Copper(II)-photocatalyzed Decarboxylative Oxygenation of Carboxylic Acids

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ARTICLE

Copper(II)-photocatalyzed Decarboxylative Oxygenation of Carboxylic Acids

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Showcasing the concept of light-induced homolysis for the generation of radicals, the Cu[II]-photocatalyzed decarboxylative oxygenation of carboxylic acids with molecular oxygen as the terminal oxidant is described. Two Cu[II]-carboxylate complexes with different coordination geometries were synthesized and characterized by X-ray analysis, correlating their structure with their ability to initiate light-induced decarboxylations.

In recent years, visible light photocatalysis became a powerful tool to enable synthetic transformations.[1] Shifting the focus from Ir- and Ru-based photocatalysts to more abundant and environmentally benign 3d-metals like Cu, Fe or Mn has gained great interest.[2,3] However, major challenges to utilize such metals as photocatalysts are their ultrashort excited-state lifetimes in the pico- or at best in the nanosecond range,[3] making bimolecular processes unlikely. One possible solution to this problem could be the precoordination of a substrate to the metal complexes, which could then undergo upon irradiation a homolysis reaction, coined as (visible) light-induced homolysis ((V)LIH), which is preceded in most cases by a LMCT transition.[4] In seminal work by Kochi, the homolysis of Cu(II)Cl$_2$ to Cu(I)Cl and a chlorine radical upon UV-irradiation was proposed in 1962.[5] More recently, we could show for a Cu(II)Clphenanthroline complex that the visible light-induced Cu(II)–Cl ➔ Cu(I) + Cl• homolysis is an ultrafast process, occurring in less than 100 fs.[6] This suggests that excited-state lifetimes of metal complexes can still be in the low picosecond range to success- fully generate radicals by a metal-ligand homolysis, while the desired metal-substrate precursor that would undergo such a process might be accessible through simple ligand exchange (Figure 1).
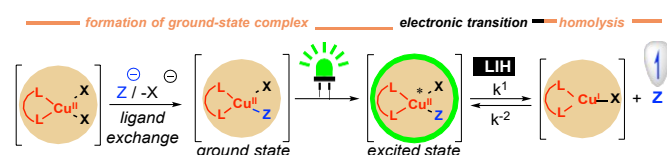

Figure 1. Concept of light induced homolysis (LIH) for Cu(II)-species)

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Little is known so far which metal-ligand combinations are amenable for light-induced homolysis. For Cu(II)-complexes, there is evidence that besides chloride- also azide-,[7] alkyl-,[8] enolate-,[9] or carboxylate-ligands[10] are all suitable substrates. We show here by UV-Vis, FT-IR, EPR, NMR, and computational studies that Cu(II)-carboxylates indeed undergo a light-induced homolysis, but that the specific coordination geometry plays a pivotal role in this process. Monodentate carboxylates are shown decisive for the success of subsequent synthetic trans-formations.

Thermal oxidative Cu(II)-catalyzed decarboxylations of carboxylic acids have been known for a long time and various synthetic transformations have been developed,[11] while fewer reports for photochemical variants have been disclosed.[12] We assumed that the underlying mechanism for such decarboxylations could be based on (V)LIH as the key step of a Cu(II)-carboxylate species, however, given the different coordination modes available for carboxylates, we set out to gain a deeper understanding on the prerequisites of this process and thus arrive at more efficient catalysts.

Copper(II)-carboxylates have been extensively investigated since the 1970s for their diverse structural properties and a broad range of applications e.g. in the field of molecular magnetism.[13] The carboxylate group can adopt various coordination modes (Figure 2), i.e. symmetric and asymmetric chelation en route to monodentate complexation, but especially the paddle-wheel-type is often encountered.[14] Complexes of the latter type have been proposed to be the active species in thermal decarboxylations of carboxylic acids.[15]
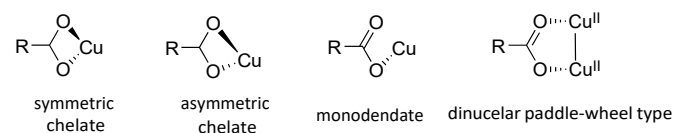

Figure 2. Common coordination modes in Cu(II)-carboxylates.

Indeed, by mixing 4-methoxyphenylacetic acid (**1a**) with CuSO$_4$ in aqueous basic media[16] and subsequent recrystallization from acetonitrile, we were able to obtain the paddle-wheel complex **3** where the carboxylates are tightly bound in a bidentate

fashion (Cu–O 197 pm). Stirring **3** in the presence of one equiv neocuproine (2,9-dimethyl-1,10-phenanthroline, dmp), the Cu(II) complex **4** was subsequently obtained, in which the carboxylates are now coordinated as monodentate (Cu–O 193 ppm, interatomic distance Cu–O 272 pm). Both complexes were characterized by X-ray structure analysis and showed a strong absorption at 367 nm as revealed by their UV-Vis spectra (see ESI for details).

Consequently, we probed these Cu(II)-complexes for their potential as catalysts to promote decarboxylations by irradiating **1a** at 367 nm in an oxygen atmosphere (Table 1). While **3** only furnished 4-metho-xybenzaldehyde (**2a**) in low yield (entry 1), complex **4** proved to be highly effective, giving rise to **2a** in 86% yield. Assuming that the low efficiency of **3** might be a consequence of the paddle-wheel coordi-nation, the reaction was also carried out in aqueous solvents taking the lead from Schröder *et al.*[17] who demonstrated that water breaks up the copper clusters. Indeed, the yield of **2a** increased to 21% (entry 2) but was still far inferior in comparison to complex **4**, which also benefitted from the addition of water (entry 4). We also noted a background reaction in the absence of the copper complex (entry 5) having the same efficiency that was observed in the presence of **3**.

Table 1. Evaluation of Paddle-wheel vs. monodentate Cu(II)-complexes **3** and **4** in the oxidative decarboxylation of **1a**.


Entry	Cu(II)-complex	Water [Vol%]	λ_{max} [nm]	Yield[b] (%)
1	Cu$_2$(**1a**)$_4$(MeCN)$_2$ (**3**)	-	367	11
2	Cu$_2$(**1a**)$_4$(MeCN)$_2$ (**3**)	2.2	367	21
3	Cu(dmp)(**1a**)$_2$ (**4**)	-	367	86
4	Cu(dmp)(**1a**)$_2$ (**4**)	2.2	367	91
5	–	-	367	10
6	Cu(OAc)$_2$ + dmp (*in situ*)	2.2	367	60
7[c]	Cu(OAc)$_2$ + dmp (*in situ*)	2.2	367	95

[a]Standard conditions: **1a** (0.25 mmol, 1.0 equiv), 10 mol% Cu[II] (12.5 μmol, for complex **3** (Dimer) or 25 μmol, for complex **4**) in MeCN (2.0 mL, 0.125 M), water (45 μL, 10 mol%), Irradiation at 367 nm with a radiant power of 160 mW under O$_2$ atmosphere for 24 h at room temperature (30 °C). [b]NMR yield using 1,1,2,2-tetrachloroethane as internal standard. [c]LED irradiation at 367 nm with a radiant power of 400 mW.

Aiming at a general applicable catalyst system, we evaluated the combination of Cu(OAc)$_2$, i.e. having an innocent carboxylate ligand present along with dmp. Gratifyingly, this reagent combination proved to be also suitable, although somewhat less efficient than **4** in the transformation of **1a** to **2a** (entry 6), which was remedied by applying a more powerful light source (entry 7).

Indeed, this catalyst system allowed the conversion of a variety of primary and secondary phenyl acetic acids to the corresponding C1-truncated aldehydes and ketones (Table 2).

Table 2. Oxidative decarboxylation of carboxylic acids **1**
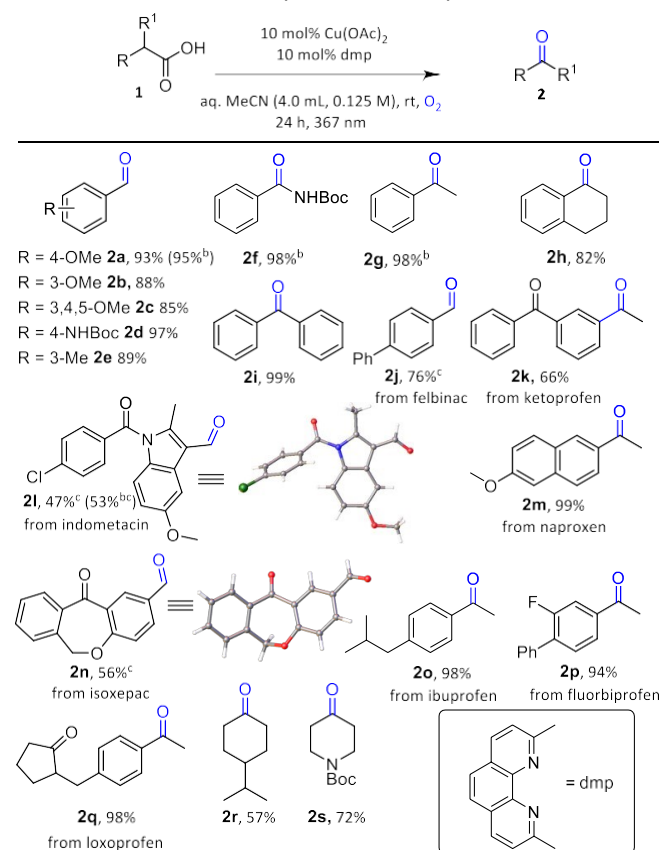
[a]Standard conditions: carboxylic acid (0.5 mmol, 1.0 equiv), Cu(OAc)$_2$ (50 μmol, 10 mol%), dmp (50 μmol, 10 mol%) in MeCN (4.0 mL), water (90 μL, 2.2 Vol%), distributed over two Schlenk tubes. Irradiation at 367 nm with a radiant power of 400 mW under O$_2$ atmosphere for 24 h at room temperature (30 °C). [b]NMR yield using 1,1,2,2- tetrachloroethane as internal standard. [c] With a radiant power of 160 mW.

With a view to identifying possible degradation pathways of non-steroidal anti-inflammatory drugs (NSAIDs) for removal from the environment, we were especially pleased that widely used agents such as felbinac, ibuprofen, or naproxen gave rise to the corres-ponding decarboxylated products **2j-2q** in high yields.
Likewise, cyclohexyl substituted carboxylic acids could be converted to the corresponding cyclohexanones **2r** and **2s**. However, primary alkyl carboxylic acids were not suitable substrates: Apparently, CO$_2$-extrusion upon homolysis of the carboxylate ligand from Cu(II) is not

possible due to the low stability of the resulting alkyl radical, and in turn, recombination of the carboxyl radical with Cu(I) might reverse the initial homolysis. Moreover, all attempts to intercept the radical formed after decarboxylation with other reagents besides oxygen failed, pointing to mechanistic implications of the process (*vide infra*).

The lack of activity for the light-induced decarboxylation of paddle wheel complex **3** might be explained by an effective rebound mechanism if an initial homolysis does indeed occur (Scheme 1a). In contrast, monodentate Cu(II)-carboxylate in **4** likely generates a free carboxylate radical upon homolysis with a sufficient lifetime to undergo decarboxylation provided the resulting radical benefits from stabilization, i.e. being benzylic or secondary (Scheme 1b).

a) Rebound mechanism (dinucelar paddlee-wheel type Cu(II)-carboxylates)
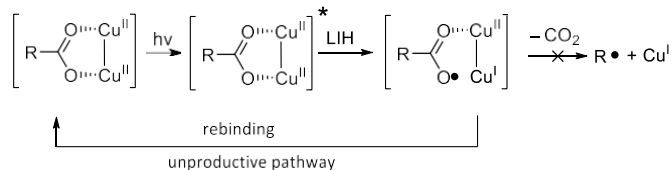
b) Homolytic cleavage mechanism (monodentate Cu(II)-carboxylates)
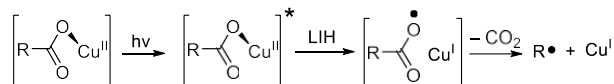
Scheme 1. Mechanistic proposal for the Cu(II)-mediated oxidation of carboxylic acids.

EPR-spectral analysis of the two Cu(II) complexes in ACN with 2 % water (v/v) indicated that a significantly larger proportion of monomeric Cu(II) species are present in complex **4** relative to that in **3** (see ESI). Hence it was concluded that indeed monomeric Cu(II) species are necessary in the title transformation to achieve good conversion in the decarboxylation step.

Consequently, a plausible catalytic cycle driven by the monomeric Cu(II)-dmp complex **3** for the oxidative decarboxylation can be proposed, being supported by DFT calculations and additional kinetics and trapping studies (Scheme 2). The generation of the radical **I** by homolytic Cu-O bond cleavage as the key step was calculated to be a significantly up-hill process ($\Delta_R G$ = 41.3 kcal/mol), but is still feasible through irradiation at the wavelength at which **4** absorbs most strongly, i.e. λ_{max} = 367 nm delivering approximately 78 kcal/mol per photon. **I** is too short-lived for direct observation or trapping given that the release of CO_2, which was monitored by solution phase IR (Figure 2b), giving rise to **II** (trapped by TEMPO (see ESI) and *N-tert*-butyl-α-phenylnitrone (PBN), Figure 2c) which is strongly exothermic by − 35.4 kcal/mol. Concurrently, a species of type Cu(I)dmp (**III**) is formed, which was confirmed by detecting [Cu(I)dmp$_2$]$^+$ by UV-Vis (Figure 2a), TDDFT and NMR (see SI). In agreement with recent mechanistic studies of oxygenase-catalyzed transformations[18], coordination of O_2 and back-binding of **II** to **III** would lead to the peroxo-complex **V**, being again highly exothermic by −21.1 kcal/mol. The high efficiency of this latter step also provides an explanation

why all our attempts to trap radical **II** with nucleophiles, being known as the terminating step in Cu(I)-catalyzed
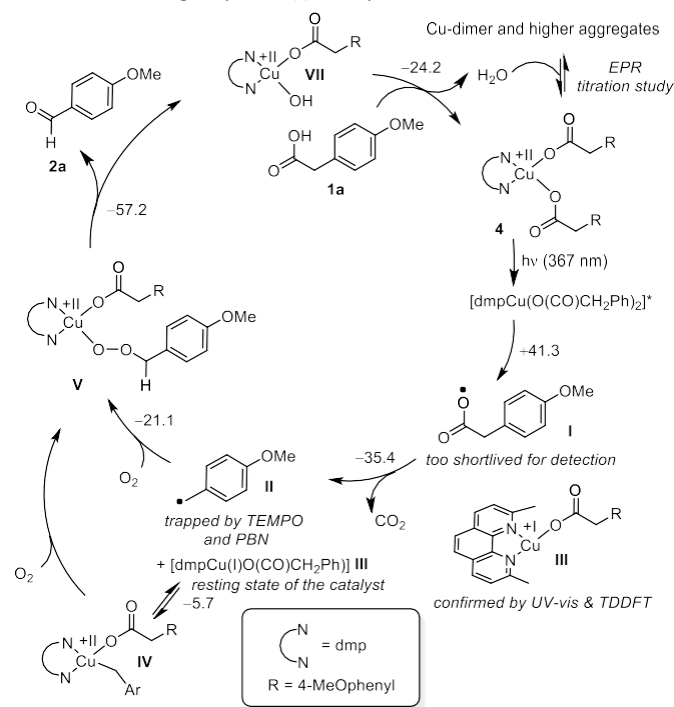
Scheme 2. Proposed Mechanism based on experimental and computational investigations. $\Delta_R G$ values of each indicated step in kcal/mol.
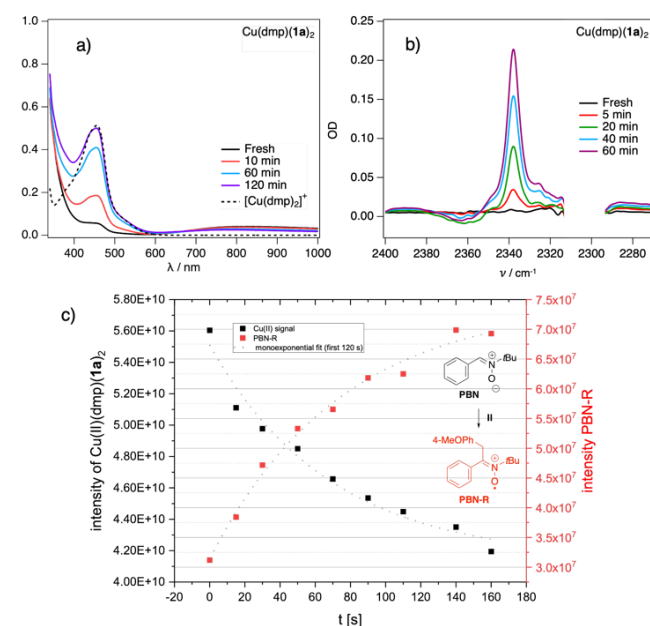

Figure 3. a) UV-Vis absorption spectra of fresh and irradiated Cu(dmp)(**1a**)$_2$ (**3**), and independently prepared [Cu(dmp)$_2$]$^+$ (dashed line) as reference; b) Solution-phase IR spectra of fresh and irradiated Cu(dmp)(**1a**)$_2$ (**3**) showing the emergence of the CO_2 absorbance band at 2335 cm^{-1} growing with irradiation time; c) Kinetic traces of Cu(II) signal (black squares) with $k_{initial}$ = 0.015 ± 0.004 s^{-1} and of the growth of the **PBN-R** signals (red squares) with $k_{initial}$ = 0.013 ± 0.002 s^{-1}. Fitted at early times with a single exponential function and assuming pseudo-first order conditions for the **PBN-R** formation.

reductive ATRA reactions,[2] in the presence of oxygen have been unsuccessful. Indeed, carrying out the decarboxylation under an inert gas atmosphere, the coupling product **5** that forms by trapping of radical **II** with carboxylic acid **1** is observed (Scheme 3). However, the required oxidation back to Cu(II) cannot take place in the absence of an oxidant, thus making such processes stoichiometric[19] rather than catalytic in copper. Therefore, our future attempts are directed to find oxidative conditions that would not interfere with an initial coupling or radicals of type **II** with nucleophiles.
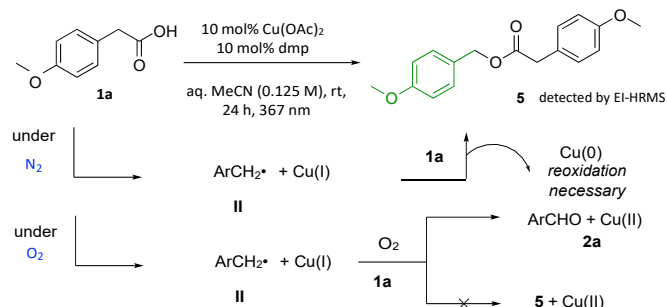
Scheme 3. Cu(II)-mediated decarboxylation under oxygen and inert gas atmosphere.

Conclusions

In summary, we have developed an efficient protocol for the Cu(II)-photocatalyzed oxidative decarboxylation of phenylacetic acids to the corresponding aldehydes or ketones with oxygen as terminal oxidant. The light-induced homolysis of a Cu(II)-carboxylate is suggested to be the key step in the process, for which monodentate coordination rather than chelation of the paddle-wheel type appears to be required, which can be forced by using sterically demanding neocuproine as ligand. Upon Cu(II)-carboxylate homolysis and decarboxylation, the resulting radical is efficiently captured by oxygen and the resulting Cu(I)-complex which delivers aldehydes and Cu(II) closing the catalytic cycle.

Author Contributions

OR, JR and FNC conceived the project, AR, HS, RF and PK carried out the experiments. The manuscript was written with contribution from all authors.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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