Selective Oxidation of Organic Compounds—Sustainable Catalytic Reactions with Oxygen and without Transition Metals?**

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Oxidation reactions belong to the repertoire of organic chemistry. Over the past few years a series of sustainable oxidation methods have been developed in which tailor-made transition-metal complexes serve as catalysts. In these reactions the chemoselectivity, regio-, stereo-, and enantioselectivity can be controlled under relatively mild reaction conditions and the products obtained with optimal yield. Recent results from research focusing on two important reactions are discussed here: 1) the selective homogeneously catalyzed oxidation of alcohols to give aldehydes/ketones and 2) the complete oxidation of pollutants. Although every synthesis begins in the laboratory, oxidation reactions also play a very important role in industrial chemistry. However, these large-scale industrial production processes will not be considered here.

Selective Oxidation of Alcohols

The selective oxidation of alcohols is an important preparative method in organic chemistry. The textbook classic by J. March lists 65 references to classical oxidation methods. The database “ISI Web of Science” provides 4715 entries on this topic for the period January 1996 to July 2005. In Table 1 three familiar oxidation methods and five more recent approaches are compared with respect to their sustainability parameters. In each case the reactions result in yields of 80–98%. In methods 1–4 the oxidation agent is a metal oxide or non-metal oxide in a high oxidation state, methods 5–8 are more recent catalytic oxidations with hydrogen peroxide or dioxygen.

Atom economy and the environmental factor \( E \) are measures for the amount of waste produced in a reaction relative to the amount of desired product. The heading atom economy in Table 1 refers to the reaction stoichiometry; the environmental factor \( E \) also takes into account the solvent and auxiliaries that must be disposed of. The ecotoxicity of the reaction must also be considered: toxic compounds are used in the Jones and Swern oxidations (methods 1 and 2 in Table 1). The assessment in terms of the atom economy and the environmental factor \( E \) is particularly poor for the Swern and Dess–Martin oxidations owing to the large amount of waste produced. In oxidations with hydrogen peroxide and oxygen (methods 5–8 in Table 1) only water is formed in addition to the desired carbonyl compound, and it is not waste in a strict sense. The cost of the oxidizing agent listed in Table 1 is calculated for a one-mole scale. The price of chemicals reflects the cost of their preparation from basic compounds including energy requirements. If one assumes that the costs for auxiliaries are similarly high for all eight methods, the price of the oxidizing agent is then a measure for the economy and the ecology. It can be seen from Table 1 that the price for one oxidation equivalent (removal of two electrons) is highly dependent upon the oxidizing agent used and ranges from 185 Euro for the Swern reagent to 0.038 Euro for dioxygen. An improvement with respect to atom economy and cost is particularly recognizable for catalytic methods with molecular oxygen or air. In past years such methods have been developed on the laboratory scale, mainly with transition-metal complexes based on copper, palladium, and ruthenium, and they are clearly superior with respect to sustainability parameters such as atom economy, cost of the oxidizing agent, and (eco)toxicity of the starting compounds and reaction products. In Table 1 the sustainability of the methods listed improves from top to bottom, also because the amount of waste decreases significantly.

Molecular oxygen does indeed have considerable oxidation potential, but at room temperature it does not react with most organic compounds owing to high activation barriers. At higher temperatures, oxygen, which exists as diradical in the ground state, takes part preferably in nonselective radical reactions, for example, the autoxidation of hydrocarbons. To achieve selective oxidations with oxygen, transition-metal complexes have been developed as homogeneous catalysts. Method 7 in Table 1 illus-

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trates the diversity of more recent, sustainable oxidation methods.

Since compounds of the transition metals described are expensive and often not available commercially and also potentially (eco)toxic (Table 1), the Chinese research group lead by X. Hu and X. Liang at the Dalian Institute of Chemical Physics has introduced the combination of TEMPO/bromine/sodium nitrite as an alternative catalyst (method 8 in Table 1).[6] A variant of this new method uses 1,3-dibromo-5,5-dimethylhydantoin or N-bromosuccinimide in place of bromine. [6b] Benzyl alcohols (eight examples), aliphatic alcohols (four examples), and an allyl alcohol may be oxidized selectively with air in aqueous solution or CH₂Cl₂ to give the corresponding carbonyl compounds in high yield (Scheme 1). A pyridine-3-carbinol was oxidized to the aldehyde without the addition of acid. Reaction times were 1–5 h. However, one disadvantage of this method is the high cost of the apparatus: an autoclave is required to achieve the oxygen partial pressure necessary (0.4 Mpa). Working in water as solvent[7] can be an advantage for the process, but organic solvents are preferable since contaminated aqueous solutions are more difficult to dispose of.

A three-stage catalytic reaction cascade has been suggested as the mechanism (Scheme 2). Coupled cyclic processes of redox pairs of different catalysts can explain many oxidation reactions such as method 7 (Table 1).[5,8] It is known that TEMPO itself can react as a stoichiometric oxidant,[4f] but as a cocatalyst with sodium bromide it can also bring about the oxidation of alcohols with sodium hypochlorite (method 4 in Table 1).

Table 1: Comparison of the sustainability of eight selective oxidation methods with benzyl alcohol as example.[6]

<table>
<thead>
<tr>
<th>Method</th>
<th>Name</th>
<th>Reagent</th>
<th>Catalyst</th>
<th>Solvent</th>
<th>T [°C]</th>
<th>Atom economy [%]</th>
<th>Environmental factor E [kg kg⁻¹]</th>
<th>Cost [€]</th>
<th>(Eco)toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1[4a]</td>
<td>Jones oxidation</td>
<td>CrO₃/H₂SO₄</td>
<td>no</td>
<td>acetone</td>
<td>0–20</td>
<td>38.8</td>
<td>ca. 6</td>
<td>17</td>
<td>CrO₃ is carcinogenic</td>
</tr>
<tr>
<td>2[4b]</td>
<td>Swern oxidation</td>
<td>(CH₃)₂SO,(COCl)₂, N(C₂H₅)₃</td>
<td>no</td>
<td>CH₂Cl₂</td>
<td>–60</td>
<td>20.6</td>
<td>ca. 58</td>
<td>185</td>
<td>toxic reactants and products</td>
</tr>
<tr>
<td>3[4c]</td>
<td>Dess–Martin oxidation</td>
<td>periodinane (DMP)</td>
<td>no</td>
<td>CH₂Cl₂/H₂O</td>
<td>–20</td>
<td>19.9</td>
<td>ca. 1800</td>
<td>160</td>
<td>DMP is unstable and explosive</td>
</tr>
<tr>
<td>4[4d]</td>
<td>according to Anelli et al.</td>
<td>NaOCl/NaBr</td>
<td>TEMPO[c]</td>
<td>CH₂Cl₂/H₂O</td>
<td>0</td>
<td>58.1</td>
<td>ca. 58</td>
<td>110</td>
<td>low</td>
</tr>
<tr>
<td>5[4e]</td>
<td>according to Sasson et al.</td>
<td>H₂O₂ (30%)</td>
<td>RuCl₃/phase-transfer cat.</td>
<td>CH₂ClCH₂Cl/ toluene</td>
<td>80</td>
<td>74.7</td>
<td>ca. 12</td>
<td>20</td>
<td>low</td>
</tr>
<tr>
<td>6[4f]</td>
<td>according to Sheldon et al.</td>
<td>O₂</td>
<td>TEMPO</td>
<td>various</td>
<td>80</td>
<td>85.5</td>
<td>–</td>
<td>0.038</td>
<td>low</td>
</tr>
<tr>
<td>7[5]</td>
<td>see Ref. [5]</td>
<td>O₂</td>
<td>Complexes of Cu, Pd, Ru</td>
<td>different</td>
<td>80</td>
<td>85.5</td>
<td>ca. 26</td>
<td>0.038</td>
<td>none</td>
</tr>
<tr>
<td>8[6]</td>
<td>according to Liu et al.</td>
<td>O₂ or air</td>
<td>TEMPO, Br₂, NaNNO₂</td>
<td>H₂O or CH₂Cl₂</td>
<td>80</td>
<td>85.5</td>
<td>ca. 15</td>
<td>0.038</td>
<td>low</td>
</tr>
</tbody>
</table>

[a] Stoichiometric equations can be found in Ref. [1a] and the respective literature citations. [b]Prices for pure chemicals from the Aldrich catalogue (2003), Price from the company Linde for O₂ (50 L, 99.95 % purity). [c] TEMPO = 2,2,6,6-tetramethyl-1-piperidinyloxy.

Scheme 1. Selective oxidation of alcohols with the system TEMPO/Br₂/NaNO₂.[6]

Scheme 2. Reaction cascade for the oxidation of alcohols.[6]
In addition to the desired selectivity, turnover number and frequency (TON and TOF values), the substrate/catalyst ratio and the formation of toxic by-products must also be considered in the assessment of catalytic reactions. The data given in Table 1 are a criterion for the efficiency of a method and should therefore be taught in chemistry courses. In the Jones oxidation, which is indeed convenient and relatively inexpensive, a carcinogenic oxidizing agent (CrO₂) is used. Since there are better, more environmentally friendly methods that do not require toxic reagents, two alternative methods are given in the Introduction of the Sustainable Organic Laboratory Course (NOP). In special cases such as the Dess–Martin reaction (method 3 in Table 1) very poor sustainability parameters are disregarded in favor of milder reaction conditions (oxidation in the presence of sensitive groups). Of the methods listed in Table 1 both method 7 and method 5 (oxidation with H₂O₂/RuCl₃ described by Sasson) are particularly advantageous, because all of the reagents and cheap and readily available.

Sustainability plays an important role in industrial oxidations of alcohols on a large scale. Moreover, the global effects of competing industrial processes can be compared based on an ecoefficiency analysis. This was demonstrated recently with the comparison of five alternative indigo syntheses by a group at BASF. In a detailed evaluation of the reactions listed in Table 1 by the EATOS method the mass flows of all starting compounds and reaction products and auxiliaries are balanced (the E value in Table 1 is an approximate summation parameter for this). The values given in Table 1 show a clear trend with respect to the sustainability of the different oxidation processes on a laboratory scale; they are indicative for synthesis on an industrial scale.

Oxidation of Pollutants (Complete Oxidation)

Most dissolved contaminants are mineralized in the environment, in other words, they undergo complete oxidative degradation to carbon dioxide and water. (S, N, and Cl compounds also give rise to sulfate, nitrate, and chloride, respectively.) For most materials in waste water this takes place by the microbiocenosis of the sewage plant. Only contaminants such as perhalogenated compounds, the so-called persistent organic pollutants (POPs), resist biological oxidation. Therefore a plurality of chemical oxidation processes (advance oxidation processes, AOPs) have been developed in which hydrogen peroxide and dioxygen play a pivotal role. The Fenton reagent consisting of iron(II) salts and hydrogen peroxide is not selective enough for effective oxidation because the most of the H₂O₂ is converted into water and unreactive oxygen by redox disproportionation (catalase activity). This is also true for the use of H₂O₂ in the oxidation of alcohols (method 5 in Table 1). For this reason H₂O₂ is combined with metal catalysts such as complexed metal salts of iron and manganese, which have lower catalase activity. None of the known oxidation processes converts organic compounds and H₂O₂ to CO₂ and H₂O quantitative— the degree of mineralization lies at only 40%.

Selected isomers of chlorophenols, the five key compounds earmarked by the U.S. Environmental Protection Agency as “priority pollutants”, have been used as models for the oxidation of persistent impurities with H₂O₂ or oxygen in the presence of metal catalysts. Meunier et al. have employed iron phthalocyanine and iron porphin catalysts in the oxidation of 2,4,6-trichloro- and pentachlorophenol with H₂O₂ and Lente and Espensen have recently described reactions with five different iron cyclam complexes. Application of these processes is made difficult in that the organic solvents must be added to the aqueous solutions. To address this problem the group lead by Collins has developed the Fe-TAML catalyst (Figure 1; TAML = macroyclic tetraamido ligand). The oxidation of 2,4,6-trichloro- and pentachlorophenol with hydrogen peroxide and this system was recently investigated in detail. The mass balance for carbon showed for TCP that CO₂ and CO account for 35% in addition to six low-molecular-weight, readily biodegradable organic acids: oxalic acid (11%), formic acid (5%), chloromalic acid (16%), malonic acid (7.5%), hydroxymalonic acid (6.5%), and chloromalonic acid (4.5%). Organically bound chlorine is mineralized to about 85%. Unlike other oxidation processes for chlorophenols, toxic chlorinated dibenzodioxins and dibenzofurans are not detectable even in trace amounts.

Other pollutants such as azo dyes and alkyl sulfides or effluent from paper and pulp production can be decomposed oxidatively and thus disposed of with this method. According to the Daphnia test, the reaction products from the oxidation of “Orange II”, a widely used azo dye, are less toxic than the starting compound. The mechanism of the oxidation with H₂O₂/Fc-TAML is still not completely understood, but it probably proceeds via iron(v) complexes.

In analogy to their work on selective oxidations of alcohols without heavy metals (method 8 in Table 1) the same Chinese group succeeded in the oxidation of 2,4,6-trichlorophenol (TCP) with dioxygen as the oxidant and sodium nitrite as the catalyst in an autoclave at a pressure of 0.5 Mpa. Possibly the chlorophenol acts through the phenol/phenoxyl radical redox pair with nitrite (redox pair NO₂/NO) as cocatalyst. The intermediate formation of peroxyxinitrite or nitrate would offer an alternative explanation, but there are no indications of the formation of these species based on the results of NO and O₂ in atmospheric chemistry. The method was optimized with respect to the reaction conditions, whereby equimolecular amounts of substrate and nitrite were used. Oxidation of TCP at 210°C leads after six hours to mineralization (CO₂ and CO) of 75% besides the four acids: formic acid (4.3%), acetic acid (5.3%).
pyruvic acid (2.4 %), and succinic acid (2.5 %). Organically bound chlorine was mineralized to about 90 %. The new method[18] is thus an interesting alternative to the method of Collins, as sodium nitrite is significantly cheaper than TAML, although on an industrial scale it would be necessary to recycle or dispose of it. The relatively high energy requirement and the apparatus expenditure must also be taken into account. The method of Collins et al. with H₂O₂/Fe-TAML requires 10–30 min at room temperature with a catalyst/substrate ratio of 1:2000. However, hydrogen peroxide is a more expensive oxidant than oxygen (Table 1). Therefore a detailed comparison that includes the energy balance of both methods would be of interest for industrial application.

**Conclusion**

A number of catalytic oxidation reactions of organic substrates with molecular oxygen are possible even without transition metals,[6,19] but transition metals cannot (yet) be dispensed with in most oxidations.[3] The (eco)toxicological assessment of metal-catalyzed reactions is currently possible only as an approximation, for the toxicity of a metal is essentially dependent upon its speciation (bonding state).[20] The toxicity of the most frequently used transition-metal catalysts is not known. Since many compounds may be toxic, they should not come into contact with personnel or the environment. If there is a choice between different catalysts and reagents in a catalytic reaction, the less toxic alternative should be given preference. The new methods described here[6,19] can contribute. The Fe-TAML catalyst[6,19] for total oxidations exhibits very low toxicity, and the system with oxygen and sodium nitrite for the total oxidation of chlorophenols is characterized by a high degree of mineralization.[19]


