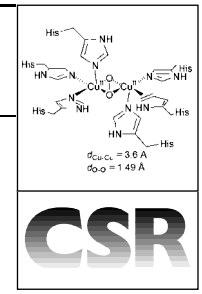
Homogeneous bio-inspired copper-catalyzed oxidation reactions



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The controlled oxidation of C–H bonds is one of the most challenging and difficult reactions in organic chemistry. Generally, it requires either stoichiometric amounts of toxic heavy metal salts or very expensive catalysts containing

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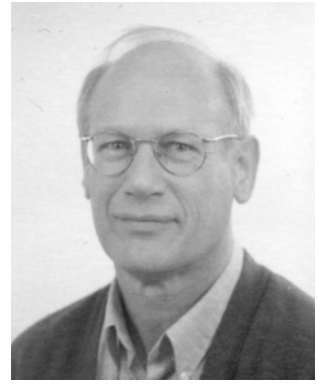
Peter Aubel graduated in inorganic chemistry at the University of Amsterdam with insertion reactions into Pd–C bonds as his final research topic. Before graduating, he worked as a trainee at the Shell Research and Technology Center in Amsterdam for six months, on the development of new catalyst precursors for polymerization reactions. He subsequently started to work for a PhD at Leiden University on the copper-catalyzed oxidative coupling of 2,6-dimethylphenol.

Willem L. Driessen (1941, Sassenheim, The Netherlands) studied chemistry at Leiden University, where he also took his PhD with E. W. Gorter and W. L. Groeneveld in 1971 on first row transition-metal compounds of weakly coordinating oxygen donor ligands. He is involved as Senior Lecturer in the teaching of (bio)inorganic and coordination chemistry and of topics in X-ray crystallography. His major research area comprises the coordination chemistry of (mostly) first row transition metals, in particular copper compounds. Specific research themes are: copper biomimetics and oxidation catalysis, and recovery of (heavy) metal ions (e.g. Cu, Cd, Rh) with specifically designed chelating ion exchangers. He is (co-)author of more than 200 publications.

Jan Reedijk (1943, Westmaas, The Netherlands) is currently Professor of Chemistry at the Leiden Institute of Chemistry, Leiden University, The Netherlands. After obtaining an MSc and PhD from Leiden University (1968) and occupying a Junior Lectureship, he lectured in Delft University of Technology until 1979, when he accepted his present position. His current research interests include: coordination chemistry of transition-metal ions; bioinorganic chemistry (active-site structure and mechanism; models; metal–DNA interactions); applications of coordination chemistry in catalysis, medicine, ion-exchange, surface chemistry; extended (magnetic, electric) interactions in coordination compounds (dimers, clusters, chains); molecular recognition and intermolecular interactions (catalysis; biomacromolecules). He has over 750 (co-)authored, refereed research publications and patents (1966–2001) and has supervised over 90 postdocs and graduate students (1973–2001). Some of his major professional activities, honours and awards are: Director, Leiden Institute of Chemistry (1993–present); Executive Secretary of the International Conference of Coordination Chemistry (ICCC) and Member of the International Advisory Board of a number of International Conference Organisations, such as the EURASIA Conferences of Chemistry, Macromolecular Metal Complexes Conferences, EUROBIC and ICBIC. Other honours include: awardee of the Max-Planck Research Award in Chemistry (1992); elected Member Finnish Academy of Sciences (1997); elected Member of the Royal Netherlands Academy of Sciences (1996). He is and has been a member of the Editorial Boards of over 15 major chemistry journals, most recently including New Journal of Chemistry and the Journal of Biological Inorganic Chemistry. He is currently one of the Editors of the rapidly growing European Journal of Inorganic Chemistry (a merger from several European Chemical Society Journals).


Patrick Gamez


Peter Aubel


Willem L. Driessen


Jan Reedijk

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transition metals such as palladium, rhodium or ruthenium. The scientific community used to focus their investigations towards these relatively rare and costly elements while neglecting to look at how Nature performs these types of reactions. Biological systems only employ abundantly available metals like iron, zinc and copper. This review summarizes the background and the state of the art of enzymatic and biomimetic oxidation catalysts involving copper as the active metal center. Recent developments have shown the first very promising results in this incipient field.

1 Introduction

The accumulation of free dioxygen (from the Greek words 'oxy genes' meaning 'acid' and 'forming') during the Precambrian era (4600 to 544 million years ago) has promoted, without any doubt, the development of Life on Earth. Spirulina, Earth's oldest living plant, is the first photosynthetic life form that created our oxygen atmosphere. This blue–green algae utilizes phycocyanin, a so-called 'light-harvesting pigment', to absorb light and initiate an electron-transfer sequence, ultimately leading to oxidation of H_2O to O_2.[1] Subsequently, further enzymatic-mediated processes could take place to produce organic compounds such as glucose from CO_2. An increasing amount of biotransformations performed by enzymes, rendered possible the appearance of more and more evolved living beings. Enzymes have been studied since the early 1900's, but even today this is a field of research still in its infancy. In 1930, only about 80 enzymes were known to exist. Today, thousands of enzymes have been discovered, but still many reactions have been identified for which the enzymes responsible remain unknown. Enzymatic reactions are known to be highly selective and to proceed under very mild conditions. Thus, the study and the modelling[2] of the active site of these bio-catalysts is a field of great interest within the scientific community, as new and very effective homogeneous catalysts for common reactions may be discovered.[3] Several copper proteins are found in Nature, with copper being the third most abundant essential trace mineral in the human body after iron and zinc, and many of them have been the starting point of the elaboration of very active copper catalysts, especially in oxidation reactions.[4]

The present review deals with the background on the enzymes involving copper ions as metal centers to bind dioxygen for transport, or to use dioxygen for biochemical transformations. These isolated metalloproteins can be used in enzymatic oxidations, while the understanding of the structure–function relationship and the modelling of their active sites will allow the design of effective complexes. Recent developments have shown high turnover numbers and high selectivities for the oxidation of alkanes, alkenes or alcohols and for oxidative coupling reactions including polymerizations.

2 Transport of molecular oxygen

One of the first problems in the development of aerobic life was the ability to bind dioxygen and transport it into the organism to allow its chemical processes. Hemoglobin, an iron-containing pigment, has this function in our bodies. In some invertebrates, hemocyanin (Fig. 1),[5] a copper-containing protein, is responsible for dioxygen transport. Since the late 80's, the outstanding spectral characteristics of oxyhemocyanin have attracted the attention of many chemists.

To provide better insight into the binding mode of dioxygen in oxyhemocyanin, extensive synthetic efforts have been made

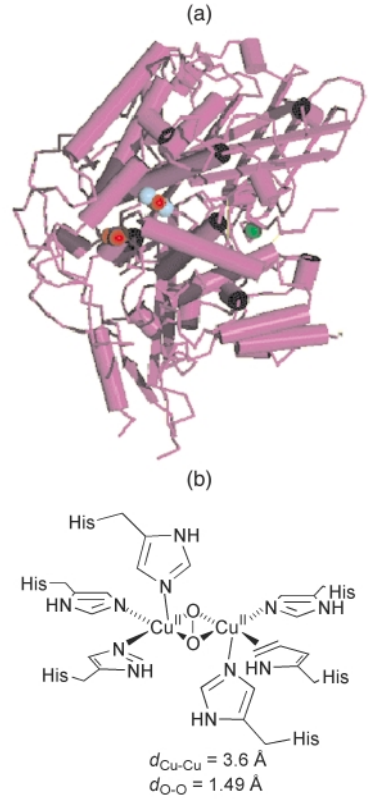
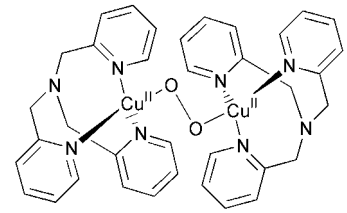
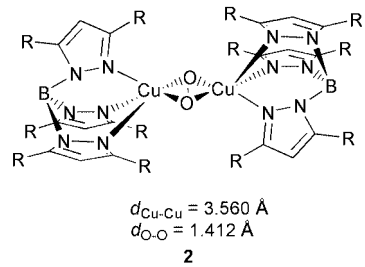


Fig. 1 The global structure and the schematic dinuclear μ-η^2:η^2 peroxo copper active site of oxyhemocyanin from *Limulus polyphemus*, from a single-crystal X-ray determination.[5]

to prepare μ-peroxo dicopper complexes using various ligands.[6–8] The first structurally characterized Cu_2O_2 species (Fig. 2, **1**) was reported in 1988 by the group of Karlin.[6]





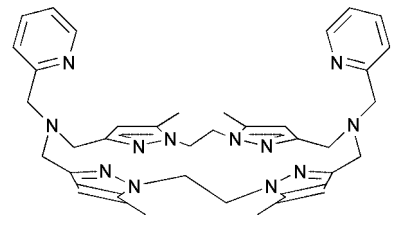


Fig. 2 Model hemocyanin systems: *trans*-μ-1,2-peroxo model of Karlin[6] (**1**), μ-η^2:η^2 peroxo model developed by Kitajima[7] (**2**), and the macrocycle MePy22Pz (**3**) reported by Reedijk.[8]

Complex **1** is intensely purple, whereas oxyhemocyanin is intensely blue. Complex **1** shows strong UV–Vis absorptions at 440, 525, and 590 nm and an additional d–d band at 1035 nm. Both an intraperoxide O–O stretch at 832 cm^{-1} and a copper–oxygen stretch at 561 cm^{-1} have been identified using resonance Raman spectroscopy. The three UV–Vis bands have been assigned to peroxo-to-copper charge transfer transitions. The 832 cm^{-1} stretching vibration indicates the oxidation state of the dioxygen moiety to be O_2^{2-}. X-Ray data of the thermally and moisture sensitive material were obtained at 90 °C. It contains an end-on *trans* μ-1,2 peroxo group (*viz*. μ-1,2-O_2^{2-}) bridging the two copper(II) ions (Fig. 2, **1**).

A very important breakthrough in copper–dioxygen biomimetics occurred in 1989 when Kitajima[7] reported copper complex **2** with a substituted anionic tripyrazolylborate ligand (Fig. 2, **2**). This intensely purple coloured compound is a stable solid (when R is an isopropyl group) at room temperature or even in non-coordinating solvent (*e.g*. $CHCl_3$, CH_2Cl_2) at 20 °C. The most remarkable feature observed in its X-ray structure is the side-on μ-η^2:η^2-peroxo coordination that holds the two copper units together. Furthermore, the physical properties reported are qualitatively and quantitatively very similar to those of oxyhemocyanin. Complex **2** shows UV–Vis absorptions at 349 nm (ε = 21000) and 551 nm (ε = 800), while for oxyhemocyanin the values are: 340 nm (ε = 20000) and 580 nm (ε = 1000). The particularly low value of the O–O stretch of 741 cm^{-1} (resonance Raman) also matches the value found for oxyhemocyanin (744–752 cm^{-1}).

Recently, the use of the macrocyclic ligand MePy22Pz (**3**) (Fig. 2) by some of us[8] also produced a room-temperature stable Cu_2O_2 species. Single crystals suitable for X-ray diffraction could not be obtained, but the spectroscopic data (*viz*. UV–Vis, resonance Raman) are comparable to those observed by Karlin for **1**. Thus, a *trans*-μ-1,2-peroxo-dicopper(II) structure has been assigned.

A key step in the use of this bound dioxygen in bioreactions is then to cleave the O–O bond. Tolman and co-workers reported the interconversion between dioxygen copper complexes having μ-η^2:η^2-peroxo and bis-μ-oxo coordination modes (Scheme 1),[9] demonstrating the viability of this transformation in biological systems.

Complex **5** was obtained in dichloromethane at −78 °C. The UV–Vis absorptions at 366 (ε = 22,500) and 510 nm (ε = 1,300) and the Raman ν_{O-O} stretch at 722 cm^{-1} clearly indicate the presence of a (μ-η^2:η^2-peroxo)dicopper(II) core. When the oxygenation of **4** is carried out in tetrahydrofuran, a different species, complex **6**, was obtained quantitatively. This EPR-silent molecule exhibits quite different spectral properties from those of **5**. Intense UV–Vis absorptions are observed at 324 (ε = 11000) and 448 nm (ε = 13000). The Raman feature at 600 cm^{-1} is assigned to a symmetric stretching vibration of the $\{Cu_2(\mu\text{-}O)_2\}^{2+}$ core. Thus, the oxygenation of **4** can produce either **5** or **6**, depending on the solvent. More interestingly, **5** interconverts with **6** simply upon a change of solvent (Scheme 1).

The formation of a 1:1 Cu–O_2 adduct is also probably important in copper oxygenase activity. Recently, Jitsukawa and Masuda[10] reported a structurally characterized mononuclear copper(II)–superoxo complex prepared with a tripodal tetradentate ligand, tris[(6-(pivaloylamino)-2-pyridyl)methyl]-amine (TPPA). The direct addition of dioxygen at −80 °C to a Cu(I)–TPPA complex in methanol results in instantaneous spectral changes. Two well-separated absorptions in the d–d region (657 and 803 nm) suggest that the copper ion is divalent. A shoulder at *ca*. 315 nm is assigned to an $O_2^- \rightarrow$Cu(II) ligand-to-metal charge transfer (LMCT) band. Moreover, the spectrum is very similar to that for complex **1** previously reported by Karlin.[6] The solution of the complex is EPR-silent at −80 °C, probably due to a strong magnetic coupling between the copper(II) ion and the superoxide. The structure was clarified by analyzing its crystal structure. The presence of a superoxo group was proven.[10]

3 Copper enzymes and oxidation reactions

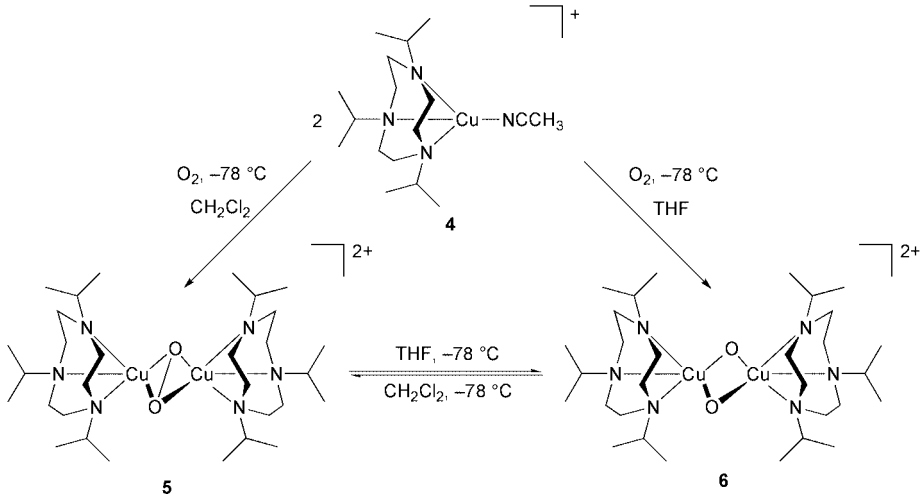
3.1 Introduction

New catalytic synthetic methods in chemistry that satisfy increasingly strict environmental constraints are in great demand by the pharmaceutical and chemical industries. In addition, novel catalytic procedures are necessary to produce the new classes of compounds that are becoming the targets of molecular and biomedical research. Enzyme-catalyzed chemical transformations are now widely recognized as practical alternatives to traditional (non-biological) organic synthesis, and as convenient solutions to certain synthetic problems like oxidation reactions.

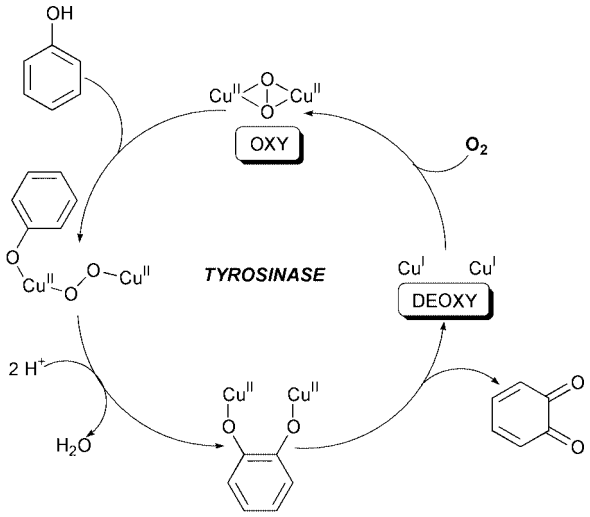
In biological systems, once inside the target cells, dioxygen is involved in a multitude of bioreactions performed by enzymes. In the following subsections, the most important copper-containing biological systems will be briefly discussed.

3.2 Copper oxygenases

3.2.1 Tyrosinase. This enzyme has been known for over 80 years. It is a dinuclear copper(II)-containing protein similar to hemocyanin, which activates dioxygen and functions as a mono-oxygenase that *ortho*-hydroxylates monophenols and



Scheme 1 Interconversion between synthetic complexes having $[Cu_2(\mu\text{-}\eta^2\text{:}\eta^2\text{-}O_2)]^{2+}$ and $[Cu_2(\mu\text{-}O)_2]^{2+}$ cores.[9]

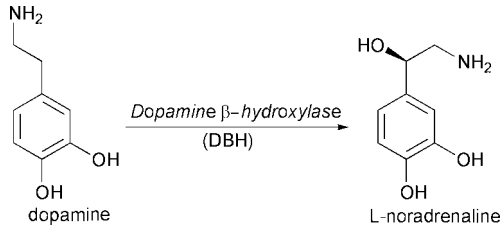


Scheme 2 Catalytic cycle of tyrosinase phenol *ortho*-hydroxylation.[11]

further oxidizes the *o*-diphenol to an *o*-quinone (Scheme 2).[4,11] It is responsible for the occurrence of the enzymatic browning reaction in bruised or cut fruits and vegetables upon contact with oxygen.

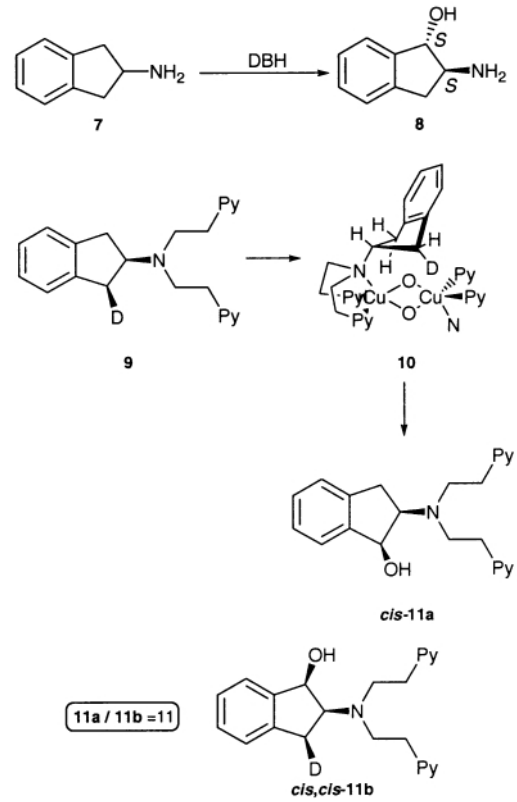
For many years, the biocatalysis of tyrosinase has been investigated in order to optimize its use in organic solvent media.[12] Furthermore, considerable progress has been made in the chemical modelling of tyrosinase-like mono-oxygenase activity. Since the first model reported in 1984, by Karlin *et al*.,[6] much research has been done and numerous biomimetic examples have been published.[13] The copper-catalyzed *para*-hydroxylation of phenol to *p*-benzoquinone is also an important bioinspired oxidation reaction.[14] The reduction of *p*-benzoquinone leads to hydroquinone, an important commodity chemical used in antioxidant and photographic chemistry.

3.2.2 Dopamine β-hydroxylase (DBH). The mechanism of O_2 activation of dopamine β-hydroxylase (DBH), which catalyzes the benzylic hydroxylation of dopamine into neurotransmitter noradrenaline (Scheme 3), is of current interest.[15]



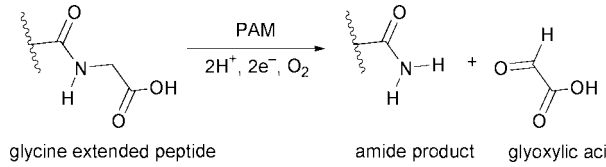
Scheme 3 Benzylic hydroxylation of dopamine promoted by DBH, a mammalian copper-containing mono-oxygenase.[15]

Recently, the group of Réglier[16] reported outstanding comparative studies on the activities of DBH and biomimetic models for the benzylic hydroxylation of 2-aminoindane derivatives (Scheme 4). The two equivalent benzylic positions in 2-aminoindane can be differentiated by benzylic mono-substitution with a deuterium atom. In this way, the process involving an insertion into a C–H bond can be distinguished from a process involving an insertion into a C–D bond. With deuterium-labeled starting compound **9**, it was demonstrated that the reaction occurs by a stereospecific process with retention of configuration and a deuterium kinetic isotope effect (DKIE) of 11 was determined (Scheme 4, products **11a** and **11b**). In both the enzymatic and the biomimetic cases, the O-atom transfers occur in a two-step process involving radical intermediates.



Scheme 4 Enzymatic and biomimetic benzylic hydroxylation of 2-aminoindane derivatives.[16]

3.2.3 Peptidylglycine α-amidating mono-oxygenase (PAM). This bifunctional enzyme mediates the conversion of C-terminal glycine-extended peptides to their active α-amidated products (Scheme 5). This oxidative cleavage of the



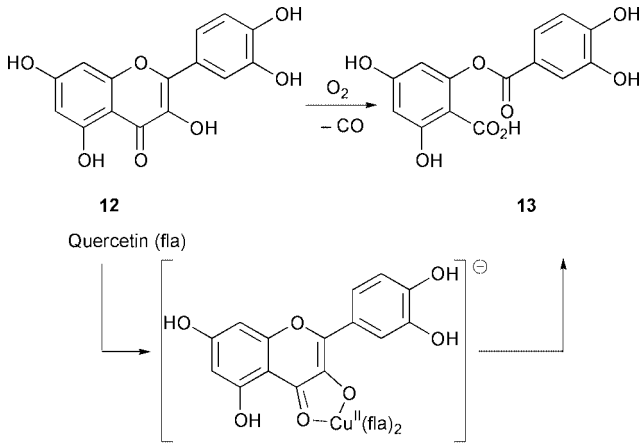
Scheme 5 Reaction mediated by peptidylglycine α-amidating mono-oxygenase (PAM).[18]

carboxy-terminal glycine-extended precursor is the basis of the bioactivation of many peptide hormones and neuropeptides. A range of chemical models of PAM has been developed,[17] however, the detailed reaction mechanism of the cleavage of the C–N bond is not clear at present, although crystallographic data have provided considerable insight into part of the mechanism.[18]

3.2.4 Copper dioxygenases. Dioxygenases incorporate both atoms of O_2 into a substrate. Keevil and Mason[19] have listed three types of copper dioxygenases: 2,3-dihydroxybenzoate-2,3-dioxygenases that effect 1,2-cleavage of arene-1,2-diols; indole dioxygenases; and quercetin 2,3-dioxygenases (quercetinases), which catalyze the oxygenolysis of 3-hydroxyflavone (**12**) to the corresponding product (**13**) as a result of the oxidative cleavage of the heterocyclic ring (Scheme 6).[20] The copper ion is thought to bind at the 3-hydroxy and 4-carbonyl groups. Copper may serve to activate the substrate, allowing O_2 attack to give an organic peroxide that subsequently cleaves to give product **13**.

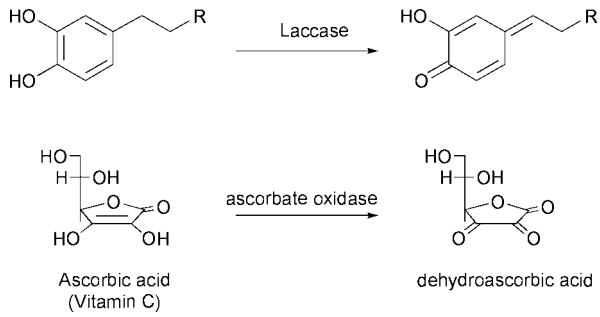
3.3 Copper oxidases

3.3.1 'Blue' multicopper oxidases. These include laccases, ascorbate oxidase, and ceruloplasmin, which contain a trinu-



Scheme 6 Oxygenolysis of **12** catalyzed by quercetinase.[20]

clear copper cluster.[21] These enzymes couple the four-electron reduction of O_2 to water with four sequential one-electron oxidations of the substrate *via* a ping-pong mechanism (Scheme 7).



Scheme 7 Laccase- and ascorbate oxidase-mediated oxidation reactions.[3]

Ceruloplasmin can play several roles *in vivo*. It is multifunctional as an enzyme, being able to utilize diverse substrates. Ceruloplasmin is also multifunctional as a protein, likely able to serve as a copper reservoir for both metal transport and cellular signaling purposes.

Laccase has been used together with a mediator to oxidize different compounds such as alkenes, mainly to the corresponding ketones or aldehydes.[22]

3.3.2 'Non-blue' copper oxidases. These include galactose oxidase and amine oxidases, which produce hydrogen peroxide by two-electron reduction of O_2. Galactose oxidase is a fungal enzyme containing a mononuclear copper ion which catalyzes the oxidation of primary alcohols to aldehydes. Models for the active site of this enzyme have been reported.[23] Amine oxidases catalyze the oxidative deamination of primary amines by transferring two electrons from the amines to molecular oxygen.[24] The catalytic mechanism can be divided in two steps, namely enzyme reduction by the substrate [eqn. (1)] followed by enzyme re-oxidation by molecular oxygen [eqn. (2)].

$$E_{ox} + R\text{–}CH_2\text{–}NH_3^+ \rightarrow E_{red}\text{–}NH_2 + R\text{–}CHO \quad (1)$$

$$E_{red}\text{–}NH_2 + O_2 \rightarrow E_{ox} + NH_3 + H_2O_2 \quad (2)$$

3.3.3 Cytochrome-c oxidase. This enzyme has been extensively studied.[25] It is involved in the respiratory chains of mitochondria and aerobic bacteria and catalyzes the four-electron–four-proton reduction of dioxygen to water (*i.e.*, $O_2 + 4e^- + 4H^+ \rightarrow 2H_2O$). A cysteine-bridged dinuclear copper center acts as the initial site of electron entry and transfer. A heme-α_3–copper center ($d_{Cu–Fe}$ = 4–5 Å) is the site of dioxygen binding, reduction, and O–O cleavage. The detailed mechanism of the catalytic cycle has not yet been fully elucidated, but considerable advances have been made from recent protein X-ray structures. Several models of the oxygen metabolic site have been reported.[25]

3.3.4 Other copper oxidases. Several additional multicopper oxidases have been discovered,[11] including phenoxazinone synthase. This enzyme catalyzes the overall six-electron oxidative coupling of 2-aminophenols to create 1-aminophenoxazinone, the final step in the bacterial (*Streptomyces*) biosynthesis of the antineoplastic agent actinomycin.

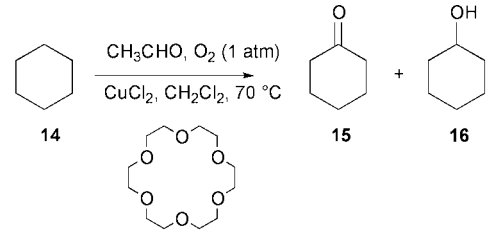
4 Homogeneous copper oxidation catalysts

4.1 Introduction

The exciting results, reported during the last three decades, on the role of metal ions in enzymatic systems have raised the question: *how can we make use of what Nature is teaching us through biomimetic catalysts?* The sections below deal with these processes, where both well-known transformations will be discussed and major challenges, starting with C–H activation, will be addressed. The aerobic oxidation of alkanes and alkenes is of importance from enzymatic and synthetic points of view.[26] For example, the catalytic oxidation of cyclohexane to adipic acid (hexane-1,6-dioic acid), an industrial compound of great importance, continues to be a challenge.

4.2 C–H activation

4.2.1 Oxidation of alkanes. Model studies for the copper-containing mono-oxygenases such as PAM (Scheme 5), which catalyze the oxidation of aliphatic C–H bonds, are limited to a few cases. Recently, the group of Murahashi found that the combination of copper chloride and crown ethers gives high catalytic efficiency for the aerobic oxidation of alkanes with acetaldehyde (Scheme 8).[27] The catalytically active species in



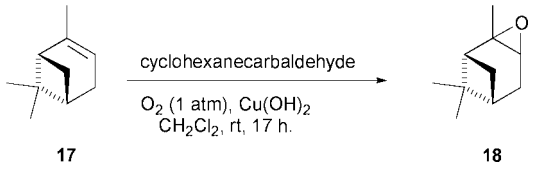
Scheme 8 $CuCl_2$–18-crown-6-catalyzed oxidation of alkanes with molecular oxygen in the presence of acetaldehyde.[27]

these reactions seems to be an oxometal species, as in the presence of macrocyclic ligands more reactive oxometal species are generated.[27]

The efficacy of this catalyst is demonstrated by extremely high turnover numbers in the aerobic oxidation of cyclohexane (**14**) under mild conditions. Actually, the oxidation of cyclohexane in the presence of $CuCl_2$ (2.5×10^{-4} mol%), 18-crown-6 (2.5×10^{-4} mol%) and acetaldehyde (10 mol%) at 70 °C under a dioxygen atmosphere (1 atm) gave cyclohexanone (**15**) (61% yield based on acetaldehyde) and cyclohexanol (**16**) (10%) with a turnover number of 1.62×10^4. The mechanism has not yet been elucidated, but it is believed that the reaction of aldehydes with molecular oxygen in the presence of copper salts gives peracids, which subsequently react with copper to afford the reactive species, Cu(III)–O· or Cu(IV)═O. Hydrogen abstrac-

tion of alkanes by the above-mentioned reactive copper species, followed by electron transfer leads to the formation of alcohols and Cu(II). These alcohols can be further oxidized to ketones under the same conditions.

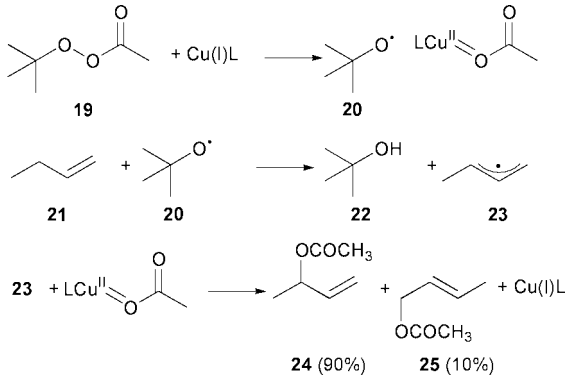
4.2.2 Oxidation of alkenes. The epoxidation of alkenes was also achieved by Murahashi with slight modifications of the previously mentioned catalytic system.[27] The epoxidation of α-pinene (**17**) using copper(II) hydroxide (0.02 mmol) and cyclohexanecarbaldehyde (6.00 mmol) at room temperature under a dioxygen atmosphere (1 atm) gave α-pinene oxide in 84% yield (Scheme 9).



Scheme 9 $Cu(OH)_2$-catalyzed epoxidation of α-pinene with molecular oxygen in the presence of cyclohexanecarbaldehyde.[27]

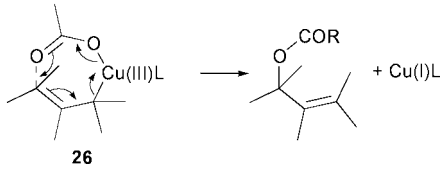
4.2.3 Oxidation of allylic C–H bonds. The allylic oxidation, originally reported by Kharasch *et al*.,[28] can be considered as an attractive alternative for direct functionalization of alkenes that takes advantage of the special nature of the allylic C–H bond. A number of copper complexes have been found to mediate the oxidation of alkenes to allylic esters.[28]

The peroxy ester reaction is a redox chain with copper (Scheme 10), where the *tert*-butoxyl radical (**20**) has been



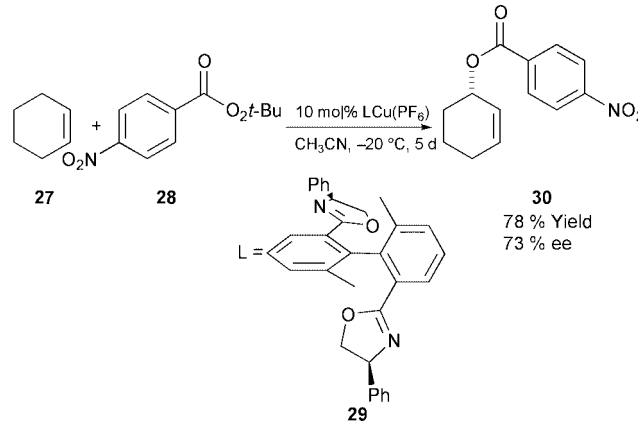
Scheme 10 Allylic oxidations by peroxy esters catalyzed by copper salts.[28]

demonstrated to be the species abstracting the allylic hydrogen. The distribution of the allylic esters obtained (**24** and **25**) is unusual since reactions of allyl radical **23** generally give products in which the thermodynamically more stable, non-terminal double bond prevails, as might be expected. Zavitsas'[28] suggestion for the preponderance of the less substituted alkene **24** involves an organo-copper(III) intermediate (Scheme 11, **26**) in a pericyclic reaction.



Scheme 11 Mechanism proposed for the copper-catalyzed allylic oxidation.[28]

The catalytic enantioselective allylic oxidation of alkenes is a particularly challenging goal in asymmetric synthesis and reports of the utilization of chiral copper complexes have increased in number during the last five years.[29] For example, the allylic oxidation of cyclohexene (**27**) was achieved in 78% yield and 73% enantiomeric excess (ee) by Andrus and Asgari, with a biarylbisoxazoline (**29**)–copper complex as the catalyst (Scheme 12).[29]

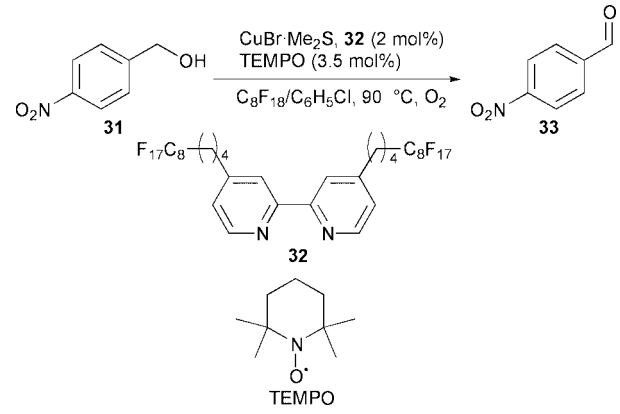


Scheme 12 Allylic oxidation of cyclohexene with a biarylbisoxazoline–copper(I) catalyst.[29]

Recently, Fahrni[29] described the first significant result for this reaction (up to 37% ee) through the use of chiral dinucleating ligands. Despite rather low enantioselectivities, the application of dinuclear metal complexes as catalysts for oxygenation reactions should be an especially promising approach, since such systems are principally able to support multielectron transfers, similar to several biological assemblies.

4.3 Oxidation of alcohols

The oxidation of primary and secondary alcohols to aldehydes and ketones is one of the most important transformations in organic synthesis.[26] Knochel and co-workers have reported a very efficient biphasic catalytic system (Scheme 13).[30] The



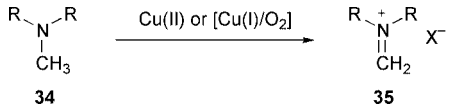
Scheme 13 Copper-catalyzed aerobic oxidation of 4-nitrobenzyl alcohol (**31**).[30]

catalyst obtained *in situ* from $CuBr{\cdot}Me_2S$ and the perfluoroalkylated bipyridine **32** is selectively soluble in perfluorooctane. With 2 mol% of this catalyst and 3.5 mol% of 2,2,6,6-tetramethylpiperidine-*N*-oxyl (TEMPO), the oxidation of 4-nitrobenzylalcohol (**31**) to 4-nitrobenzaldehyde (**33**) has been carried out in a biphasic system of perfluorooctane and chlorobenzene at 90 °C under oxygen. The aldehyde **33** was isolated in 93% yield after 4 h reaction time. The catalyst

solution (fluorous phase) was reused eight times without any significant decrease in reactivity.

4.4 Oxidation of amines

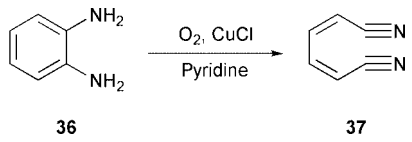
The oxidation of amines (**34**) to the corresponding iminium salts (**35**) can be catalyzed by copper complexes (Scheme 14).[31]



Scheme 14 Copper-induced synthesis of iminium ions.[31]

Iminium ions are important synthetic intermediates involved in transformations like the Mannich reaction. This method, reported by Capdevielle and co-workers,[31] can be a very nice alternative to the classical ways to prepare iminium ions from tertiary amines, which involve oxidizing reagents like potassium dichromate, peroxides and lead and mercury salts. Furthermore, multicopper oxidases laccase and human ceruloplasmin are able to convert tertiary amines to iminium ions, which can then react with a nucleophile in a subsequent step. The study of these reactions is therefore also interesting with regard to the enzymatic mechanism.

Tsuji and co-workers described in 1972 a simple stereospecific synthesis of *cis*,*cis*-muconononitrile (**37**) based on the oxidation of *o*-phenylenediamine with molecular oxygen catalyzed by cuprous salts (Scheme 15).[32]

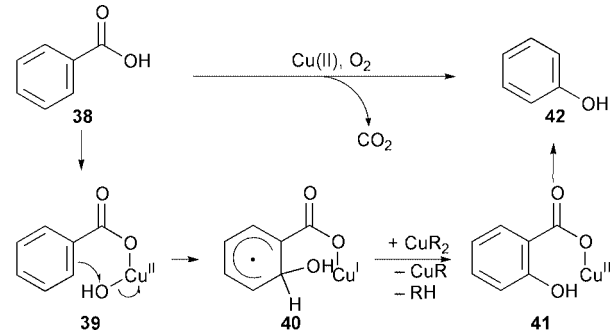


Scheme 15 Copper-catalyzed oxidation of *o*-phenylenediamine to muconitrile.[32]

Moreover, the study of this transformation has relevance to catechol 1,2-dioxygenase since *o*-phenylenediamine is isoelectronic with catechol (see Section 3.2.1).

4.5 Oxidative decarboxylation of acids

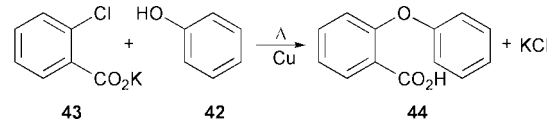
Copper salts catalyze the oxidative decarboxylation of benzoic acid and its derivatives and this has been used commercially for the manufacture of phenol.[33] The proposed mechanism of the reaction is represented in Scheme 16. It is based on an attack of the *ortho*-position by an incipient benzoate radical. The arenium radical **40** thus formed is oxidized by a second copper(II) ion to produce the observed copper(I) species **41** which decarboxylates rapidly at 230–250 °C to form phenol. A few years ago, some of us reported the possibility of applying this reaction to aliphatic carboxylic acids.[34]



Scheme 16 Proposed mechanism for the copper-catalyzed oxidative decarboxylation of benzoic acid.[33]

4.6 Oxidative coupling reactions

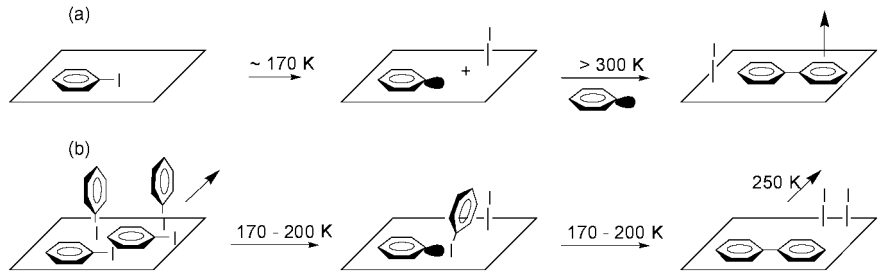
4.6.1 Oxidative biaryl coupling: Ullmann coupling. Ullmann described in 1904 the copper-catalyzed coupling between potassium 2-chlorobenzoate (**43**) and phenol (**42**) to produce 2-phenoxybenzoic acid (**44**) (Scheme 17).[35]



Scheme 17 Ullmann coupling of phenol.[35]

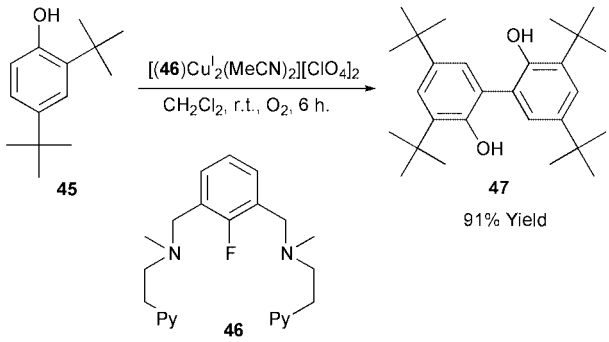
Several efficient alternatives to the Ullmann ether synthesis involving other metals or copper salts like copper(I) bromide–dimethyl sulfide complex, have been reported,[35] but the work of Ullmann is better known for the C–C coupling of aromatic derivatives. The Ullmann reaction is a classical organic synthesis method[36] reported more than 100 years ago by Ullmann and Bielecki, which uses copper powder as a stoichiometric reagent.[36] However, the reaction mechanism remains unknown. The latest mechanism proposal was reported by Xi and Bent in 1993.[36] A schematic summary of the possible mechanisms for the coupling reaction of iodobenzene is depicted in Scheme 18.

Panel (a) shows the low-coverage, high-temperature (300–400 K) pathway in which iodobenzene dissociates to form adsorbed phenyl groups which subsequently couple to form biphenyl. Panel (b) shows the high-coverage, low-temperature (< 210 K) coupling reaction between adsorbed groups and molecularly intact iodobenzene. Since its discovery at the beginning of the 20th century, this reaction has been extensively studied and a multitude of catalytic couplings have been published.



Scheme 18 Proposed mechanisms for the Ullmann coupling reaction of iodobenzene in adsorbed monolayers on Cu(111).[36]

The oxidative C–C coupling of hindered phenols can also be catalyzed by dinuclear copper complexes biomimicking tyrosinase (see section 3.1.1). Thus, a dicopper(I) complex bearing ligand **46**, catalytically converts 2,4-di-*tert*-butylphenol (**45**) to the C–C coupled bisphenol product **47** (Scheme 19).[37]



Scheme 19 Catalytic oxidation of 2,4-di-*tert*-butylphenol (**45**) by dicopper(I) complex and dioxygen.[37]

4.6.2 Coupling of acetylenes. Oxidative condensation of mono-substituted acetylenes to corresponding disubstituted butadiynes is generally performed by using oxygen as oxidant in the presence of a copper(I) catalyst.[38] The mechanism of this reaction, discovered by Glaser in 1869, is depicted in Scheme 20.[38]

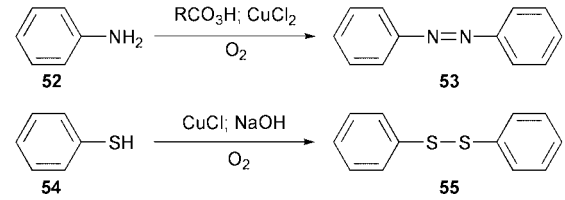
The catalytic cycle begins with the formation of a copper(I) acetylide (**49**) from a copper(I) salt and a terminal acetylene (**48**). Oxidation of **49** by a copper(II) salt is proposed to give an unstable dimeric copper(II) acetylide (**50**). Decomposition of **50** forms the observed diacetylene product (**51**) and completes the catalytic cycle by regeneration of copper(I) ions.

4.6.3 Other coupling reactions. Copper salts can also catalyze the oxidative coupling of aromatic amines and aromatic thiols, respectively to the corresponding diazo compounds (**53**) or disulfides (**55**) (Scheme 21).[39] However, these last two examples of oxidative couplings have not frequently been applied to organic syntheses.

5 Two important industrial applications

5.1 Introduction

Several industrial catalytic oxidation processes involving copper ions are known and two of them especially have received much more attention. Each of these, *viz*. the Wacker oxidation



Scheme 21 Other copper-catalyzed oxidative coupling reactions.[39]

with copper and palladium, and the oxidative polymerisation of 2,6-dimethylphenol, will be discussed in more detail.

5.2 Wacker oxidation

The most important and extensively studied alkene oxidation is the conversion of ethylene to acetaldehyde, which is best known as the Wacker Process.[40] The invention of this reaction was a triumph of common sense. It had been known since 1894 that ethylene is oxidized to acetaldehyde by palladium chloride as a stoichiometric reagent [eqn. (3)]. However, it was not until 1956 that this reaction was combined with the known reactions (4) and (5) to achieve a catalytic acetaldehyde synthesis [eqn. (6)]

$$C_2H_4 + PdCl_2 + H_2O \rightarrow CH_3CHO + Pd(0) + 2\ HCl \quad (3)$$

$$Pd(0) + 2\ CuCl_2 \rightarrow PdCl_2 + Cu_2Cl_2 \quad (4)$$

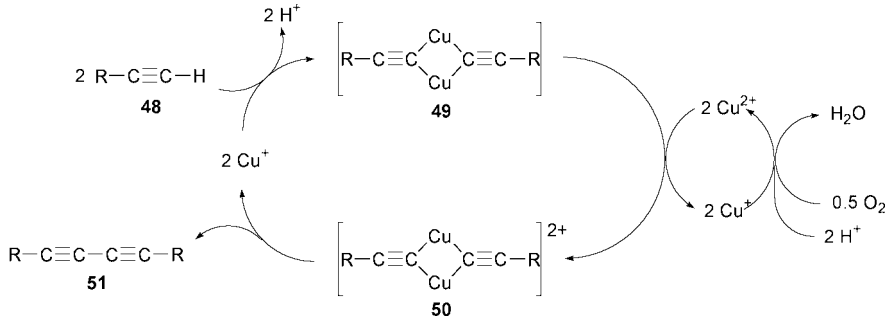
$$Cu_2Cl_2 + 2\ HCl + \tfrac{1}{2}\ O_2 \rightarrow 2\ CuCl_2 + H_2O \quad (5)$$

$$C_2H_4 + \tfrac{1}{2}\ O_2 \rightarrow CH_3CHO \quad (6)$$

Thus, the use of a copper salt as a co-catalyst permits the precious metal salt to be used in a catalytic sense. Since the discovery of this reaction, numerous examples of Wacker type oxidations have been reported.

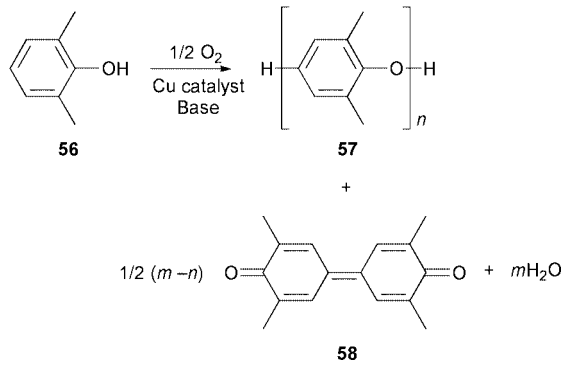
5.3 Polymerization of 2,6-dimethylphenol: copper-catalyzed synthesis of PPE

Homogeneous catalysis is of considerable commercial importance in the production of chemicals, and particularly in polymerization processes. The copper-catalyzed polymerisation of 2,6-dimethylphenol (DMP, **56**) leading to poly(2,6-dimethyl-1,4-phenylene ether) (PPE, **57**), an industrial amorphous high-performance thermoplastic of great importance, and to the



Scheme 20 Proposed mechanism for the catalytic oxidative coupling of acetylenes.[38]

undesirable 4-(3,5-dimethyl-4-oxocyclohexa-2,5-dienylidene)-2,6-dimethylcyclohexa-2,5-dienone (DPQ, **58**, Scheme 22) has



Scheme 22 Copper-catalyzed oxidative coupling of DMP.[41]

been known for more than 40 years.[41] Due to its inherent chemical composition, PPE exhibits unusually low moisture absorption. Therefore, good electrical insulating properties are realized over a wide range of humidities and temperatures. PPE is also very resistant, chemically, to water, most salt solutions, acids, and bases and has very good mechanical properties.[41] This polymer, therefore, finds many industrial applications, such as computer and television housings, keyboard frames, automotive parts or interface boxes.

This polymerisation reaction has been extensively studied and early proposals involve mononuclear copper–phenoxo complexes as active species , whereas recent ones advocate biorelated dinuclear copper–phenoxo complexes producing phenoxonium cations as active species. Despite the huge amount of impressive work published, the mechanism of this polymerisation has not yet been well clarified.[41] It is therefore necessary to study this mechanism further, also with the aim of optimizing the catalytic activity. Recently, we reported that the ligand 1,2-dimethylimidazole combined with acetonitrile as the solvent is a very efficient catalytic system. Acetonitrile induces a spectacular increase of the initial dioxygen-uptake rate R_0. It seems that acetonitrile plays an important role as a labile ligand and by favouring water scattering and so avoiding catalyst poisoning. Increasing the water amount by more than 3% in acetonitrile leads to a 75% drop of catalytic activity. The use of several imidazole derivatives has provided more insight into the understanding of this reaction. In all cases, monodentate ligands led to more active catalysts in comparison with bidentate ones. The more basic the ligand is, the greater is the activity of the copper catalyst. It is believed that the imidazole moiety acts not only as a ligand, but probably also as a base. The steric hindrance near the donor atom also appeared important, providing much better activity, probably through easier formation of very active dinuclear copper species.[41]

6 Concluding remarks

Oxidation reactions are probably the most challenging and difficult reactions in chemistry. Usually, it requires stoichiometric amounts of toxic heavy metal salts, or very expensive catalysts involving noble metals such as ruthenium, rhodium or palladium. Copper is an abundant metal in the earth's crust and it can be found in numerous metalloproteins, especially in enzymes implicated in the binding of molecular oxygen or in mild and highly selective aerobic oxidation transformations. Thus, it is really surprising that only a few examples using *cheap* and 'green' copper catalysts and molecular oxygen or hydrogen peroxide are known so far. Although this field of chemistry is still in its infancy, during the last decade it has been increasingly explored and significant advances have been achieved in the understanding of naturally occuring copper oxidations. Therefore, many outstanding results can be expected in the near future in the field of homogeneous copper catalysis. So it can be safely predicted that copper will gradually replace the rare and costly elements used nowadays.

7 Acknowledgements

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