EurJIC
European Journal of Inorganic Chemistry

Full Papers
doi.org/10.1002/ejic.202100185

Chemistry Europe
European Chemical Societies Publishing

Aerobic C–H Hydroxylation by Copper Imine Complexes: The Clip-and-Cleave Concept – Versatility and Limits

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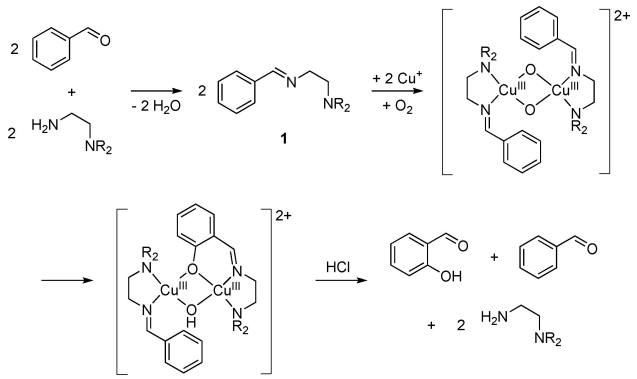
The intramolecular ligand hydroxylation of a series of copper(I) imine complexes during their reaction with dioxygen had been systematically studied. The so-called clip-and-cleave concept offers a facile way to oxygenate aldehydes or ketones. A copper(I) complex for example, with an imine ligand derived from an ethylenediamine derivative and cyclohexanone was oxidized. Decomposing the complex after the reaction with hydrochloric acid showed a 50% conversion of the cyclohexanone to 2-hydroxycylohexanone. Depending on the ligand system, three different reaction pathways have been identified that can cause hydroxylation reactions. While the radical based mechanisms are more difficult to identify, the reactions that go through a copper bis(μ-oxido) complex as active species can be analyzed by low temperature stopped-flow techniques. In an ideal case the formation and decomposition of this reactive intermediate can be spectroscopically observed. It was shown that this depends strongly on the ligand system: steric effects, chelate ring size and coordination number play an important role for the mechanism and the outcome of the reaction.

Introduction

Copper monooxygenases such as e.g. tyrosinase or methane monooxygenase are important enzymes for the oxygenation of organic substrates (tyrosine to L-DOPA and methane to methanol).[1] Besides the interest in a better understanding of the biological function, these enzymes demonstrate that it is possible to perform selective oxidation reactions under ambient conditions (aqueous solutions, room temperature) using dioxygen from air as the sole oxidant.[2] Due to the importance of catalytic selective oxidation reactions in industry,[3] low molecular weight complexes have been "designed" to model the reactivity of the copper enzymes.[4,5]

In that regard we recently developed a so called "clip-and-cleave" system that allows stoichiometric C–H hydroxylation in the γ-position of aromatic and aliphatic aldehydes utilizing a copper imine complex system,[6,7] similar to the initial oxygenation step of tyrosinase, which catalyzes the *ortho*-hydroxylation of L-tyrosine to L-DOPA prior to the further oxidation to L-DOPA quinone in melanin biosynthesis.[8] In contrast to our previous work, the nomenclature has been adapted to the nomenclature of Garcia-Bosch and co-workers for the carbon that is hydroxylated.[9] In Scheme 1 the general reaction mechanism is presented using benzaldehyde as a substrate. In a first step the imine ligand is prepared, here from benzaldehyde and *N*,*N*-diethylethylenediamine, leading to *N*′-benzylidene-*N*,*N*-diethylethylenediamine (BDED, **1**). BDED was then reacted with a copper(I) salt e.g. $[Cu(CH_3CN)_4]OTf$, to form the copper(I) complex [Cu(**1**)]OTf in situ (most likely one or two CH_3CN molecules are coordinated as ligands additionally). Reaction with dioxygen caused formation of a copper bis(μ-oxido) complex as an intermediate followed by intramolecular ligand hydroxylation. Yields of salicylaldehyde were close to the limiting 50% (theoretical maximum yield in this reaction)[6,7] and the formation and decomposition of the intermediate, the copper bis(μ-oxido) complex, could be followed spectroscopically by low temperature stopped-flow measurements. Copper bis(μ-oxido) complexes have been investigated in great detail during the last years with regard to ligand variation, reaction conditions etc.[5,10]



Scheme 1. Intramolecular hydroxylation of $[Cu^{I}(\mathbf{1})]^{+}$ complex (R = Et) with dioxygen. The hydroxylation proceeds via a copper bis(μ-oxido) intermediate.[6]

More recently an excellent extensive study on intramolecular ligand hydroxylation was reported by Garcia-Bosch and co-workers, using camphor derivatives and steroids as

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Supporting information for this article is available on the WWW under https://doi.org/10.1002/ejic.202100185

substrates.[11] This work is based on results obtained earlier by Schönecker and later by Baran and co-workers.[12–15] In contrast to the mechanism described above (Scheme 1), they did not observe formation of a copper bis(μ-oxido) complex at all. Their detailed kinetic analysis showed that for these reactions obviously a different mechanism takes place.[9,11] Their proposed reaction mechanism for the hydroxylation of sp^2 C–H bonds is presented in Scheme 2. Here, using imino pyridine ligands, they assigned a hydroperoxido complex ($LCu^{II}(OOH)$) as active species. By optimizing the reaction conditions, they were able to achieve yields close to 100% of hydroxylated product.

With regard to the importance of selective oxidation reactions we were interested to learn more about the occurrence of the two different mechanisms and investigated these reactions in more detail.

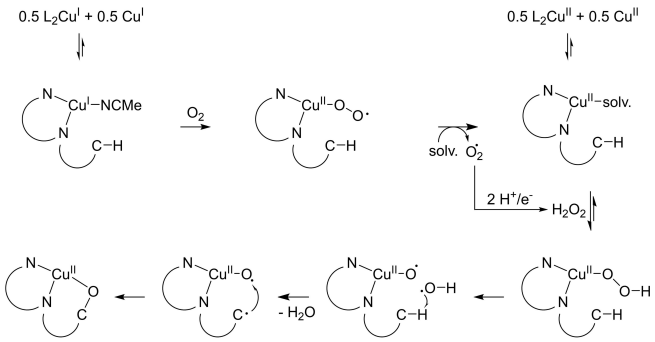
Results and Discussion

Influence of solvent and ligand backbone

Many of the reactions leading to selective oxygenation reactions rely on the formation of a mononuclear copper complex in a 1:1 ratio of copper(I):ligand.[6,7,9,11,16] However, when ligands are utilized that do not provide necessary sterically features/hindrance a strong tendency is observed that a complex in a copper(I) to ligand ratio of 1:2 forms. These complexes often are nearly unreactive towards dioxygen. This problem was observed for the copper BDED system described above as well.[6] Depending on the conditions, the unreactive complex $[Cu(\mathbf{1})_2]X$ (X = different anions) is easily formed leading herewith to complete suppression of the hydroxylation reaction. Often these complexes exhibit a more intensive color and furthermore decreased solubility. Figure 1 shows the difference between solutions containing [Cu(**1**)]OTf and $[Cu(\mathbf{1})_2]$OTf in acetone.

To avoid this problem, it was decided to modify the ligand system e.g. by introducing sterically more demanding, bulkier groups into the ethylenediamine unit. Therefore, the ligands **L** presented in Scheme 3 were prepared. Furthermore, due to the fact that the formation of the $[Cu(\mathbf{L})_2]$OTf complex is also depending on the solvent used, the influence of different solvents was tested. While being used successfully in the past, acetonitrile (or propionitrile) and methanol had to be excluded for our studies because no hydroxylation reaction was observed using these two solvents. Methanol can be a problem because it is a protic solvent, thus leading to decomposition of intermediates prior to a reaction with the ligand and nitrile solvents might suppress any further reaction because nitriles coordinate strongly to the copper(I) ion (blocking it against dioxygen activation).[17] Acetone so far proved to be the best solvent for the investigations described herein, however it was also possible to use dichloromethane, despite some problems described earlier (low yield and ligand decomposition at low temperatures), that can occur with this solvent.[6]

Ligands **1** to **7** were investigated under the same conditions that were applied previously for the hydroxylation reaction using [Cu(**1**)]OTf. The results obtained according to Scheme 1 are presented in Table 1 together with the original findings for this complex (entry 1) for which a ligand conversion to the hydroxylated product, salicylaldehyde, of almost 50% were achieved. In our new measurements we had some more problems with the precipitation of a yellow/orange solid discussed above in combination with some formation of



Scheme 2. Proposed mechanism for the intramolecular hydroxylation of sp2C–H bond. Redrawn from Trammell *et al.*[11]

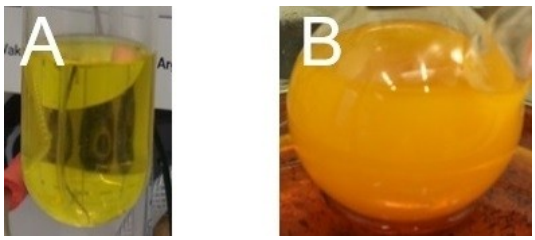
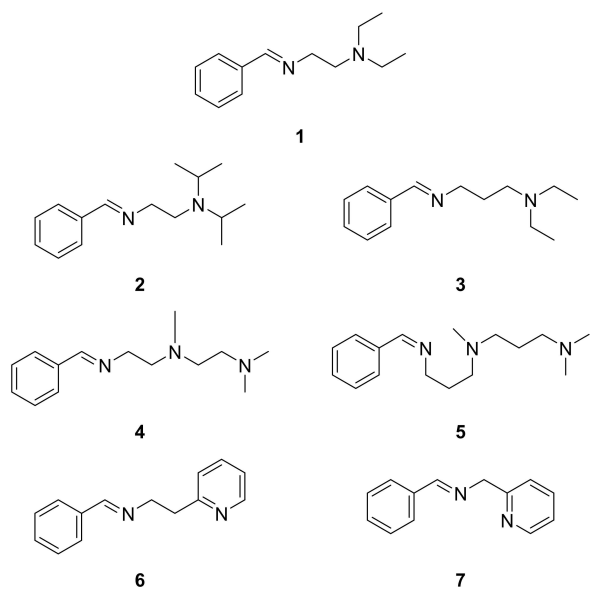


Figure 1. (A) The 1:1 [Cu:L] complex [Cu(**1**)]OTf in acetone and (B) the 1:2 [Cu:L_2] complex $[Cu(\mathbf{1})_2]$OTf in acetone.



Scheme 3. Ligands used in this study: BDED (**1**), BDiPED (**2**), BDPD (**3**), BTED (**4**), BTPD (**5**), BEP, (**6**) and BMP (**7**).

Table 1. Conversion of the substrate into hydroxylated products using ligands **1**–**7** (Scheme 3) with benzaldehyde as substrate.

Entry	Ligand	Acetone[a] Conversion [%]	Dichloromethane
1[b]	BDED (**1**)	Close to 50	–
2[c]	BDED (**1**)	34	33
3	BDiPED (**2**)	45	41
4	BDPD (**3**)	0	0
5	BTED (**4**)	0	0
6	BTPD (**5**)	0	0
7	BEP (**6**)	5	8
8	BMP (**7**)	5	3

[a] Traces of diisopropylamine after hydroxylation experiment detected. [b] J. Becker *et al.*[6] [c] Reproduced results of Entry 1.

diisopropylamine in acetone. Nevertheless, hydroxylation conversions of 34% in acetone and 33% in dichloromethane were observed. The occurrence of diisopropylamine had been puzzling at first, however it can be explained by a reaction with the solvent acetone according to the mechanism presented in Figure S53 (see Supporting Information). In an imine equilibrium free benzaldehyde can react with acetone followed by a 1,3-H-shift. Cleavage of the imine allows the reaction with a second acetone molecule and through a hydride transfer, similar to a Cannizzaro type reaction, diisopropylamine is formed. The additionally formed side products were most likely extracted during the aqueous work-up and therefore could not be detected in GC-MS measurements.

A look at Table 1 immediately shows two important aspects that are essential for the intramolecular ligand hydroxylation under these conditions:

1.) Here "wrong" chelate ring sizes seem to completely suppress ligand hydroxylation. With ligand **3** a six-membered chelate ring size is achieved in contrast to ligand **1** and **2** that form 5-membered chelate rings. Six-membered chelate rings are well known to often stabilize copper(I) complexes better and that might be one of the reasons for the completely suppressed hydroxylation reaction.[18] However, this is not generally the case because hydroxylation reactions also can be observed with copper(I) complexes with ligands in six-membered chelate rings.[19]

2.) Independent of chelate ring sizes it seems that tridentate ligands such as e.g. **4** and **5** are not suitable here as well. For copper(I) complexes with these ligands no hydroxylation was observed at all. Our intention to avoid formation of [Cu(**L**)$_2$]X complexes by using tridentate ligands obviously was counterproductive. Most likely a bidentate ligand is necessary (at least in our reactions) to keep the coordination sites open for their reactivity towards hydroxylation. Further investigations with these two ligands were not carried out due to the lack of a hydroxylation reaction as well as due to the high cost and time-consuming preparation of the reactants for ligand syntheses.

Our approach to introduce more bulky groups to suppress the 1:2 copper:ligand formation was valid because copper(I) complexes with ligand **2** showed higher hydroxylation conversions in comparison to complexes with ligand **1** in both solvents under our conditions. Still, it is possible to achieve a conversion of up to 50% with both ligands **1** (entry 1 in Table 1) and **2** but it is obviously more difficult with **1**. Furthermore, despite the slightly higher conversion in acetone, small amounts of diisopropylamine were again detected, indicating that dichloromethane is the better solvent to perform these reactions.

However, quite surprisingly and despite the structural similarity of **2** with **1**, no copper bis(μ-oxido) complex could be spectroscopically detected as an intermediate during the reaction of its copper(I) complex with dioxygen (see Supporting Information). Two possibilities could account for that: a) if the formation of the copper bis(μ-oxido) complex (or another "dioxygen adduct" complex) is rate determining then consecutive hydroxylation is fast and there is no chance to observe the intermediate or b) hydroxylation occurs according to the mechanism proposed by Garcia-Bosch and co-workers (Scheme 2).[11] From our data we cannot really say which of the two cases is more likely here.

In contrast to the formation of a quite stable copper bis(μ-oxido) complex with ligand **1**, the sterically more demanding isopropyl groups in **2** could lead to some shielding and thus exclude formation of such a binuclear unit. To some extent this is supported by the molecular structure of the copper(I) complex [Cu(**2**)]Cl (Figure 2, crystallographic data are reported in the Supporting Information and selected bond lengths and angles are reported in Table 2) in which the two isopropyl groups definitely require some space. This steric shielding furthermore allowed us to crystallize this complex in a 1:1 copper to ligand ratio. With ligand **1** it only had been possible to crystallize the 1:2 complex [Cu(**1**)$_2$]SbF_6.[6] In general, it is not easy to crystallize and structurally characterize copper(I) com-

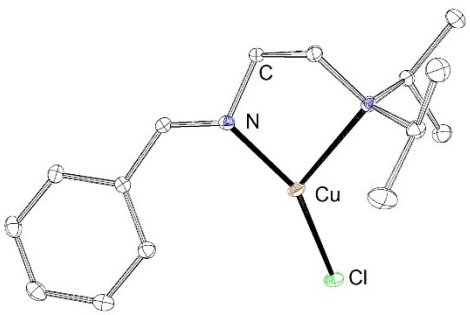


Figure 2. ORTEP plot of molecular structure of [Cu(**2**)Cl]. Hydrogen atoms are omitted for clarity. Anisotropic displacement ellipsoids set to 50% probability.

Table 2. Selected bond length [Å] and angles [°] for complex [Cu(**2**)Cl] (Figure 2).

Cu(1)–N(1)	1.9415(9)	N(1)–Cu(1)–Cl(1)	153.44(3)
Cu(1)–Cl(1)	2.1577(3)	N(1)–Cu(1)–N(2)	84.09(3)
Cu(1)–N(2)	2.3727(9)	Cl(1)–Cu(1)–N(2)	122.17(2)
Cu(1)–C_{oxid}	3.263(1)	Dihedral angle[a]	158.8

[a] C_{oxid}.–Cu(1)–N(2) angle.

plexes of this type. Therefore, chloride or iodide as co-ligands have been used.[20]

[Cu(**2**)]Cl shows a trigonal coordination of copper by the imine and amine nitrogen atoms and chloride. Whether the amine-copper bond is a strong coordinative bond is worth discussing, since the bond length is relatively long. The copper-amine nitrogen distance is 2.3727(9) Å, whereas the distance between imine nitrogen and copper is 1.9415(9) Å. In the copper(I) BDED complex, the largest distance between nitrogen and copper is 2.239(3) Å. Cu–N amine distances higher than 2.37 Å are less common, nevertheless, similar bond lengths were determined with structurally very similar ligands and also the Cu–N imine distances fit very well.[21]

Only low reactivity was achieved with ligands **6** and **7** (entry 7 and 8 in Table 1). Here a pyridyl group with an ethylene respectively a methylene bridge was introduced instead of the ethylene diamine backbone. The conversion is well below that of **1** and **2**, however, See *et al.* have shown that higher yields with copper(I) complexes with this type of imino pyridine functionalized ligands (steroids) were possible under slightly different reaction conditions.[15] We also tried to apply these reaction conditions, using a reducing agent and dioxygen as oxidant, but instead of a clean hydroxylation reaction with high yields we observed overoxidation of the aromatic substrate and the formation of various by-products.

Recently, Trammell *et al.* reported the molecular structure of the copper(I) complex with **7** as a ligand ([(**7**)Cu(CH_3CN)]PF_6).[9] The complex shows a trigonal planar coordination geometry which is comparable to the molecular structure of the copper(I)-**2** complex with chloride (Figure 2). Within estimated standard deviation there is no difference of the N–Cu–N angles (84.09(3)° vs. 84.4(4)°). Also, the Cu–$C_{oxid.}$ distance is very similar (3.263(1) Å vs. 3.243(13) Å), only the dihedral angle ($C_{oxid.}$–Cu–N) is slightly more angled (158.8° vs. 178.8°) in case of the copper(I)-**2** complex.

The hydroxylation of benzaldehyde with this complex was performed using hydrogen peroxide instead of dioxygen. In comparison with their other investigated systems the conversion of 39% was quite low but still significantly higher than in our experiment with dioxygen (entry 8 in Table 1). Stopped-flow measurements of the reaction of dioxygen with the copper(I) complexes with the ligands **6** and **7** did not indicate the formation of a "dioxygen adduct" complex as an intermediate and only showed a slow oxidation to corresponding copper(II) complexes.

Aliphatic hydroxylation

A particular challenge is the hydroxylation of aliphatic substrates (non-activated C–H bonds), which already has been described by Réglier *et al.*[22] In comparison to a selective aromatic hydroxylation, very few examples for selective aliphatic hydroxylations are known in the literature. Based on the BDED ligand, Becker *et al.* reported the selective hydroxylation of trimethylacetaldehyde, an adamantane carboxaldehyde as well as of an diadamantane-1-carboxaldeyde.[7]

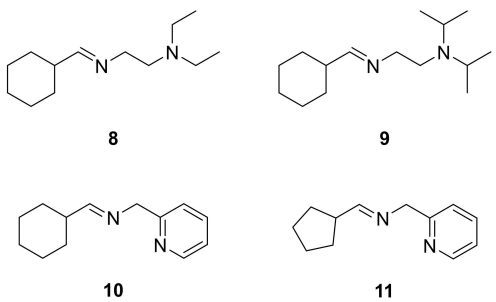
Cyclohexane is an important basic chemical in industry, e.g. for the manufacturing of polymers such as 6,6 nylon where it is oxidized in a first reaction sequence to cyclohexanol and cyclohexanone. With regard to this, new possibilities for the derivatization of cyclohexane could become interesting. Therefore, experiments with cyclohexane derivatives, cyclohexane carboxaldehyde as well as cyclopentane carboxaldehyde and cyclohexanone (see further below) were carried out to expand the range of substrates and to investigate reaction parameters for possible selective hydroxylation reactions. Ligands **8**, **9**, **10** and **11** (Scheme 4) were synthesized in good yields and applied in analogy to the aromatic systems described above. However, in contrast to these systems investigations with the ligands **8**, **9**, **10** and **11** turned out to be much more problematic.

While the copper(I) complex with ligand **11** did not seem to react at all with dioxygen copper(I) complexes with ligands **8**, **9** and **10** at least showed some reactivity. However, GC-MS results of the product mixtures only showed cyclohexane carboxaldehyde (the substrate) while the expected product, 2-hydroxycyclohexane-1-carboxaldehyde was not detected at all. Instead, formation of some other products was observed which could not be identified so far. Most likely this is caused by decomposition reactions during the oxidation process, either directly or of the hydroxylated product (if it actually was formed in the process). Aspects that control C–C cleavage versus C–H bond hydroxylation by copper complexes was previously discussed by Schoenebeck and co-workers.[23]

Efforts to crystallize copper(I) complexes with ligands **8**, **9**, **10** and **11** only were successful with ligand **9** and chloride as a co-ligand. However, in contrast to our expectations that [Cu(**9**)Cl] would be obtained, the molecular structure revealed that [Cu(**9**)$_2$][$CuCl_2$] formed instead (Figure 3, crystallographic data are reported in the Supporting Information).

Despite the fact that the molecular structure in the solid state might not represent the actual molecule in solution, it gives an idea why no hydroxylation reaction was observed. A chelate complex, necessary at least for the formation of a copper bis(μ-oxido) complex, obviously is avoided.

In addition, it was tried to obtain single crystals of the corresponding copper(II) complexes with ligands **8**, **9**, **10** and **11**. Again, we only succeeded with ligand **9** by reacting it with copper(II) chloride dihydrate in either acetone or in acetonitrile.



Scheme 4. Ligands CyDED (**8**), CyDiPED (**9**) and CyMPy (**10**), substrate: cyclohexane carboxaldehyde and ligand CypMPy (**11**), substrate: cyclopentane carboxaldehyde.

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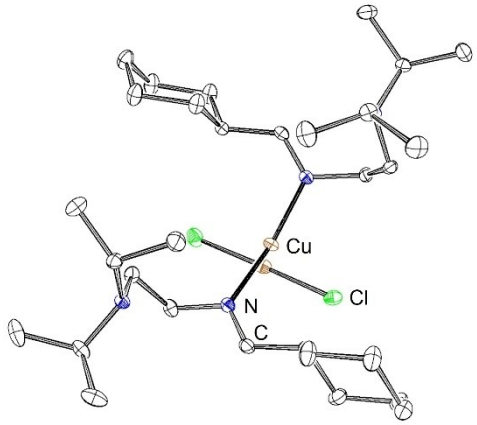


Figure 3. ORTEP plot of the molecular structure of $[Cu(\mathbf{9})_2][CuCl_2]$. Hydrogen atoms are omitted for clarity. Anisotropic displacement ellipsoids set to 50% probability.

Dark green crystals were obtained in both solvents after a few days with the same orthorhombic unit cell. The molecular structure of the complex $[Cu_2(O–CyDiPED)_2Cl_2]$ that crystallized in the orthorhombic space group *Pba*2 in a 2:2 copper to ligand ratio with two coordinated chloride anions is presented in Figure 4 (crystallographic data are reported in the Supporting Information and selected bond lengths and angles are reported in Table 3).

This result is surprising in so far, that obviously a β-hydroxylation of the ligand had occurred under ambient conditions (presence of air and moisture) during the crystallization process. Reactions of copper(II) complexes with dioxygen and water are well known (a few selected examples are given in the references)[24] and according to these previous results we propose the mechanism presented in Scheme 5 for this hydroxylation reaction.

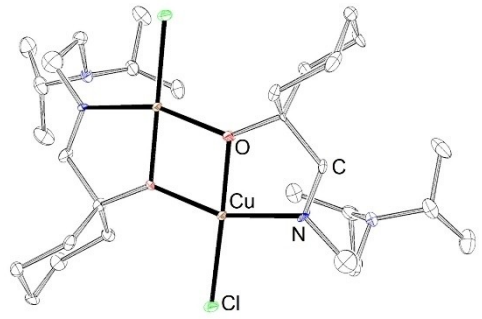


Figure 4. ORTEP plot of molecular structure of $[Cu_2(O–CyDiPED)_2Cl_2]$. Hydrogen atoms are omitted for clarity. Anisotropic displacement ellipsoids set to 50% probability.

Table 3. Selected bond length [Å] and angles [°] for complex $[Cu_2(O\text{-}\mathbf{9})_2Cl_2]$ (Figure 4).

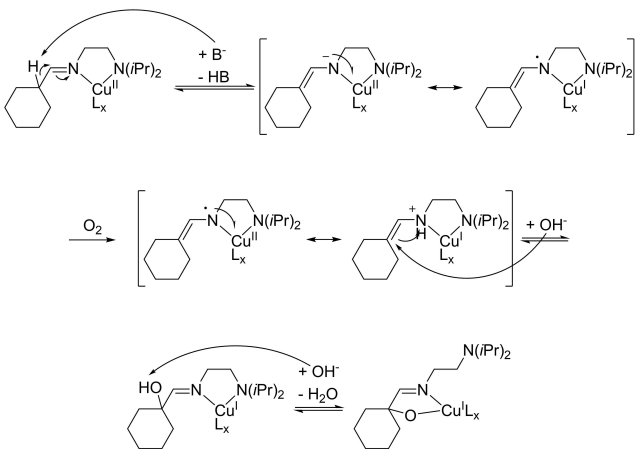
Cu(1)–O(1)#1	1.921(3)	O(1)#1–Cu(1)–O(1)	76.15(12)
Cu(1)–Cl(1)	1.925(3)	O(1)#1–Cu(1)–Cu(1)#1	38.13(8)
Cu(1)–N(4)	1.977(3)	O(1)#1–Cu(1)–N(4)	81.78(12)
Cu(1)–Cl(5)	2.2185(11)	O(1)–Cu(1)–N(4)	157.78(13)
Cu(1)–Cu(1)#1	3.0274(9)	O(1)#1–Cu(1)–Cl(5)	176.98(17)
		O(1)–Cu(1)–Cl(5)	102.79(8)

In a first step deprotonation at the β-position of the ligand leads to formation of an enamine. The Cu^{II} enamine complex is in resonance with a Cu^{I} complex coordinated by a radical ligand. The Cu^{I} is oxidized by oxygen from air to Cu^{II}. The resulting complex is again in resonance with a Cu^{I} complex that is coordinated by a positively charged ligand. The last steps are a nucleophilic attack of a hydroxide anion in the β-position, subsequent deprotonation of the alcohol and coordination to the copper center.

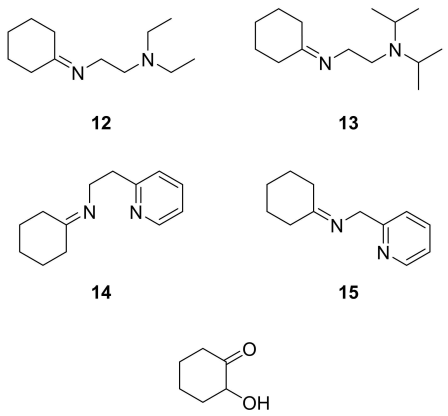
Unfortunately, so far, we did not find a way to perform this reaction efficiently to allow the synthesis of 1-hydroxycyclohexane-1-carboxaldehyde by removing the copper ions similar to the synthesis of salicylaldehyde in Scheme 1. While this reaction definitely has to be investigated further it presents a third possible mechanism for copper-mediated hydroxylation of organic substrates that is promising with regard to an alternative facile way for further oxygenation reactions.

Furthermore, this reaction also can give a hint, why the expected reaction of a β-hydroxylation with a copper(I) complex and oxygen (see general hydroxylation procedure) does not result in the expected product. In contrast to all the other aliphatic substrates, which can be hydroxylated with a BDED based ligand system, the substrates do not have a hydrogen at the β-carbon (e.g. adamantane carboxaldehyde or trimethylacetaldehyde).

To investigate this further and by avoiding this kind of β-hydroxylation we switched from cyclohexane carboxaldehyde to cyclohexanone as a substrate. Therefore, ligands **12**, **13**, **14** and **15** were synthesized (Scheme 6). It turned out that the synthesis of these imine ligands starting from a ketone as a substrate are much more difficult than expected. The imine condensation could not be performed under the same mild conditions as described for the ligands above: reaction temperature needed to be elevated, a change of solvent was necessary, and *p*-toluene sulfonic acid was added in catalytic amounts. Furthermore, it turned out that these imine ligands



Scheme 5. Proposed mechanism for β-hydroxylation of **9** with copper(II).



Scheme 6. Ligands CyonDED (**12**), CyonDiPED (**13**), CyonEPy (**14**), and CyonMPy (**15**), bottom: hydroxylated product 2-hydroxycyclohexanone.

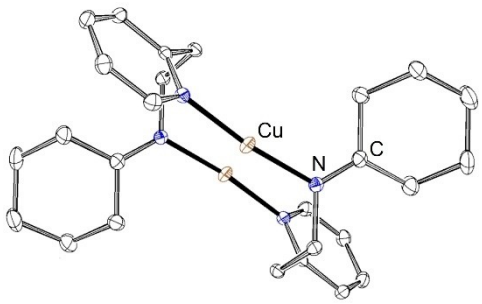


Figure 5. ORTEP plot of molecular structure of $[Cu_2(\mathbf{14})_2](OTf)_2$. Hydrogen atoms and counter ions are omitted for clarity. Anisotropic displacement ellipsoids set to 50% probability.

Table 4. Selected bond length [Å] and angles [°] for complex $[Cu_2(\mathbf{14})_2](OTf)_2$ (Figure 5).

Cu(1)–N(2)	1.9074(12)	N(2)–Cu(1)–N(1)#1	172.95(5)
Cu(1)–N(1)#1	1.9164(13)		
Cu(1)–Cu(1)#1	3.284		

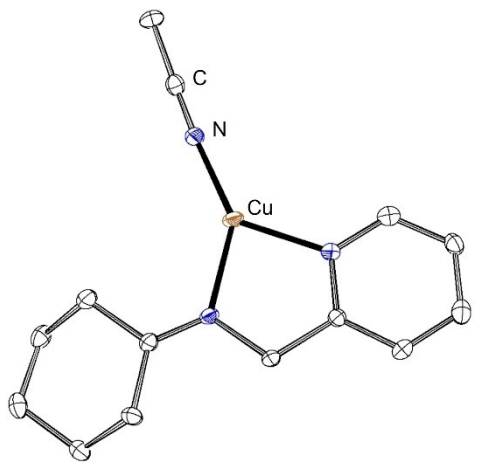


Figure 6. ORTEP plot of the molecular structure of the cation of [Cu-(**15**)(MeCN)]OTf. Hydrogen atoms are omitted for clarity. Anisotropic displacement ellipsoids set to 50% probability.

were extremely sensitive towards water which led to a back reaction to the reactants despite applying a drying agent. Thus, working under inert conditions together with a drying agent was essential to prepare these ligands. Furthermore, all ligands were purified by "Kugelrohr" distillation. Caused by these problems, only decent yields of all four of these ligands were obtained.

With ligands **14** and **15** we succeeded in crystallizing the corresponding copper(I) complexes that turned out to be quite different with regard to their molecular structures. The binuclear complex $[Cu_2(\mathbf{14})_2](OTf)_2$ in which two copper(I) are bridging two ligands is shown in Figure 5 (Crystallographic data are reported in the Supporting Information and selected bond lengths and angles in Table 4).

In contrast, the copper(I) complex with ligand **15** crystallized as expected. The molecular structure of the cation of [Cu-(**15**)(MeCN)]OTf is presented in Figure 6 (Crystallographic data are reported in the Supporting Information). The molecular structure shows the same trigonal planar coordination geometry of copper(I) which was also observed with similar ligands (see Figure 2 and Trammel *et al.* 2019).[9] The N–Cu–N angle is very similar with 84.01° (average of both angles), the dihedral angle 178.5° and the Cu–$C_{oxid.}$ distance is 3.267 Å and has a comparable length towards the other molecular structures.

Despite the problems with the ligand handling described above, no changes were necessary for the experiments of the intramolecular ligand hydroxylation and they could be carried out according to our general procedure in acetone and dichloromethane. The hydroxylation of the substrate cyclohexanone to 2-hydroxycyclohexanone (Scheme 6) could be carried out successfully with the copper(I) complexes of all four ligands and conversions are presented in Table 5.

It was observed that with imine amine-based ligands **12** and **13** higher conversion to the hydroxylated product (close to the limiting 50% if a copper bis(μ-oxido) complex is the reactive intermediate; see below under kinetic measurements) were achieved in comparison with the imino pyridyl ligands (**14** and **15**). Furthermore, acetone turned out to be the better solvent compared to conversions in dichloromethane. Again, as discussed above, diisopropylamine was detected after the hydroxylation reaction in acetone (as well as some other small amounts of by-products).

So far, we did not manage to obtain 2-hydroxycyclohexanone in pure form from the reaction mixtures. Therefore, trying to increase the conversion/yield, hydroxylation experi-

Table 5. Conversion of the substrate into hydroxylated products using ligands **12**–**15** with cyclohexanone as substrate.

Entry	Ligand	Acetone[a] Conversion/%	Dichloromethane
1	CyonDED (**12**)	47	35
2	CyonDiPED (**13**)	46	21
3	CyonEPy (**14**)	22[b]	7
4	CyonMPy (**15**)	16	3[b]

[a] Traces of diisopropylamine detected. [b] Blue precipitate after oxygen treatment.

ments were performed with copper(II) complexes with **12** and **13** as ligands and hydrogen peroxide as the oxidant according to the reaction conditions reported by Trammell *et al.*[4,11] However, in both cases only the non-hydroxylated substrate, cyclohexanone, could be detected and no conversion to a hydroxylated product was observed. This is particularly interesting with regard to our observations by UV-vis spectroscopy (see kinetic investigations below).

Kinetic investigations

The reaction of dioxygen with the copper(I) complexes with ligands **12** and **13** in acetone and dichloromethane was investigated with low temperature stopped-flow measurements.

The reaction of dioxygen with the copper(I) complex with ligand **12** is very fast in both solvents. Time resolved spectra at −93.0 °C in acetone are shown in Figure 7. An absorbance increase is observed with maxima at 405 nm and at 490 nm. The spectrum fits perfectly well to a copper bis(μ-oxido) complex as an intermediate and is in line with our previous observations for the copper(I) complex with ligand **1** (Scheme 1).[6] The formation of this intermediate is complete in about 7 s with a rate constant $k_{obs} = 2 \cdot 10^{-3}\ s^{-1}$ under these conditions (calculated from the absorbance time trace shown as an inset in Figure 7). Analysis of the same reaction in dichloromethane gave the same result, however only half of the height of the absorbance maxima was observed (see Supporting Information). Therefore, a kinetic analysis herein is only reported for the reaction in acetone.

Stopped-flow measurements in the temperature range between −94 °C and −55 °C allowed to obtain activation parameters of $\Delta H^{\neq} = +24.2 \pm 0.2\ kJ\,mol^{-1}$ and $\Delta S^{\neq} = -115 \pm 1\ J K^{-1} mol^{-1}$, calculated from an Eyring plot (see Supporting Information). These data are well in line with the results reported previously for the hydroxylation of trimethylacetaldehyde as a substrate.[7] The negative activation entropy indicates an associative mechanism, the formation of a copper superoxido complex as the rate-determining step and a fast consecutive reaction to the copper bis(μ-oxido) complex.[16]

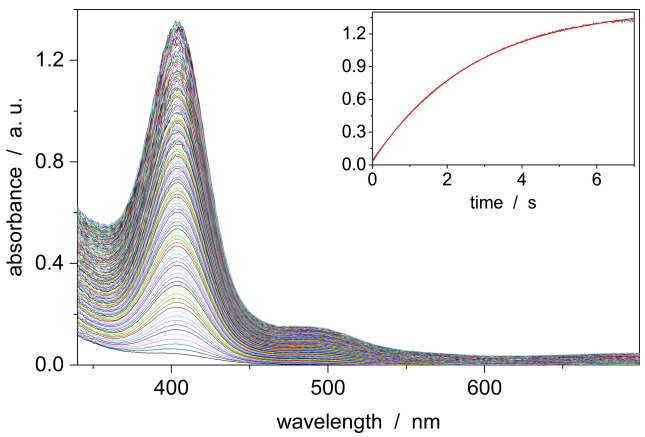


Figure 7. Time resolved stopped-flow UV-vis spectra of the formation of copper(I) bis(μ-oxido) complex with ligand **12** in acetone ($c_{complex} = 0.50 \cdot 10^{-3}\ mol\,L^{-1}$, $c_{O2} = 5.7 \cdot 10^{-3}\ mol\,L^{-1}$, after mixing) at −93.0 °C. Inlay (time trace): Absorbance vs. time at 405 nm (black: experimental, red: exponential fit).

In contrast, during the reaction of dioxygen with the copper(I) complex with ligand **13** in acetone (measurements in dichloromethane were excluded due to disproportionation of the complex), no copper bis(μ-oxido) complex as an intermediate was spectroscopically observed (see Supporting Information). However, while the mechanism is not quite clear for the reaction of the copper(I) complex with the ligand **2** as described above, the situation is different here. The lack of reactivity of the copper(II) complex with ligand **13** towards H_2O_2 speaks against the hydroxylation mechanism described in Scheme 2.[11,15] Instead and most likely here the formation of the copper bis(μ-oxido) complex is rate determining while the consecutive hydroxylation is fast and therefore does not allow to observe the intermediate.

No kinetic studies were performed with the copper(I) complexes of ligands **14** and **15**. Here the formation of a solid during the reaction with dioxygen precluded the stopped-flow measurements.

Conclusions

Over time, different new findings have helped a lot to gain better understanding of stoichiometric or catalytic oxygenation reactions with copper complexes either in the active site of enzymes or applied in form of their model complexes in the lab. For a long time, it was thought that only ligands preorganized for the formation of binuclear copper complexes were suitable for these reactions, however, Tolman and coworkers could demonstrate that this is not required and that mononuclear copper complexes can self-organize themselves to form a binuclear copper bis(μ-oxido) complex.[25] While the ligand system by Tolman was excellent as proof of concept it was not suitable for synthetic applications. By introducing our clip-and-cleave concept it became possible to perform hydroxylation reactions of different aldehydes and ketones.[6,7] We believe that this concept has a great potential for future applications due to the easy handling and the mild reaction conditions. However, one of the problems that comes with this approach is the formation of copper(I) complexes in a copper to ligand ratio of 1:2 that can completely suppress the hydroxylation reaction. Our systematic study on ligand modification to avoid this (reported in here) showed how difficult it is to optimize such a system. Furthermore, the formation of the binuclear copper bis(μ-oxido) complex limits the maximum yield of the hydroxylation to 50%. Based on earlier work by Schönecker[12–14] with the same limitations Baran, Garcia-Bosch and coworkers could increase the yields in their synthetic applications on steroids close to 100% by applying an additional reducing agent (e.g. ascorbate) or working with copper (II) complexes and hydrogen peroxide.[9,11,15] While it seemed that this problem was solved we now could show that this only

might work if a radical mechanism takes place (as reported by Trammell *et al.*)[11] but not if a copper bis(μ-oxido) complex is formed. Furthermore, with two different mechanisms at place for ligand hydroxylation we now would like to add a third possible reaction pathway starting from simple copper(II) complexes in the presence of air and moisture. While this type of reaction is well known since a long time, to the best of our knowledge it has not been really applied in the context of selective ligand hydroxylation. Our results show how sensitive the oxygenation reaction is towards small changes in the whole system that can lead either (depending on the mechanism) to β- or γ- hydroxylation of the substrate or completely suppress the reaction. With the new findings we now hope to design a system that would allow its application in synthetic chemistry. Once such a complex system is identified it could be optimized e.g. by immobilization (and chemical reactivation) or by reactivating it through electrochemistry or photochemistry. Our goal still remains to identify simple copper complexes that can be used to selectively oxidize organic substrates in good yields with dioxygen from air. That this is possible has been demonstrated previously by Lumb and co-workers who showed that they could catalytically oxidize phenols and derivatives with dioxygen.[26]

Experimental Section

Materials and methods

Solvents and reagents used were of commercially available reagent quality. ^{13}C-NMR and ^{1}H-NMR spectra were measured on a Bruker Avance II 400 MHz and Avance III 400 MHz HD spectrometer. Electrospray-ionization MS (ESI-MS) measurements were performed on a Bruker micro-TOF mass spectrometer. All measurements under inert conditions were carried out in argon or nitrogen atmosphere by standard Schlenk techniques or working in a glove box (MBraun, Garching, Germany). For these experiments extra dry solvents were distilled under an argon atmosphere with a drying agent and transferred into the glove box. For gas chromatography with coupled mass spectrometry (GC-MS) a HP-GC 5890 Series II with coupled HP 5972 Series mass detector and Agilent Technologies 5977B MSD with 7820 A GC system was used. For gas chromatography (GC) a 5890 Series II GC was used. For low-temperature stopped-flow measurements HI-TECH Scientific SF-61SX2 instrument (TgK Scientific, Bratford on Avon, UK) was used. Setup and kinetic measurements procedure were described in detail previously.[27] Kinetic data were analysed with the integrated software Kinetic Studio (Version 5.02 Beta, TgK Scientific). For the reactions of copper(I) complex solutions with dioxygen a gastight syringe was filled with argon saturated solvent and saturated with dioxygen by bubbling a dioxygen stream through the solvent for 15 min ($c_{max}(O_2) = 11.44$ mmol L^{-1} in acetone, $c_{max}(O_2) = 11.08$ mmol L^{-1} in dichloromethane).[28] Due to the mixing of the complex and dioxygen solutions in the stopped-flow instrument, the maximum concentrations have to be divided by two resulting in $c(O_2) = 5.72$ mmol L^{-1} in acetone and $c(O_2) = 5.54$ mmol L^{-1} in dichloromethane. Diffraction data for all samples were collected at low temperatures (100 K) using ϕ- and ω-scans on a BRUKER D8 Venture system equipped with dual IμS microfocus sources, a PHOTON100 detector and an OXFORD CRYOSYSTEMS 700 low temperature system. Mo–Kα radiation with a wavelength of 0.71073 Å and a collimating Quazar multilayer mirror were used. Semi-empirical absorption correction from equivalents was applied using SADABS-2016/2[29] and the structures were solved by direct methods using SHELXT2014/5.[30] Refinement was performed against F^2 on all data by full-matrix least squares using SHELXL2018/3.[31] All non-hydrogen atoms were refined anisotropically and C–H hydrogen atoms were positioned at geometrically calculated positions and refined using a riding model. The isotropic displacement parameters of all hydrogen atoms were fixed to 1.2× or 1.5× (CH_3) the U_{eq} value of the atoms they are linked to.

Ligand syntheses

General procedure for the syntheses of ligands 1–15: The substrate (aldehyde or ketone functionalized) and the ligand backbone (amine functionalized) were dissolved in diethyl ether and stirred over sodium sulfate for one hour at room temperature and were kept for another hour under reflux. After the reaction mixture was filtered the solvent was removed using a rotary evaporator. Finally, the product was dried under oil pump vacuum. The general procedure is based on the ligand synthesis of BDED (**1**) published previously.[6] Amounts of reactants, yields, analyses and notes (in case that ligand synthesis deviates from the general procedure) are listed for each ligand in the supporting information.

Ligand hydroxylation

General procedure for ligand hydroxylation: Depending on the ligand 1.00 mmol (**1**–**3** and **6**–**15**) or 0.10 mmol of ligand (**4**–**5**) were dissolved in 5–10 ml solvent (absolute dichloromethane, acetone, methanol or acetonitrile) and added to a solution of 377 mg (1.00 mmol, for **1**–**3** and **6**–**15**) or 37.7 mg (0.10 mmol, for **4**–**5**) [Cu(MeCN)$_4$]OTf in 5–10 ml solvent in a Schlenk tube. Subsequently dioxygen was passed through the solution for 15 min. For the workup 10 ml hydrochloric acid (1 mol L^{-1}) were added and stirred for one hour at room temperature and additionally for one hour under reflux. After cooling the organic solvent was removed and the remaining reaction mixture extracted three times with dichloromethane. The combined organic phases were dried over sodium sulfate, filtered and concentrated using a rotary evaporator for GC-MS analysis. The conversion rate was estimated on the basis of the integrals of the different fractions of hydroxylated product and reactant.

Low-temperature stopped-flow measurements

[Cu(CyonDED)]OTf with dioxygen in acetone: 96 mg (0.25 mmol) [Cu(MeCN)$_4$]OTf and 50 mg (0.25 mmol) CyonDED (**12**) were dissolved in 10 ml of absolute acetone. The solution was diluted to a complex concentration of 0.50 mmol L^{-1} and filled into a gastight syringe. Measurements were performed between −94 °C and −55 °C

[Cu(CyonDED)]OTf with dioxygen in dichloromethane: 107 mg (0.283 mmol) [Cu(MeCN)$_4$]OTf and 56 mg (0.28 mmol) CyonDED (**12**) were dissolved in 10 ml absolute dichloromethane. The solution was diluted to a complex concentration of 0.56 mmol L^{-1} and filled into a gastight syringe. Measurements were performed between −93 °C and −39 °C.

[Cu(CyonDiPED)]OTf with dioxygen in acetone: 92 mg (0.24 mmol) [Cu(MeCN)$_4$]OTf and 55 mg (0.24 mmol) CyonDiPED (**13**) were dissolved in 10 ml absolute acetone. The solution was diluted to a complex concentration of 0.96 mmol L^{-1} and filled in a gastight syringe. Measurements were performed between −92 °C and −49 °C.

Single crystals

[Cu(BDiPED)Cl]: 23 mg (0.10 mmol) BDiPED (**2**) and 9.9 mg (0.10 mmol) copper(I) chloride were dissolved in acetonitrile each. The ligand solution was added to the copper(I) salt solution dropwise and stirred for about 30 min. After a few days at room temperature crystals were obtained.

[Cu_2(O–CyDiPED)$_2$$Cl_2$]: 119 mg (0.500 mmol) CyDiPED (**9**) and 85.2 mg (0.500 mmol) copper(II) chloride dihydrate were dissolved in 3 ml acetone (or acetonitrile) each. Under stirring the ligand solution was added to the copper(I) salt solution dropwise. Subsequently a few drops of diethyl ether were added, and the solution was stirred for 30 min. After three days at room temperature dark green crystals were obtained. Crystals with the same orthorhombic unit cell and molecular structure of the complex were obtained, but the co-crystallized solvent was acetonitrile instead of acetone.

[Cu(CyDiPED)$_2$][$CuCl_2$]: In a glovebox 119 mg (0.500 mmol) CyDiPED (**9**) and 49.5 mg (0.500 mmol) copper(I) chloride were dissolved in 3 ml dry acetonitrile (or dichloromethane) each. The ligand solution was added to the copper(I) salt solution dropwise and stirred for 30 min. After a few days at room temperature crystals were obtained. Crystals with the same triclinic unit cell and molecular structure of the complex were obtained, just with dichloromethane instead of acetonitrile.

[Cu_2(CyonEPy)$_2$](OTf)$_2$: 20.2 mg (0.100 mmol) CyonEPy (**14**) and 37.7 mg (0.100 mmol) [Cu(MeCN)$_4$]OTf were dissolved in THF each. The ligand solution was added to the copper(I) salt solution dropwise and stirred for about 30 min. After a few days at room temperature crystals were obtained.

[Cu(CyonMPy)(MeCN)]OTf: 18.8 mg (0.100 mmol) CyonMPy (**15**) and 37.7 mg (0.100 mmol) [Cu(MeCN)$_4$]OTf were dissolved in methanol each. The ligand solution was added to the copper(I) salt solution dropwise and stirred for about 15 min. After a few days at room temperature colourless crystals were obtained.

Deposition Numbers 2050690 (for [Cu(**2**)Cl]), 2050691 (for [Cu(**9**)$_2$][$CuCl_2$]), 2050692 (for [Cu_2(**14**)$_2$](OTf)$_2$), 2050693 (for [Cu(**15**)(MeCN)]OTf), and 2050694 (for [Cu_2(O-**9**)$_2$$Cl_2$) contain the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service www.ccdc.cam.ac.uk/structures.

Acknowledgements

Open access funding enabled and organized by Projekt DEAL.

Conflict of Interest

The authors declare no conflict of interest.

Keywords: Copper · Dioxygen activation · Kinetics · Selective hydroxylation · Stopped-flow

[1] a) E. I. Solomon, D. E. Heppner, E. M. Johnston, J. W. Ginsbach, J. Cirera, M. F. Qayyum, M. T. Kieber-Emmons, C. H. Kjaergaard, R. G. Hadt, L. Tian, *Chem. Rev.* **2014**, *114*, 3659–3853; b) M. H. Sazinsky, S. J. Lippard in *Metal Ions in Life Sciences. Sustaining Life on Planet Earth: Metalloenzymes Mastering Dioxygen and Other Chewy Gases.* Methane Monooxygenase: Functionalizing Methane at Iron and Copper (Eds.: A. Sigel, H. Sigel, R. K. O. Sigel, P. M. H. Kroneck, M. E. S. Torres), Vol.15, Springer, Cham, Switzerland, **2015**, pp. 205–256; c) D. A. Quist, D. E. Diaz, J. J. Liu, K. D. Karlin, *J. Biol. Inorg. Chem.* **2017**, *22*, 253–288; d) M. O. Ross, F. MacMillan, J. Wang, A. Nisthal, T. J. Lawton, B. D. Olafson, S. L. Mayo, A. C. Rosenzweig, B. M. Hoffman, *Science* **2019**, *364*, 566–570.

[2] a) L. Que, W. B. Tolman, *Nature* **2008**, *455*, 333–340; b) S. D. McCann, S. S. Stahl, *Acc. Chem. Res.* **2015**, *48*, 1756–1766.

[3] a) J. I. van der Vlugt, F. Meyer in *Organometallic Oxidation Catalysis* (Eds.: F. Meyer, C. Limberg), Vol. 22, Springer, Berlin Heidelberg, **2007**, pp. 191–240; b) S. E. Allen, R. R. Walvoord, R. Padilla-Salinas, M. C. Kozlowski, *Chem. Rev.* **2013**, *113*, 6234–6458; c) M. E. Ali, M. M. Rahman, S. M. Sarkar, S. B. A. Hamid, *J. Nanomater.* **2014**, *2014*, 1–23.

[4] R. Trammell, K. Rajabimoghadam, I. Garcia-Bosch, *Chem. Rev.* **2019**, *119*, 2954–3031.

[5] C. E. Elwell, N. L. Gagnon, B. D. Neisen, D. Dhar, A. D. Spaeth, G. M. Yee, W. B. Tolman, *Chem. Rev.* **2017**, *117*, 2059–2107.

[6] J. Becker, P. Gupta, F. Angersbach, F. Tuczek, C. Näther, M. C. Holthausen, S. Schindler, *Chem. Eur. J.* **2015**, *21*, 11735–11744.

[7] J. Becker, Y. Y. Zhyhadlo, E. D. Butova, A. A. Fokin, P. R. Schreiner, M. Förster, M. C. Holthausen, P. Specht, S. Schindler, *Chem. Eur. J.* **2018**, *24*, 15543–15549.

[8] a) A. Bijelic, M. Pretzler, C. Molitor, F. Zekiri, A. Rompel, *Angew. Chem. Int. Ed.* **2015**, *54*, 14677–14680; b) M. M. Del Garcia-Molina, J. L. Muñoz-Muñoz, F. Garcia-Molina, P. A. García-Ruiz, F. Garcia-Canovas, *J. Agric. Food Chem.* **2012**, *60*, 6447–6453; c) J. N. Hamann, B. Herzigkeit, R. Jurgeleit, F. Tuczek, *Coord. Chem. Rev.* **2017**, *334*, 54–66.

[9] R. Trammell, L. D'Amore, A. Cordova, P. Polunin, N. Xie, M. A. Siegler, P. Belanzoni, M. Swart, I. Garcia-Bosch, *Inorg. Chem.* **2019**, *58*, 7584–7592.

[10] a) M. Paul, M. Teubner, B. Grimm-Lebsanft, C. Golchert, Y. Meiners, L. Senft, K. Keisers, P. Liebhäuser, T. Rösener, F. Biebl, et al., *Chem. Eur. J.* **2020**, *26*, 7556–7562; b) W. Keown, T. A. G. Large, L. Chiang, E. C. Wasinger, T. D. P. Stack, *Chem. Commun.* **2019**, *55*, 7390–7393.

[11] R. Trammell, Y. Y. See, A. T. Herrmann, N. Xie, D. E. Díaz, M. A. Siegler, P. S. Baran, I. Garcia-Bosch, *J. Org. Chem.* **2017**, *82*, 7887–7904.

[12] B. Schönecker, T. Zheldakova, Y. Liu, M. Kötteritzsch, W. Günther, H. Görls, *Angew. Chem. Int. Ed.* **2003**, *42*, 3240–3244.

[13] B. Schönecker, T. Zheldakova, C. Lange, W. Günther, H. Görls, M. Bohl, *Chem. Eur. J.* **2004**, *10*, 6029–6042.

[14] B. Schönecker, C. Lange, T. Zheldakova, W. Günther, H. Görls, G. Vaughan, *Tetrahedron* **2005**, *61*, 103–114.

[15] Y. Y. See, A. T. Herrmann, Y. Aihara, P. S. Baran, *J. Am. Chem. Soc.* **2015**, *137*, 13776–13779.

[16] A. Hoffmann, M. Wern, T. Hoppe, M. Witte, R. Haase, P. Liebhäuser, J. Glatthaar, S. Herres-Pawlis, S. Schindler, *Eur. J. Inorg. Chem.* **2016**, 4744–4751.

[17] K. D. Karlin, D. H. Lee, S. Kaderli, A. D. Zuberbühler, *Chem. Commun.* **1997**, 475–476.

[18] M. Schatz, M. Becker, F. Thaler, F. Hampel, S. Schindler, R. R. Jacobson, Z. Tyeklár, N. N. Murthy, P. Ghosh, Q. Chen, et al., *Inorg. Chem.* **2001**, *40*, 2312–2322.

[19] O. Sander, A. Henß, C. Näther, C. Würtele, M. C. Holthausen, S. Schindler, F. Tuczek, *Chem. Eur. J.* **2008**, *14*, 9714–9729.

[20] O. Bienemann, A. Hoffmann, S. Herres-Pawlis, *Rev. Inorg. Chem.* **2011**, *31*, 83–108.

[21] O. Bienemann, R. Haase, A. Jesser, T. Beschnitt, A. Döring, D. Kuckling, I. Dos Santos Vieira, U. Flörke, S. Herres-Pawlis, *Eur. J. Inorg. Chem.* **2011**, 2367–2379.

[22] I. Blain, M. Giorgi, I. de Riggi, M. Réglier, *Eur. J. Inorg. Chem.* **2000**, *2000*, 393–398.

[23] A. S.-K. Tsang, A. Kapat, F. Schoenebeck, *J. Am. Chem. Soc.* **2016**, *138*, 518–526.

[24] a) E. C. Constable, *Metals and Ligand Reactivity. An Introduction to the Organic Chemistry of Metal Complexes*, VCH Verlagsgesellschaft mbH, Weinheim, **1996**; b) M. Schatz, M. Becker, O. Walter, G. Liehr, S. Schindler, *Inorg. Chim. Acta* **2001**, *324*, 173–179; c) T.-D. J. Stumpf, M. Steinbach, C. Würtele, J. Becker, S. Becker, R. Fröhlich, R. Göttlich, S. Schindler, *Eur. J. Inorg. Chem.* **2017**, 4246–4258.

[25] P. L. Holland, K. R. Rodgers, W. B. Tolman, *Angew. Chem. Int. Ed.* **1999**, *38*, 1139–1142.

[26] a) K. V. N. Esguerra, Y. Fall, L. Petitjean, J. P. Lumb, *J. Am. Chem. Soc.* **2014**, *136*, 7662–7668; b) Z. Huang, J. P. Lumb, *Angew. Chem. Int. Ed.* **2016**, *55*, 11543–11547; c) K. V. N. Esguerra, J. P. Lumb, *Angew. Chem. Int. Ed.* **2018**, *57*, 1514–1518; d) Z. Huang, O. Kwon, H. Huang, A. Fadli, X.

Marat, M. Moreau, J.-P. Lumb, *Angew. Chem.* **2018**, *130*, 12139–12143; e) M. S. Askari, L. A. Rodríguez-Solano, A. Proppe, B. McAllister, J.-P. Lumb, X. Ottenwaelder, *Dalton Trans.* **2015**, *44*, 12094–12097.
[27] M. Weitzer, M. Schatz, F. Hampel, F. W. Heinemann, S. Schindler, *J. Chem. Soc. Dalton Trans.* **2002**, 686–694.
[28] H. Sterckx, B. Morel, B. U. Maes, *Angew. Chem. Int. Ed.* **2019**, *58*, 7946–7970.
[29] L. Krause, R. Herbst-Irmer, G. M. Sheldrick, D. Stalke, *J. Appl. Crystallogr.* **2015**, *48*, 3–10.
[30] G. M. Sheldrick, *Acta Crystallogr. Sect. A* **2015**, *71*, 3–8.
[31] G. M. Sheldrick, *Acta Crystallogr. Sect. C* **2015**, *71*, 3–8.

Manuscript received: March 4, 2021
Revised manuscript received: March 31, 2021
Accepted manuscript online: April 1, 2021