroxylation of alkenes using catalytic amounts of OsO_4, and H_2O_2 as the terminal oxidant.

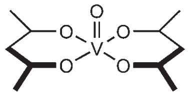
Entry	Olefin	Method[a]	Yield [%]	*ee* [%]
1		A	80	95
		B	75	95
2		A	94	91
		B	89	90
3		A	88	99
		B	81	90
4		A	67	96
		B	61	99
5		A	50	92
		B	58	70

[a] In Method A, NMM and $(DHQD)_2PHAL$ were used, see Ref. [89b]; in Method B only $(DHQD)_2PHAL$ was used, see Ref. [90].

Flavin **9** is an efficient ETM, but is rather unstable; therefore, replacement of the flavin by other ETMs is of interest. Various transition-metal complexes such as methyltrioxorhenium (MTO; **11**) and vanadyl acetylacetonate (**12**) are known to activate hydrogen peroxide. Different procedures were developed in which the flavin was substituted by these redox catalysts, and it was found that **11** and **12** can be used as catalysts for the N oxidation of NMM in the three-component catalyst system.[91,92]

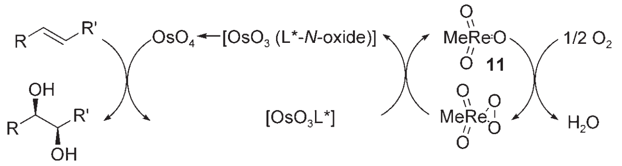


11



12

MTO (**11**) was also used as an ETM in the asymmetric osmium-catalyzed dihydroxylation of various alkenes (up to 98% *ee*), and here the chiral ligand $(DHQD)_2PHAL$ also played the role of an ETM.[92b] The principle of this oxidation system is shown in Scheme 16. This new system constitutes a robust dimetallic system for the dihydroxylation of alkenes.

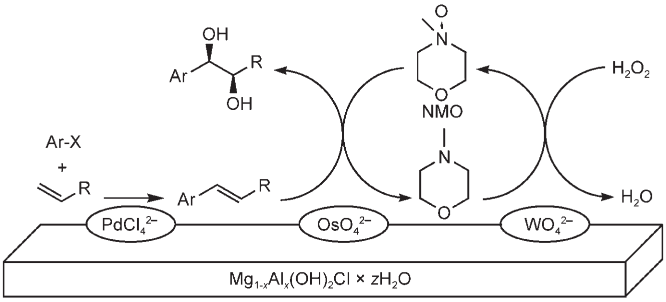


Scheme 16. Asymmetric biomimetic dihydroxylation of olefins with the $Os/(DHQD)_2PHAL/MeReO_3$ system.

It was subsequently found that the entire three-component catalyst system of Scheme 15 can be immobilized in an ionic liquid.[93] The use of 1-*n*-butyl-3-methylimidazolium hexafluorophosphate ($[bmim]PF_6$) as the ionic liquid with acetone as a cosolvent gave a high yield of the dihydroxylation product. After extraction of the diol product, the osmium, NMM (NMO), and flavin were retained within the ionic liquid and could be reused after addition of new portions of alkene and hydrogen peroxide. The reaction was repeated five times without loss of activity. The immobilization of other three-component catalyst systems and using **11** and **12** as co-catalysts (ETMs) has also been carried out.[94] The results from recycling the latter catalytic system demonstrated that it can be reused with no loss or only moderate loss of activity.

The biomimetic oxygen-transfer cascades were rationalized by DFT calculations.[95] It was indeed shown that stepwise transfer of oxygen from the peroxorhenium species via an amine *N*-oxide proceeds along a low-energy electron-transfer pathway whereas direct oxygen transfer from the peroxorhenium to an Os^{VI} species requires a much higher activation energy.

Choudary et al. have developed an electron-transer-based catalytic synthesis of chiral diols by using a trifunctional solid-state catalyst consisting of active palladium, tungsten, and osmium species immobilized onto a layered Mg/Al double hydroxide (LDH-PdOsW).[96] The $PdCl_4^{2-}$, OsO_4^{2-}, and WO_4^{2-} were ion-exchanged with the LDH as their potassium or sodium salts. A prochiral olefin was obtained from a palladium-catalyzed Heck reaction and was continuously asymmetrically dihydroxylated by the osmium(VIII) in very good yields and high enantioselectivity. The osmium(VI) is reoxidized by a coupled catalytic system consisting of NMO/WO_4/H_2O_2 (Scheme 17). The LDH-PdOsW can be recovered by filtration and reused up to five times with maintained activity. It was claimed that the all three metal catalysts stay bound to the LDH matrix during the reaction, but there is little evidence that the osmium catalyst is effectively immobilized. For example, while the Os^{VI} (OsO_4^{2-}) can be ion-



Scheme 17. Catalytic cycle in the LDH-PdOsW-catalyzed synthesis of chiral diols using H_2O_2 as the terminal oxidant.

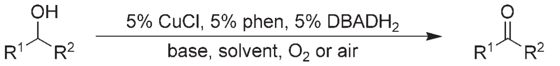
exchanged, Os^{VIII} cannot, and this will result in severe leaching. The synthetic utility of the heterogeneous LDH-PdOsW catalyst was demonstrated by the synthesis of diltiazem and the taxol side chain. Chiral diols derived from cinnamates were used as starting materials with this coupled catalytic system.[97]

The oxidation of primary and secondary benzylic and allylic alcohols using a OsO_4/Cu/air system has been reported.[98] Low catalyst loadings are used in the method and it can be run at room temperature to give the aldehyde or ketone in high selectivity without any overoxidation products.

5. Copper-Catalyzed Biomimetic Oxidation

Many of the aerobic oxidation reactions carried out in organic chemistry usually employ transition metals such as palladium and ruthenium, while living organisms make use of transition metals such as copper or iron. Copper is found in enzymes responsible for the binding and transport of oxygen in a variety of biological oxidation reactions.[99] However, there are only a few examples of the use of copper as a substrate-selective catalyst in aerobic oxidations in the presence of ETMs.[100]

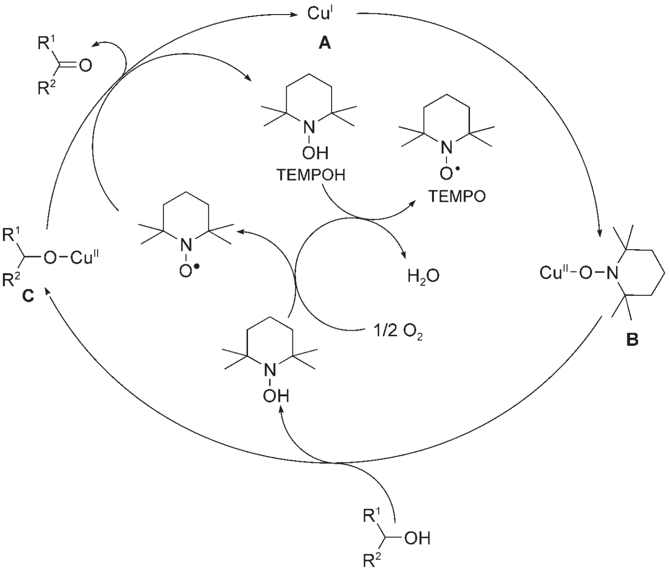
Markó et al. reported the efficient aerobic oxidation of a variety of alcohols to aldehydes and ketones in the presence of a copper catalyst.[101] The use of CuCl, 1,10-phenanthroline (phen), di-*tert*-butylhydrazine-1,2-dicarboxylate ($DBADH_2$), and K_2CO_3 (2 equiv) as a base in toluene at 70–90 °C and under O_2 led to the products in good to excellent yields [Eq. (6)]. Air can be used in place of molecular oxygen without affecting the outcome of the reaction, but longer reaction times are needed. The major drawback of the procedure is the need for two equivalents of strong base and the inefficiency in the oxidation of primary aliphatic alcohols. Further studies showed that it was possible to perform the reaction with only catalytic amounts of the base in the presence of 4-Å MS or in fluorobenzene.[102] Suitable conditions for the oxidation of sensitive alcohols were achieved by using KO*t*Bu and the copper catalyst in a 1:1 ratio, with no racemization observed in substrates with chiral centers at the α-position.[103] Additional studies on the reaction conditions showed that the addition of *N*-methylimidazole allowed the efficient oxidation of a wide range of primary aliphatic alcohols to the corresponding aldehydes without overoxidation to the carboxylic acids.[104] This is an elegant study, but has a disadvantage in that it is necessary to use many co-catalysts in relatively high amounts.



$$R^1CH(OH)R^2 \xrightarrow[\text{base, solvent, } O_2 \text{ or air}]{5\%\ \text{CuCl, } 5\%\ \text{phen, } 5\%\ DBADH_2} R^1C(=O)R^2 \qquad (6)$$

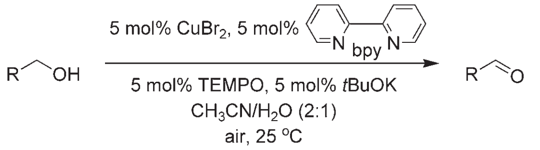
In this system, copper is reoxidized by molecular oxygen and the DBAD/$DBADH_2$ serves as the ETM of the redox reaction. The oxidized form of the ETM (DBAD) acts as a hydrogen acceptor and the reduced form ($DBADH_2$) as a hydrogen donor when it facilitates the oxidation of the metal by O_2.

Another important catalytic system for aerobic oxidations in the presence of copper species is the copper/TEMPO/O_2 system. The first aerobic copper-catalyzed oxidation was described by Semmelhack et al., who employed the CuCl/TEMPO/O_2 system to oxidize benzyl and allyl alcohols at room temperature to the corresponding carbonyl compounds.[105] Although TEMPO was proposed by Semmelhack et al. to be the oxidant of the alcohol, with copper chloride acting as a co-catalyst for the recycling of the TEMPO, recent mechanistic studies performed by Sheldon and co-workers, indicate that, based on their previous studies of the Ru/TEMPO/O_2 system,[74] copper is the substrate-selective redox catalyst and TEMPO the reoxidant of the copper catalyst.[2,106] The catalytic cycle starts with the reaction of copper(I) species **A** with TEMPO to form a (piperidinyloxyl)copper(II) complex **B** which reacts with an alcohol to give a copper(II) alkoxide complex **C** and TEMPOH (Scheme 18). The reaction of **C** with a second molecule of TEMPO leads to the formation of the carbonyl compound, a second molecule of TEMPOH, and the original copper(I) complex **A**. The TEMPOH obtained during the formation of the carbonyl compound is reoxidized by molecular oxygen, thereby closing the catalytic cycle.



Scheme 18. Proposed mechanism for the CuCl/TEMPO-catalyzed aerobic oxidation of alcohols.

In addition to their mechanistic studies, Sheldon and co-workers evaluated different copper salts, solvents, and N-containing ligands and developed a mild procedure for the oxidation of primary alcohols to give aldehydes in which [$CuBr_2$(bpy)], TEMPO, and air were used at room temperature [Eq. (7)].[107] It is noteworthy that this system shows high chemoselectivity for primary alcohols: when a mixture of benzylic alcohol and α-methyl benzyl alcohol was used, only conversion of the former was observed. This chemoselectivity towards primary alcohols was explained as a consequence of steric hindrance.

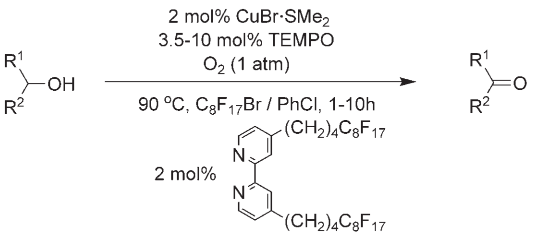


(7)

Punniyamurthy and co-workers have developed a related system in which {Cu(salen)} is used as the subtrate-selective catalyst together with TEMPO as a co-catalyst.[108] The system offers an advantage over that described by Sheldon and co-workers in that it does not require the use of additives, and the catalyst can be recycled and reused up to three times without loss of activity. However, this new system has the disadvantages that it requires pure oxygen in place of air and that it has to be performed at 100 °C instead of at room temperature.

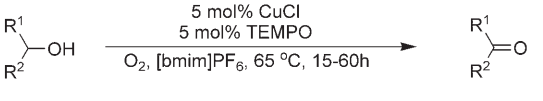
Other examples of the Cu/TEMPO system are given below, and in these studies the aim was to recover the catalysts by using nontraditional solvents such as perfluorinated solvents[109] and ionic liquids.[110,111]

Knochel and co-workers[109] described the use of perfluoroalkylated bipyridines as ligands for copper in the Cu/TEMPO system. The reaction is carried out in a biphasic perfluorinated/organic solvent mixture; the catalyst is soluble in the perfluorinated phase while the reagents and products are soluble in the organic phase. Thus, the method allows an easy separation of the catalyst from the product so that the catalyst can be recovered and reused for further reactions. The system was applied to the aerobic oxidation of a number of alcohols including primary and secondary benzylic, allylic, and aliphatic alcohols in good yields [Eq. (8)].The fluorous phase containing the catalyst was reused eight times without significant decrease of activity.

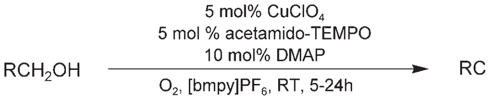


(8)

Ansari and Gree[110] employed the CuCl/TEMPO system in the ionic liquid [bmim]PF$_6$ for the successful aerobic oxidation of primary and secondary alcohols to the corresponding aldehydes and ketones, without any trace of overoxidation products [Eq. (9)]. However, only the ionic liquid was recycled with this method and it was not possible to recover the catalyst. In a later report, Jiang and Ragauskas[111] developed a room-temperature aerobic oxidation of primary alcohols to aldehydes by using the Cu/acetamido-TEMPO system in 1-*n*-butyl-4-methylpyridinium hexafluorophospate ([bmpy]PF$_6$) [Eq. (10)]. In this new system the 4-acetamido-substituted TEMPO can, in contrast to unsubstituted TEMPO, be recycled in the ionic liquid. It was possible to oxidize a variety of primary alcohols including benzylic, allylic, and aliphatic alcohols; no reaction was observed for secondary alcohols. The catalysts can be recovered and reused five times without any significant loss of activity.



(9)

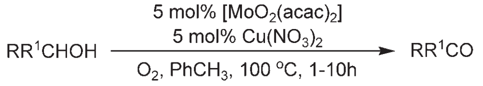


$$RCH_2OH \xrightarrow[O_2,\ [bmpy]PF_6,\ RT,\ 5\text{-}24h]{\substack{5\ mol\%\ CuClO_4 \\ 5\ mol\ \%\ acetamido\text{-}TEMPO \\ 10\ mol\%\ DMAP}} RCHO \qquad (10)$$

The combination of Mn^{II}/Cu^{II} nitrates with TEMPO also permits the aerobic oxidation of primary and secondary alcohols to give aldehydes and ketones in excellent yields under very mild conditions.[112]

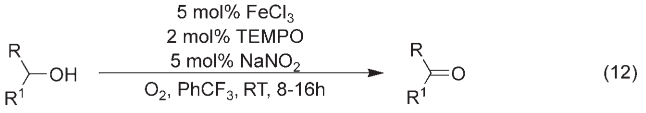
6. Other Metal-Catalyzed Biomimetic Oxidations

There are only a few examples of coupled redox systems for aerobic oxidation in which other transition metals are used as the substrate-selective redox catalysts and electron-transfer mediators. In one example, the oxidation of activated primary and secondary alcohols to the corresponding aldehydes and ketones, respectively, was performed with molecular oxygen in the presence of a molybdenum/copper system as the catalyst [Eq. (11)].[113] In this catalytic system, molybdenum acts as the oxidant of the alcohol and the copper salt acts as the co-catalyst (ETM) which activates the molecular oxygen. The authors evaluated different molybdenum complexes, with benzylic alcohol used as the substrate, and showed that the nature of the ligand is decisive for the success of the reaction, with acetylacetonate (acac) being the most effective ligand. They also studied different transition metals known to activate O$_2$ such as Co^{II}, Fe^{II}, and Mn^{II}, but copper gave the most efficient reaction. The best catalytic system found, [MoO$_2$(acac)$_2$]/Cu(NO$_3$)$_2$, was examined for the oxidation of various alcohols. Benzylic primary alcohols gave good yields and selectivity whereas secondary benzylic alcohols or aliphatic alcohols furnished low yields and poor selectivity.



$$RR^1CHOH \xrightarrow[O_2,\ PhCH_3,\ 100\ ^{\circ}C,\ 1\text{-}10h]{\substack{5\ mol\%\ [MoO_2(acac)_2] \\ 5\ mol\%\ Cu(NO_3)_2}} RR^1CO \qquad (11)$$

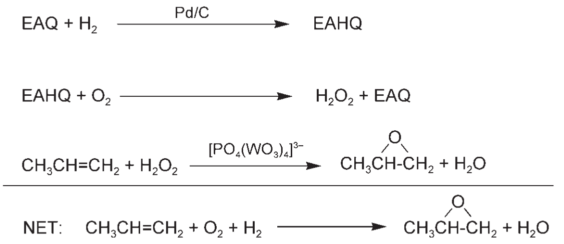
In 2005 Liang and co-workers reported an iron/TEMPO/NaNO$_2$ catalyst system for the selective and mild aerobic oxidation of a wide range of alcohols, even those containing C−C double bonds as well as nitrogen and sulfur atoms [Eq. (12)].[114] Benzylic and secondary alcohols were fully converted into the corresponding carbonyl compounds in high selectivity. It is worth noting that compounds containing



(12)

sulfur, which are problematic with many other transition-metal-catalyzed aerobic oxidations, did not interfere with the reaction. In a control experiment, a mixture of alcohol (benzyl alcohol or 2-octanol) and methyl phenyl sulfide was treated with the iron/TEMPO/nitrite catalyst: the alcohol was oxidized selectively to the aldehyde while the sulfide remained unchanged. The mechanism is analogous to that of the Cu/TEMPO systems (see above). The alcohol would be oxidized by the action of the Fe/TEMPO system and the role of the $NaNO_2$ would be to provide NO_2, which would reoxidize the Fe/TEMPO system to give NO. Finally, the NO can be easily oxidized by molecular oxygen.

Zuwei et al. developed an efficient epoxidation of propylene which was performed with H_2O_2 and a tungsten-containing catalyst. The process is coupled with the 2-ethylanthraquinone/2-ethylanthrahydroquinone (EAQ/EAHQ) redox process for the production of H_2O_2 from O_2; the net effect is that the reaction consumes O_2, H_2 (the EAQ is transformed into EAHQ by catalytic hydrogenation by Pd/C and H_2), and propylene to produce propylene oxide with high selectivity (Scheme 19).[115] This system offers some advantages over the previously described methods for the tungstate-catalyzed epoxidation of olefins by H_2O_2;[9a,116] the first is that in this case the terminal oxidant is molecular oxygen instead of H_2O_2; the second is that the tungsten catalyst is based on a quaternary ammonium heteropolyoxotungstate and is soluble in the reaction mixture when it is oxidized, but insoluble when reduced. In this way the catalyst can be recovered by simple filtration and reused again; therefore it has the advantages of both a homogeneous and a heterogeneous catalyst. However, the authors state that the recovery of only 90 % of the catalyst is possible after the precipitation. This is presumably due to the fact that precipitation/dissolution of the reduced/oxidized catalyst is not absolute, and in this case the recycling of the catalyst would not be effective after a few cycles.



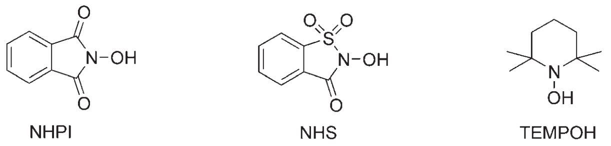
Scheme 19. Epoxidation of propylene using the EAQ/H_2O_2/tungsten-catalyst system. The phosphotungstate was used in the form of an *N*-hexadecylpyridinium salt.

Recently, an iron-catalyzed biomimetic epoxidation of olefins by hydrogen peroxide was reported by Beller and co-workers.[117]

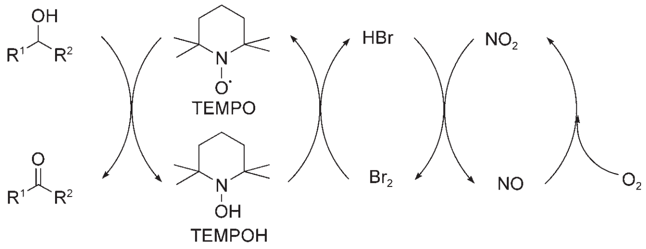
7. Metal-Free Catalyzed Biomimetic Oxidation

There are coupled catalytic systems in which ETMs are used for the oxidations with O_2 or H_2O_2 where the substrate-selective catalyst is not a transition metal. Since the aim of this Review is to survey coupled catalytic systems with transition metals as the substrate-selective catalyst, we will only cite a few selected systems.

In most of these oxidations the substrate-selective catalyst is a nitroxyl radical derived from compounds such as *N*-hydroxyphthalimide (NHPI),[106b,118] *N*-hydroxysaccharin (NHS),[106b,119] and TEMPOH.[106b,120] Some typical ETMs that are commonly used in combination with the previous catalysts are metal salts, usually Co, Cu, and Mn salts. It is also worth mentioning that laccase, a multicopper oxidase, has been used together with NHPI, TEMPOH, and other nitrogen-based ETMs.[121]



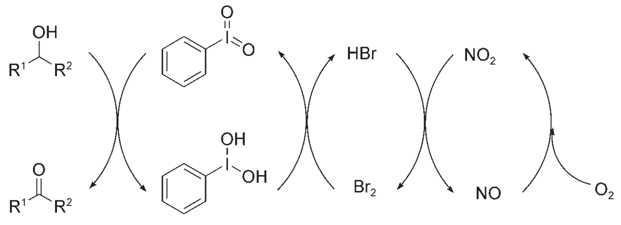
Hu and co-workers have recently reported a transition-metal-free system for the aerobic oxidation of benzylic alcohols and heteroaromatic analogues, with TEMPO used as the oxidant.[122] In this example, Br_2 and $NaNO_2$ are used as the co-catalysts and a wide range of primary benzylic alcohols and secondary alcohols were effectively oxidized. The overall mechanism of this transition-metal-free system is depicted in Scheme 20. The same authors proposed another catalytic system for the aerobic oxidation of alcohols with TEMPO, in which bromine was substituted by 1,3-dibromo-5,5-dimethylhydantoin; by using this system it is possible to perform the reaction with water as a solvent.[123]



Scheme 20. Aerobic oxidation of alcohols with a TEMPO/Br_2/$NaNO_2$ system.

Another system for the oxidation of alcohols involves the use of hypervalent iodine (iodoxybenzene) as the oxidant and bromine and $NaNO_2$ as ETMs.[124,125] The reactions are conducted in water under air, and the system is suitable for the oxidation of primary benzylic alcohols and secondary aromatic and aliphatic alcohols to give excellent yields of the aldehydes and ketones, respectively. However, low conversions and yields are achieved with primary aliphatic alcohols.

The mechanism is similar to that proposed for the TEMPO/Br_2/$NaNO_2$ system developed by Hu and co-workers (Scheme 21).

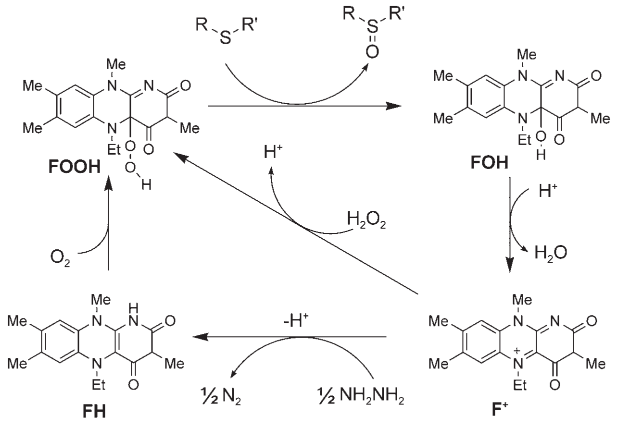


Scheme 21. Aerobic oxidation of alcohols with a $PhIO_2$/Br_2/$NaNO_2$ system.

A catalytic system for the oxidation of alcohols related to the two previous ones (TEMPO/Br_2/$NaNO_2$ and $PhIO_2$/Br_2/$NaNO_2$) has recently been reported. This system is composed of TEMPO/[bis(acetoxy)iodobenzene]/$NaNO_2$ with oxygen as the terminal oxidant, and has been effectively employed for the oxidation of primary benzylic alcohols, but with less success for the oxidation of secondary benzylic or aliphatic alcohols. The analogous immobilized hypervalent iodine reagent was also used. It could be recycled up to three times in the oxidation of benzylic alcohol to benzaldehyde, with essentially the same high yield as for the free reagent, although longer reaction times were required.[126]

Espenson et al. developed a method to oxidize alcohols by bromine using methyltrioxorhenium (**11**) as a co-catalyst and hydrogen peroxide as the terminal oxidant in acetic acid at room temperature.[127] With this system it is possible to oxidize secondary alcohols and benzylic primary alcohols to the carbonyl compounds in high yields. However, the reactions are not totally selective and in some cases different amounts of products derived from the esterification of the alcohols with the solvent were detected. The method is also suitable for the oxidation of 1,3-dioxolanes to give glycol monoesters and for the conversion of aldehydes into methyl esters by using methanol as a solvent. The oxidative cleavage of ethers can be performed with this catalytic system, although the yields for this reaction were always lower than 60%.

It is worth mentioning that in some cases flavins, which have been typically used as ETMs (see Section 4), can be used as the substrate-selective redox catalyst for the mild oxidation of amines and sulfides at room temperature, with hydrogen peroxide used as the sole reoxidant.[87,128] In nature, flavins occurring in monooxygenases use molecular oxygen as the oxidant. This process requires a cofactor that reduces the hydroxyflavin that is produced after the hydroperoxyflavin has oxidized the substrate, and in nature this cofactor is NADPH. In an elegant study Imada, Murahashi, and co-workers mimicked this process with the development of an aerobic flavin-catalyzed oxidation of sulfides to sulfoxides at ambient temperature.[129] Hydrazine is used as a stoichiometric ETM (reductant), and constitutes a mimic of the NADPH cofactor. The catalytic cycle of this biomimetic oxidation starts with oxidation of the sulfide by a hydroperoxyflavin (**FOOH**) species to give the sulfoxide and hydroxyflavin (**FOH**), of which the latter undergoes dehydration to give an oxidized flavin (**F**$^+$). At this point, **F**$^+$ can be transformed to **FOOH** by hydrogen peroxide or it can be reduced by hydrazine to give the reduced flavin (**FH**), which can be oxidized by molecular oxygen to the hydroperoxyflavin (**FOOH**, Scheme 22). The catalytic reaction also works with tertiary amines, but only at 60 °C.



Scheme 22. Catalytic cycle for the oxidation of sulfides by hydrogen peroxide or molecular oxygen.

8. Conclusions and Outlook

Oxidation reactions are among the most commonly used reactions in industry. However, many of the industrial processes still use stoichiometric amounts of high-oxidation-state metal reagents. Moreover, there is currently an active search for environmentally friendly procedures, which are based on the use of catalytic amounts of the metal. Thus, the development of new methodologies that employ environmentally friendly oxidants such as molecular oxygen or hydrogen peroxide is one of the most important goals in oxidation chemistry today. A better understanding of the mechanisms of various electron-transfer reactions is of central importance and will stimulate further achievements in this area. Enantioselective oxidation reactions based on the biomimetic approach and involving ETMs should also be further developed.

There are systems where the catalyst is oxidized directly by molecular oxygen or hydrogen peroxide. However, this strategy fails in some cases, and one can search for ligands which facilitate the direct oxidation or make use of co-catalysts as electron-transfer mediators (ETMs). The use of coupled catalytic systems with electron-transfer mediators (ETMs) is an important complement to the direct oxidation approach which expands considerably the use of O_2 and H_2O_2 as oxidants in catalytic oxidation reactions.

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