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Photochemically Mediated Toluene Oxidation through a Copper Complex

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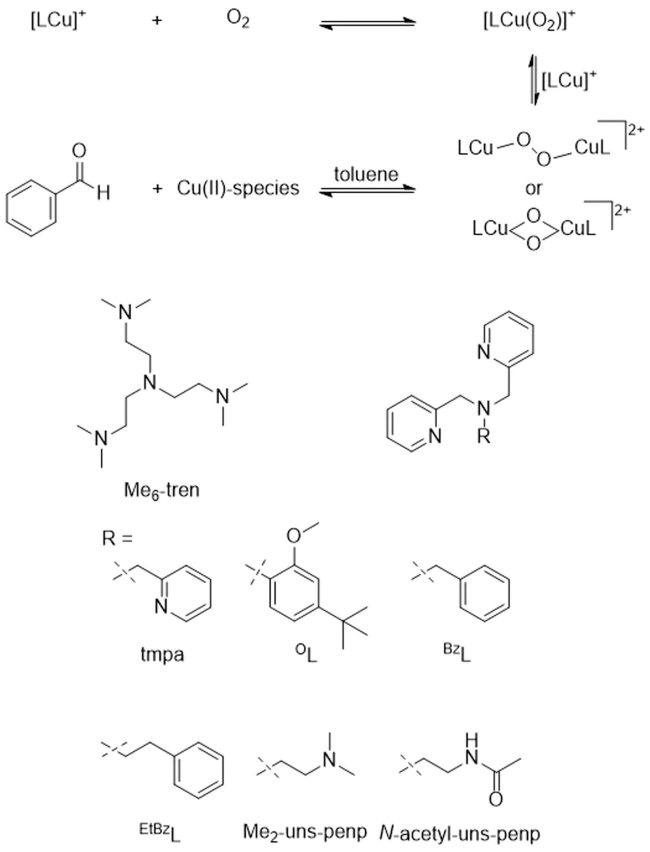
Dedicated to Prof. Dr. Reinhard W. Hoffmann on his 90th birthday

Abstract: A method is described to photochemically oxidize toluene selectively to benzaldehyde, an essential compound in the chemical industry. Copper(I) complexes with different ligands were applied in combination with $[Ru(bipy)_3](PF_6)_2$ and dioxygen as the oxidant. As a result, a "dioxygen adduct" copper complex, for example, a peroxido complex, is formed as the active species. The copper(II) complex obtained after oxidation can be photochemically reduced to the starting copper(I) species, and the process can be repeated continuously. The ligand tris(2-methylpyridyl)amine (tmpa) led to the highest conversion rates.

Introduction

Benzaldehyde is a widely used reactant in the chemical industry being applied, for example, in the synthesis of cosmetics, drugs, and dyes.[1] It is currently produced by either the chlorination of toluene with subsequent hydrolysis, the Gattermann-Koch synthesis, or the direct, transition metal oxide-catalyzed oxygenation of toluene.[2–4] Unfortunately, these procedures either require quite toxic reagents/catalysts (e.g., the chromyl chloride in Etard's reaction),[5] lead to unwanted byproducts, and/or consume much energy for the final separation of the product mixtures.[2–4] Many publications (only a few selected examples are listed) report alternative approaches; however, so far, none of them solves these problems for different reasons.[5,6] Therefore, especially concerning sustainability, it would be desirable to find a way to synthesize benzaldehyde by selective oxidation of toluene at room temperature using a catalyst and solely dioxygen (or air) as an oxidation agent.

Previously, we demonstrated that it is possible to oxygenate toluene to benzaldehyde using solid binuclear *end-on* copper peroxido complexes $[LCu{-}O_2{-}CuL](BPh_4)_2$ (with L =, for example Me_6tren, Scheme 1)[7] or by applying the same compounds immobilized on silica.[8] Furthermore, Karlin and co-workers reported that the corresponding peroxido copper complexes with L = tris(2-methylpyridyl)amine (tmpa) – or derivatives of this ligand – are capable of oxidizing toluene in solution.[9] With



Scheme 1. Oxygenation of toluene by using copper(I) complexes $[LCu]^+$ with the different ligands L described herein. Please replace Scheme 1 with revised Scheme 1

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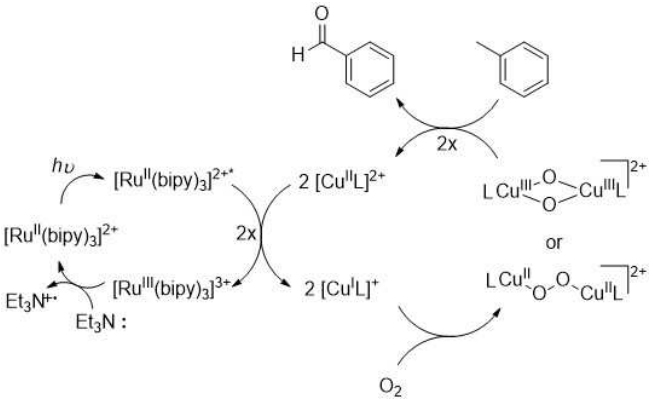
these complexes, it was possible to oxidize benzaldehyde at low temperatures with conversions up to 40%, according to Scheme 1. The syntheses of these complexes have been inspired by nature where copper "dioxygen adduct" complexes in the active site of copper enzymes, such as tyrosinase[10] or galactose oxidase (here the dioxygen adduct complex is only an intermedidate, not the active species),[11] are responsible for the selective oxygenation of organic substrates. While so far neither the binuclear *end-on* peroxido nor the bis(*μ-oxido*) unit have been observed in nature, a mononuclear *end-on* superoxido copper complex is well known in enzymes such as peptidylglycine-α-hydroxylating monooxygenase (PHM).[12] Such a complex is observed when a mononuclear copper(I) complex with a tripodal ligand such as tmpa reacts with dioxygen before the formation of the binuclear peroxido complex (Scheme 1).[13,14]

Oxygenation reactions with copper complexes and dioxygen often only proceed stoichiometrically with maximum yields of 50% due to the formation of copper(II) complexes as products that do not react with dioxygen anymore.[15] Excellent work by Garcia-Bosch, Baran, and co-workers demonstrated that in some cases, yields could be increased close to 100% by adding a reductant or by working with hydrogen peroxide.[16] Still, there are exceptions to this approach.[17] Reactivating the copper(II) complex by reducing it electrochemically might be an interesting alternative.[18] However, applying photochemistry to regenerate the active species could be a more elegant solution.

That this attractive approach principally is possible was demonstrated previously by Avenier et al., who reported a photoassisted generation of a binuclear iron(III) peroxido species.[19] To achieve this, the well-known ruthenium bipyridine complex $[Ru(bipy)_3](PF_6)_2$ was applied in combination with triethylamine (TEA) as a sacrificial compound. Furthermore, Iali et al. used a copper bispyridine (bpa) complex (Scheme 1) attached via a linker to a Rubipy unit.[20] They as well could show that the copper(II) complex could be reduced by light and allowed them to catalytically oxidize different organic substrates such as thioanisole derivatives or triphenylphosphine. However, as has been pointed out by Avenier et al., it does not seem to be necessary to attach the complex to the Rubipy unit covalently, and simply $[Ru(bipy)_3]^{2+}$ could be added instead (in their case, it even improved the reduction of the iron(III) complex).[19] Based on these results, we became interested in investigating if we could apply this strategy to the oxygenation of toluene according to Scheme 2. While, in principle, different active species could form from the reaction of copper(I) complexes with dioxygen, we leave it to the binuclear *end-on* peroxido, and the bis(*μ-oxido*) copper complexes that up to now have been observed in this oxygenation. Furthermore, from the results reported by Iali et al., we assume that the copper(I) complexes are reformed through oxidative quenching.[20]

Results and Disscussion

The reactions were performed in pure toluene (for details, see the experimental part in the Supporting Information). The anion



Scheme 2. General strategy fo the photochemical reduction of the $[LCu^{II}]^{2+}$ complexes.

$B(C_6F_5)_4^-$ was used for the complexes to achieve decent solubility.[9] TEA was applied as a sacrificial compound. We tested the reaction with the copper tmpa system in a first experiment. The complex was prepared in situ under argon by mixing stoichiometric amounts of tmpa and $[Cu(MeCN)_4]B(C_6F_5)_4$ in toluene. Bubbling dioxygen for two minutes through the solution at room temperature did lead to a color change from yellow to deep purple, the typical color of the binuclear peroxido complex (Figure 1). After stirring the solution overnight, a color change to a pale blue colored solution and a small amount of a solid in the same color was detected (a copper(II) complex of tmpa). The solution was analyzed by GC-MS (details are provided in the Supporting Information), and conversion of around 10% was observed in line with the report by Karlin and co-workers with 8%.[9] The conversion is calculated in relation to the copper complex. After removing dioxygen by bubbling with nitrogen, $[Ru(bipy)_3]PF_6$ and TEA

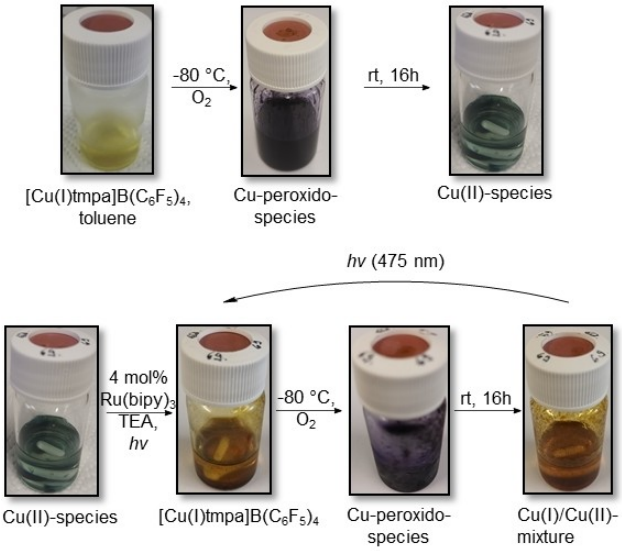


Figure 1. Stepwise oxygenation of toluene.

were added. The mixture was irradiated with light ($\lambda = 475$ nm) for two hours leading to a color change to a yellow color (the copper(I) tmpa complex had reformed), and the solid had disappeared. When dioxygen was introduced again to this sample, the purple color of the peroxido complex was regained. The reaction mixture was left for 18 h and analyzed afterward. The same procedure was repeated five times leading to a linear conversion rise after each reaction cycle (Supporting Information). After six cycles, a conversion of 42% was achieved.

This stepwise procedure demonstrated that photochemically reforming the copper(I) complex was possible and that this reaction deserved further investigation. However, the tedious approach could be simplified by changing the experimental procedure to a one-pot reaction (details of the experimental design are described in the Supporting Information) that furthermore could be performed without any cooling at room temperature. The copper(I) tmpa complex was again prepared in toluene under inert conditions; however, $[Ru(bipy)_3]PF_6$ and TEA were added directly to the copper(I) complex solution. Afterward, pure dioxygen was lead through the solution and irradiated with light ($\lambda = 475$ nm). Samples were analyzed after 18, 36, 54, and 72 h. After 72 h, a conversion of 136% was observed. Because this is related to the copper complex, a conversion above 100% accounts for a catalytic reaction under these conditions. Figure 2 (black squares) shows the conversion's linear rise. No conversion was observed if the reaction was performed without the copper complex. Compared to the stepwise procedure, the one-pot reaction thus showed a much higher efficiency.

Karlin and co-workers reported that the copper(I) complex with the ligand ^{O}L (Scheme 1) oxidized toluene to benzaldehyde with a much higher conversion of 40% (together with an additional 5% of benzyl alcohol) in comparison with the copper tmpa system of 8%.[9] Therefore, we also applied this ligand in the one-pot procedure. However, under our conditions, we observed that the complex, with a conversion of 39% after 72 h (Figure 2), did not perform as well as the copper tmpa system.

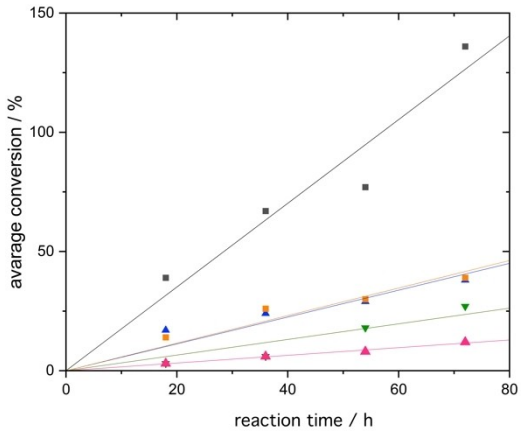


Figure 2. Average conversion observed during the one-pot reaction procedure (50 µmol copper complex, 2 µmol $[Ru(bipy)](PF_6)_2$, 200 µL TEA, RT, toluene) with different copper complexes (■ tmpa, ■ ^{O}L, ▼ ^{EtBz}L, ▲ Me_2-uns-penp, ▲ *N*-acetyl-uns-penp).

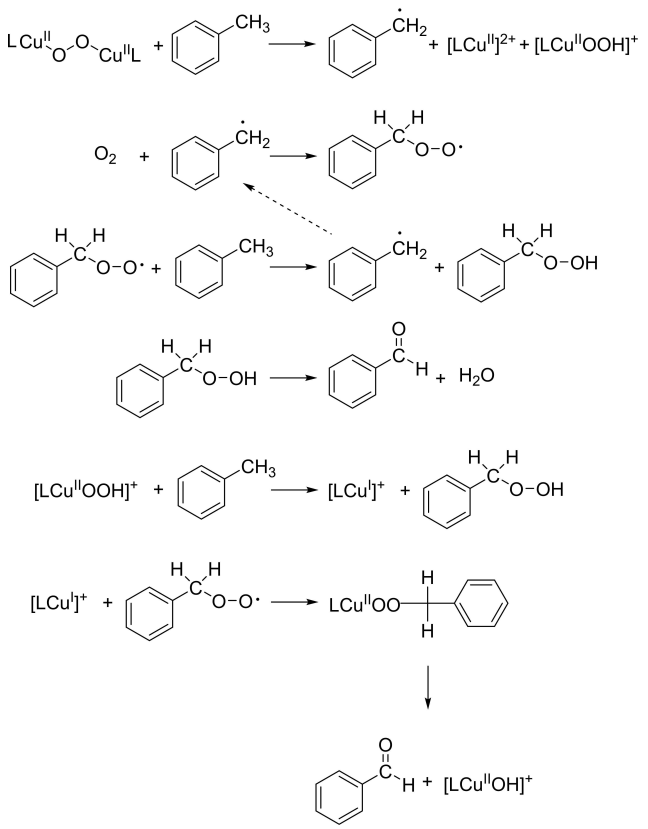
It has been suggested that the copper peroxido complex is in equilibrium with the bis-μ-oxido complex (Scheme 1) and that this species might be the primary oxidant.[9] This was furthermore supported when the copper(I) complex with ^{Bz}L as a ligand (Scheme 1) was investigated; solely a bis-μ-oxido complex was formed, and a conversion almost identical to the copper ^{O}L system was observed.[9] However, under our conditions, close to 100% conversion after 18 h could be measured, and no further rise of the conversion could be achieved over time. This observation made us suspect that with this ligand, intramolecular oxygenation (with cleavage of the benzyl nitrogen bond leading to benzaldehyde and bispicolylamine) might be preferred over the intermolecular oxygenation of toluene. To support this assumption, the reaction was repeated in d_8-toluene. In the GC-MS, isotopically labeled and unlabeled benzaldehydes were observed, whereby the signal of the unlabeled one was double as high as the signal of the labeled one. This leads us to conclude that these copper oxygen species prefer intramolecular oxidation instead of the proposed intermolecular oxidation of toluene. The ligand's decomposition leads to the high conversion after one cycle.

Chelate ring sizes play an essential role in this kind of chemistry, and thus we applied the copper complex with the ligand ^{EtBz}L instead of ^{Bz}L (Scheme 1). This system had been investigated previously by Itoh and co-workers, who here as well proposed the formation of a bis-μ-oxido complex as an intermediate.[21] Under our conditions, the complex led to increased conversion of toluene to benzaldehyde over time (in contrast to the copper complex with ^{Bz}L as a ligand), however, with even lower yields than the copper complex with ^{O}L (Figure 2).

Somewhat related to the ^{O}L ligand is *N*-acetyl-uns-penp (Scheme 1). Both ligands can provide a slightly loose fourth coordination site (O or N/O donor atoms) that could support the formation of a binuclear *end-on* peroxido complex instead of a bis-μ-oxido complex.[9] This was supported to some extent by the observation that the conversion of toluene (38%) with the copper complex with the *N*-acetyl-uns-penp ligand was nearly the same as with the ^{O}L ligand (Figure 2).

While copper complexes with Me_6tren as a ligand usually behave pretty similarly to the corresponding complexes with tmpa as a ligand,[22,14] here we observed complete failure of this system under our conditions. Obviously, substituting pyridyl groups with aliphatic amine groups is bad for the overall reaction cascade. This was further confirmed by applying Me_2-uns-penp (Scheme 1) as a ligand where two pyridyl groups of tmpa were substituted with aliphatic amine groups.[23] While conversion was observed, it was quite low (12%, Figure 2).

From the results obtained (and combined with previous work by us and by Karlin and co-workers),[9] we propose the mechanism according to Scheme 3. While alternative mechanisms still could be considered, several pathways can be excluded: for example, no benzyl alcohol was detected, and thus, a hydroxylation followed by oxidation does not occur; furthermore, we did not observe a reaction with a superoxido complex excluding another possible pathway.



Scheme 3. Proposed reaction mechanism for the oxygenation of toluene.

The binuclear peroxido copper complex is formed by toluene hydrogen atom abstraction, leading to the benzyl radical $PhCH_2^{\bullet}$ together with $[LCu^{II}OOH]^+$ and $[LCu^{II}]^{2+}$. Next, the benzyl radical will react with dioxygen to form the benzyl peroxo radical $PhCH_2OO^{\bullet}$ that also abstracts hydrogen from toluene, leading back to the starting radical $PhCH_2^{\bullet}$ and the hydroperoxide $PhCH_2OOH$. The hydroperoxide then reacts further to benzaldehyde and water, a well-known reaction.[24]

Depending on conditions, further side/consecutive reactions can occur; however, they were not observed in our system. In principle, this would allow a catalytic cycle started by a copper complex in combination with dioxygen. However, it is well known that copper(II) compounds would react with alkyl radicals, thus stopping the conversion. Therefore it is necessary to constantly reduce formed copper(II) complexes back to copper(I) species (here done photochemically according to Scheme 2) to keep the reaction going. Furthermore, additional reactions can take place that would lead to benzaldehyde as a product: the copper complex $[LCu^{II}(OOH)]^+$ could react with $PhCH_2^{\bullet}$ leading to $[LCu^{I}]^+$ and $PhCH_2OOH$ and thus again to the products (benzaldehyde and water) while reforming the starting copper(I) complex. Last but not least, the benzyl peroxo radical $PhCH_2OO^{\bullet}$ could react with the copper(I) complex $[LCu^{I}]^+$ to form $PhCH_2OOCu^{II}L$ that would form benzaldehyde and a hydroxido copper(II) complex.

Conclusion

In conclusion, it could be demonstrated that it is possible to successfully convert toluene to benzaldehyde (and a decent conversion could be achieved) under ambient conditions by using dioxygen (air) as an oxidant, a copper complex, and Rubipy as a photochemical reducing agent. Compared to the alternatives described in the Introduction, our system works quite well, avoiding higher pressures, higher temperatures, or more toxic chemicals. Furthermore, it is important to point out that the oxygenation reaction is selective, and no formation of benzyl alcohol or benzoic acid was observed. However, the problems that still have to be solved (and will be addressed in the near future) are a) improving the solubility of the copper complex in toluene (or finding an alternative solvent), b) avoiding a sacrificial compound and c) finding a good way to separate the product benzaldehyde from toluene in a simple setup.

Experimental Section

The syntheses and characterizations of the ligands and the copper salt ($[Cu(MeCN)_4]B(C_6F_5)_4$) were performed according to the literature, and details are reported in the Supporting Information.

One-pot reaction using the tmpa ligand: In an argon-filled glove box 14.5 mg (50.0 μmol) tmpa was dissolved in 1.983 g toluene. Separately 45.3 mg (50.0 μmol) $[Cu(MeCN)_4]B(C_6F_5)_4$ was dissolved in 5.144 g toluene. The copper salt solution was added dropwise to the ligand solution while stirring, leading to a yellow solution. To the mixture, 2 mg (2 μmol) tris(2,2′-bipyridine)ruthenium(II)hexafluorophosphate and 200 μL triethylamine were added.* Subsequently, pure oxygen was bubbled through the solution (1 bubble per second) while the solution was irradiated with light ($\lambda = 475$ nm) at room temperature (22 °C). After 18 h, the oxygen was removed by bubbling nitrogen through the solution for 2 min. A sample of the reaction mixture (150 μL) was taken in a nitrogen glove box. 2 μL of a 0.106 mol/L solution of dibenzyl ether (in toluene) was added to the solution. The conversion to benzaldehyde was measured using GC-MS technics and dibenzyl ether as internal standard. The procedure highlighted with an asterisk was repeated after 36, 54, and 72 h. After 72 h, a conversion of 136% related to the copper complex was observed.

A detailed description for the stepwise and the one-pot reaction for the other ligands is reported in the Supporting Information. Furthermore, the data and calculations of the conversions are described in the Supporting Information.

Supporting Informartion

Additional references are cited in the Supporting Information.[25]

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Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Keywords: copper peroxido complexes · photooxidation · benzaldehyde · toluene oxidation · ruthenium bipyridine

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