Organocatalyzed oxidation of alcohols to aldehydes with molecular oxygen

Petro Lahtinen [a], Jahir Uddin Ahmad [a], Elina Lankinen [a], Petri Pihko [b],
Markku Leskelä [a], Timo Repo [a,*]

[a] *Department of Chemistry, Laboratory of Inorganic Chemistry, University of Helsinki, P.O. Box 55, FIN-00014, Finland*
[b] *Laboratory of Organic Chemistry, Helsinki University of Technology, P.O. Box 6100, 02015 TKK, Finland*

Abstract

The first direct organocatalytic system for oxidizing alcohols to aldehydes with molecular oxygen is described. The catalytic activity of 9,10-diaminophenanthrene with and without the presence of transition metals was studied in the oxidation of benzylic alcohols to corresponding aldehydes. The catalytic reaction occurs at elevated dioxygen pressure and temperature in alkaline aqueous solutions. Up to 80% conversions were observed in organocatalytic oxidation of 3,4-dimethoxybenzyl alcohol to corresponding aldehydes. Addition of transition metal ions to reaction solution increased the catalytic activity significantly. Complete conversions of 3,4-dimethoxybenzyl alcohol to aldehydes were observed in the presence of copper and iron ions.
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1. Introduction

The oxidation of alcohols to aldehydes is a fundamental chemical transformation in synthetic chemistry [1]. In recent years, significant progress has been made in replacing the traditional stoichiometric inorganic oxidants with environmentally more benign catalytic methods [2]. In this respect, several sophisticated oxidation catalyst systems which are able to use molecular oxygen as the end oxidant have been introduced [3–5].

Most of the dioxygen activating catalysts are transition metal compounds. These can be roughly divided into two subclasses: inorganic oxidation catalysts and transition metal complexes with organic ligands. Inorganic catalysts are mainly polyoxometalates (POM) which are typically metal oxides of molybdenum and vanadium, but also many other are known [6]. On the other hand the transition metal complexes are composed from a central metal atom and a surrounding organic ligand

[5]. According to basic rules of thermodynamics an organic molecule, e.g. alcohol with singlet electronic configuration cannot directly react with an unactivated dioxygen molecule which has a triplet electronic configuration [7]. Hence, all these traditional oxidation catalysts are mechanistically connected by the fact that the electron transfer is mediated by a metal atom which induces the formation of singlet oxygen. In this context the search for the organic oxidation catalyst capable of activating dioxygen is an interesting as well as challenging task.

Although, metal-free catalytic systems have been described for the oxidation of sulfides, amines, and activated hydrocarbons [8–11], the examples about the direct oxidation of alcohols to aldehydes with metal-free catalysts are sparse. To the best of our knowledge, the direct oxidation of alcohols to aldehydes with metal-free catalysts and molecular oxygen is possible only with non-persistent nitroxyl radicals derived from *N*-hydroxyphthalimide (NHPI) [8]. Herein we describe a simple diamine organocatalyst capable of direct oxidation of benzylic alcohols to aldehydes with molecular oxygen. Also the effect of an added transition metal into the reaction solution is discussed.

* Corresponding author. Fax: +358 9 191 50198.
  E-mail address: timo.repo@helsinki.fi (T. Repo).

2. Experimental

All chemicals were purchased from Sigma–Aldrich (>99% purity) and used as received.

In a typical oxidation experiment the 9,10-diaminophenanthrene (10 mg, 0.048 mmol), metal chloride (0.048 mmol, if used), and substrate (0.24–4.8 mmol) were dissolved in 10 mL of the 0.25 M NaOH solution in a 30 mL test tube. A steel reactor was loaded with 14 of such test tubes and the oxygen pressure was set from a gas cylinder. The pressurized reactor was heated in an oil bath and reaction solution was stirred with a magnetic stirrer. The reaction time was typically 3 h.

Samples for GC analysis were prepared by extracting the reaction products in test tubes with 10 mL of ethyl acetate. A sample from the ethyl acetate phase was injected to GCMS (HP-5, 30 m × 0.32 mm i.d. × 0.25 μm film thickness, Agilent 6890N Gas Chromatograph, Agilent 5973Network MS detector). Oxidation results were calculated from the integrated peak areas and expressed in terms of percentages of formed aldehyde. The MS measurements were made with JEOL JMS-SX102 mass spectrometer.

3. Results and discussion

We have previously reported the catalytic activity of in situ prepared Cu-9,10-diaminophenanthrene (DAPHEN) complex in the oxidation of benzylic alcohols in basic aqueous media [12]. Although moderately active, the Cu-DAPHEN catalyst maintains its activity only for 2 h due to extensive DAPHEN dimerization in the oxidation conditions [13]. In further studies with DAPHEN-based oxidation catalysts, it came apparent that the DAPHEN ligand possesses redox-activity and is fully capable of aqueous oxidation catalysis even in the absence of a metal cofactor. Veratryl alcohol was selected as the test substrate for the present study due to its water solubility [12,13].

The effect of the reaction conditions on the catalytic activity of DAPHEN catalysts were studied by carrying out experiments was one reaction parameter at a time was varied. The activation temperature of DAPHEN catalysed oxidation is approximately 60 °C and from there the catalytic activity increases linearly with increasing temperature up to 120 °C (Fig. 1). The pressure of O_2 was observed to have only a slight effect on the activity and the highest conversions were obtained at 5–7 atm.

The pH of the reaction solution has the most visible effect on the catalytic activity. The highest conversions are obtained in 0.25 M NaOH. (Fig. 2) If the NaOH concentration is lower than this, the catalytic activity is diminished and side reactions (oxidative coupling, etc.) are observed. The increase in activity at 0.25 M NaOH solution is probably caused by increased deprotonation of alcohol substrate making it more susceptible to oxidation to aldehyde. At higher alkali concentrations no side reactions are observed but the activity is decreased. Therefore, 0.25 M NaOH was selected as solvent for the rest of the experiments.

As was earlier observed, the lifetime of DAPHEN in these conditions is approximately 2 h. This sets the limit for reaction
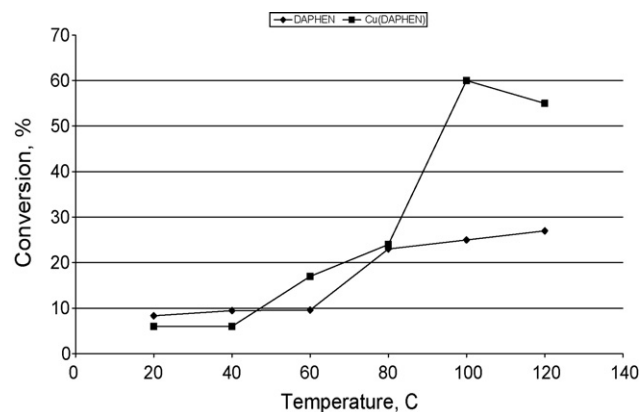

Fig. 1. The effect of reaction temperature on the DAPHEN and Cu-DAPHEN catalysed 3,4-dimethoxybenzyl alcohol oxidation. Reaction conditions in DAPHEN oxidations: 10 bar O_2, 10 ml of 0.25 M NaOH, 10 mg DAPHEN (0.048 mmol, 10 mol%), 81 mg 3,4-dimethoxybenzyl alcohol (0.48 mmol) and 3 h reaction time. Cu-DAPHEN results were taken from our earlier report; 10 bar O_2, 10 mg $CuSO_4$ (0.063 mmol, 5 mol%), 26 mg DAPHEN (0.126 mmol, 10 mol%), 230 mg 3,4-dimethoxybenzyl alcohol (1.38 mmol), 10 ml 0.25 M NaOH and 3 h reaction time [12].

time for every DAPHEN catalyst systems. Under standardized reaction conditions (0.25 M NaOH, 100 °C, 10 bar O_2 pressure, 1 mol% catalyst concentration and 3 h reaction time) turn over numbers (TON) up to 50 were achieved in the oxidation of veratryl alcohol catalysed by DAPHEN. In the same conditions, 80% conversion is reached with 20 mol% catalyst concentration. In a reference experiment without any catalyst veratryl alcohol is not oxidized under the standardized reaction conditions.

The presence of some transition metals enhances the DAPHEN catalysed oxidation reaction. The level of activity is depending on the metal ion, the most efficient metal cations being Cu(II), Fe(III), Mn(II) and Co(II) in this order (Fig. 3). In the presence of transition metals, the response to dioxygen pressure and temperature (Fig. 1) differs somewhat from the organocatalyzed reaction. With added metals, no clear activation temperature could be observed, as the catalysts were
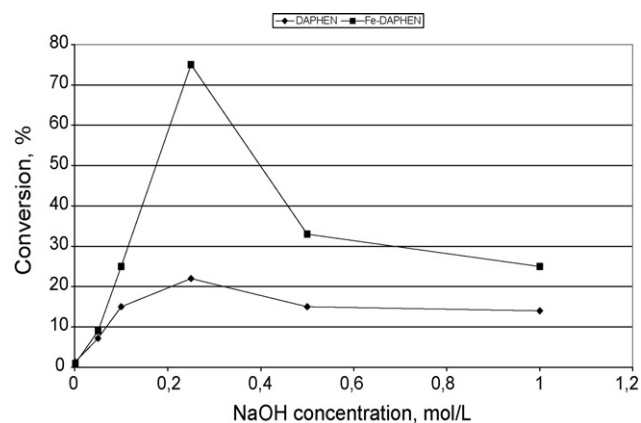

Fig. 2. The effect of pH on the DAPHEN and Fe-DAPHEN catalysed 3,4-dimethoxybenzyl alcohol oxidation. Reaction conditions: 10 bar O_2, 10 mol% catalyst (48 mmol/L $FeCl_3$, 48 mmol/L DAPHEN), 80 °C and 3 h. Proposed catalytic cycle for 9,10-diaminophenanthrene catalysed alcohol oxidation.
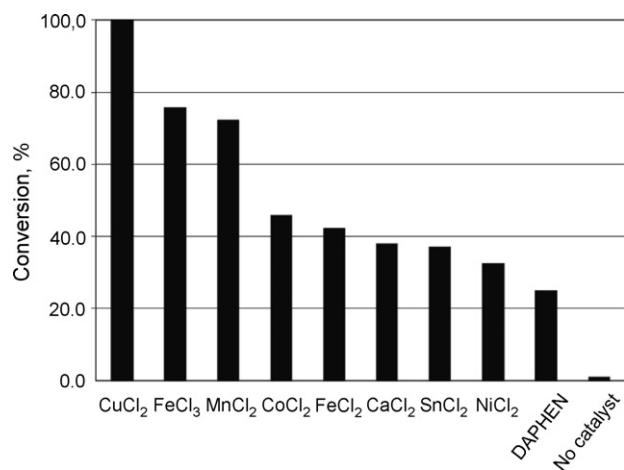
Fig. 3. Oxidation of 3,4-dimethoxybenzyl alcohol to corresponding aldehyde catalysed by selected metal-DAPHEN catalysts. Reaction conditions: 10 bar O_2, 0.25 M NaOH, 1 mol% DAPHEN/Metal (48 mmol/L DAPHEN and metal), 100 °C and 3 h.
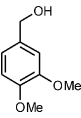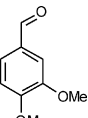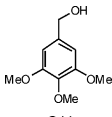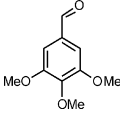
slightly active already at room temperature. The catalytic activity increased linearly with increasing temperature and dioxygen pressure. In general, every metal-DAPHEN combination had a similar response on the variations in the reaction conditions. For example, the ratio of DAPHEN and metal does not have significant effect on conversions although equimolar c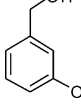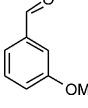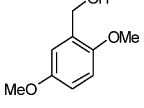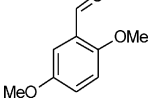oncentrations were observed to give optimal conversions and thus were used in all experiments. In the oxidation of veratryl alcohol, quanti-

tative conversions can be reached with most catalyst systems by increasing the catalyst concentration.

The effect of pH on the catalytic activity is clearer in the presence of transition metals. Also in the presence of transition metals the highest activities were observed in 0.25 M NaOH solutions. (Fig. 2) The base is needed for the deprotonation of alcohols and for the formation of active metal-DAPHEN complex. In aqueous solution hydroxide ions and ligand molecules (DAPHEN in this case) are competing to coordinate to metal atom. When metal and ligand concentrations are kept constant, the concentration of the active species is determined by the pH of the solution. When the concentration of the active species is at maximum it is logical to expect the highest catalytic activity. In this case it seems that in the 0.25 M NaOH solution the deprotonation of alcohol and the concentration of the catalytically active species is at optimum equilibrium. The deactivation of the catalyst at higher alkali concentrations is probably due to metal hydroxide formation which removes the added metal from the reaction solution.

The activities of various DAPHEN catalysts towards other substrates were studied under the optimized conditions. (Table 1) The water soluble *n*-butanol is oxidized with low conversions while sparingly soluble *n*-octanol remained unreacted. Similarly, benzyl alcohol is only poorly oxidized. This suggests to us that the solubility of the alcohols into alkaline water solutions appears to be a crucial factor. Importantly, in contrast with the previously reported NHPI-metal systems, the DAPHEN oxidations afford clean conversions to

Table 1
Conversions of selected alcohols to corresponding aldehydes catalysed by DAPHEN catalyst systems

Substrate	Product	Cu-DAPHEN (%)	Fe-DAPHEN (%)	No metal (%)
(benzyl alcohol)	(benzaldehyde)	20	20	8
(3,4-dimethoxybenzyl alcohol)	(3,4-dimethoxybenzaldehyde)	99	99	50 / 80[a]
(3,4,5-trimethoxybenzyl alcohol)	(3,4,5-trimethoxybenzaldehyde)	99	99	40
(3-methoxybenzyl alcohol)	(3-methoxybenzaldehyde)	80	73	5
(2,5-dimethoxybenzyl alcohol)	(2,5-dimethoxybenzaldehyde)	58	30	16
1-Butanol	1-Butanal	57	30	8
1-Octanol	1-Octanal	5	3	3

Reaction conditions: 100 °C, 10 atm O_2, 0.25 M NaOH, 5 mol% DAPHEN/metal chloride and 3 h.
[a] 20 mol% of DAPHEN catalyst was used.

the aldehyde, and no over oxidation to the carboxylic acid is observed.

The study of the DAPHEN catalyzed oxidation turned out to be a challenging task due to low solubility of the molecule into aqueous solutions. The most helpful method proved to be direct EI-MS measurements from the reaction solutions. This enabled us to identify DAPHEN intermediates. In the samples taken before the initiation of the reaction (no O_2 added), only the peaks at 168 *m/z* (veratryl alcohol) and 208 *m/z* (DAPHEN) were visible. Thus, spontaneous interaction between alcohol and the DAPHEN catalyst can be excluded. In the samples taken during the reaction (after O_2 addition), new peaks at 166, 206 and 207 *m/z* appeared in addition to those at 168 and 208 *m/z*. The peak at 166 *m/z* corresponds to veratrylaldehyde and 206 *m/z* to iminoquinone form of DAPHEN. The 207 *m/z* can be assigned to semi-iminoquinone radical of DAPHEN which probably forms in the ionization process from the corresponding hydroperoxide radical of DAPHEN. During the progress of the reaction, a new peak appeared at 380 *m/z*. This has been previously assigned to a DAPHEN dimer [13].

Aromatic diamines can be dehydrogenated to iminoquinones in oxidative reaction conditions. This transformation is similar to a redox reaction observed in quinone-hydroquinone transformation [14]. The net reactions in both of these transformations are addition and reduction of two hydrogen atoms, the same which is needed for alcohol dehydrogenation. Apparently, the organocatalytic activity of DAPHEN relies in part on the ability of diamine groups to release and accept two hydrogens and

in part on the polyaromatic structure which hosts radical reactions. The latter is supported by work of Bromberg and Muzkat, where the reaction between O_2 and dihydrophenantrene has been reported [15]. This is a radical reaction in which O_2 is reduced to hydrogen peroxide via a hydroperoxo radical.

This together with MS data opens a possibility to propose the organocatalytic dehydrogenation mechanism (Fig. 4). In the case of DAPHEN, an imine resonance isomer provides a reactive hydrogen–carbon bond. Therefore, it is reasonable to assume that the imine isomer is involved in the initiation of the oxidation reaction. It forms a hydroperoxo semi-iminoquinone in the presence of O_2, which reacts further to give hydrogen peroxide and an iminoquinone (*m/z* 206). The formation of hydrogen peroxide was confirmed by iodometric titration from the reaction solution. Iminoquinone is then reduced back to DAPHEN by alcohol in a two step radical reaction. In this respect the deactivation of the catalyst by a recombination of two semiquinone radicals and formation of the DAPHEN dimer is understandable. The catalytic cycle proposed here finds its similarities with the mechanism previously described for flavin-based organocatalysts [11].

4. Conclusions

In conclusion, the organocatalytic oxidation activity of DAPHEN is significant, as it provides a new and intriguing concept for the oxidation of alcohols to aldehydes using O_2 as a terminal oxidant. Although, the reaction is enhanced by the addition of Cu, Fe, Co or Mn salts, the fact that the polyaromatic diamine alone is capable of direct O_2 activation is remarkable since usually a transition metal is needed for O_2 activation. We believe the diamine structure of DAPHEN is relevant since it enables the formation of iminoquinone which ultimately transfers hydrogen atoms from the substrate to O_2. Apparently, the polyaromatic structure and the ability to accept and release hydrogen atoms reversibly are the main criteria for potential organocatalytic molecules of this type. Further studies on the redox properties of DAPHEN as well as the development of novel organocatalysts with enhanced reactivity for O_2 oxidations are in progress.

Fig. 4. Proposed catalytic cycle for 9,10-diaminophenanthrene catalysed alcohol oxidation.

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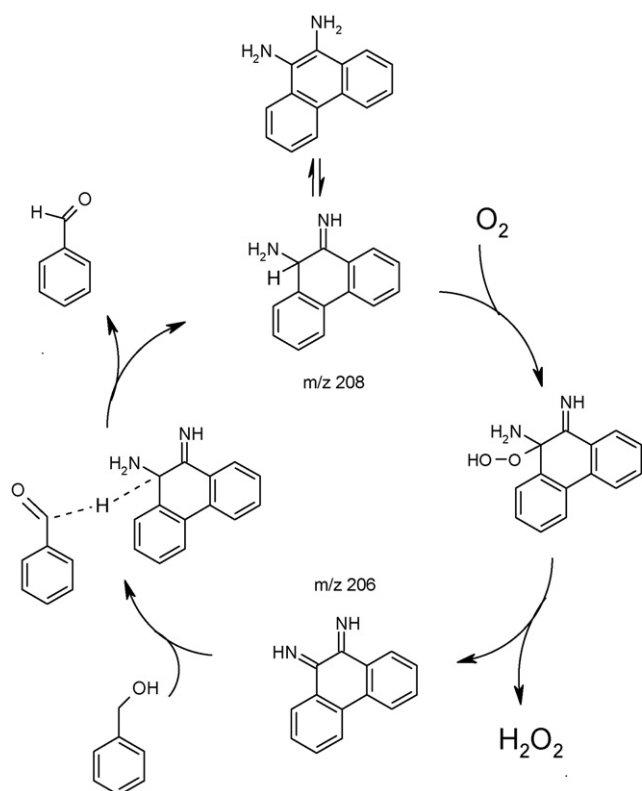
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