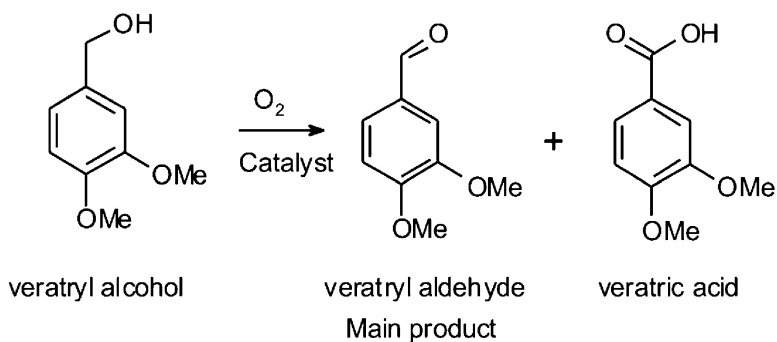Article

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Parallel Screening of Homogeneous Copper Catalysts for the Oxidation of Benzylic Alcohols with Molecular Oxygen in Aqueous Solutions

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A simple and efficient parallel screening method to evaluate the catalytic activities of homogeneous copper complexes for the oxidation of benzylic alcohols in aqueous solutions with molecular oxygen is reported. Copper(II) sulfate was treated in situ with 22 nitrogen donor ligands, and the catalytic activities of these combinations were studied at four different pH values with two substrates (benzyl alcohol and 3,4-dimethoxy benzyl alcohol (veratryl alcohol)), resulting in 176 oxidation experiments in the primary screening stage. Copper complexes based on *N,N,N',N'*-tetramethyl ethylenediamine (TMEDA), 9,10-diaminephenanthrene (DAPHEN), and 1,2-diaminocyclohexane (DACH) were determined to be the most active catalysts. In the second screenings, the influence of reaction conditions on Cu(DACH)-, Cu(TMEDA)-, and Cu(DAPHEN)-catalyzed reactions were investigated in more detail. It was found that highly basic reaction conditions favor the reaction with the exception of Cu(TMEDA), which is active at a lower pH range. Under optimized conditions, Cu(DAPHEN) catalyzes the transformation of veratryl alcohol to the corresponding aldehyde with 100% conversion.

Introduction

Molecular oxygen is an attractive choice as a nonpoisonous and inexpensive oxidant for industrial processes, and its applications may vary from pulp and textile bleaching to petroleum and synthetic chemistry.[1] The processes that are based on molecular oxygen can also be considered to be ecologically benign processes, because water or hydrogen peroxide are the main side products derived from the oxidant. In addition, water as a reaction solvent would be highly desirable in the terms of green chemistry. Because of inherent spin restrictions,[2] these oxidation reactions still require an appropriate catalyst to activate molecular oxygen. The importance of the catalytic oxidation has stimulated intensive research activities, and several elegant approaches for efficient dioxygen activation have been developed.[3,4] Most of the oxygen-activating homogeneous transition-metal catalysts are investigated in organic solvents; however, only a few are known to be active in water.

The development of new catalysts by traditional synthetic methods is a laborious and time-consuming area of research, often with an uncertain outcome, and new experimental methods are required to enhance catalyst development. At early stages, combinatorial methods were used in biochemical applications (e.g., for peptide libraries);[5,6] however, because of the effectiveness of these methods, the high-throughput screening method has emerged recently in the synthesis of organic compounds,[7,8] in catalytic reactions,[9,10] and in polymer chemistry.[11,12] Combinatorial chemistry has also

been experiencing increased importance in modern catalyst research.[13,14] On this basis, we have developed a parallel screening method for a fast evaluation of the oxidation properties of various homogeneous catalysts.

The importance of copper-based enzymes in various biological oxidation reactions has stimulated intensive research activities.[15] Because of the inherent complexity of natural enzymes, numerous models for the active sites have been synthesized and investigated instead. Most of the model complexes are based on nitrogen-containing ligands (for example, derivatives of ethylenediamine). In these complexes, the role of the Cu ion is usually to bind the substrate and oxidant either simultaneously or separately and mediate the transfer of electrons between the oxidant and the substrate.[16,17] Because of their reactivity, copper diamine complexes have previously also been applied as catalysts in oxidative polymerization,[18] the oxygenation of 2-nitropropane,[19] and oxidative coupling reactions.[20] In addition, isolated Cu-diamine complexes that have a bis-*μ*-oxo-dicopper(II) core are able to promote stoichiometric oxidations of phenols and benzylic alcohols.[21,22] Diamine-type ligands leave the active Cu center open for the required external coordination, and what is important from the screening point of view is that various diamines are commercially available and synthetically easy to modify. Therefore, we have decided that diamine-based copper complexes are rather attractive candidates for the catalytic oxidation of benzylic alcohols.

Selective oxidation of alcohols to corresponding aldehydes is a highly desirable reaction, and its importance is observed

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Figure 1. Photograph of the reaction setup; the left-hand side shows an opened reaction autoclave with 14 glass reactors inside, and the right-hand side presents the autoclave as it appears during the reactions.

in the pharmaceutical and fine chemicals industries. In addition, 3,4-dimethoxy benzyl alcohol (veratryl alcohol) can be considered as a model compound for lignin substructures,[23] which allows the possibility of evaluating catalyst properties also for pulp-bleaching purposes, as described earlier.[24,25] We report herein the reactor setup and parallel screening method, as well as our results concerning the primary screening of the catalytic activity of various copper—ligand combinations in aqueous solution. The primary screening was used to identify active catalyst combinations for the oxidation of benzylic alcohols, and second screenings were used to study the effects of reaction conditions on the catalytic activity.

Results and Discussion

The Method. To enhance development of oxidation catalysts, we have established a simple reactor setup, which consists of an 1-L steel autoclave embedded with 14 small glass reactors (Figure 1). After the ingredients are loaded, the autoclave is closed, pressurized, and heated to the desired reaction temperature. All the reactors have a common headspace. With this setup, a broad range of reaction temperatures and pressures (maximum of 20 bar) can be applied. To facilitate a fast and accurate analysis of the oxidation reactions, the sample preparation also was optimized. A small amount of reaction solution (0.5 mL) and ethyl acetate (1.5 mL) are combined in a sample vial. The sample vial was then shaken to extract oxidation products into the organic phase and then placed on the plate of a gas chromatography (GC) autosampler, which was programmed to draw a sample from the organic phase. The method described by the aforementioned procedure provides fast and

quantitative evaluation of the studied reaction, and the accuracy between two parallel samples is 1%.

Primary Screening. The catalytic properties of a certain metal complex generally are highly dependent on the ligand framework around the metal center, and by varying the ligand substituents, the electronic character, geometry, and steric protection of the catalytic center can be reasonably modified. For an efficient screening of new catalyst candidates, a series of ligands should be large enough to cover the influence of different steric and electronic properties, as well as with different bite-angle, hapticity, and coordination strength on the catalytic activity. The chosen reaction conditions gave an additional challenge for the catalyst design; catalytic species must withstand alkaline-water solutions, combined with high temperature and an oxidizing (O_2) atmosphere. Particularly for this study, ethylenediamine-type ligands were determined to be suitable, because they are generally soluble in water and they have high complex formation constants in aqueous solutions,[26] which is a major requirement to prepare metal complexes in situ. The ligands used in the primary screening are presented in Figure 2, and copper sulfate was used as a metal source.

The catalytic activity of in situ prepared copper complexes was investigated in the oxidation of benzyl and veratryl alcohol with the parallel screening method (Figure 3). The main product of the catalyzed reaction is aldehyde; however, a small amount of veratric acid also is formed. The reaction conditions for the primary screening were derived from our earlier experiments where veratryl alcohol was oxidized with Co(salen) complexes.[24,25] The results from the primary screening studies are summarized in Figure 4.

The columns in Figure 4 clearly illustrate that the highest conversions for veratryl alcohol are obtained under basic reaction conditions, whereas benzyl alcohol is less susceptible to the oxidation and, hence, the recorded conversions under similar conditions are significantly lower. Nevertheless, from these results, an apparent correlation can be determined; the oxidation of benzyl and veratryl alcohol requires similar catalytic species, with only difference being activity. The most efficient catalysts were copper complexes based on *N,N,N′,N′*-tetramethyl ethylenediamine (**5**, TMEDA), 1,2-diaminocyclohexane (**8**, DACH), and 9,10-diaminophenantrene (**20**, DAPHEN).

The activity of copper catalysts that are based on ligands **1**−**4** decreases as the length of the alkyl bridge between the coordinating amines increases. In fact, the stability constants for the copper complexes also decrease in the same order.[26] A similar trend for the *N,N,N′,N′*-tetramethyl-substituted analogues **5**−**7** was observed. The strongly coordinating ligand **5** forms an active copper complex, whereas complexes with ligands **6** and **7** gave negligible activities. According to these results, the bridge, which consists of two C atoms between the amines, favors the formation of the catalytically active copper species. Cyclohexyl diamines **8**−**10** obey the same rule and possess high activities. Note that the racemic mixture of 1,2-diaminocyclohexane (**8**) is more active than either of the diastereomerically pure forms (cis (**9**) or trans (**10**)). This suggests that a catalytic active species is formed
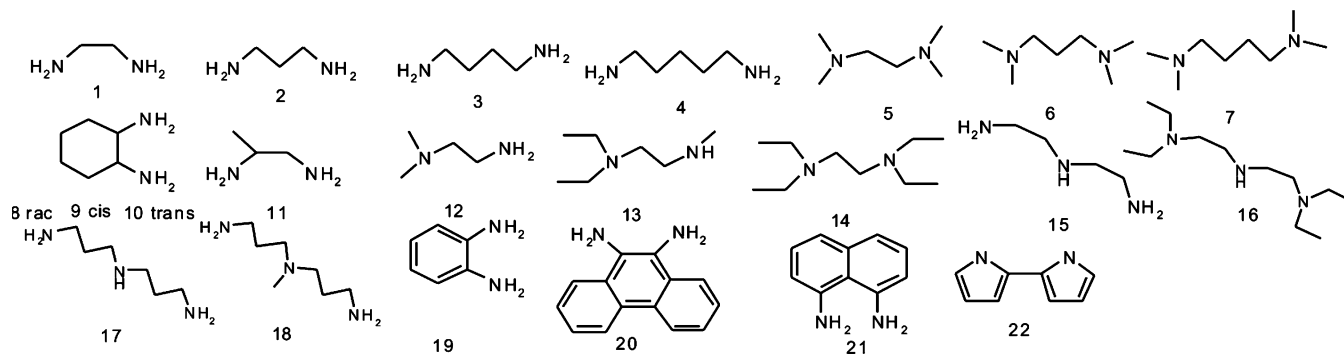
Figure 2. Schematics of the structures of ligands used in the primary screenings.
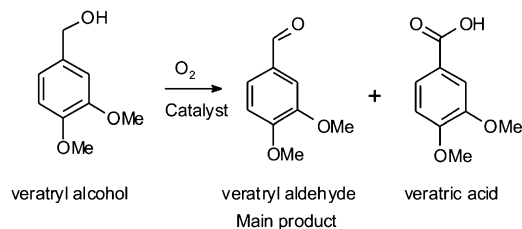

Figure 3. Schematics of the oxidation of veratryl alcohol to veratraldehyde and veratric acid.

from two ligands, and a complex containing one of each stereoisomer is sterically favored, from the reaction point of view.

Unsymmetric ligands (1-methyl ethylenediamine (**11**) and *N,N*-dimethyl ethylenediamine (**12**)) gave activities similar to those of their symmetric counterparts (**1** and **5**, respectively), whereas the ethyl substituents (**13** and **14**) have a negative influence on oxidation activity. A series of tridentate ligands follows the same trend as that outlined previously. The ligand with the ethylene bridge between two adjacent nitrogens (**15**) gave an activity similar to that of the bidentate **1**, whereas an elongation of the bridge (**17** and **18**) or the ethyl substitution (**16**) decreases the activity. The replacement of the cyclohexyl backbone by an aromatic phenyl (**19**) slightly decreases the activity, whereas the additional conjugation, as in the case of 9,10-diaminophenanthrene (**20**), has a considerably positive effect on activity.

In alkaline-water solutions, the coordination of hydroxide ions is competing with the original anions and the added ligand. Therefore, ligands with a high complex formation constant are needed. Increasing the number of secondary or tertiary amines in ligands, such as that observed in **5**, **12**, **13**, and **16**, shifts the area of maximum activity of the studied system to a lower pH range. We assume that this is due to a weaker coordination of secondary and tertiary amines to the Cu cation. Under strongly alkaline conditions, the coordination of hydroxide ions is dominant over the coordination of the desired ligands to copper, and various copper hydroxide species are formed instead of an active catalyst. Generally, the active catalyst seems to require sufficiently high pH solutions, and, as a result of mixed coordination of ligands and hydroxyl ions, an active species is formed. In this context, the observed activity of copper with ligand **5** over a broad pH range is noteworthy.

Second Screening. The most-active catalysts—Cu(DACH) and Cu(DAPHEN), as well as Cu(TMEDA), because of its interesting activity over a wide pH range—were chosen for

the second screening (Figure 5). The effect of reaction conditions on the catalytic activity, including reaction temperature, metal-to-ligand molar ratio, and pH, was further investigated. The reaction conditions for the oxidation were otherwise the same as those used for the primary screening. Benzyl alcohol was omitted, and only veratryl alcohol was used as a substrate.

Results from the second screening experiments are collected in Figure 6. The effect of a counteranion was investigated by replacing CuSO$_4$ with other copper(II) compounds. The results presented in graph a of Figure 6 indicate that the counteranions have no significant role in formation of a catalytic active species. The only exception in the series is CuO, because it is not completely soluble in alkaline water and, therefore, gives lower activities. These results justified the use of CuSO$_4$ for the second screening.

As indicated in the primary screening, the substrate conversion is highly dependent on the pH of the reaction solution and alkaline conditions are preferred. In graph b of Figure 6, the conversions as a function of initial pH are presented for Cu(TMEDA), Cu(DAPHEN), and Cu(DACH). For each catalyst, different optimal pH values are recorded. The highest conversions for Cu(TMEDA) are obtained in pH 10.5, whereas higher pH values of 13 and 14 were required for the maximum activity of Cu(DAPHEN) and Cu(DACH), respectively. The results corroborate the observation from the primary screening that Cu(TMEDA) functions under milder conditions than the other catalysts and has the widest active pH range. This makes it interesting, although the absolute conversion is not the highest in the series of catalysts.

To have a greater understanding about the catalytic species, the effect of increasing the ligand-to-metal molar ratios were investigated (see graph c in Figure 6). By increasing the amount of ligand in the reaction solution, the catalytic activity is enhanced and maximum conversions for Cu(DACH), Cu(DAPHEN), and Cu(TMEDA) are reached when the applied ligand-to-metal molar ratios are 5, 10, and 30, respectively. In the case of Cu(DAPHEN), the conversion increases very rapidly as the ligand-to-copper ratio increases; however, because of the limited solubility of DAPHEN in the alkaline-water solution, conversions with ligand-to-copper ratios of >10 turned out to be unreliable. Nevertheless, both TMEDA and DACH are very soluble in water and also extended ligand-to-copper ratios were applied. The catalytic activity of Cu(TMEDA) increases slowly as the ligand concentration
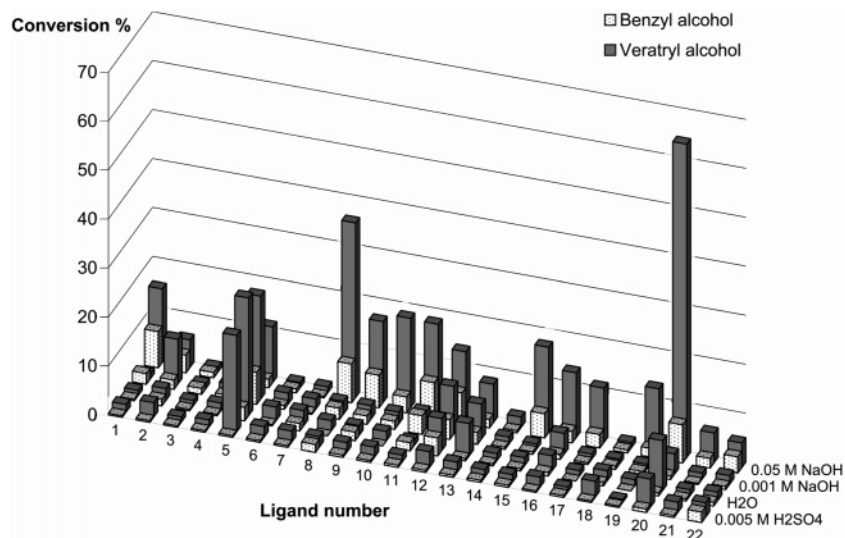
Figure 4. Results from the primary screening experiments. The reaction conditions used were 80 °C, a dioxygen (O_2) pressure of 10 bar, a ligand-to-metal molar ratio of 2, and a catalyst-to-substrate molar ratio of 1:20. The solvents used are listed on the *y*-axis to the right. The ligands that correspond to the ligand numbers are shown in Figure 2.
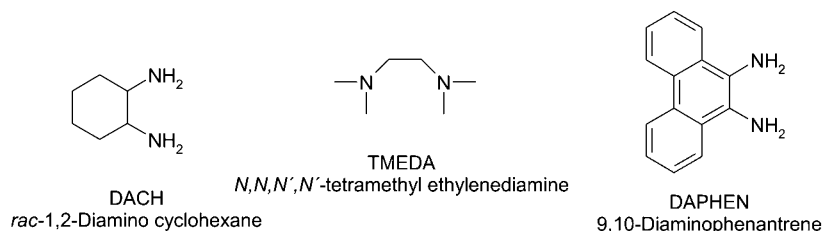

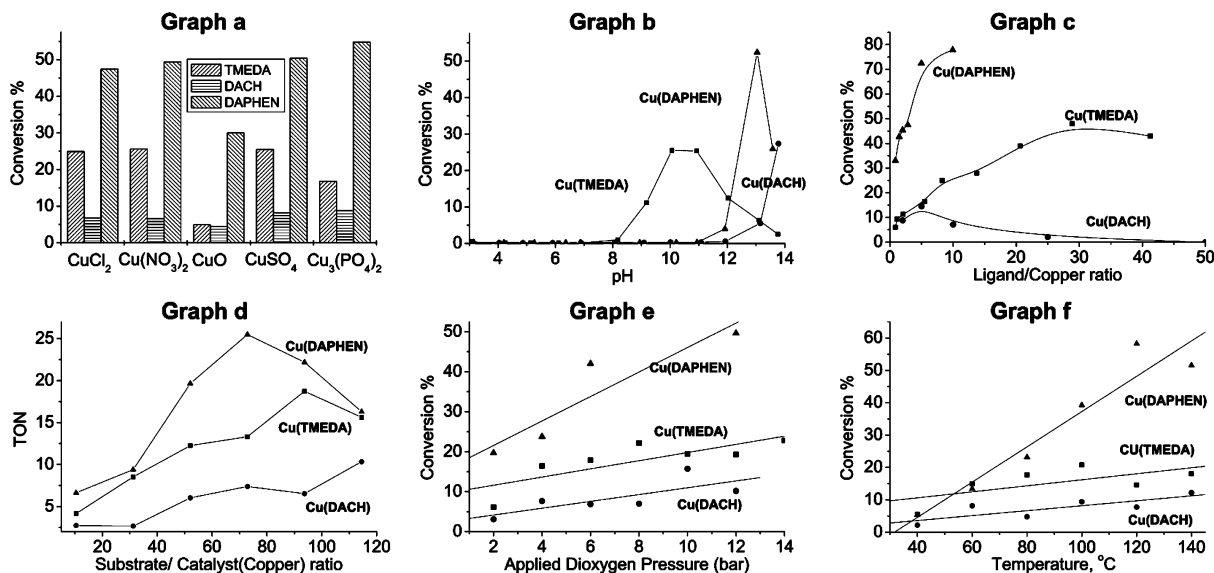**Figure 5.** Schematic diagrams of the structures of the ligands chosen for the second screening.

Figure 6. (a) Effect of copper compound used on conversion of oxidation reaction. (b) Effect of the initial pH on the activity of Cu(TMEDA), Cu(DAPHEN), and Cu(DACH) catalysts. (c) Effect of ligand-to-metal ratio on the activity of the catalysts. (d) Effect of substrate-to-catalyst ratio on the reaction rate (turnover number (TON), number of catalytic cycles). (e) Effect of applied O_2 pressure on conversion. (f) Effect of reaction temperature on conversion. (The lines in graphs b−f are in place only to guide the eye.)

increases until a ligand-to-copper ratio of 30 is achieved, after which point the activity starts to decrease. With Cu-(DACH), the activity declines shortly after reaching a ligand-to-copper ratio of 5. Because DACH is a more strongly coordinating ligand than TMEDA, it is plausible that DACH saturates the coordination sphere of copper centers at a lower ligand concentration than TMEDA.

The influence of the substrate concentration on the activity was investigated, and the results are plotted in graph d of Figure 6 in terms of turnover number, TON (TON is the number of moles of oxidized substrate per one mole of catalyst). Generally, high monomer concentrations increase the reaction rate but the actual conversions are diminished. In the case of Cu(TMEDA) and Cu(DACH), the reaction
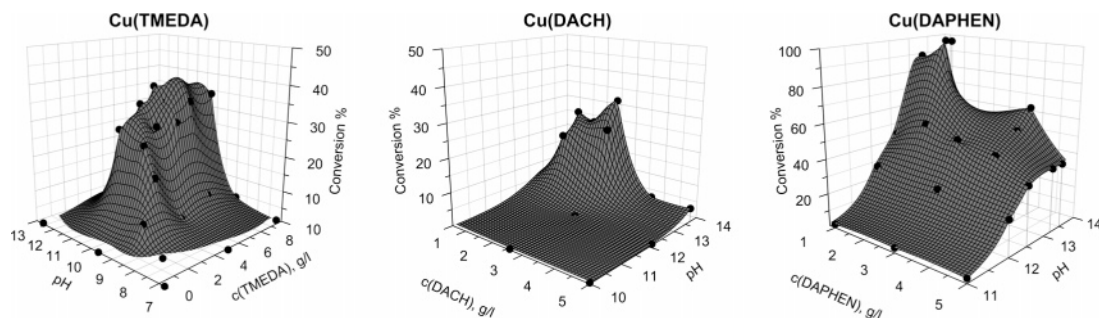
Figure 7. Results from the conversion optimization with Cu(TMEDA), Cu(DACH), and Cu(DAPHEN) catalysts. Maximum conversions are as follows: 40% for Cu(TMEDA), 32% for Cu(DACH), and 100% for Cu(DAPHEN). Reaction conditions were 10 bar O₂ and 80 °C, with the following solvents: 0.1 mL of veratryl alcohol (10 g/L), 10 mg of CuSO₄ (1 g/L), and 10 mL of NaOH solution. Initial pH of the reaction solution was adjusted with 0.1 M H₂SO₄ and 1 M NaOH.

rate increases rather linearly as the alcohol concentration increases, whereas Cu(DAPHEN) behaves differently. At high veratryl alcohol concentrations, its catalytic activity decays, which implies the appearance of dormant Cu-species, e.g., via ligand exchange reactions.

The effect of applied O₂ pressure and reaction temperature on the conversion of the reaction was also investigated, and the respective results are presented in graphs e and f of Figure 6. Conversions are directly proportional to the applied O₂ pressure and reaction temperature. Increased O₂ pressure increases the oxygen concentration in the reaction solution, thereby providing more oxygen to the catalyst.[27,28] On the other hand, increased reaction temperature reduces the solubility of oxygen in water. Still, the reaction rate seems to increase linearly with increasing temperature, which means that the temperature effect on the reaction rate is more dominant than the effect of oxygen concentration in the reaction solution.

The stability constants for known TMEDA and DACH complexes of copper(II) vary over the ranges of 7.28−13.7 and 10.6−20, respectively.[26] The stability constants for Cu(DAPHEN) are not known, which might be due to its limited solubility in water. Based on the results, it can be concluded that strongly coordinating ligands require more-basic reaction conditions for catalytic activity than loosely coordinating ligands. Also, a high ligand-to-copper ratio seems to inhibit the reaction with strongly coordinating ligands. Because DACH coordinates strongly to copper, large/high ligand concentrations saturate the coordination sphere of copper, leaving no place for the dioxygen and the substrate. TMEDA, as a weakly coordinating ligand, does not easily block the coordination of other components. This evidence suggests that the ligand molecules and OH⁻ ions are competing to coordinate to copper, and the active species should contain both. Only a large number of OH⁻ ions is able to prevent strongly coordinating DACH ligands from saturating the coordination sphere of copper. Correspondingly, the Cu(TMEDA) catalyst loses activity at high pH when the OH⁻ ions prevent TMEDA from coordinating to copper.

Conversion Optimization. To obtain maximum conversions, further optimization of the reaction parameters was needed. For these experiments, a reaction time of 3 h was sufficient, because conversions after 3 h or, e.g., 24 h are

basically the same. Based on the results from the second screening, the pH and ligand-to-metal molar ratio (ligand concentration) have a strong effect on the reaction rate. It was also concluded that these parameters have interactions in the sense that ligand and hydroxyl ions are competing for the copper coordination. While keeping other reaction parameters constant, the ligand concentration and pH were varied in a parallel manner. The results are presented in Figure 7, where the conversion is plotted as a function of the ligand concentration and pH values.

The optimum pH range for Cu(TMEDA) was 10.5−11 with a ligand concentration of 6−8 g/L, which is equal to the ligand-to-copper molar ratio of 8−11, and the maximum conversion was 40%. With Cu(DACH) catalysts, the highest conversion (30%) was observed at ligand concentrations of 1−2.5 g/L (ligand-to-copper molar ratio of 1.5−3.5) at pH 13.5−14. Experiments under optimized reaction conditions revealed that conversions with Cu(TMEDA) and Cu(DACH) catalysts remained low, although the reaction rate can be increased by increasing the substrate concentration. However, Cu(DAPHEN) can reach 100% conversion at an optimum ligand concentration of 1.8 g/L and pH 13.2. This is equal to a ligand-to-metal molar ratio of <2. The poor solubility of DAPHEN raises doubts about the true concentration of the ligand in the reaction mixture; however, for calculation purposes, it was estimated to be complete. In the cases of Cu(TMEDA) and Cu(DACH), these results are in accordance with results from second screenings; however, for the Cu-(DAPHEN) catalyst, the optimum combination of ligand concentration and pH could not be determined with separate optimization of these interdependent reaction parameters.

The optimized reaction conditions for Cu(DAPHEN) also were applied for the oxidation of other benzylic alcohols (Table 1). Under the same reaction conditions, 2,4-dimethoxybenzyl alcohol gave 80% conversion, whereas yields with 3-methoxybenzyl alcohol and benzyl alcohol were modest. Low conversions could be due to limited solubility of the substrates in alkaline water and their different susceptibility for oxidation. It is plausible that reaction conditions that are optimized for one substrate do not apply for other substrates. Thus, after any modification on the catalytic system, the reaction conditions should be re-evaluated.

Table 1. Results from Oxidation Experiments Catalyzed by Cu(DAPHEN)[a]

substrate	conversion to aldehyde (%)
3,4-dimethoxybenzyl alcohol (veratryl alcohol)	100
2,4-dimethoxybenzyl alcohol	80
3-methoxybenzyl alcohol	30
benzyl alcohol	22

[a] Reactions were conducted under conditions that were optimized especially for veratryl alcohol.

Table 2. Reaction Conditions Used in Second Screenings

studied reaction parameter[a]	range	amount of veratryl alcohol (mL)
pH	pH 3−14, adjusted with 0.1 M H_2SO_4 and 1 M NaOH	0.3
ligand-to-metal ratio	1−50, by increasing the ligand concentration	0.4
substrate concentration		0.1−1.1
anion		0.4
O_2 pressure	1−12 atm	0.4
temperature	40−140°C	0.4

[a] Results are displayed in Figure 6.

Conclusion

Catalyst screening based on in situ complexation was determined to be an efficient way to find new active compounds to catalyze the oxidation of veratryl alcohol. In situ complexation and a fast assessment of the reaction products with gas chromatography (GC) analysis are vital to this method. In situ complexation also creates problems such as uncertainty about the catalyst structure and active species. However, the benefits outweight the disadvantages when new catalyst candidates are found. To the best of our knowledge, the catalytic properties of Cu(DAPHEN) have not been reported previously. Further studies concerning the structure of the catalytically active species, as well as the reaction mechanism, are in progress.

The reaction rate of catalytic veratryl alcohol oxidation is strongly dependent on the reaction conditions, such as pH, substrate concentration, ligand-to-metal ratio, dioxygen (O_2) pressure, and temperature. The catalysts are typically able to catalyze the oxidation of veratryl alcohol only in a narrow, specific pH range. An increase in substrate concentration, reaction temperature, or O_2 pressure generally results in an increase in the reaction rate. In addition, catalysts based on weakly coordinating ligands need a surplus of ligands for the optimum performance; the ligand concentration can be up to 30 times greater than the copper concentration, under certain conditions. The anion of the copper compound does not affect the reaction rate as long as the copper precursor is water-soluble.

The separate screening of reaction conditions does not necessarily lead to the optimum conditions for the oxidation. As recognized from the second screening, the ligand concentration and pH have interdependent effects on conversion, and, therefore, a two-dimensional (pH and Cu(ligand)) conversion optimization scheme was developed. By varying the ligand concentration and pH at the same time, it was possible to increase the conversion of veratryl alcohol oxidation with Cu(DAPHEN) up to 100%. Although the conversions with Cu(TMEDA) and Cu(DACH) catalysts remained low, it is possible to increase the reaction rate and overall turnover number (TON), using higher substrate concentrations or O_2 pressures.

The parallel screening method presented here is an example of an inexpensive and efficient method to find novel catalytic active combinations for the oxidation of benzylic alcohols. With small modifications, this same setup could be used to explore other types of catalyst or reaction systems.

Experimental Section

Chemicals and Equipments. Commercially available copper compounds and amines were used without further purification. Veratryl alcohol (3,4-dimethoxybenzyl alcohol, 96%) and benzyl alcohol were purchased from Acros and used as received. Oxidation products were analyzed via gas chromatography/mass spectroscopy (GC/MS) (Varian model Saturn2100 and model GC/Fid Agilent 5890N equipped with an autosampler) using a Hewlett−Packard model HP-5 capillary column (with dimensions of 30 m × 320 μm × 0.25 μm). Oxidation results are calculated from integrated peak areas and expressed in terms of percentages of formed aldehyde.

Primary Screening. All oxidation experiments were conducted using the following procedure and molar amounts of reagents, unless otherwise stated. Copper(II) sulfate (10 mg, 63 μmol) and a ligand (ligand-to-metal ratio of 1:2, 0.126 mmol) were dissolved in 10 mL of solvent (0.005 M H_2SO_4, distilled H_2O, 0.001 M NaOH, or 0.05 M NaOH) in a 30-mL glass reactor. Veratryl or benzyl alcohol (0.2 mL, 1.38 mmol) was added and 14 glass vessels with magnetic stir bars were fitted inside a 1-L steel autoclave. A small amount of deionized water was added to the bottom of the autoclave, to serve as a heat-transfer medium, and the desired O_2 pressure (10 bar) was set from an O_2 gas cylinder bottle. The autoclave was placed in an oil bath, and the reaction mixture was stirred at a temperature of 80 °C for 3 h. After 3 h, the pressure was released and the autoclave was opened. From the hot reaction solution, a 0.5-mL sample was taken and extracted in a 2.5-mL sample vial with 1.5 mL of ethyl acetate. Samples were measured via GC by programming the autosampler to inject 1 μL of the ethyl acetate phase.

Second Screening. The second screening experiments were performed and analyzed using the same procedures as those for the primary screenings, with the following exceptions. Only veratryl alcohol was used as a substrate, and its amount changed between experiments. With Cu(TMEDA), distilled water was used as a solvent, whereas Cu(DACH) and Cu(DAPHEN) experiments were conducted in 0.05 M

NaOH, except when the pH was adjusted prior to reaction. The molar amount of copper was 62 μmol in every experiment, and copper sulfate was used as a copper source, except when the anion effect was studied. Variable reaction parameters are presented in Table 2.

Conversion Optimization. The reaction setup was used for the conversion optimizations was the same as that used for primary screening experiments, but the ligand concentration and pH were varied. NaOH solutions with concentrations of 0.001, 0.05, 0.1, or 1 M were used as a solvent. The final pH of the reaction solution was adjusted with 0.1 M H_2SO_4 and 1 M NaOH. The substrate-to-catalyst (copper) ratio used was 10.

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CC0499136