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Reactivity of Copper(I) Complexes Containing Ligands Derived from (1*S*,3*R*)-Camphoric Acid with Dioxygen

Fabian Stöhr,[a, b] Niclas Kulhanek,[b] Jonathan Becker,[a] Richard Göttlich,*[b] and Siegfried Schindler*[a]

Amine derivatives prepared from camphoric acid were used as ligands for the synthesis of corresponding copper(I) complexes. Their reactivity towards dioxygen was analyzed. The formation of a short-lived bis(μ-oxido)copper complex was spectroscopically observed during the reaction of the copper(I) complex with (1*R*, 3*S*)-N^1,N^1,N^3,N^3-Tetramethyl-1,2,2-trimethylcyclopentane-1,3-diamine as a ligand. Furthermore, a regioselective demethylation of the ligand system was detected. Deuteration of the methyl groups of the ligand allowed crystallization and characterization of the bis(μ-oxido)copper complex. Derivatives of the ligand with pyridine residues caused suppression of the reactivity of the corresponding copper(I) complexes towards dioxygen. Additionally, the ligand system could be modified for intramolecular oxygenation reactions with benzaldehyde that led to the formation of salicylaldehyde, a selective hydroxylation in *ortho* position.

Introduction

Copper enzymes are able to activate dioxygen under ambient conditions and thereby catalyze the oxidation of organic substrates.[1] Examples include the enzyme tyrosinase, which catalyzes the selective oxidation of tyrosine to dopaquinone[2] and furthermore methane monooxygenase, which is capable to oxidize methane selectively to methanol.[3]

In order to understand the binding of dioxygen to the active site in these enzymes, various copper(I) complexes as model compounds were synthesized and investigated in the past.[4,5–9] A wide variety of so called "oxygen adduct" complexes could thus be detected and in some cases also structurally characterized e.g. bis(μ-oxido)copper complexes.[10,11,12–14] These compounds are usually highly reactive and often lead to intramolecular ligand hydroxylations.[5–7,15,16,17,18] To take advantage of this reactivity, ligand systems were functionalized with substrates to be oxidized.[6,7,17,18] For this purpose, aldehydes and ketones are typically bound to ligands *via* imine condensations in order to simply release the oxidized substrates by cleaving the imine after the reaction. With this "click and cleave" method, non-activated, aliphatic[7] and aromatic[6] systems up to complex steroid systems[17,18] could be hydroxylated *via* C–H activation. In addition, this method has already been used successfully as a key step in the synthesis of C-12 hydroxylated steroids in high yields.[18] Moreover, external substrates have already been successfully oxygenated using these active oxygen adduct intermediates.[8,19]

Rigid ligand systems can stabilize dinuclear *trans*-μ-1,2-peroxo-dicopper(II) complexes.[12,20] *Tolman* and co-workers observed an equilibrium between *side-on* peroxido copper complexes and bis(μ-oxido)copper complexes applying an alkylated derivative of the small macrocycle triazacyclononane as ligand.[13] Furthermore, *Itoh* and co-workers could demonstrate for a series of tridentate ligands based on a cyclic diamine unit that a higher rigidity of these ligand systems led to a preferred formation of bis(μ-oxido)copper complexes.[21] In this context we therefore looked for a system that was as easily accessible and as rigid as possible, to allow for a possible crystallization of an oxygen intermediate complex. Based on previous work ligands derived from camphoric acid should satisfy these claims.[22]

Ligand systems containing guanidine residues have been used successfully to stabilize "oxygen adduct" complexes.[23,24,25] These include, among others, the ligand TMG_3tren[26] or ligands based on 1,3-propanediamine, where corresponding copper(I) complexes were able to hydroxylate phenolates using dioxygen.[24] In addition, the guanidine-containing ligands **1** and **2** (Figure 1) could be synthesized from camphoric acid. Copper(I) complexes with these ligands reacted with dioxygen to form bis(μ-oxido) copper complexes. However, so far they have not been used for oxidation reactions of substrates.[27]

With this background we decided to adapt other groups than guanidine residues to the system. For this purpose, the use of various residual groups (Scheme 1, **3a**–**3c**) was first investigated to test corresponding copper(I) complexes with these ligands for possible dioxygen activation. Selective intra-

[a] *F. Stöhr, Dr. J. Becker, Prof. Dr. S. Schindler*
Institute for Inorganic and Analytical Chemistry,
Justus-Liebig-University Gießen,
Heinrich-Buff-Ring 17, 35392 Gießen, Germany
E-mail: siegfried.schindler@ac.jlug.de
https://www.uni-giessen.de/fbz/fb08/Inst/iaac/schindler
[b] *F. Stöhr, N. Kulhanek, Prof. Dr. R. Göttlich*
Institute for Organic Chemistry,
Justus-Liebig-University Gießen,
Heinrich-Buff-Ring 17, 35392 Gießen, Germany
E-mail: richard.goettlich@org.chemie.uni-giessen.de
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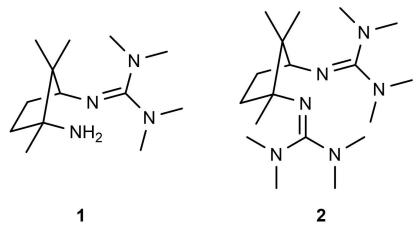


Figure 1. Camphor-like ligands used in previous work.[27] Complexation with Cu(I) and reaction with dioxygen resulting in a bis-(μ-oxido) copper complex.

3a: R^1, R^2, R^3, R^4 = Me
3b: R^1 = 2-Methylpyridine; R^2, R^3, R^4 = Me
3c: R^1, R^3 = 2-Methylpyridine; R^2, R^4 = Me
4a: R^1, R^2 = Me
4b: R^1 = Me, R^2 = Et
4c: R^1, R^2 = Et

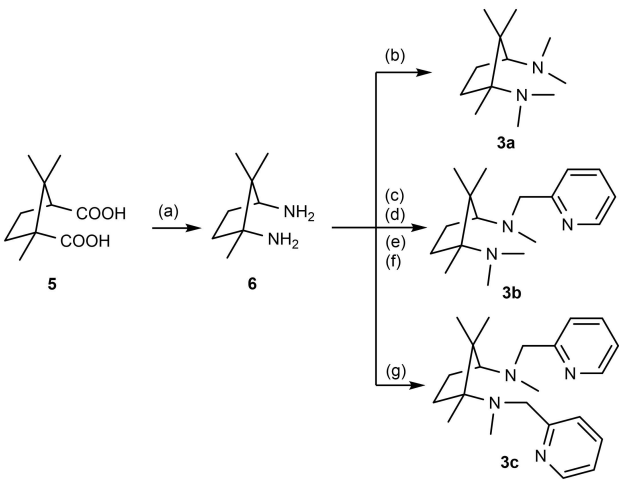
Scheme 1. Camphor-like ligands used in this work.

molecular ligand hydroxylation should be achieved afterwards by further modification of this ligand system (Scheme 1, **4a**–**4c**).

Results and Discussion

Synthesis of the Ligands and Characterization of Corresponding Copper Complexes

Camphoric acid (**5**) is commercially available and therefore, the synthesis of the ligand systems **3a**–**3c** (Scheme 2) started with the conversion of **5** in a Schmidt reaction to diamine **6**,[28] which functions as a common precursor for all further ligands described herein. Ligand **3a** could be obtained in good yields applying Eschweiler-Clarke conditions (Scheme 2b).[29] To prepare ligand **3b**, diamine **6** was first selectively protected at the sterically less hindered amine function with benzoyl chloride (Scheme 2c).[30] The subsequent methylation of the free amine function was carried out again applying Eschweiler-Clarke conditions (Scheme 2d).[30] After deprotection (Scheme 2e),[31] an imine condensation was carried out with 2-formylpyridine. This was followed by reduction with $NaBH_4$ and subsequent reductive methylation (Scheme 2f), which led to ligand **3b**. Ligand **3c** could be obtained from diamine **6** by adapting the reaction conditions of step f (Scheme 2) and by an increase of the equivalents of the reagents.



Scheme 2. (a) NaN_3, H_2SO_4, $CHCl_3$, 55 °C, 77%. (b) Formic acid, formaldehyde, reflux, 83%. (c) Benzoyl chloride, EtOH 69%. (d) Formic acid, formaldehyde, reflux, 83%. (e) HCl reflux, 81%. (f) 1.) 2-Formylpyridine, Na_2SO_4, MeOH, reflux 2.) $NaBH_4$, MeOH 3.) Formaldehyde, $NaCNBH_3$, MeOH 72%. (g) 1.) 2-Formylpyridine, Na_2SO_4, MeOH, reflux 2.) $NaBH_4$, MeOH 3.) Formaldehyde, $NaCNBH_3$, MeOH 26%.

With these ligands at hand, their complexation properties in combination with copper ions were examined. Starting with **3a**, it was first reacted with $[Cu(CH_3CN)_4]OTf$ in a ratio of 1:1 in acetone. Crystals could be obtained, which were structurally analyzed. However, in contrast to the expected copper complex the protonated triflate salt of **3a** was obtained (The crystallographic data are presented in the Supporting Information). The protons presumably came from the solvent acetone. Therefore, DCM was used instead but still it was not possible to obtain/crystallize a copper complex as a product. A possible reason for this could be that a complex in a 2:1 ratio of ligand to copper ion is formed as well and thus leading to a product mixture that did not allow to obtain a clean product. Problems with bidentate ligands that tend to form complexes in a ligand to copper(I) ratio of 1:2 have already been described previously.[6,10]

To avoid this problem, one equivalent of PPh_3 was added to the complex solution, on the one hand to block a free coordination site at the copper, and on the other hand to enforce crystallization. Thus, yellow colored crystals of a copper (I) complex were obtained in which, as expected, the copper(I) ion is coordinated in a trigonal planar geometry by PPh_3 and the chelating diamine **3a** (Figure 2).

The reaction of ligand **3b** with $[Cu(CH_3CN)_4]ClO_4$ led to the formation of crystals in which two ligands bind to the copper center. Interestingly, one ligand chelates *via* a pyridine and an amine residue, while a second ligand coordinates to the copper

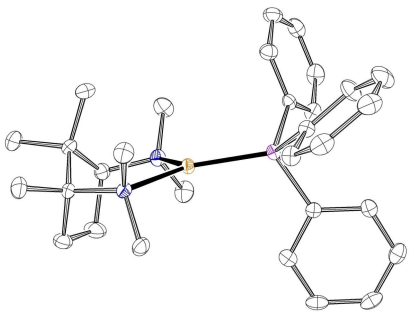


Figure 2. Molecular Structure of $[Cu(3a)(PPh_3)]^+$. Hydrogen atoms and the triflate anion are omitted for clarity. Ellipsoids are drawn at 50% probability.

center only *via* a pyridine residue (Figure 3). The ligand obviously does not act as tridentate ligand. This could be caused by a *syn*-pentane interaction.[32]

When ligand **3c** was reacted with $[Cu(CH_3CN)_4]OTf$ in a 1:1 ratio a yellow colored oil was obtained. Complexation with CuCl in THF caused formation of yellow colored and crystalline small plates, which could be examined using SC-XRD (Figure 4). Here **3c** acts as tetradentate ligand, as has already been described in the literature for other N^4 ligands,[33] however with $CuCl_2^-$ as an anion.

Attempting to react the ligand with two equivalents of $[Cu(CH_3CN)_4]OTf$ resulted in a disproportionation reaction. After filtration (to remove the metallic copper) and evaporating the solvent under ambient conditions, a blue powder was obtained. Dissolving the residue in methanol followed by a slow evaporation, led to blue colored crystals, which turned out to be the copper(II) complex with **3c** as ligand (The crystallographic data are presented in the Supporting Information).

To investigate the influence of methyl and ethyl groups on possible ligand hydroxylation, the ligands **4a**–**4c** were synthesized to obtain more detailed information on selective ligand hydroxylation. Benzaldehyde was selected as a test substrate to be oxygenated, since previous studies have already been successful in demonstrating high-conversion hydroxylations near the maximum of 50% on aromatic systems using copper(I) and dioxygen with bis(μ-oxido)copper complexes as reactive intermediates.[6,15,34] The synthesis started from the benzoyl-protected amine **7** which was initially prepared by slight

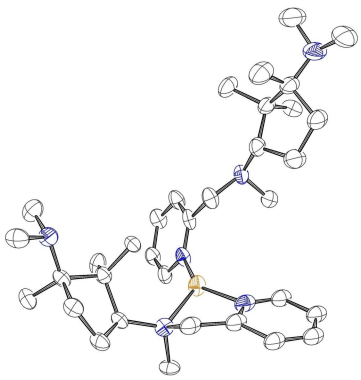


Figure 3. Molecular Structure of $[Cu(3b)_2]^+$. Hydrogen atoms and perchlorate anion are omitted for clarity. Ellipsoids are drawn at 50% probability.

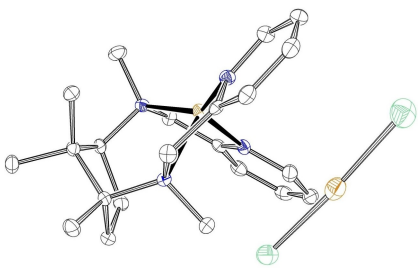
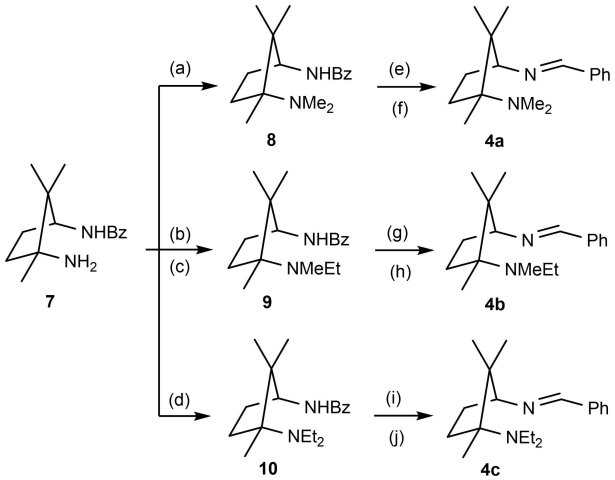


Figure 4. Molecular Structure of [Cu(3c)] $[CuCl_2]$. Hydrogen atoms are omitted for clarity. Ellipsoids are drawn at 50% probability.



Scheme 3. (a) Formic acid, formaldehyde, reflux, 83%. (b) EtI 5 eq., Na_2CO_3, EtOH, reflux 81%. (c) Formaldehyde, $NaCNBH_3$, rt, 96%. (d) EtI 10 eq., Na_2CO_3, MeCN, reflux 65%. (e),(g),(i) HCl, reflux, 81–91%. (f),(h),(j) Benzaldehyde, Na_2SO_4, MeOH reflux, 56–81%.

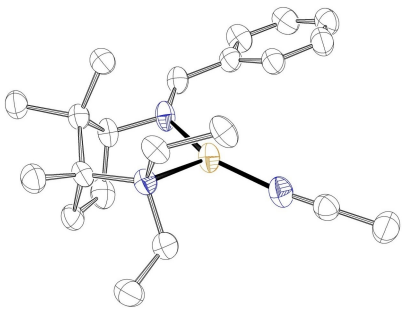


Figure 5. Molecular Structure of $[Cu(4c)(CH_3CN)]^+$. Hydrogen atoms and triflate anion are omitted for clarity. Ellipsoids are drawn at 50% probability.

modifications to the literature.[30] This was followed by different alkylation reactions to receive the alkylated amines **8**–**10**.[30] After deprotection with HCl[31] and subsequent imine condensations the ligands **4a**–**4c** were obtained (Scheme 3).

Single crystals could be obtained from the HCl salts of the ligand systems **4a** and **4b**. The crystallographic data are presented in the Supporting Information. Quite unexpected, these imines turned out to be quite stable, even under acidic conditions.

Additionally it was possible to obtain single crystals from the complex of $[Cu(CH_3CN)_4]OTf$ and **4c**. This ligand acts as a chelate ligand, and one acetonitrile molecule coordinates to the copper center (Figure 5).

Reactivity of the Copper(I) Complexes with Dioxygen

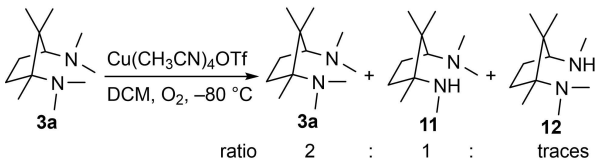
Due to the problems with obtaining copper(I) complexes as simple 1:1 (copper ion to ligand ratio) $[Cu(L)]^+$ solids the reactions with dioxygen were performed by mixing solutions of

copper(I) salts with the ligand in an equimolar ratio as described previously.[35]

When a solution of ligand **3a** and $[Cu(CH_3CN)_4]OTf$ in DCM was reacted with dioxygen at −80 °C in a bench top experiment an immediate color change from a yellow to a very dark brown colored solution was observed. After warming to room temperature, the solution turned irreversibly to a dark green color. After decomplexation with aqueous ammonia, demethylation of the ligand system was indicated by means of ESI-MS. Using GC-MS, two demethylated species could be detected and the position of the demethylation could be determined on the basis of the fragmentation pattern. An approximate ratio of 2:1 and traces of **12** could be found (Scheme 4).

The two demethylated species **11** and **12** could be separated as a mixture from ligand **3a** by means of column chromatography and the structures of these compounds were confirmed by NMR. Conversion to the corresponding HCl salts of the mixture of the demethylated species yielded crystals which were structurally examined. It turned out as the demethylated component **11** in form of an HCl salt (The crystallographic data are presented in the Supporting Information).

Related dealkylation reactions were reported previously by Stack and co-workers including the observation of a bis(μ-oxido)copper complex as the reactive intermediate.[10] In order to clarify whether such an oxygen intermediate leads to the observed demethylation here as well, the complex solution of ligand **3a** and $[Cu(CH_3CN)_4]OTf$ was examined using low temperature stopped-flow techniques. At low temperatures, a transient intermediate could be observed spectroscopically, characterized by two significant absorbance maxima near 300 nm (limit of the detector) and 414 nm (Figure 6). Based on earlier work, this result supports the formation of bis(μ-oxido) copper complex[6–9,24,27,36] and, furthermore, is in excellent agreement with our previous investigation of related copper(I) complexes with the monoguanidine ligand 2-[3-(dimethylamino)propyl]-1,1,3,3-tetramethylguanidine (TMGdmap) and the related bis(guanidine) 1,3-bis(*N*,*N*,*N*′,*N*′- tetramethylguanidino)propane (btmgp).[25]



Scheme 4. Observed oxidation products after the reaction at −80 °C.

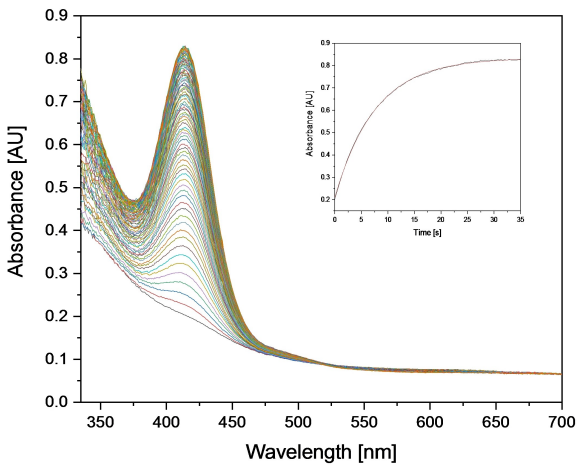


Figure 6. Time-resolved UV/Vis spectra of the reaction of [Cu(3a)]OTf ($c = 0.5 \times 10^{-3}$ M) with dioxygen ($c = 2.15 \times 10^{-3}$ M) in DCM at −89 °C for 35 s. The inset shows the absorbance vs time at λ = 414 nm.

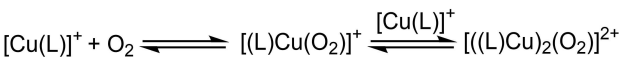
The absorbance vs. time trace at 414 nm can be fitted with a one exponential function and a rate constant of $k_{obs} = 0.13\ s^{-1}$ could be calculated, in line with our results for the reaction of dioxygen with the complexes $[Cu(TMGdmap)]^+$ and $[Cu(btmgp)]^+$. Therefore, no further kinetic measurements were performed. In a first step a mononuclear superoxido copper complex is formed that reacts in a fast consecutive step to the bis(μ-oxido)copper complex according to Scheme 5.

As described in great detail previously the rate limiting step is the formation of a superoxido complex.[25] With an excess of dioxygen a first order rate law (Eq. 1) can be applied.

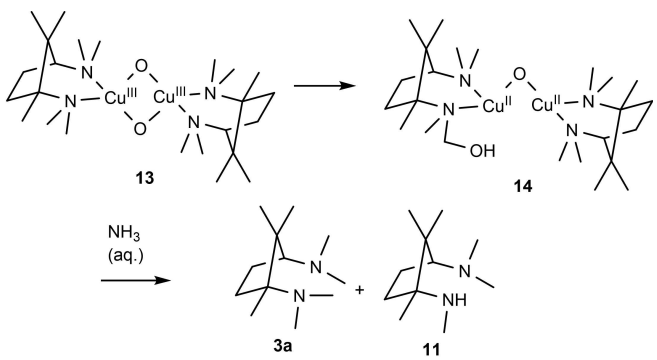
$$v = k_{obs} \times c_{[Cu(L)]+} \quad \text{with } k_{obs} = k_1[O_2] \tag{1}$$

Detailed kinetic investigations by *Stack* and co-workers on similar complexes with cyclohexane derivatives as ligands can be applied here for a mechanistic explanation and the cleavage of the methyl groups (Scheme 6).[10] The bis(μ-oxido)copper complex **13** leads to intramolecular ligand hydroxylation. The intermediate hemiaminal **14** is split into formaldehyde and the amine **11** after aqueous work-up. Based on previous work, this also explains that the conversion of the reaction to the demethylated ligands cannot exceed 50 %.[6]

It is well known by us and others, that deuteration of alkyl groups can be used to suppress an attack on these groups.[37] Deuteration of diamine **6** with deuterated formaldehyde and



Scheme 5. Formation of the bis(μ oxido)copper complex.



Scheme 6. Proposed pathway for the demethylation of amine **3a** to amine **11**. Charges omitted.

deuterated formic acid yielded a D-12 analogue of **3a**. Reaction of the deuterated ligand together with $[Cu(CH_3CN)_4]PF_6$ and dioxygen at −80 °C in DCM yielded brown crystals, which turned out to be the proposed bis(μ-oxido)copper complex (Figure 7).

The distance between the oxygen atoms is 2.218 Å, which indicates a cleavage of the dioxygen bond. The distance is smaller than in *Stack's*[10] bis(μ-oxido)copper complex (2.334 Å), while the distance between the two copper ions is longer (2.851 Å vs. 2.744 Å). However, in both cases the copper atoms are ligated in nearly square planar fashion.

The observed selectivity in the cleavage of the methyl groups might be caused by the closer distance between the protons on the labile methyl groups and the oxygen atoms (2.108 Å vs. 2.234 Å) which corresponds to observed selectivity above. The closer distance is presumably directed by the methyl group carried by the carbon 1*R*. One possibility for the hydroxylation mechanism of aliphatic C–H bonds is described as the radical abstraction of hydrogen and subsequent rebinding of the oxygen.[17,18,38] This mechanism might apply to our system, at least with regard to selectivity.

When the tridentate ligand **3b** was reacted with $[Cu(CH_3CN)_4]$Otf and dioxygen at −80 °C in DCM with dioxygen only an irreversible color change to a dark green color could be observed. After warming to room temperature and decomplexation with aqueous ammonia, it turned out that only traces of the ligand system were demethylated and/or hydroxylated by means of ESI-MS. Isolation of these species was unsuccessful due to the minimal conversion that could not be detected by GC-MS. Furthermore, stopped-flow measurements did not show the formation of a reactive intermediate. Most likely, this is caused due to the formation of a complex with a 2:1 ratio of ligand to copper (despite the equimolar premixing), which was detected in the solid.

More or less expected from the molecular structure of the copper(I) complex with the ligand **3c**, a mixture of this ligand together with $[Cu(CH_3CN)_4]$OTf in DCM turned out to be inert towards dioxygen. No color change of the yellow colored solution was observed. This suggests that the complex cannot activate dioxygen under these conditions, presumably, due to its steric and electronic properties.

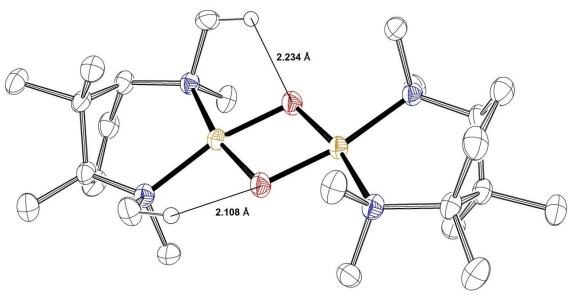


Figure 7. Molecular structure of $[Cu_2(3ad_{12})_2O_2]^{2+}$. Hydrogen atoms (except the nearest C–H's to O), the PF_6 anions and solvent molecules are omitted for clarity. Ellipsoids are drawn at 50% probability.

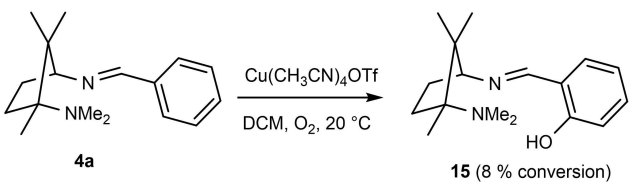
The reactivity of copper(I) complexes with the ligands **3a**–**3c** was investigated especially to detect dioxygen adduct complexes as intermediates. This was important prior to the investigations with ligands **4a**–**4c** that were chosen for possible intramolecular hydroxylation reactions because more recently an alternative radical reaction pathway was observed based on the formation of a hydroperoxido complex instead of a bis(μ-oxido)copper intermediate.[34]

When ligand **4a** was reacted with copper triflate in DCM with dioxygen (Scheme 7) at room temperature a color change from a yellow to a green color was observed. After treating the solution with aqueous ammonia to remove the copper(II) ions and separating it from the organic phase, the organic residue was analyzed by means of ESI-MS and NMR. Ligand hydroxylation could be determined, and an NMR analysis showed that a hydroxylation in the *ortho* position had occurred. With the integral ratio of the imine proton signals, a ratio of 92 to 8 could be determined.

The low conversion observed in this reaction could be caused by the fact that a possible oxygen adduct intermediate might not be sufficiently stabilized at room temperature. Therefore, the influence of temperature on the reaction was investigated. It was observed that the conversion increased with lower temperatures and approached a maximum of 17% (Table S1).

Additionally, the reaction was carried out in different solvents. However, in contrast to previous findings, applying acetone,[6,7] acetonitrile or methanol suppressed the hydroxylation reaction completely. Furthermore, since an influence of the anions on the formation of oxygen intermediates had been described in the literature,[39] various copper(I) salts were investigated for this reaction (Table S2). Not surprisingly, no conversion to a hydroxylated product could be detected when CuCl was used. The chloride anion coordinates strongly to the copper ion, competes with the incoming dioxygen and thus binding of oxygen is suppressed. The highest conversion (28%) was observed when the weakly coordinating BF_4 anion was used.

Since the conversion was highest when using $[Cu(CH_3CN)_4]BF_4$, a stopped-flow measurement of the reaction was carried out. The formation of a band at 392 nm could be detected (Figure 8). Since it was not possible, to fit the absorbance vs. time trace at 414 nm with a one exponential function, we thought the band shows the formation of the copper(II) complex with the hydroxylated ligand **15**. For that we decided to synthesize the ligand **15** by an imine condensation reaction with salicylaldehyde. A mixture of this ligand together



4a **15** (8 % conversion)

Scheme 7. First attempt at hydroxylation of ligand **4a**. Conversion was determined using the integral of the imine proton signals.

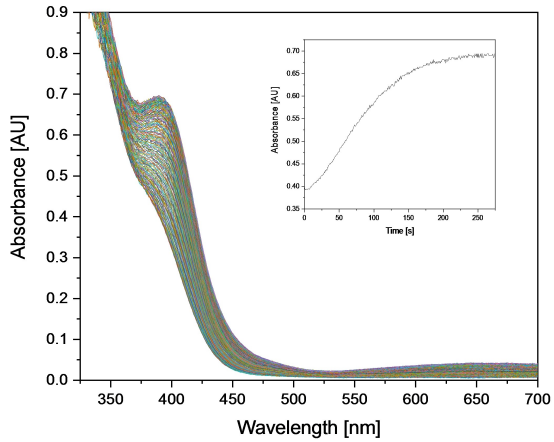


Figure 8. Time-resolved UV/Vis spectra of the reaction of **4a** and $[Cu(CH_3CN)_4]Otf$ ($c = 2\times10^{-3}$ M) with Dioxygen ($c = 2.15\times10^{-3}$ M) in DCM at −89 °C.

with copper(II) triflate was examined by means of UV/Vis. The resulting spectra is presented in the Supporting Information and is in agreement with the final spectrum in the stopped flow measurement. This suggests that the rate limiting step is the formation of the reactive intermediate and the consecutive hydroxylation reaction is much faster. However, it is unclear *via* which intermediate the reaction proceeds.

The reaction of dioxygen with the copper complexes with the ligands **4b** and **4c** under the same conditions did not show any oxygenation reactions at all. Most likely substitution of one – or both – methyl groups by ethyl groups increased the sterical hinderance to such an extent that no dinuclear bis(μ-oxido) copper complex can form and therefore no hydroxylation was observed. Obviously, the alternative reaction pathway through a hydroperoxido complex mentioned above also did not take place here.

Conclusion

C–H activation is a very important area in chemistry, and with our previous developed clip-and-cleave system we could demonstrate that facile oxygenation reactions of aldehydes and ketones are possible by applying simple copper(I) complexes and dioxygen as the sole oxidant. However, there is still room for optimization of this reaction and therefore we have been looking for additional ligand systems that might provide even better results. In this regard we investigated copper complexes with ligand systems based on camphor derivatives. We found that the copper(I) complex of the tetramethylated ligand (1*R*, 3*S*)-N^1,N^1,N^3,N^3-tetramethyl-1,2,2-trimethylcyclopentane-1,3-diamine caused a selective, intramolecular demethylation when reacted with dioxygen. A stopped-flow analysis of this reaction showed the formation of a bis(μ-oxido)copper complex as a reactive intermediate. Following up on this, we were able to successfully crystallize and structurally characterize the oxygen intermediate through deuteration of the sensitive methyl groups. In contrast, functionalization of the ligand framework with pyridine residues lead to absence of any detectable oxygen intermediate.

However, it was possible to modify the ligand system in such a way that an intramolecular ligand hydroxylation on benzaldehyde in *ortho* position became accessible and salicylaldehyde was obtained. This kind of reactivity could only be observed for one of our ligands, the twice methylated one. The introduction of ethyl groups again suppressed this reactivity. We are currently working on increasing the conversion of these reactions and furthermore we believe we now have a good basis for to achieve stereoselective oxygenation reactions of substrates in the near future.

Experimental Section

General: Chemicals and solvents were purchased from commercial sources. The solvents were distilled and, if necessary, dried using standard procedures. Oxygen free solvents were obtained by redistillation under argon. Preparation under anaerobic conditions were carried out in a glovebox (MBraun) under Argon atmosphere. ^{1}H and ^{13}C spectra were measured on a Bruker Avance II 400 MHz and Bruker Avance III HD 400 MHz spectrometer. The ^{1}H- and ^{13}C-NMR spectra were calibrated against the residual proton and carbon signals of chloroform (δ = 7.26). HRMS(ESI) was measured with an ESI-MS Bruker Mikro-TOF. Elemental analysis was performed by a Thermo FlashEA-1112 Series. GC-MS analysis was carried out using an Agilent Technologies 7820 A GC System coupled with an Agilent Technologies 5977B MSD.

Stopped-Flow measurements: The copper(I) complex solutions were prepared in a glove box by adding the ligand solution to the copper salt solution under stirring and were filled in glass syringes. Saturated solutions of dioxygen were prepared by bubbling dry oxygen through dry DCM in a syringe for 10 minutes. The saturated dioxygen concentration in DCM is 4.3×10^{-3} M at 25 °C.[40] The measurements were performed by a commercial HI-TECH SF-61SX2 instrument (TgK Scientific, Bradford-on-Avon, UK) at −89 ± 1 °C.

(1*R*,3*S*)-Diamino-1,2,2-trimethylcyclopentane (6): Following the literature procedure[28], (1*S*,3*R*)-camphoric acid (9.52 g, 47.5 mmol) was dissolved in 150 ml chloroform and 25 ml conc. H_2SO_4 were added. NaN_3 (9.02 g, 138.7 mmol) was added to the solution in small portions over three hours. The mixture was heated to 55 °C for 18 h. After cooling to rt, 500 ml H_2O were added, the aqueous phase was separated and NaOH was added until the aqueous phase was strongly basic. The aqueous phase was extracted with DCM (3x300 ml) and the combined organic phases were dried with $MgSO_4$. After filtration and removing of the solvent, a colorless solid was obtained (5.21 g, 36.6 mmol, 77 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.02 (dd, J = 8.4, 6.3 Hz, 1H), 2.11–1.99 (m, 1H), 1.93 (s, 4H), 1.72–1.62 (m, 2H), 1.41–1.29 (m, 1H), 1.05 (s, 3H), 0.85 (s, 3H), 0.80 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 61.6, 61.0, 46.4, 38.2, 30.2, 25.6, 22.5, 16.5. HRMS (ESI): calcd. for $C_8H_{18}N_2$ [M + H$^+$] 143.1544, found 143.1544. Crystals of the HCl salt, which were structurally characterized, were obtained by adding HCl in Et_2O (2 m) to 6 dissolved in methanol, evaporating of the solvent, followed by dissolving of the residue in methanol/acetonitrile 1:1 and slow evaporating of the solvent mixture. The crystallographic data are presented in the Supporting Information.

(1*R*,3*S*)-N^1,N^1,N^3,N^3-Tetramethyl-1,2,2-trimethylcyclopentane-1,3-diamine (3a): Diamine 6 (1.092 g, 7.677 mmol) was added to 4 ml formic acid over a period of 20 min at 0 °C. Then 4.5 ml formaldehyde solution (37wt. %) was added dropwise. The solution

refluxed for 18 hours. After cooling to *rt*, the solution was made basic with NaOH solution and extracted with DCM (4×50 ml). The organic phases were combined and dried with Na_2SO_4. After filtration and removing of the solvent, the colorless residue was purified by column chromatography (DCM, MeOH 9:1, 1% NEt_3; silica). The product was obtained as a colorless liquid (1.267 g; 6.388 mmol; 83%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.42 (t, J=9.3 Hz, 1H), 2.28 (s, 6H), 2.23 (s, 6H), 1.90–1.77 (m, 1H), 1.75–1.61 (m, 2H), 1.59–1.48 (m, 1H), 1.10 (s, 3H), 0.99 (s, 3H), 0.90 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 74.8, 67.0, 48.1, 45.8, 40.4, 37.2, 24.7, 21.5, 17.9, 11.5. HRMS (ESI): calcd. for $C_{12}H_{26}N_2$ [M+H$^+$] 199.2169, found 199.2168. $C_{12}H_{26}N_2$: calcd. C 72.66, H 13.21, N 14.12; found C 72.64, H 13.24, N 14.05.

(1*R*,3*S*)-*N*^{1},*N*^{1},*N*^{3},*N*^{3}-Tetramethyl-1,2,2-trimethylcyclopentane-1,3-diamine (d_{12}) ($3ad_{12}$): The reaction was carried out by upscaling the reaction conditions of the synthesis of 3a. (Diamine 6 (2.012 g, 14.14 mmol), formaldehyde d_2 (20 wt%, 20 ml), formic acid d_2 (5 ml), reaction time 48 h) The product was obtained as a colorless liquid (2.419 g, 11.50 mmol, 81%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.42 (t, J=9.3 Hz, 1H), 1.90–1.77 (m, 1H), 1.77–1.60 (m, 2H), 1.60–1.49 (m, 1H), 1.10 (s, 3H), 0.99 (s, 3H), 0.90 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 74.72, 67.23, 48.04, 44.87, 39.54, 37.07, 24.68, 21.55, 17.95, 11.76. HRMS (ESI): calcd. for $C_{12}H_{14}D_{12}N_2$ [M+H$^+$] 211.2922, found 211.2923.

***N*-((1*S*,3*R*)-3-Amino-2,2,3-trimethylcyclopentyl)benzamide (**Scheme 2c **or 7)**: Based on a modified synthesis[30], diamine 6 (1.421 g, 10.00 mmol) was placed in 20 ml dry EtOH and cooled to 0 °C. Benzoyl chloride (1.05 ml, 9.11 mmol) in 20 ml dry EtOH was added dropwise to the solution over 20 min. After slowly warming to *rt*, the solution was stirred for 21 h. After removing of the solvent, the solution was made basic with sat. $NaHCO_3$ solution, extracted with DCM (3x30 ml) and dried with Na_2SO_4. The product was obtained as a colorless solid after purification by column chromatography (DCM, MeOH 9:1, 1% NEt_3; silica) (1.556 g; 6.316 mmol; 69%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.74 (d, J=9.2 Hz), 7.83–7.75 (m, 2H), 7.49–7.36 (m, 3H), 4.34 (ddd, J=9.6, 7.8, 1.7 Hz, 1H), 2.38–2.21 (m, 1H), 1.94–1.79 (m, 1H), 1.74–1.54 (m, 2H), 1.22 (bs, 2H), 1.16 (s, 3H), 0.96 (s, 3H), 0.96 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 165.7, 135.5, 131.0, 128.5, 127.0, 62.4, 59.8, 47.7, 38.4, 30.0, 26.8, 25.1, 16.9. HRMS (ESI): calcd. for $C_{15}H_{22}N_2O$ [M+H$^+$] 247.1805, found 247.1803.

***N*-((1*S*,3*R*)-3-Dimethylamino-2,2,3-trimethylcyclopentyl)-benzamide (Scheme 2d or 8)**: Following the literature procedure[30], the benzoyl protected amine (obtained by Scheme 2c or 7) (1.601 g, 6.500 mmol) was added to 1.5 ml formic acid over a period of 20 min at 0 °C. Then 1.7 ml formaldehyde solution (37wt.%) was added dropwise. The solution refluxed for 18 hours. After cooling to *rt*, the solution was made basic with NaOH solution and extracted with DCM (4x50 ml). The organic phases were combined and dried with Na_2SO_4. After filtration and removing the solvent, the colorless residue was purified by column chromatography (DCM, MeOH 9:1, 1% NEt_3; silica). The product was obtained as a colorless solid (1.480 g; 5.393 mmol; 83%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80–7.72 (m, 2H), 7.53–7.38 (m, 3H), 6.48 (d, J=9.7 Hz, 1H), 4.46 (q, J=9.5 Hz, 1H), 2.26 (s, 6H), 2.22–2.08 (m, 1H), 2.05–1.88 (m, 1H), 1.72–1.58 (m, 1H), 1.50–1.35 (m, 1H), 1.06 (s, 3H), 1.04 (s, 3H), 1.03 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 167.1, 135.2, 131.5, 128.7, 126.9, 67.4, 58.0, 48.1, 40.5, 36.7, 27.4, 23.5, 18.0, 11.7. HRMS (ESI): calcd. for $C_{17}H_{26}N_2O$ [M+H$^+$] 275.2118, found 275.2120. Crystals, which were structurally characterized, were obtained by dissolving 8 in DCM and slow evaporating of the solvent. The crystallographic data are presented in the Supporting Information.

(1*R*,3*S*)-*N*^{1},*N*^{1}-Dimethyl-1,2,2-trimethylcyclopentane-1,3-diamine (Scheme 2e **or** Scheme 3e**)**: Following the literature procedure[31], concentrated HCl (10 ml) was added to the methylated amine (obtained by Scheme 2d or 8) (1.480 g, 5.393 mmol). Then 7.5 ml water was added. The mixture was refluxed for 48 hours. The suspension was then made basic with NaOH solution and extracted with 3x50 ml DCM and 3x50 ml ethyl acetate. The combined organic phases were dried with sodium sulfate. After filtration and removing of the solvent, the product was obtained as a colorless liquid (741 mg, 4.35 mmol, 81%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.89 (t, J=9.2 Hz, 1H), 2.17 (s, 6H), 2.05 (s, 2H), 1.93 (m, 1H), 1.85–1.71 (m, 1H), 1.54–1.40 (m, 1H), 1.25 (m, 1H), 0.94 (s, 3H), 0.85 (s, 3H), 0.82 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 67.4, 61.2, 46.8, 40.1, 36.7, 29.0, 22.7, 16.1, 11.3. HRMS (ESI): calcd. for $C_{10}H_{22}N_2$ [M+H$^+$] 171.1856, found 171.1854.

(1*R*,3*S*)-*N*^{1},*N*^{1},*N*^{3} -Trimethyl- *N*^{3}-(2-pyridinylmethyl)-1,2,2-trimethylcyclopentane-1,3-diamine (3 b) : The amine (obtained by Scheme 2e or **3 e**) (1.920 g, 11.27 mmol) was dissolved in 50 ml MeOH. 2-Formylpyridine (1.8 ml, 19 mmol) and Na_2SO_4 (4 g) were added and the mixture was refluxed under nitrogen for three days. After cooling to room temperature and filtration, $NaBH_4$ (701 mg, 18.5 mmol) was added to the solution. After 17 h the solvent was removed, the residue was made basic with NaOH solution and extracted with DCM (3x150 ml). The organic phases were combined, and the solvent was removed. The residue was dissolved in 20 ml MeOH and 7 ml formaldehyde solution (37wt.%), 100 µL AcOH and $NaCNBH_3$ (1.212 mg, 19.29 mmol) were added. After 20 h the solvent was removed and extracted with DCM (3x150 ml). The organic phases were combined, and the solvent was removed. The residue was purified by column chromatography (diethyl ether, 2% NEt_3; silica gel). The product was obtained as a colorless oil (2.224 g; 8.074 mmol; 72%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51 (m, 1H), 7.71–7.58 (m, 2H), 7.13 (m, 1H), 3.94 (d, J=15.0 Hz, 1H), 3.67 (d, J=15.0 Hz, 1H), 2.89 (t, J=9.3 Hz, 1H), 2.31 (s, 3H), 2.20 (s, 6H), 1.88–1.64 (m, 4H), 1.61–1.52 (m, 1H), 1.07 (s, 3H), 0.96 (s, 3H), 0.88 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 161.5, 149.0, 136.5, 122.5, 121.8, 72.7, 66.1, 63.4, 49.0, 42.3, 40.3, 37.2, 24.1, 19.1, 18.2, 11.4. HRMS (ESI): calcd. for $C_{17}H_{29}N_3$ [M+H$^+$] 276.2434, found 276.2434. $C_{17}H_{29}N_3$: calcd. C 74.13, H 10.61, N 15.26; found C 73.74, H 10.65, N 15.04.

(1*R*,3*S*)-*N*^{1},*N*^{3} -Dimethyl- *N*^{1},*N*^{3}-bis(2-pyridinylmethyl)-1,2,2-trimethylcyclopentane-1,3-diamine (3 c): Diamine **6** (1.01 g, 7.10 mmol) was dissolved in 50 ml MeOH. 2-formylpyridine (2.1 ml, 22 mmol) and 4 g Na_2SO_4 were added and the mixture was refluxed under nitrogen for four days. After cooling to room temperature, the mixture was filtered and $NaBH_4$ (970 mg, 25.6 mmol) was added to the solution. After 24 h the solvent was removed, made basic with NaOH solution and extracted with DCM (3x150 ml). The organic phases were combined and the solvent was removed. The oily, brown residue was taken up in 20 ml AcOH. 1.6 ml Formaldehyde solution (37wt.%) and $NaCNBH_3$ (2.664 g, 42.39 mmol) were added at 0 °C. After warming to room temperature, the solution was made basic with NaOH solution and extracted with DCM (3x150 ml). The combined organic phases were dried with Na_2SO_4. After filtration and removing of the solvent, the residue was purified by column chromatography (diethyl ether, 2% NEt_3; silica). The product was obtained as a colorless oil (648 mg; 1.84 mmol; 26%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.66–8.36 (m, 2H), 7.71–7.57 (m, 4H), 7.17–7.06 (m, 2H), 3.97 (d, J=15.0 Hz, 1H), 3.79–3.64 (m, 3H), 2.93 (t, J=9.4 Hz, 1H), 2.34 (s, 3H), 2.15 (s, 3H), 2.00–1.55 (m, 5H), 1.13 (s, 3H), 1.05 (s, 6H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 162.3, 161.4, 149.0, 148.9, 136.6, 136.5, 122.4, 122.0, 121.8, 121.6, 72.6, 66.6, 63.3, 58.8, 49.5, 42.4, 37.2, 24.3, 18.9, 18.5, 14.1. HRMS (ESI): calcd. for $C_{22}H_{32}N_4$ [M+H$^+$] 353.2700, found 353.2700. $C_{22}H_{32}N_4$: calcd. C 74.96, H 9.15, N 15.89; found C 73.63, H 9.01, N 15.50.

***N*-((1*S*,3*R*)-3-Ethylamino-2,2,3-trimethylcyclopentyl)-benzamide (Scheme 3b)**: Following the literature procedure[30], amine **7** (1.01 g,

4.10 mmol) was dissolved in 20 ml EtOH and Iodoethane (1.3 ml, 16 mmol) and K_2CO_3 (2.20 g, 16.0 mmol) were added. The mixture was refluxed overnight. After evaporation of the solvent the residue was dissolved in 50 ml H_2O and was made basic with sat. $NaHCO_3$ solution. The aqueous phase was extracted three times with 50 ml DCM and the combined organic phases were dried with Na_2SO_4. After filtering and evaporation, the residue was purified with column chromatography (diethyl ether, 2% NEt_3; silica). The product was obtained as colorless solid (912 mg, 3.32 mmol, 81%).^{1}H NMR (400 MHz, $CDCl_3$) δ 8.86 (d, J = 9.6 Hz, 1H), 7.86–7.72 (m, 2H), 7.49–7.35 (m, 3H), 4.34–4.25 (m, 1H), 2.75–2.48 (m, 2H), 2.38–2.22 (m, 1H), 2.08–1.94 (m, 1H), 1.63–1.49 (m, 2H), 1.15 (t, J = 7.1 Hz, 3H), 1.08 (s, 3H), 0.98 (s, 3H), 0.95 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 165.5, 135.6, 131.0, 128.5, 127.0, 66.1, 59.5, 48.7, 36.5, 32.0, 30.2, 25.5, 19.2, 16.8. HRMS (ESI): calcd. for $C_{17}H_{26}N_2O$ [M + H^+] 275.2118, found 275.2120. Crystals, which were structurally characterized, were obtained by dissolving the amine in DCM and slow evaporating of the solvent. The crystallographic data are presented in the Supporting Information.

***N*-((1*S*,3*R*)-3-Ethyl,methylamino-2,2,3-trimethylcyclopentyl)-benzamide (9)**: The monoethylated amine (obtained by Scheme 3b) (3.41 g, 12.4 mmol) was dissolved in 70 ml MeCN and 1.2 ml formaldehyde solution (37 wt.%) was added. After stirring for 30 min., $NaCNBH_3$ (0.86 g, 13.6 mmol) and 13.6 ml AcOH was added at 0 °C. The solution was stirred overnight at *rt*. H_2O (150 ml) was added and the solution was made basic with NaOH. The aqueous phase was extracted with DCM (3x100 ml) and the combined organic phases were dried with Na_2SO_4. After filtration and evaporation of the solvent the product was obtained as colorless solid (3.44 g, 11.9 mmol, 96%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81–7.73 (m, 2H), 7.52–7.39 (m, 3H), 6.89 (d, J = 9.7 Hz, 1H), 4.46–4.35 (m, 1H), 2.74–2.44 (m, 1H), 2.34–2.12 (m, 5H), 2.09–1.93 (m, 1H), 1.72–1.57 (m, 1H), 1.49–1.35 (m, 1H), 1.11–0.94 (m, 12H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 166.9, 135.3, 131.4, 128.7, 127.0, 68.5, 58.3, 48.4, 46.4, 36.3, 35.9, 28.0, 24.27, 18.5, 14.4, 13.3. HRMS (ESI): calcd. for $C_{18}H_{28}N_2O$ [M + H^+] 289.2274, found 289.2272. Crystals, which were structurally characterized, were obtained by dissolving **9** in DCM and slow evaporating of the solvent. The crystallographic data are presented in the Supporting Information.

***N*-((1*S*,3*R*)-3-Diethylamino-2,2,3-trimethylcyclopentyl)-benzamide (10)**: Amine **7** (3.26 g, 13.2 mmol) was dissolved in 20 ml dry MeCN and Iodoethane (10.7 ml, 132 mmol) and K_2CO_3 (18.3 g, 132 mmol) were added. The mixture was refluxed over four days under N_2. After cooling to *rt*, the solvent was evaporated, and 100 ml H_2O was added. The mixture was made basic with sat. $NaHCO_3$ solution and extracted with DCM (3x100 ml). After filtration and evaporation of the solvent the product was obtained as colorless solid after column chromatography (diethyl ether, 2% NEt_3; silica). (2.60 g, 8.60 mmol, 65%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74–7.67 (m, 2H), 7.45–7.26 (m, 4H), 4.31–4.20 (m, 1H), 2.65–2.47 (m, 4H), 2.24–1.99 (m, 2H), 1.65–1.51 (m, 1H), 1.46–1.33 (m, 1H), 1.02 (s, 3H), 1.00–0.92 (m, 12H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 166.7, 135.4, 131.2, 128.5, 127.0, 69.3, 58.8, 49.1, 46.3, 43.9, 35.4, 28.8, 24.7, 19.1, 17.4, 15.3, 11.4. HRMS (ESI): calcd. for $C_{19}H_{30}N_2O$ [M + H^+] 303.2431, found 303.2428. Crystals, which were structurally characterized, were obtained by dissolving **10** in DCM and slow evaporating of the solvent. The crystallographic data are presented in the Supporting Information.

Deprotection of (9) and (10)

(1*R*,3*S*)-*N*^{1}-Ethyl-*N*^{1}-methyl-1,2,2-trimethylcyclopentane-1,3-diamine (Scheme 3g): Concentrated HCl (75 ml) was added to amine **9** (3.442 g, 11.93 mmol). Then water (55 ml) was added. The mixture was refluxed for 48 hours. The suspension was then made basic with NaOH solution and extracted with DCM (3x100 ml) and ethyl acetate (3x100 ml). The combined organic phases were dried with sodium sulfate. After filtration and removing the solvent, the product was obtained as a colorless liquid (2.006 mg, 10.88 mmol, 91%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.92–2.84 (m, 1H), 2.59–2.44 (m, 1H), 2.30–2.17 (m, 1H), 2.15 (s, 3H), 2.00–1.87 (m, 1H), 1.86–1.74 (m, 1H), 1.69–1.44 (m, 3H), 1.32–1.19 (m, 1H), 1.06–0.93 (m, 6H), 0.89 (s, 3H), 0.82 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 68.2, 61.1, 47.1, 45.9, 36.7, 35.7, 29.2, 23.2, 16.3, 14.4, 13.1. HRMS (ESI): calcd. for $C_{11}H_{24}N_2$ [M + H^+] 185.2012, found 185.2014.

(1*R*,3*S*)-*N*^{1},*N*^{1}-Diethyl-1,2,2-trimethylcyclopentane-1,3-diamine (Scheme 3i): Concentrated HCl (55 ml) was added to amine **10** (2.600 g, 8.600 mmol). Then water (40 ml) was added. The mixture was refluxed for 48 hours. The suspension was then made basic with NaOH solution and extracted three times with DCM (3x100 ml) and ethyl acetate (3x100 ml). The combined organic phases were dried with sodium sulfate. After filtration and removing the solvent, the product was obtained as a colorless liquid (1.523 g, 7.678 mmol, 89%).^{1}H NMR (400 MHz, $CDCl_3$) δ 2.90–2.80 (m, 1H), 2.60–2.42 (m, 4H), 2.01–1.82 (m, 2H), 1.73–1.40 (m, 3H), 1.32–1.21 (m, 1H), 1.04–0.99 (m, 6H), 0.97 (s, 3H), 0.95 (s, 3H), 0.83 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 60.9, 47.5, 45.0, 35.7, 29.3, 23.2, 16.9, 16.8, 16.6. HRMS (ESI): calcd. for $C_{12}H_{26}N_2$ [M + H^+] 199.2169, found 199.2172. Crystals of the HCl salt, which were structurally characterized, were obtained by slow evaporating of the NMR sample. The crystallographic data are presented in the Supporting Information.

(1*R*,3*S*)-*N*^{1},*N*^{1}-Dimethyl-*N*^{3}-(phenylidene)-1,2,2-trimethyl-cyclopentane-1,3-diamine (4a): The deprotected amine (obtained by Scheme 2e or Scheme 3e) (731 mg, 4.29 mmol) was dissolved in 25 ml dry MeOH and Benzaldehyde (470 µl, 4.6 mmol) and Na_2SO_4 (2 g) were added. The mixture was refluxed overnight. After cooling to *rt*, filtration and evaporation of the solvent, the residue was purified by column chromatography (diethyl ether, 2.5% NEt_3; silica). The product was obtained as colorless solid (619 mg, 2.40 mmol, 56%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (s, 1H), 7.79–7.71 (m, 2H), 7.43–7.36 (m, 3H), 3.39 (t, J = 9.0 Hz, 1H), 2.28 (s, 6H), 2.18–2.05 (m, 1H), 1.98–1.75 (m, 2H), 1.72–1.62 (m, 1H), 1.12 (s, 3H), 1.01 (s, 3H), 0.94 (s, 3H).^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 159.4, 136.8, 130.5, 128.7, 128.3, 79.3, 67.9, 49.0, 40.5, 38.3, 26.9, 22.9, 18.2, 11.6. HRMS (ESI): calcd. for $C_{17}H_{26}N_2$ [M + H^+] 259.2169, found 259.2171. Crystals of the HCl salt, which were structurally characterized, were obtained by slow evaporating of the NMR sample. The crystallographic data are presented in the Supporting Information.

(1*R*,3*S*)-*N*^{1}-Ethyl-*N*^{1}-methyl-*N*^{3}-(phenylidene)-1,2,2-trimethyl-cyclopentane-1,3-diamine (4b): The deprotected amine (obtained by Scheme 3g) (2.01 g, 10.9 mmol) was dissolved in 50 ml dry MeOH and Benzaldehyde (1.4 ml, 13.1 mmol) and Na_2SO_4 (5 g) were added. The mixture was refluxed overnight. After cooling to *rt*, filtration and evaporation of the solvent, the residue was purified by column chromatography (diethyl ether, 2.5% NEt_3; silica). The product was obtained as yellow oil (2.40 g, 8.81 mmol, 81%).^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (s, 1H), 7.78–7.72 (m, 2H), 7.42–7.37 (m, 3H), 3.36 (t, J = 8.9 Hz, 1H), 2.63–2.47 (m, 5H), 2.34–2.01 (m, 3H), 1.95–1.60 (m, 1H), 1.15–0.86 (m, 13H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 159.4, 136.8, 130.4, 128.7, 128.3, 79.2, 68.5, 49.1, 46.1, 38.3, 36.0, 26.9, 23.3, 18.3, 14.4, 13.3. HRMS (ESI): calcd. for $C_{18}H_{28}N_2$ [M + H^+] 273.2325, found 273.2326. $C_{18}H_{28}N_2$: calcd. C 79.36, H 10.36, N 10.28; found C 79.39, H 10.10, N 10.25. Crystals of the HCl salt, which were structurally characterized, were obtained by adding HCl in Et_2O (2 M) to **4b** dissolved in $CDCl_3$, evaporating of the solvent, followed by dissolving of the residue in methanol/acetonitrile 1:1 and slow evaporating of the solvent mixture. The crystallographic data are presented in the Supporting Information.

(1*R*,3*S*)-*N*^{1},*N*^{1}-Diethyl-*N*^{3}-(phenylidene)-1,2,2-trimethyl-cyclopentane-1,3-diamine (4c): The deprotected amine (obtained by Scheme 3i) (1.52 g, 7.66 mmol) was dissolved in 50 ml dry MeOH and Benzaldehyde (0.93 ml, 9.2 mmol) and Na_2SO_4 (5 g) were added. The mixture was refluxed for 48 h. After cooling to *rt*, filtration and evaporation of the solvent, the residue was purified by column chromatography (diethyl ether, 2.5% NEt_3; silica). The product was obtained as yellow oil (1.26 g, 4.40 mmol, 57%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (s, 1H), 7.78–7.72 (m, 2H), 7.42–7.37 (m, 3H), 3.31 (t, J = 8.9 Hz, 1H), 2.62–2.49 (m, 4H), 2.21–2.10 (m, 1H), 1.94–1.73 (m, 2H), 1.65–1.55 (m, 1H), 1.10–1.01 (m, 12H), 0.92 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 159.3, 136.9, 130.4, 128.6, 128.3, 79.1, 69.4, 49.4, 45.4, 37.1, 27.0, 23.2, 18.6, 17.2, 16.8. HRMS (ESI): calcd. for $C_{19}H_{30}N_2$ [M + H$^+$] 287.2482, found 287.2483. $C_{19}H_{30}N_2$: calcd. C 79.66, H 10.56, N 9.78; found C 79.80, H 10.53, N 9.60.

(1*R*,3*S*)-*N*^{1},*N*^{1}-Dimethyl-*N*^{3}-(salicylidene)-1,2,2-trimethyl-cyclopentane-1,3-diamine (15): The deprotected amine (obtained by Scheme 2e or Scheme 3e) (345 mg, 2.03 mmol) was dissolved in 20 ml dry MeOH and Salicylaldehyde (211 µl, 2.03 mmol) and Na_2SO_4 (2 g) were added. The mixture was refluxed for 4 days. After cooling to *rt*, filtration and evaporation of the solvent, the residue was purified by column chromatography (diethyl ether; silica). The product was obtained as yellow solid (322 mg, 1.17 mmol, 58%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.79 (s, 1H), 8.26 (s, 1H), 7.30 (ddd, J = 8.6, 7.3, 1.7 Hz, 1H), 7.27–7.23 (m, 1H), 6.96 (d, J = 8.3 Hz, 1H), 6.87 (td, J = 7.5, 1.1 Hz, 1H), 3.41 (t, J = 9.0 Hz, 1H), 2.28 (s, 6H), 2.18–2.02 (m, 1H), 2.00–1.79 (m, 2H), 1.74–1.63 (m, 1H), 1.09 (s, 3H), 1.02 (s, 3H), 0.97 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 163.7, 161.6, 132.3, 131.3, 118.9, 118.6, 117.2, 78.3, 68.0, 48.5, 40.4, 37.9, 27.3, 22.8, 18.1, 11.8. HRMS (ESI): calcd. for $C_{17}H_{26}N_2O$ [M + H$^+$] 275.2118, found 275.2121.

Triflate salt of 3a: Under inert gas in a glove box: to a solution of $[Cu(CH_3CN)_4]OTf$ (75,8 mg, 0.20 mmol) in approx. 1 ml aceton was added a solution of **3a** (39.9 mg, 0.20 mmol) in approx. 1 ml aceton. Ether diffusion led to the formation of some colorless crystals, which were structurally characterized.

[Cu(3a)(PPh$_3$)]OTf: Under inert gas in a glove box: to a solution of $[Cu(CH_3CN)_4]OTf$ (67.7 mg, 0.18 mmol) in approx. 1 ml DCM was added a solution of **3a** (35.7 mg, 0.18 mmol) in approx. 1 ml DCM. PPh_3 (47.2 mg, 0.18 mmol) was added. Ether diffusion led to the formation of some yellow colored crystals, which were structurally characterized.

[Cu(3b)$_2$]ClO$_4$: Under inert gas in a glove box: to a solution of $[Cu(CH_3CN)_4]ClO_4$ (34.7 mg, 0.11 mmol) in approx. 1 ml DCM was added a solution of **3b** (29.2 mg, 0.11 mmol) in approx. 1 ml DCM. Ether diffusion led to the formation of some colorless crystals, which were structurally characterized.

[Cu(3c)][CuCl$_2$]: Under inert gas in a glove box: to a solution of CuCl (7.3 mg, 0.07 mmol) in approx. 1 ml THF was added a solution of **3c** (21.9 mg, 0.06 mmol) in approx. 1 ml THF. Pentane diffusion at −40 °C led to the formation of some yellow colored crystals, which were structurally characterized.

[Cu(3c)(H$_2$O)]OTf$_2$: Under inert gas in a glove box: to a solution of **3c** (11.7 mg, 0.03 mmol) in approx. 3 ml DCM was added a solution of $[Cu(CH_3CN)_4]OTf$ (25.1 mg, 0.07 mmol) in approx. 3 ml DCM, which led to a disproportionation reaction. After filtration of the copper, the blue colored solution was evaporated, and the residue was dissolved in MeOH. Slow evaporation led to the formation of some blue colored crystals, which were structurally characterized.

[Cu(4c)(CH$_3$CN)]OTf: Under inert gas in a glove box: to a solution of $[Cu(CH_3CN)_4]OTf$ (30.4 mg, 0.08 mmol) in approx. 1 ml DCM was added a solution of **4c** (23.2 mg, 0.08 mmol) in approx. 1 ml DCM. PPh_3 (21.3 mg, 0.08 mmol) was added. Ether diffusion at −40 °C led to the formation of some yellow colored crystals, which were structurally characterized. Interestingly PPh_3 does not act as ligand.

[Cu$_2$(3ad$_{12}$)$_2$O$_2$][PF$_6$]$_2$: Under inert gas in a glove box: to a solution of $[Cu(CH_3CN)_4]PF_6$ (40.7 mg, 0.11 mmol) in approx. 1 ml DCM was added a solution of **3ad$_{12}$** (23.0 mg, 0.11 mmol) in approx. 1 ml DCM. The glass vessel was placed inside a bigger glass vessel filled with pentane and was closed with a septum. After cooling to −80 °C dry oxygen was bubbled through the reaction solution for one minute and then placed in the refrigerator at −80 °C. Pentane diffusion led to the formation of brown colored crystals after about a week, which were structurally characterized.

Demethylation of amine 3a: Under inert gas in a glove box: to a solution of $[Cu(CH_3CN)_4]OTf$ (310.0 mg, 0.82 mmol) in approx. 10 ml DCM was added a solution of **3a** (163.2 mg, 0.82 mmol) in approx. 10 ml DCM. After cooling to −80 °C dry oxygen was bubbled through the reaction solution for 10 minutes. After warming to *rt*, conc. aqueous NH_3 (50 ml) was added and extracted with DCM (3x50 ml). The combined organic phases were dried with sodium sulfate and analyzed by HRMS (ESI) and GC-MS. It turned out that the system was demethylated (HRMS (ESI): calcd. for $C_{11}H_{24}N_2$ [M + H$^+$] 185.2012, found 185.2013, GC-MS data are available in the Supporting Information). The two demethylated species **11** and **12** could be separated as a mixture from ligand **3a** by means of column chromatography (DCM, MeOH 9:1, 1% NEt_3; silica). (^{1}H-NMR and ^{13}C{^{1}H}-NMR spectra of the mixture of **11** and **12** with minor impurities are available in the Supporting Information). HCl in Et_2O (2 M) was added to the mixture. After evaporation of the solvent the colorless solid was dissolved in MeOH. Slow evaporation led to the formation of some colorless crystals, which were structurally characterized. It turned out as the demethylated component **11** as HCl salt.

Hydroxylation of 4a (general procedure): Under inert gas in a glove box: to a solution of the copper salts (0.03 mmol) in approx. 3 ml solvent was added a solution of **4a** (7.8 mg, 0.03 mmol) in approx. 3 ml solvent. Dry oxygen was passed through the reaction solutions for 30 min at various temperatures. After warming to *rt*, the reaction was stirred overnight. Then conc. aqueous NH_3 (20 ml) was added and extracted with DCM (20 ml). The organic phase was dried with sodium sulfate. After filtration and evaporating of the solvent the reaction mixture was analyzed by HRMS (ESI) and ^{1}H-NMR. The conversion was determined by using the integral ratio of the imine protons (one example is presented in the Supporting Information). HRMS (ESI) of **15**: calcd. for $C_{17}H_{26}N_2O$ [M + H$^+$] 275.2118, found 275.2116.

Deposition Numbers 2063860 (for triflate salt of **3a**), 2063861 (for [Cu(**3a**)(PPh$_3$)]OTf), 2063862 (for [Cu(**3b**)$_2$]ClO$_4$), 2063863 (for [Cu(**3c**)][CuCl$_2$]), 2063864 (for [Cu(**3c**)(H$_2$O)](OTf)$_2$), 2074266 for **11**×2HCl), 2063865 (for [Cu(**4c**)(CH$_3$CN)]OTf), 2063866 (for [Cu$_2$(**3ad$_{12}$**)$_2$O$_2$][PF$_6$]$_2$), 2063867 (for **6**×2HCl), 2063868 (for **8**), 2063869 (for *N*-((1*S*,3*R*)-3-ethylamino-2,2,3-trimethylcyclopentyl)-benzamide), 2063870 (for **9**), 2063871 (for **10**), 2063872 (for (1*R*,3*S*)-*N*^{1},*N*^{1}-diethyl-1,2,2-trimethylcyclopentane-1,3-diamine×HCl), 2063873 (for **4a**×HCl), and 2063874 (for **4b**×HCl) 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.

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Conflict of Interest

The authors declare no conflict of interest.

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[1] L. Que, *J. Biol. Inorg. Chem.* **2017**, *22*, 171.
[2] a) E. I. Solomon, U. M. Sundaram, T. E. Machonkin, *Chem. Rev.* **1996**, *96*, 2563; b) H. Decker, R. Dillinger, F. Tuczek, *Angew. Chem. Int. Ed.* **2000**, *39*, 1591; *Angew. Chem.* **2000**, *112*, 1656; c) Y. Matoba, T. Kumagai, A. Yamamoto, H. Yoshitsu, M. Sugiyama, *J. Biol. Chem.* **2006**, *281*, 8981; d) H. Decker, T. Schweikardt, F. Tuczek, *Angew. Chem. Int. Ed.* **2006**, *45*, 4546; *Angew. Chem.* **2006**,*118*, 4658; e) L. Que, W. B. Tolman, *Nature* **2008**, *455*, 333.
[3] a) M. H. Sazinsky, S. J. Lippard, *Metal Ions in Life Sciences: Methane Monooxygenase: Functionalization Methane at Iron and Copper*, *Vol.* 15 Springer, Amsterdam, **2015**; b) M. A. Culpepper, G. E. Cutsail, W. A. Gunderson, B. M. Hoffman, A. C. Rosenzweig, *J. Am. Chem. Soc.* **2014**, *136*, 11767; c) L. Cao, O. Caldararu, A. C. Rosenzweig, U. Ryde, *Angew. Chem. Int. Ed.* **2018**, *57*, 162; *Angew. Chem.* **2018**, *130*, 168.
[4] a) 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; b) O. Sander, A. Henss, C. Näther, C. Würtele, M. C. Holthausen, S. Schindler, F. Tuczek, *Chem. Eur. J.* **2008**, *14*, 9714; c) S. Hong, Y.-M. Lee, K. Ray, W. Nam, *Coord. Chem. Rev.* **2017**, *334*, 25; d) L. M. Mirica, X. Ottenwaelder, T. D. P. Stack, *Chem. Rev.* **2004**, *104*, 1013.
[5] M. Becker, S. Schindler, K. D. Karlin, T. A. Kaden, S. Kaderli, T. Palanché, A. D. Zuberbühler, *Inorg. Chem.* **1999**, *38*, 1989.
[6] J. Becker, P. Gupta, F. Angersbach, F. Tuczek, C. Näther, M. C. Holthausen, S. Schindler, *Chem. Eur. J.* **2015**, *21*, 11735.
[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.
[8] T.-D. J. Stumpf, M. Steinbach, C. Würtele, J. Becker, S. Becker, R. Fröhlich, R. Göttlich, S. Schindler, *Eur. J. Inorg. Chem.* **2017**, *37*, 4246.
[9] C. Citek, S. Herres-Pawlis, T. D. P. Stack, *Acc. Chem. Res.* **2015**, *48*, 2424.
[10] A. P. Cole, V. Mahadevan, L. M. Mirica, X. Ottenwaelder, T. D. P. Stack, *Inorg. Chem.* **2005**, *44*, 7345.
[11] a) K. E. Dalle, T. Gruene, S. Dechert, S. Demeshko, F. Meyer, *J. Am. Chem. Soc.* **2014**, *136*, 7428; b) G. J. Karahalis, A. Thangavel, B. Chica, J. Bacsa, R. B. Dyer, C. C. Scarborough, *Inorg. Chem.* **2016**, *55*, 1102; c) R. R. Jacobson, Z. Tyeklar, A. Farooq, K. D. Karlin, S. Liu, J. Zubieta, *J. Am. Chem. Soc.* **1988**, *110*, 3690; d) S. Mahapatra, J. A. Halfen, E. C. Wilkinson, G. Pan, X. Wang, V. G. Young, C. J. Cramer, L. Que, W. B. Tolman, *J. Am. Chem. Soc.* **1996**, *118*, 11555.
[12] T. Hoppe, S. Schaub, J. Becker, C. Würtele, S. Schindler, *Angew. Chem. Int. Ed.* **2013**, *52*, 870; *Angew. Chem.* **2013**, *125*, 904.
[13] J. A. Halfen, S. Mahapatra, E. C. Wilkinson, S. Kaderli, V. G. Young, L. Que, A. D. Zuberbühler, W. B. Tolman, *Science* **1996**, *271*, 1397.
[14] M. Kodera, K. Katayama, Y. Tachi, K. Kano, S. Hirota, S. Fujinami, M. Suzuki, *J. Am. Chem. Soc.* **1999**, *121*, 11006.
[15] P. L. Holland, K. R. Rodgers, W. B. Tolman, *Angew. Chem. Int. Ed.* **1999**, *38*, 1139; *Angew. Chem.* **1999**, *111*, 1210.
[16] a) I. Blain, P. Bruno, M. Giorgi, E. Lojou, D. Lexa, M. Réglier, *Eur. J. Inorg. Chem.* **1998**, *9*, 1297; b) M. Réglier, C. Jorand, B. Waegell, *J. Chem. Soc. Chem. Commun.* **1990**, *107*, 1752; c) B. Schönecker, T. Zheldakova, Y. Liu, M. Kötteritzsch, W. Günther, H. Görls, *Angew. Chem. Int. Ed.* **2003**, *42*, 3240; *Angew. Chem.* **2003**, *115*, 3361.
[17] B. Schönecker, C. Lange, T. Zheldakova, W. Günther, H. Görls, G. Vaughan, *Tetrahedron* **2005**, *61*, 103.
[18] Y. Y. See, A. T. Herrmann, Y. Aihara, P. S. Baran, *J. Am. Chem. Soc.* **2015**, *137*, 13776.
[19] a) L. M. Mirica, D. J. Rudd, M. A. Vance, E. I. Solomon, K. O. Hodgson, B. Hedman, T. D. P. Stack, *J. Am. Chem. Soc.* **2006**, *128*, 2654; b) H. R. Lucas, L. Li, A. A. N. Sarjeant, M. A. Vance, E. I. Solomon, K. D. Karlin, *J. Am. Chem. Soc.* **2009**, *131*, 3230.
[20] a) J. E. Bol, W. L. Driessen, R. Y. N. Ho, B. Maase, L. Que, J. Reedijk, *Angew. Chem. Int. Ed.* **1997**, *36*, 998; *Angew. Chem.* **1997**, *109*, 1022; b) H. Börzel, P. Comba, K. S. Hagen, M. Kerscher, H. Pritzkow, M. Schatz, S. Schindler, O. Walter, *Inorg. Chem.* **2002**, *41*, 5440; c) H. Börzel, P. Comba, C. Katsichtis, W. Kiefer, A. Lienke, V. Nagel, H. Pritzkow, *Chem. Eur. J.* **1999**, *5*, 1716.
[21] T. Abe, Y. Morimoto, T. Tano, K. Mieda, H. Sugimoto, N. Fujieda, T. Ogura, S. Itoh, *Inorg. Chem.* **2014**, *53*, 8786.
[22] a) M. Bouché, M. Mordan, B. M. Kariuki, S. J. Coles, J. Christensen, P. D. Newman, *Dalton Trans.* **2016**, *45*, 13347; b) K. Cox, B. M. Kariuki, A. Smyth, P. D. Newman, *Dalton Trans.* **2016**, *45*, 8485; c) J.-L. Yu, R. Guo, H. Wang, Z.-T. Li, D.-W. Zhang, *J. Organomet. Chem.* **2014**, *768*, 36.
[23] a) O. Bienemann, A. Hoffmann, S. Herres-Pawlis, *Rev. Inorg. Chem.* **2011**, *31*, 83; b) F. Strassl, B. Grimm-Lebsanft, D. Rukser, F. Biebl, M. Biednov, C. Brett, R. Timmermann, F. Metz, A. Hoffmann, M. Rübhausen, S. Herres-Pawlis, *Eur. J. Inorg. Chem.* **2017**, *27*, 3350.
[24] S. Herres-Pawlis, P. Verma, R. Haase, P. Kang, C. T. Lyons, E. C. Wasinger, U. Flörke, G. Henkel, T. D. P. Stack, *J. Am. Chem. Soc.* **2009**, *131*, 1154.
[25] A. Hoffmann, M. Wern, T. Hoppe, M. Witte, R. Haase, P. Liebhäuser, J. Glatthaar, S. Herres-Pawlis, S. Schindler, *Eur. J. Inorg. Chem.* **2016**, *29*, 4744.
[26] C. Würtele, E. Gaoutchenova, K. Harms, M. C. Holthausen, J. Sundermeyer, S. Schindler, *Angew. Chem. Int. Ed.* **2006**, *45*, 3867; *Angew. Chem.* **2006**, *118*, 3951.
[27] M. Wern, J. Ortmeyer, P. Josephs, T. Schneider, A. Neuba, G. Henkel, S. Schindler, *Inorg. Chim. Acta* **2018**, *481*, 171.
[28] J. Lam, B. A. R. Günther, J. M. Farrell, P. Eisenberger, B. P. Bestvater, P. D. Newman, R. L. Melen, C. M. Crudden, D. W. Stephan, *Dalton Trans.* **2016**, *45*, 15303.
[29] H. Urabe, T. Yamakawa, F. Sato, *Tetrahedron: Asymmetry* **1992**, *3*, 5.
[30] D. Murtinho, M. Elisa Silva Serra, A. M. d.'A Rocha Gonsalves, *Tetrahedron: Asymmetry* **2010**, *21*, 62.
[31] D. Murtinho, C. H. Ogihara, M. E. S. Serra, *Tetrahedron: Asymmetry* **2015**, *26*, 1256.
[32] R. W. Hoffmann, *Angew. Chem. Int. Ed.* **2000**, *39*, 2054; *Angew. Chem.* **2000**, *112*, 2134.
[33] a) A. Iturrospe, B. Artetxe, S. Reinoso, L. San Felices, P. Vitoria, L. Lezama, J. M. Gutiérrez-Zorrilla, *Inorg. Chem.* **2013**, *52*, 3084; b) B. J. Pella, J. Niklas, O. G. Poluektov, A. Mukherjee, *Inorg. Chim. Acta* **2018**, *483*, 71; c) M. F. Shehata, S. K. Ayer, J. L. Roizen, *J. Org. Chem.* **2018**, *83*, 5072; d) V. Vermaak, D. A. Young, A. J. Swarts, *Dalton Trans.* **2018**, *47*, 16534.
[34] 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.
[35] M. Weitzer, S. Schindler, G. Brehm, S. Schneider, E. Hörmann, B. Jung, S. Kaderli, A. D. Zuberbühler, *Inorg. Chem.* **2003**, *42*, 1800.
[36] W. B. Tolman, *Acc. Chem. Res.* **1997**, *30*, 227.
[37] a) S. Schaub, A. Miska, J. Becker, S. Zahn, D. Mollenhauer, S. Sakshath, V. Schünemann, S. Schindler, *Angew. Chem. Int. Ed.* **2018**, *57*, 5355; *Angew. Chem.* **2018**, *130*, 5453; b) J. Chen, R. J. M. Klein Gebbink, *ACS Catal.* **2019**, *9*, 3564.
[38] a) C. Citek, J. B. Gary, E. C. Wasinger, T. D. P. Stack, *J. Am. Chem. Soc.* **2015**, *137*, 6991; b) C. Citek, B.-L. Lin, T. E. Phelps, E. C. Wasinger, T. D. P. Stack, *J. Am. Chem. Soc.* **2014**, *136*, 14405.
[39] a) X. Ottenwaelder, D. J. Rudd, M. C. Corbett, K. O. Hodgson, B. Hedman, T. D. P. Stack, *J. Am. Chem. Soc.* **2006**, *128*, 9268; b) A. K. Gupta, W. B. Tolman, *Inorg. Chem.* **2010**, *49*, 3531.
[40] S. V. Kryatov, E. V. Rybak-Akimova, S. Schindler, *Chem. Rev.* **2005**, *105*, 2175.

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