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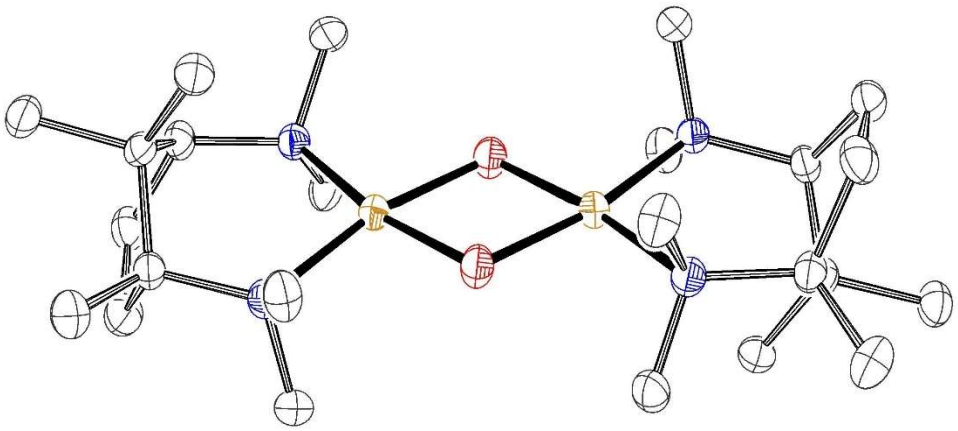

DISSERTATION

Darstellung neuartiger Kupfer(I)-Komplexe ausgehend von Camphersäure zur Aktivierung von molekularem Sauerstoff

Kumulative Dissertation zur Erlangung des Doktorgrades der Naturwissenschaften

-Dr. rer. nat.-

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Dezember 2022

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Zusammenfassung

Die selektive Oxidation von organischen Substraten unter milden Reaktionsbedingungen und der Verwendung von molekularem Sauerstoff als Oxidationsmittel ist eines der wichtigsten Ziele in der nachhaltigen organischen Chemie. Ein Ansatz hierzu bietet die Orientierung an kupferhaltigen Enzymen, welche in der Lage sind, Sauerstoff an das aktive Zentrum zu binden und diesen damit für Oxidationsreaktionen zu aktivieren. Inspiriert durch diese Reaktivität wurden in der Vergangenheit Kupfer(I)-Komplexe synthetisiert und mittels Sauerstoff verschiedenste organische Moleküle oxidiert. Begründet durch Limitierungen im Substratbereich besteht jedoch eine Notwendigkeit in der Synthese neuartiger Kupfer(I)-Komplexe für eine mögliche Substrat-Diversifizierung.

Hierfür wurden ausgehend von Camphersäure verschiedene, neuartige Kupfer(I)-Komplexe synthetisiert und deren Reaktivität mit Sauerstoff untersucht. Dabei konnte im Falle des Komplexes mit dem Liganden (1*R*,3*S*)-N^1,N^1,N^3,N^3-Tetramethyl-1,2,2-trimethylcyclopentan-1,3-diamin die Ausbildung eines kurzlebigen Bis(μ-oxido)dikupfer(III)-Komplexes beobachtet werden. Nach der Abreaktion wurde eine regioselektive Oxidation der Methylgruppen nachgewiesen. Die Deuterierung der empfindlichen Methylgruppen führte zu einer Stabilisierung der reaktiven Spezies, was letztlich die Kristallisierung und die strukturelle Analyse erlaubte. Basierend auf dieser Reaktivität wurde das Ligandensystem für eine selektive Hydroxylierung von Benzaldehyd zu Salicylaldehyd modifiziert. Die detaillierten Ergebnisse werden in **Abschnitt 3.1** vorgestellt.

Aufbauend auf dieser Arbeit wurde ein neuartiger tripodaler tetradentater Ligand aus Camphersäure synthetisiert. Der resultierende Kupfer(I)-Komplex zeigte auch hier in der Reaktion mit Sauerstoff die Ausbildung eines kurzlebigen Bis(μ-oxido)dikupfer(III)-Komplexes. Die Substitution der Methylgruppen mit sterisch anspruchsvolleren Alkylgruppen führte zu einer signifikanten Stabilisierung des Sauerstoff-Intermediates. Detaillierte kinetische Untersuchungen lieferten für die Reaktionen eine starke negative Aktivierungsentropie. Dies spricht für einen assoziativen Mechanismus im geschwindigkeitsbestimmenden Schritt. Des Weiteren konnten Hinweise auf ein vorgelagertes Gleichgewicht im Reaktionsmechanismus gefunden werden. Die Kupfer(I)-Komplexe wurden abschließend für die Oxidation verschiedener Substrate eingesetzt. Dabei konnte eine enantioselektive Umsetzung von Thioanisol zum entsprechenden Sulfoxid nachgewiesen werden. Die detaillierten Ergebnisse werden in **Abschnitt 3.2** vorgestellt.

Abstract

The selective oxidation of organic substrates under mild reaction conditions using molecular oxygen as the oxidant is one of the most important goals in sustainable organic chemistry. One approach is to focus on copper-containing enzymes, which are able to bind oxygen to the active center and thus activate it for oxidation reactions. Inspired by this reactivity, copper(I) complexes were synthesized in the past and various organic molecules were oxidized with oxygen. Due to limitations in the substrate scope, there is a need for the synthesis of novel copper(I) complexes for a possible substrate diversification.

For this purpose, various novel copper(I) complexes were synthesized starting from camphoric acid and their reactivity with oxygen was investigated. In the case of the complex with the ligand (1*R*,3*S*)-N^1,N^1,N^3,N^3-Tetramethyl-1,2,2-trimethylcyclopentane-1,3-diamine, the formation of a short-lived bis(μ-oxido)dicopper(III) complex could be observed. After the reaction, a regioselective oxidation of the methyl groups was detected. Deuteration of the sensitive methyl groups led to stabilization of the reactive species, which ultimately allowed crystallization and structural analysis. Based on this reactivity, the ligand system was modified for a selective hydroxylation of benzaldehyde to salicylaldehyde. The detailed results are presented in **section 3.1**.

Building on this work, a novel tripodal tetradentate ligand based on camphoric acid was synthesized. The resulting copper(I) complex also showed the formation of a short-lived bis(μ-oxido)dicopper(III) complex in the reaction with oxygen. The substitution of the methyl groups with sterically more demanding alkyl groups led to a significant stabilization of the oxygen intermediate. Detailed kinetic investigations revealed a strong negative activation entropy for the reactions. This indicates an associative mechanism in the rate-determining step. Furthermore, indications of a pre-equilibrium in the reaction mechanism could be found. Finally, the copper(I) complexes were used for the oxidation of different substrates. Here, the enantioselective conversion of thioanisole to the corresponding sulfoxide was detected. The detailed results are presented in **section 3.2**.

1. Einleitung

Anastas und *Warner* definierten vor über zwanzig Jahren die „12 Prinzipien der Grünen Chemie“ zur nachhaltigen Gestaltung chemischer Prozesse.[1] Eine Schlüsseltechnologie bildet die selektive Aktivierung von C-H-Bindungen unter milden Reaktionsbedingungen.[2] Besonders für Oxidationsreaktionen werden dabei umweltfreundliche Oxidationsmittel und Katalysatoren benötigt, um giftige Abfallprodukte wie zum Beispiel Chromverbindungen zu vermeiden.[3]

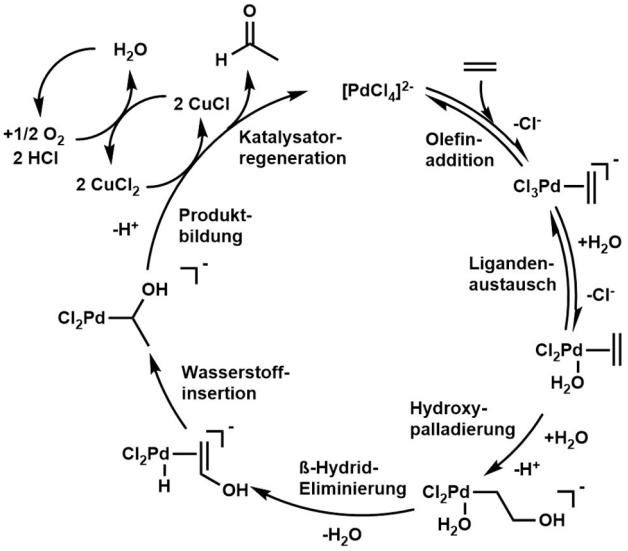


Abbildung 1: Katalysezyklus der Wacker-Oxidation.[6]

Ein möglicher Ansatz hierzu bietet die Verwendung von molekularem Sauerstoff als Oxidationsmittel.[4] Dies wird in der Industrie bereits erfolgreich im Wacker-Höchst-Verfahren genutzt.[5,6] Dabei wird mittels der Übergangsmetallkatalysatoren $PdCl_2$ und $CuCl_2$ Ethen zu Acetaldehyd oxidiert. Es findet zunächst eine Koordination von Ethen an die Pd^{2+}-Spezies statt. Nach einer Ligandenaustausch-reaktion wird das koordinierte Ethen hydroxyliert. Die Produktbildung erfolgt nach einer β-Hydrid-Eliminierung und Wasserstoff-Insertion. Die Regeneration des Katalysators wird durch eine Redoxreaktion zwischen dem zugesetzten $CuCl_2$ und der Palladiumspezies erreicht. Molekularer Sauerstoff oxidiert das dabei gebildete CuCl zu $CuCl_2$ (Abbildung 1).[6]

Die direkte Reaktion von Sauerstoff mit organischen Substraten ist in den meisten Fällen nicht möglich. Dies resultiert aus dem Triplett-Zustand des Sauerstoffs, wodurch Reaktionen mit organischen Verbindungen im Singulett-Zustand spinverboten sind. Durch Anregung mittels Strahlung kann dieser jedoch in einen Singulett-Zustand überführt werden und damit für Oxidationsreaktionen aktiviert werden. Eine weitere Möglichkeit zur Aktivierung des Sauerstoffmoleküls bietet die Anbindung an ein Metallion.[7] Dieser niederenergetische Reaktionspfad wird in dieser Arbeit mittels neuartiger, biomimetischer Kupfer-Komplexe untersucht und erweitert somit die bereits in der Literatur beschriebenen Ansätze. Die Grundlage dazu bilden kupferhaltige Proteine, welche unter anderem Oxidationen von verschiedensten Verbindungen katalysieren (Abschnitt 1.1).

1.1 Kupferproteine

In Stoffwechselprozessen verschiedenster Lebewesen sind Enzyme beteiligt, welche im aktiven Zentrum Kupfer-Ionen beinhalten. Diese fungieren unter anderem als Oxygenasen, welche Oxidationsreaktionen katalysieren und dabei Sauerstoff auf das Substrat übertragen oder als Oxidasen, welche durch Elektronenübertragungen funktionelle Gruppen oxidieren können. In Mollusken und Arthropoden findet der Sauerstofftransport über das Hämocyanin statt. Ebenfalls sind Kupferproteine, wie z.B. die Superoxid-Dismutase, am Abbau zelltoxischer Stoffe beteiligt.[8–11] Eine Übersicht der Funktion einiger kupferhaltiger Proteine zeigt Abbildung 2.

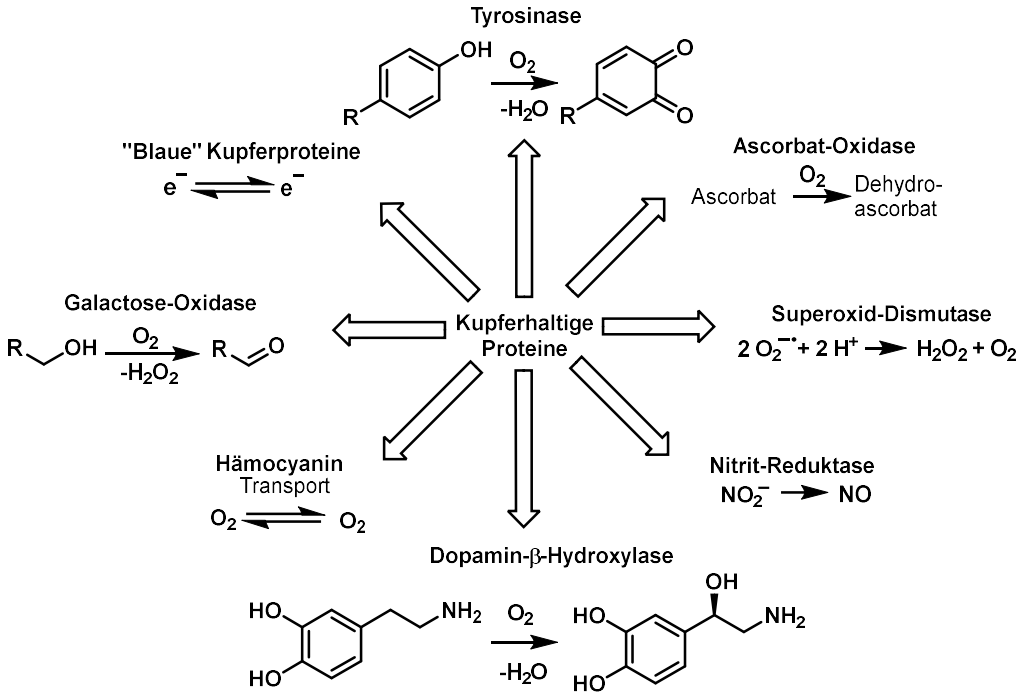


Abbildung 2: Eine Übersicht über die wichtigsten Kupferproteine und deren Funktionen.[10,12]

Kupferproteine werden dabei hinsichtlich ihrer strukturellen und spektroskopischen Eigenschaften in drei verschiedene Typen unterteilt.[8–10] Dennoch existieren auch Beispiele, die keiner dieser Klassen zugeordnet werden können.[13]

Typ-I-Kupferproteine werden auch „blaue Kupferproteine“ genannt. Durch Charge-Transfer-Übergänge zwischen der oxidierten Cu(II)-Spezies und einem Thiolatrest der Aminosäure Cystein wird eine charakteristische blaue Farbe hervorgerufen. Die Koordinationssphäre des zentralen Kupferions wird neben einem deprotonierten Cysteinrest durch zwei Histidinreste

und einem weiteren variablen Liganden, der häufig aus einem Methioninrest besteht, gebildet. Das aktive Zentrum ist dabei eine Zwischenform aus der für Kupfer(I)-Komplexe typischen tetraedrischen Koordination und der für Kupfer(II)-Komplexe bevorzugte quadratisch planaren bzw. quadratisch pyramidalen Umgebung. Dies führt zu einer tetraedrisch verzerrten Geometrie, welche die beiden Oxidationsstufen des Kupfers stabilisieren kann. Somit kann ein einfacher Wechsel der Oxidationsstufen stattfinden, was diese Proteine zu exzellenten Elektronenüberträgern macht.[8,9,13,14] In Algen und grünen Pflanzen ist unter anderem das Kupferprotein Plastocyanin **1** (Abbildung 3, Links) in der Photosynthese beteiligt.[15,16] Des Weiteren nimmt Azurin **2** (Abbildung 3, Rechts) in manchen Bakterien an Denitrifikationsprozessen teil. Eine Besonderheit im aktiven Zentrum ist dabei eine fünfte schwache Wechselwirkung des Carbonylsauerstoffs eines Glycinrestes mit dem zentralen Kupferion.[17,18]

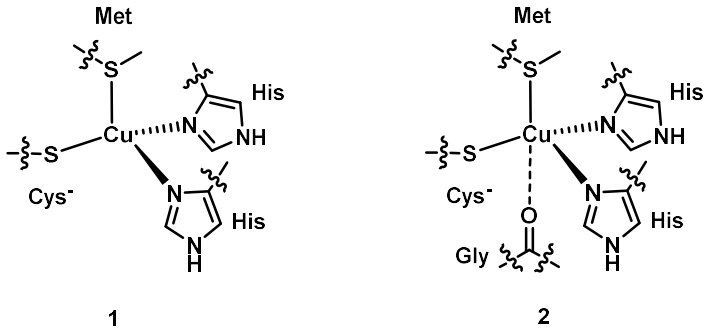


Abbildung 3: Aktive Zentren des Plastocyanin 1 und Azurin 2.[16,17]

Typ-II-Kupferproteine werden auch als „normale“ oder „nichtblaue Kupferproteine“ bezeichnet. Das Kupfer im aktiven Zentrum wird durch zwei Histidinreste und zwei variable Donoren quadratisch planar oder tetraedrisch verzerrt koordiniert. Es kann aber auch zu einer weiteren axialen Koordination eines variablen Liganden kommen. Die Funktion dieser Klasse von Proteinen besteht in der Katalyse von Oxidationsreaktionen. So können diese als Oxidasen oder auch Oxygenasen fungieren.[8,9,13,14,19] Ein wichtiger Vertreter dieser Gruppe ist die Cu-Zn-Superoxid-Dismutase **3**, welche den Abbau von zelltoxischen Superoxid-Anionen zu Sauerstoff und Wasserstoffperoxid katalysiert. Das aktive Zentrum enthält dabei ein Kupfer-Ion, welches durch drei Histidinreste koordiniert ist. Dieses wird über einen deprotonierten Imidazolat-Ring mit einem Zink-Ion verbrückt, welches durch zwei Histidinreste und einem deprotonierten Asparaginsäurerest umgeben ist. Durch die starke Verzerrung der tetraedrischen

Umgebung des Kupferions im Vergleich zum Zinkion wird eine zusätzliche Koordinationsstelle geschaffen, die durch ein Wassermolekül oder durch das Superoxid-Ion besetzt werden kann (Abbildung 4).[8,9,20]

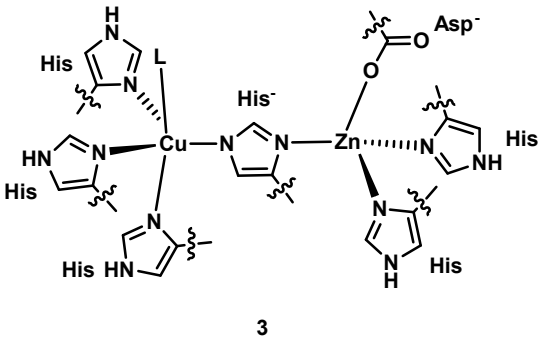


Abbildung 4: Aktives Zentrum der Cu-Zn-Superoxid-Dismutase.[9,21]

Typ-III-Kupferproteine enthalten in den aktiven Zentren dinukleare Kupferzentren. Diese sind in der Lage, Sauerstoff reversibel zu binden. So wird der Sauerstofftransport in Mollusken und Arthropoden durch das Protein Hämocyanin bewerkstelligt. Das aktive Zentrum beinhaltet in der Desoxyform **4** zwei Kupfer(I)-Zentren, welche jeweils durch drei Histidinreste koordiniert sind. Nach der Umsetzung mit Sauerstoff ändert sich die Koordinationssphäre des Kupfers von trigonal-planar zu quadratisch-pyramidal (Abbildung 5). Das Sauerstoffmolekül wird dabei reduziert und somit als *side-on* Peroxidoligand koordiniert.[8,9,13,22]

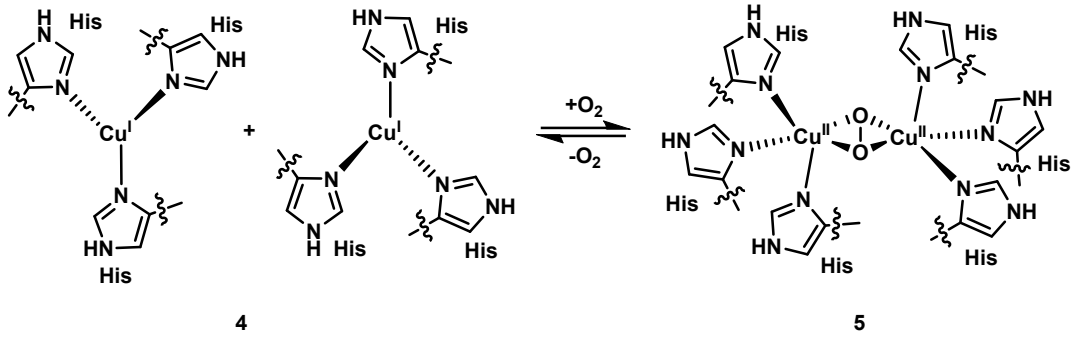


Abbildung 5: Reversible Sauerstoffanbindung an das aktive Zentrum des Sauerstofftransportproteins Hämocyanin.[8,14]

Aufgrund der Beteiligung des Typ-III-Proteins Tyrosinase an katalytischen Oxidationsprozessen unter milden Reaktionsbedingungen wird dieses als Vorbild für biomimetische Systeme verwendet (Abschnitt 1.4). Das Enzym ist in der Lage, L-Tyrosin über L-Dopa zu L-Dopachinon zu oxidieren. Das aktive Zentrum **6** besteht auch in diesem Falle aus zwei Kupfer(I)-Ionen, welche jeweils durch drei Histidinreste komplexiert sind. Nach Reaktion mit Disauerstoff bildet sich analog zum Hämocyanin eine (μ-η^2:η^2)-Peroxidodikupfer(II)-Spezies **7** aus. Nach Anbindung des Phenolatrestes an das Kupfer(II)-Zentrum **8** erfolgt die *ortho*-Hydroxylierung zu L-Dopa. Anschließend wird dieses zu L-Dopachinon oxidiert und dabei Wasser freigesetzt, wodurch die Kupfer(I)-Spezies regeneriert wird (Abbildung 6).[23,24] Verschiedene Arbeiten an Modellsystemen postulieren, dass die Hydroxylierung auch über einem im Gleichgewicht stehenden Bis(μ-oxido)dikupfer(III)-Komplex verlaufen könnte.[25–29]

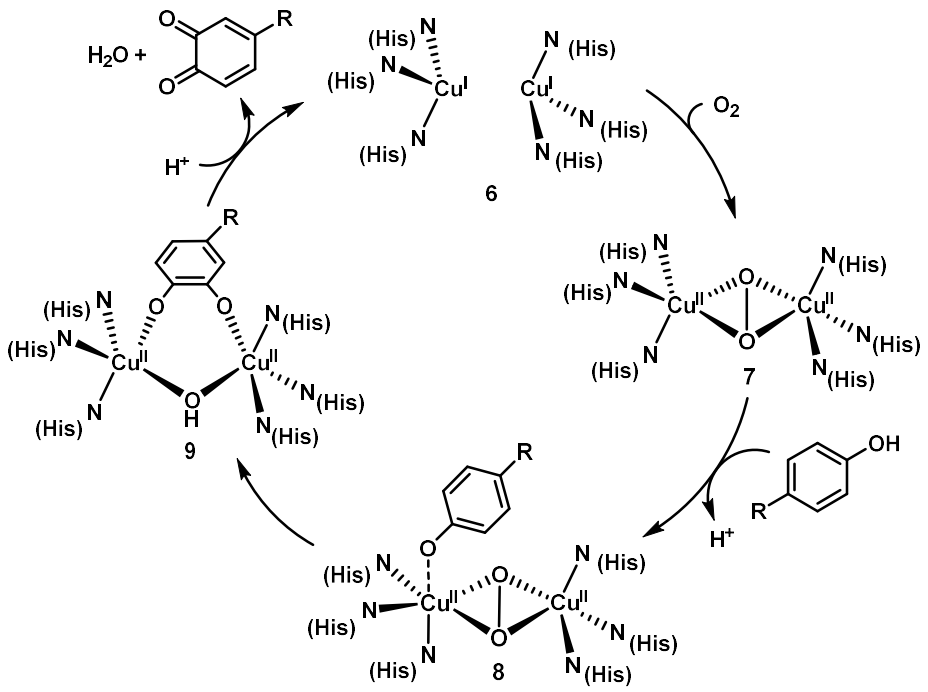


Abbildung 6: Exemplarische Umsetzung eines phenolischen Substrates mittels des Enzyms Tyrosinase.[23]

Infolge der unterschiedlichsten Funktionen der drei Typen von Kupferproteinen sind diese an Reaktionskaskaden bei der Biosynthese von Hormonen oder Neurotransmittern, wie zum Beispiel L-Adrenalin, beteiligt. Dabei wird mittels der Tyrosin-3-Monooxygenase L-Tyrosin **11** durch eine Hydroxylierung in *ortho*-Position in L-Dopa **12** umgewandelt. Nach einer Decarboxylierung zu Dopamin **13** wird eine stereoselektive Hydroxylierung zu

L-Noradrenalin **14** durch das Enzym Dopamin-β-Hydroxylase katalysiert. Eine anschließende Methylierung der Aminfunktion liefert L-Adrenalin **15** (Abbildung 7).[8,30,31]

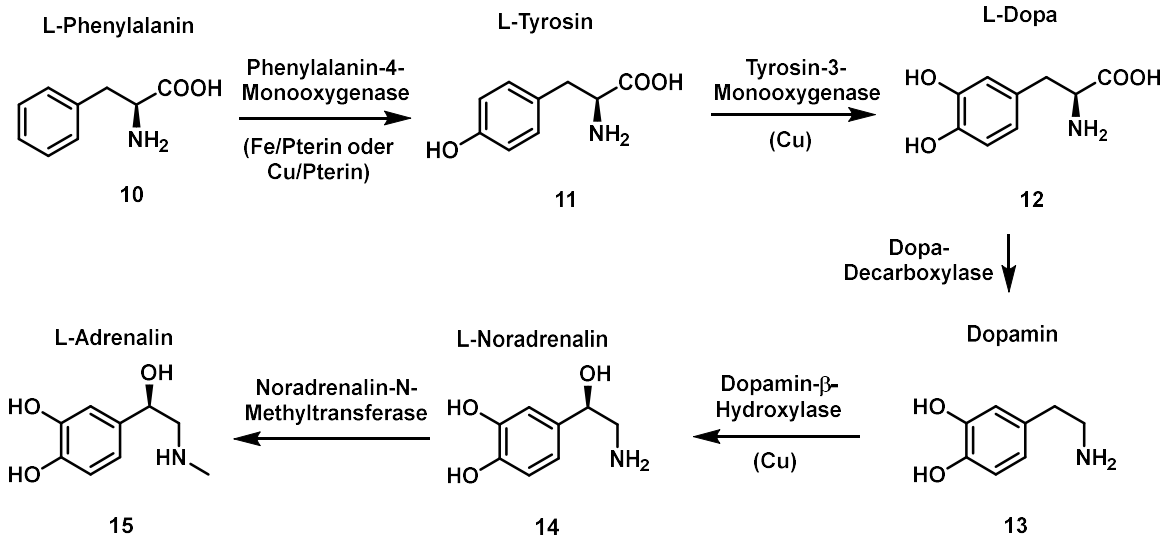


Abbildung 7: Reaktionskaskade der biologischen Oxidation von L-Phenylalanin zu L-Adrenalin.[8]

Die Funktion von Oxygenasen, wie zum Beispiel von Tyrosinasen oder auch der Dopamin-β-Hydroxlase, basieren auf der Anbindung von molekularem Sauerstoff an ein durch Aminosäurereste koordiniertes Kupfer(I)-Zentrum. Dabei konnten unterschiedliche Bindungsmodi des Sauerstoffmoleküls an das Metallzentrum nachgewiesen werden.[23,31] Zudem ist auch die Untersuchung synthetischer Kupfer-Sauerstoff-Adduktkomplexe elementarer Bestandteil der bioanorganischen Chemie (Abschnitt 1.2).

1.2 Sauerstoffanbindung an Kupfer(I)-Komplexe

Der erste kristallographische Nachweis eines synthetischen Kupfer-Sauerstoff-Adduktkomplexes wurde von der Arbeitsgruppe *Karlin* im Jahr 1988 mit dem Kupfer(I)-Komplex des Liganden Tris(2-pyridylmethyl)amin (TMPA) nach der Reaktion mit Sauerstoff beschrieben.[32] Bis zum heutigen Zeitpunkt konnten verschiedenste Bindungsmodi dieser Adduktkomplexe nachgewiesen werden (Abbildung 8).[33,34,35–41] Die Charakterisierung erfolgt dabei unter anderem mittels UV/Vis-Spektroskopie bei tiefen Temperaturen, da Vertreter dieser Verbindungsklasse oftmals eine hohe Reaktivität und Temperatursensitivität zeigen. Deshalb sind kristallographische Nachweise eher selten. Durch Charge-Transfer-Übergänge zwischen den Elektronenpaaren des Sauerstoffs leeren d-Orbitalen der Kupferionen zeigen die verschiedenen Adduktkomplexe charakteristische Extinktionsbanden im UV/Vis-Bereich. Eine weitere Möglichkeit ist die Charakterisierung mittels Raman-Spektroskopie. Dabei werden durch den Einsatz von $^{18}O_2$ charakteristische Verschiebungen der Schwingungsfrequenzen der Cu-O und O-O Schwingungsformen beobachtet.[33,35,39]

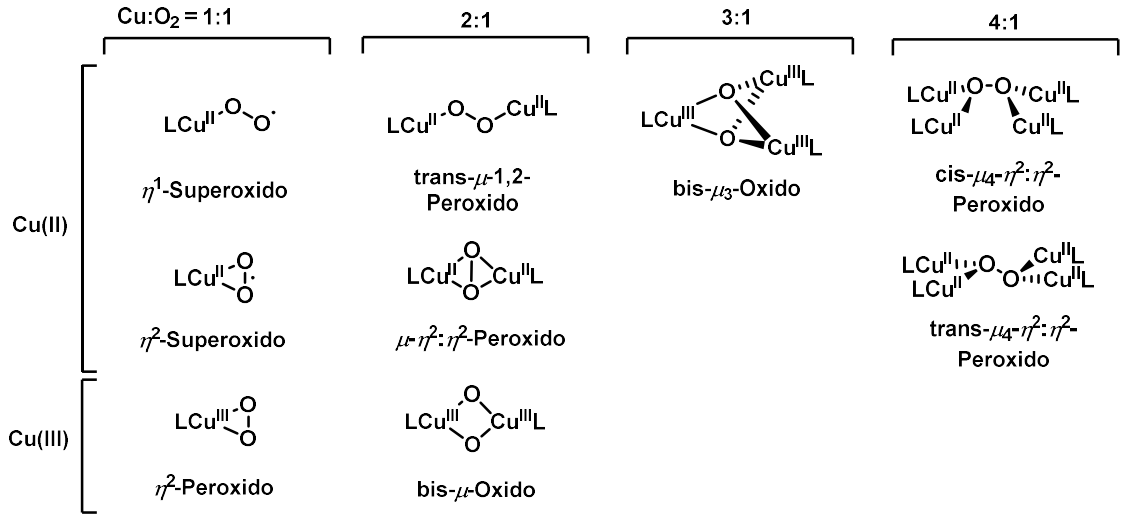


Abbildung 8: Übersicht über einige „Kupfer-Sauerstoff-Adduktkomplexe" nach der Reaktion von Kupfer(I)-Komplexen und Sauerstoff.[33]

Die Art der Sauerstoffanbindung hängt maßgeblich von den sterischen und elektronischen Eigenschaften der Liganden ab. So liefern vierzähnige Liganden häufig trans-μ-1,2-Peroxido-dikupfer(II)-Komplexe, während zweizähnige Liganden unter anderem Bis(μ-oxido)dikupfer(III)-Komplexe ausbilden.[33,35,37,39,42–45] Die Bildung von Kupfer-Sauerstoff-Adduktkomplexe erfolgt in Lösung zunächst durch Anbindung von Disauerstoff an einen

Kupfer(I)-Komplex zu einer Superoxido-Spezies. Diese kann dann durch Dimerisierung mit einem weiteren Kupfer(I)-Komplex zweikernige Sauerstoff-Adduktkomplexe ausbilden (Abbildung 9).[33,42,46] Durch geeignete Wahl der Ligandensysteme ist es möglich, eine Dimerisierung zu vermeiden.[38,41,47] Die erste Kristallisation eines η^1-Superoxido-kupfer(II)-Adduktes wurde unter Verwendung des Kupfer(I)-Komplexes mit dem superbasischen Liganden TMG_3tren durch die Arbeitsgruppe *Schindler* beschrieben (TMG_3 ≙ Tris(tetramethylguanidino); tren ≙ Tris(2-amino)ethylamin).[41] Außerdem konnte teilweise gezeigt werden, dass durch Wahl des Lösungsmittels oder des Anions das Gleichgewicht in verschiedene Richtungen gelenkt werden kann.[40,48–50] Einer der synthetischen Kupfer-Sauerstoff-Adduktkomplexe, welcher in dieser Form noch nicht in kupferhaltigen Proteinen nachgewiesen werden konnte, stellt der Bis(μ-oxido)dikupfer(III)-Komplex dar (Abschnitt 1.3).[51]

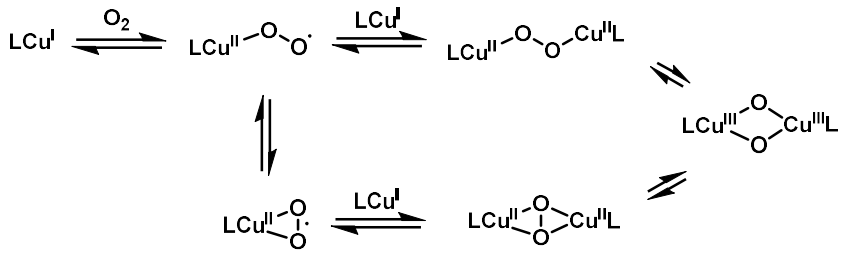


Abbildung 9: Mögliches Gleichgewicht bei der Umsetzung von Kupfer(I)-Komplexen und Sauerstoff.[33,42]

1.3 Die Eigenschaften des Bis(μ-oxido)dikupfer(III)-Komplexes

Der erste kristallographische Nachweis eines Bis(μ-oxido)dikupfer(III)-Komplexes wurde durch die Arbeitsgruppe *Tolman* mit dem synthetischen Kupfer(I)-Komplex des makrozyklischen Liganden Bz_3tacn nach der Reaktion mit Sauerstoff erbracht (Bz_3tacn ≙ 1,4,7-Tribenzyl-1,4,7-triazacyclononan).[36] Dabei konnte ein Bruch der O-O-Bindung nachgewiesen werden. Der Abstand der Sauerstoffatome in diesen Komplexen liegt dabei im Bereich von ~2,3 Å. Der Abstand der Kupferatome ist im Vergleich zu dem zweikernigen (μ-η^2:η^2)-Peroxido-dikupfer(II)-Komplex kürzer (~2,8 Å vs. ~3,6 Å), dementsprechend ist dieser auch kompakter.[33,36,44,52] Verschiedene Arbeiten konnten ein direktes Gleichgewicht zwischen der Bis(μ-oxido)- und der (μ-η^2:η^2)-Peroxido-Spezies nachweisen (Abbildung 10). Dieses konnte durch Variation des Lösungsmittels oder des Anions in eine der beiden Formen überführt werden.[40,48–50] Die Bis(μ-oxido)-Spezies wird als enthalpisch stabilisiert beschrieben, während die Peroxido-Form als entropisch stabilisiert gilt.[53]

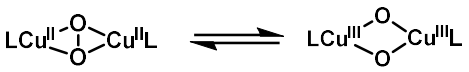


Abbildung 10: Gleichgewicht zwischen dem (μ-η^2:η^2)-Peroxido-dikupfer(II)-Komplex und dem Bis(μ-oxido)dikupfer(III)-Komplex.[40,48–50]

Vertreter dieser Verbindungsklasse zeigen zwei charakteristische Charge-Transfer-Banden bei Extinktionsmaxima im Bereich von ca. 300 und 400 nm. Die Bande bei etwa 300 nm resultiert durch einen Überlapp der π*-Orbitale des Sauerstoffs zu leeren d-Orbitalen des Kupfers, während die Bande bei 400 nm durch den Überlapp des σ*-Orbitals zu den d-Orbitalen entsteht. Mittels Raman-Spektroskopie kann eine charakteristische Atmungsschwingung des Cu_2O_2-Kerns bei etwa 600 cm^{-1} beobachtet werden, die unter Einsatz des Sauerstoffisotops $^{18}O_2$ um eine bestimmte Frequenz verschoben wird.[33,54]

Die strukturelle Ähnlichkeit zur (μ-η^2:η^2)-Peroxido-Spezies und die hohe Reaktivität der Bis(μ-oxido)dikupfer(III)-Komplexe führte zu dessen Einsatz zur selektiven Oxidation von Substraten (Abschnitt 1.4).

1.4 Die Reaktivität des Bis(*μ*-oxido)dikupfer(III)-Komplexes

Die Reaktivität der Tyrosinase, also die selektive Oxidation von Phenolatresten, konnte bereits vielfach durch den Einsatz von Modellkomplexen, welche analog zum Enzym als reaktive Spezies (μ-η^2:η^2)-Peroxido-dikupfer(II)-Komplexe ausbilden, beobachtet werden.[23,55] Ein erster Nachweis, dass diese Reaktion auch über eine Bis(*μ*-oxido)dikupfer(III)-Spezies verlaufen kann, erfolgte unter Verwendung des Kupfer(I)-DBED-Komplexes (BDED ≙ *N*,*N'*-Di-*tert.*-butylethylendiamin). Dieser bildet bei –80 °C in aprotischen Lösungsmitteln nach der Reaktion mit Sauerstoff einen (μ-η^2:η^2)-Peroxido-dikupfer(II)-Komplex **16** aus und kann Phenolatreste hydroxylieren. Jedoch kann bei extremeren Temperaturen (–120 °C) in MeTHF nach Zugabe von Phenolaten zu der reaktiven Spezies **16** die Ausbildung einer Bis(*μ*-oxido)-Spezies **17** durch Addition des Phenolates und Spaltung der O-O-Bindung beobachtet werden (Abbildung 11). Das Intermediat **17** wurde hierbei unter anderem durch UV/Vis- und Raman-Spektroskopie nachgewiesen.[23,28] Spätere spektroskopische und theoretische Analysen legen nahe, dass das 1:1 Verhältnis der Reaktionsprodukte Catechol **18** und *ortho*-Chinon **19** in der Ausbildung eines intermediär auftretenden Semichinonradikals begründet liegt, welches zu **18** und **19** disproportioniert.[29]

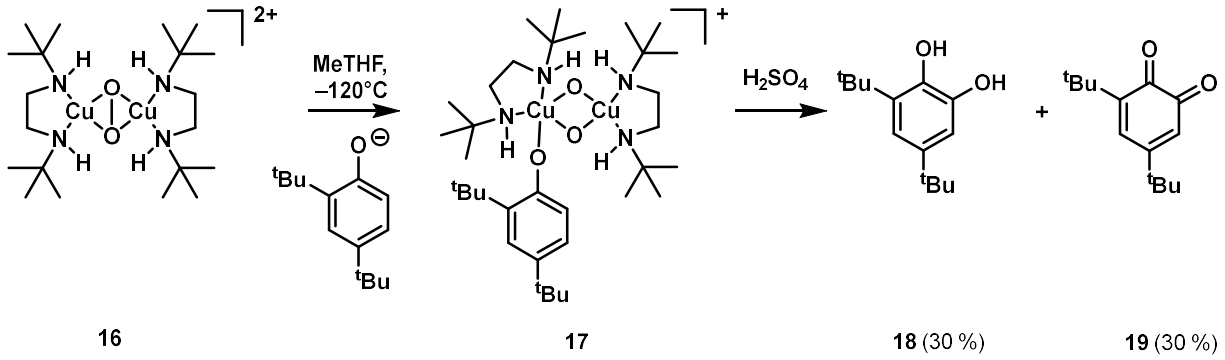


Abbildung 11: Umsetzung des Bis(*μ*-oxido)dikupfer(III)-Komplexes 16 mit einem Phenolat und anschließender Substrat-Oxidation.[28]

Die erste Beschreibung eines Modellsystems mit Tyrosinase-Aktivität, welches bereits vor der Addition eines Substrates Sauerstoff als Bis(*μ*-oxido)-Spezies bindet, erfolgte 2008 von *Company et al.* unter Verwendung eines zweikernigen Kupfer(I)-Komplexes. Dieser wurde bei tiefen Temperaturen mit Sauerstoff umgesetzt und der Sauerstoff-Addukt-Komplex **20** beobachtet (Abbildung 12). Nach Umsetzung mit *p*-Chlorphenolat wird umgehend der postulierte Komplex **21** mit neuen spektralen Eigenschaften erhalten, welcher unter anderem

auf eine Koordination des Phenolates an ein Kupferzentrum hindeutet. Aufgrund der schnellen Bildungsgeschwindigkeit konnte für den Aufbau keine kinetische Analyse durchgeführt werden. Jedoch zeigte dessen thermischer Zerfall eine Kinetik erster Ordnung und unter Verwendung verschiedener Phenolatresten konnte über einen Hammett-Plot ein negativer Proportionalitätsfaktor ($\delta = -1{,}9$) bestimmt werden. Dies deutet auf eine elektrophile aromatische Substitutionsreaktion hin. Außerdem wird Catechol als exklusives Reaktionsprodukt erhalten.[23,25] Der elektrophile Charakter von Bis(μ-oxido)dikupfer(III)-Komplexen konnte auch in anderen Arbeiten gezeigt werden.[27,56,57]

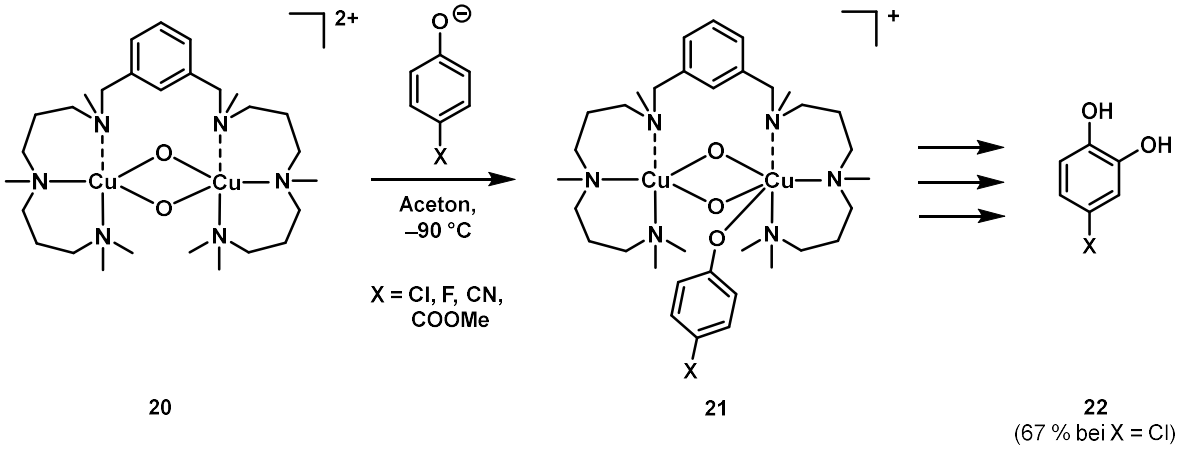
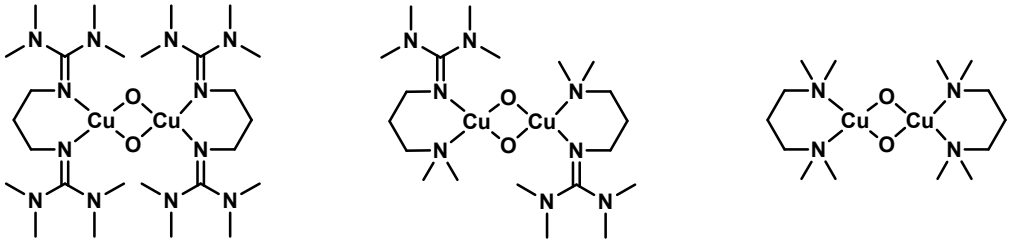


Abbildung 12: Reaktionsweg zur Oxidation von Phenolaten unter Verwendung des zweikernigen Kupfer(I)-Komplexes des Liganden *m*-XYL^{MeAN}.[25]

Neben Hydroxylierungen von Phenolaten werden auch radikalische Kupplungsreaktionen mittels Bis(μ-oxido)dikupfer(III)-Komplexen beschrieben. So zeigte eine systematische Analyse zur Oxidation von 2,4-Di-*tert*-butylphenol und 2,4-Di-*tert*-butylphenolat, dass die Funktionalisierung von zweizähnigen Liganden mit Guanidinresten zu einer signifikanten Veränderung der Reaktivität im Vergleich zu den *N*-alkylierten Derivaten führt (Abbildung 13). Bei der Verwendung des Bis-Guanidin-Komplexes **23** konnten keine Reaktionsprodukte nachgewiesen werden. Dies wird damit begründet, dass Guanidinreste im Vergleich zu alkylierten Aminresten stärkere σ-Donoren zu Kupfer-Zentren sind und somit die Oxidationsfähigkeit herabsetzen. Der bidentate Hybridkomplexes **24** führte zu radikalische Kupplungen zwischen Phenolen und Hydroxylierungen von Phenolaten. Aminkomplex **25** lieferte ausschließlich C-C-Kupplungsprodukte.[27]

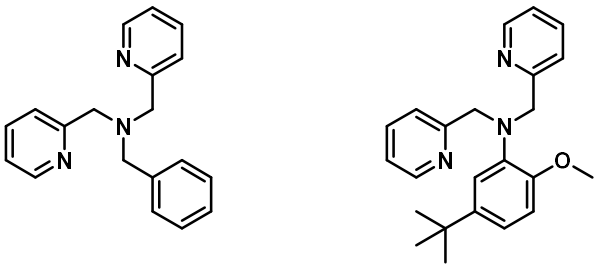


23 24 25

Substrat			
Phenol	keine Reaktion	radikalische Kupplung	radikalische Kupplung
Phenolat	keine Reaktion	Hydroxylierung	radikalische Kupplung

Abbildung 13: Unterschiedliche Reaktivität von Bis(*μ*-oxido)dikupfer(III)-Komplexen gegenüber Phenol und Phenolat.[27,35]

Des Weiteren konnten mittels Kupfer-Sauerstoff-Adduktkomplexen benzylische C-H-Bindungen oxidiert werden. Unter Einsatz von *trans*-*μ*-1,2-Peroxido-dikupfer(II)-Komplexen konnte die selektive Oxidation von Toluol zu Benzaldehyd gezeigt werden.[45,58,59] Mit den Kupfer(I)-Komplexen der Liganden **26** und **27** (Abbildung 14) konnten dabei Ausbeuten von bis zu 40 % erreicht werden. Während bei der Verwendung von **26** die Bis(*μ*-oxido)-Spezies spektroskopisch nachgewiesen werden konnte, wird bei **27** eine *trans*-*μ*-1,2-Peroxido-Anbindung beobachtet. Dennoch postuliert *Karlin*, dass auch andere, im Gleichgewicht stehende Kupfer-Sauerstoff-Spezies für die Oxidation verantwortlich sein könnten.[58] In zukünftigen industriellen Prozessen könnten die hohe Selektivität und die milden Reaktionsbedingungen dieser Methode zum Tragen kommen, da Benzaldehyd als Ausgangsverbindung für die Herstellung von Farbstoffen, Medikamenten, Kosmetika oder Lebensmitteln benötigt wird.[60]



26 27

Abbildung 14: Ligandensysteme, deren Kupfer(I)-Komplexe in der Lage sind, Toluol selektiv zu Benzaldehyd umzusetzen.[58]

Die Oxidation unterschiedlicher Substrate wurde mittels eines Bis(μ-oxido)dikupfer(III)-Komplexes **29**, welcher aus dem Liganden Bis(2-piperidyl)methan aufgebaut ist, in den Arbeitsgruppen *Schindler* und *Göttlich* untersucht. Nach dem Abbau des Intermediates **29** ohne Anwesenheit eines Substrates konnte anhand von Einkristallstrukturanalysen gezeigt werden, dass eine intramolekulare Hydroxylierung in 5-Position stattgefunden haben muss. Durch Zugabe von verschiedenen Substraten konnte in einigen Fällen eine selektive Oxidation nachgewiesen werden (Abbildung 15). Unter anderem konnte Cyclohexen zu dem entsprechenden allylischen Alkohol **30** und Keton **31** oxidiert werden. Es wird davon ausgegangen, dass der Alkohol als Intermediat auftritt, welcher anschließend zum Keton weiter oxidiert wird. Bei der Umsetzung von Benzylamin konnte das Reaktionsprodukt Benzonitril in 84 % Ausbeute generiert werden. Bei der Umsetzung von Benzylalkohol und 3,5-Di-*tert*-Butylcatechol konnten die Oxidationsprodukte **33** und **34** in moderaten Ausbeuten erhalten werden. Zu erwähnen ist jedoch, dass die Oxidation von Toluol keine Reaktionsprodukte lieferte. Dies steht im Gegensatz zu der vorher beschriebenen Arbeit von *Karlin*, die eine selektive Umsetzung von Toluol mithilfe von Kupfer-Sauerstoff-Addukten beschreibt.[43]

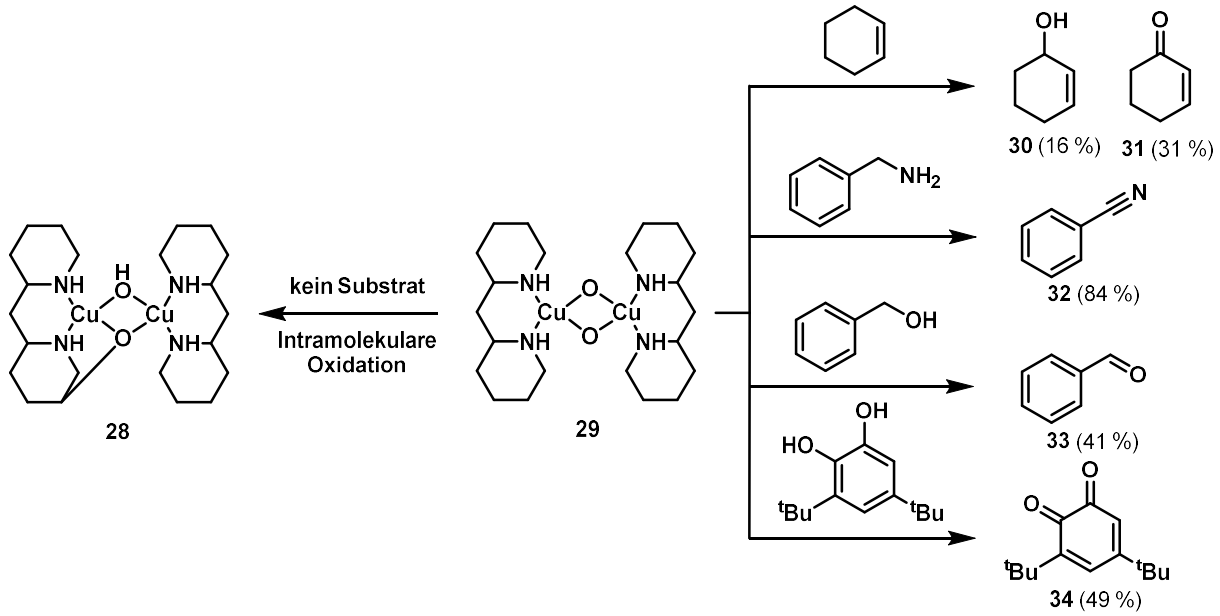


Abbildung 15: Oxidation verschiedener Substrate mit Hilfe des Kupfer(I)-Komplexes mit dem Liganden Bis(2-piperidyl)methan und Sauerstoff.[43]

Die intramolekulare Oxidation von Ligandensystemen wurde ebenfalls durch *Tolman* bei der Untersuchung des Kupfer(I)-Komplexes mit dem Liganden PPN **35** nach Umsetzung mit Sauerstoff beobachtet (PPN ≙ 2-(Diethylaminomethyl)-6-phenylpyridin). Die hohe Reaktivität der Bis(μ-oxido)-Spezies **36** induziert eine C-H-Aktivierung des aromatischen Systems, was letztlich zu einer Hydroxylierung führt (Abbildung 16). Dabei konnte ein Verhältnis von Edukt zu Produkt von 7:3 nachgewiesen werden.[56] Der Reaktionsmechanismus wurde in einer weiterführenden Arbeit mittels DFT-Rechnungen analysiert (DFT ≙ Dichtefunktionaltheorie). Dabei zeigte sich, dass die relative energetische Lage des korrespondierende (μ-η^2:η^2)-Peroxido-dikupfer(II)-Komplex um 10 kcal/mol höher liegt. Außerdem folgt aus dem Mechanismus, dass nur ein Ligand des zweikernigen Komplex **36** hydroxyliert werden kann, wodurch die Ausbeute auf 50 % limitiert ist.[57]

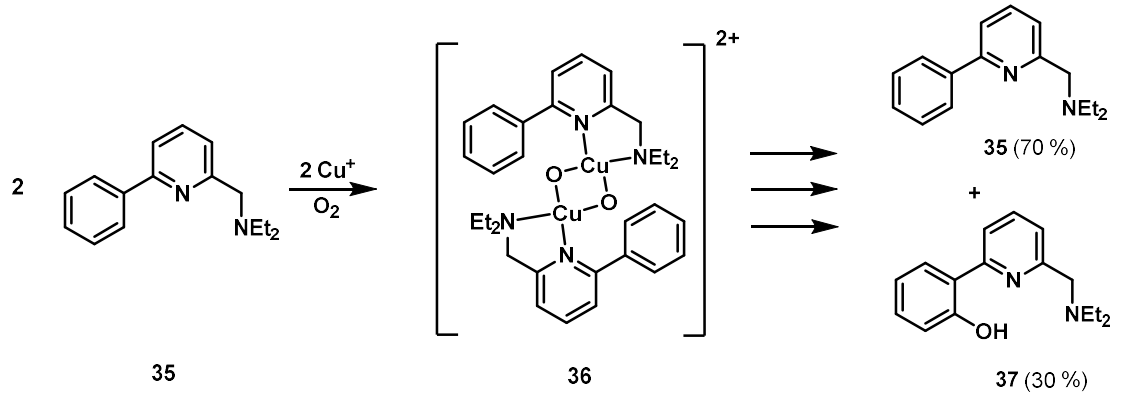


Abbildung 16: Intramolekulare Ligandenhydroxylierung des Liganden PPN nach der Reaktion mit Cu(I) und Sauerstoff.[56]

Da das PPN-System für synthetische Anwendungen sehr limitiert erschien, wurde daraus durch Becker *et al.* das so genannte „Clip-and-Cleave Concept“ entwickelt.[57,61] Dazu wurde ein zu oxidierendes Substrat über eine Carbonylverbindung an den Liganden *N*,*N*-Diethylethylendiamin über eine Iminkondensation angebracht. Zunächst wurden aromatische Systeme wie Benzaldehyd in *ortho*-position hydroxyliert (Abbildung 17). Spektroskopische und computerchemische Untersuchungen legen den Verlauf der Reaktion über eine Bis(μ-oxido)-Spezies **39** nahe. Das hydroxylierte Substrat kann anschließend mittels saurer Aufarbeitung gewonnen werden.[57]

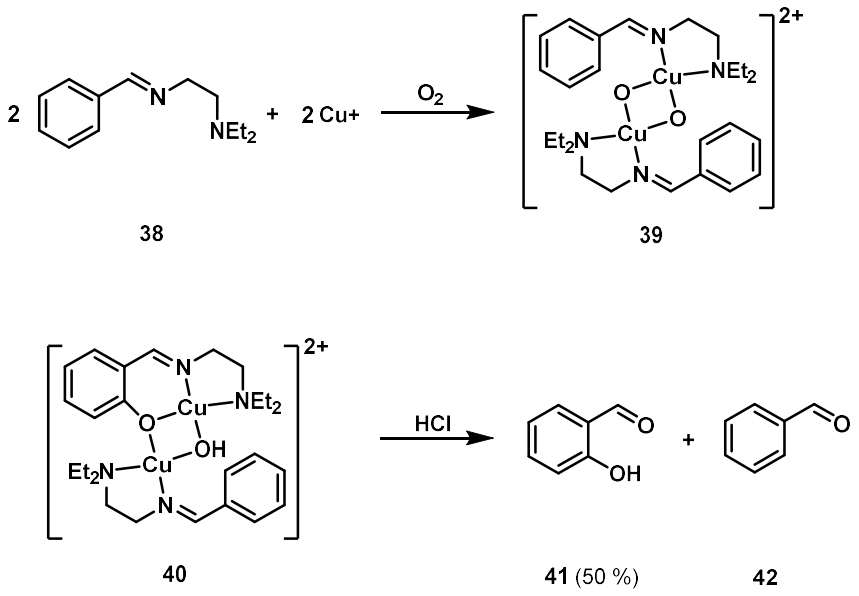


Abbildung 17: Das in der Arbeitsgruppe Schindler entwickelte „Clip-and-Cleave Concept".[57]

Dazu führte *Specht et al.* eine systematische Analyse des Einflusses des Linkers, aber auch der Substitution der Ethylgruppen der Aminfunktion von Ligand **38** durch verschiedene Alkylreste auf den Umsatz der Ligandenhydroxylierung durch. Die Substitution der Ethylgruppen durch Isopropylgruppen lieferte ähnliche Ausbeuten in Bezug auf Salicylaldehyd. Es konnte spektroskopisch jedoch kein Sauerstoff-Addukt-Komplex als reaktive Spezies nachgewiesen werden. Dementsprechend müssen auch radikalische Mechanismen für die Hydroxylierung in Betracht gezogen werden.[62] Diese werden ebenfalls von *Garcia-Bosch* für Kupfer induzierte sp^3-C-H-Hydroxylierungen postuliert.[63]

In weiterführenden Arbeiten gelang es, das Konzept auf aliphatische Substrate zu adaptieren (Abbildung 18). Die Hydroxylierungen in β-Position weisen dabei eine hohe Selektivität auf. Besonders hervorgehoben wird die synthetisch simple Darstellung von 1,2-disubstituierten Adamantylresten.[61,62]

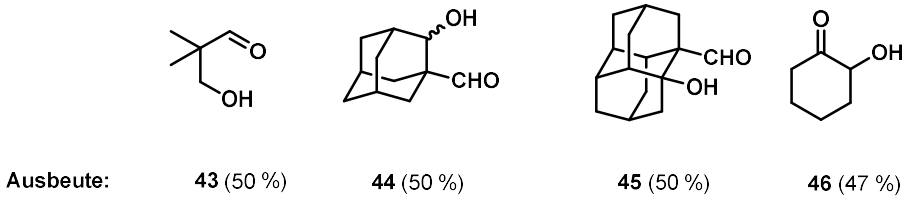


Abbildung 18: Erweiterung des „Clip-and-Cleave Concept" auf aliphatische Systeme.[61,62]

Ein Ansatz zur Überschreitung der Ausbeutenlimitierung von 50 % wird durch die Arbeitsgruppe *Baran* bei der stereoselektiven Hydroxylierung von Steroidsystemen beschrieben. Dabei wurde das Reduktionsmittel Natriumascorbat zur Reaktionslösung gegeben (Abbildung 19). Dieses reduziert die nach der Reaktion gebildete, inaktive Cu(II)- zurück zur Cu(I)-Spezies, wodurch erneut Sauerstoff aktiviert werden kann und somit auch Ausbeuten über 50 % ermöglicht werden. Es konnte gezeigt werden, dass die Umsätze stark von der Funktionalisierung des eingesetzten Pyridinrestes und vom Lösungsmittel abhängen. Des Weiteren wird eine Abhängigkeit des Reduktionsmittels auf die Ausbeuten gezeigt.[64]

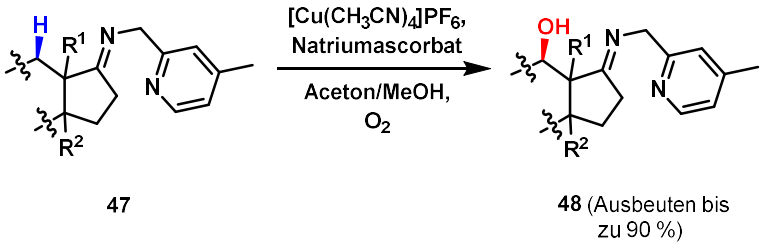


Abbildung 19: Selektive Hydroxylierung von Steroidsystemen mittels einer Cu(I)-Quelle, Natriumascorbat und Sauerstoff.[64]

Eine weitere Möglichkeit für hohe Reaktionsumsätze bei regioselektiven Hydroxylierungen wird durch die Verwendung von Wasserstoffperoxid als Oxidationsmittel gegeben. Dadurch werden reaktive Kupfer(II)-Hydroperoxido-Komplexe gebildet, welche zur Hydroxylierung des Ligandensystems führen (Abbildung 20). Da es sich dabei um einkernige Adduktkomplexe handelt, kann dabei die Ausbeute von 50 % überschritten werden. Die Methodik erlaubt Hydroxylierungen an sp^3- und an sp^2-Zentren unter kurzen Reaktionszeiten (30 min).[65]

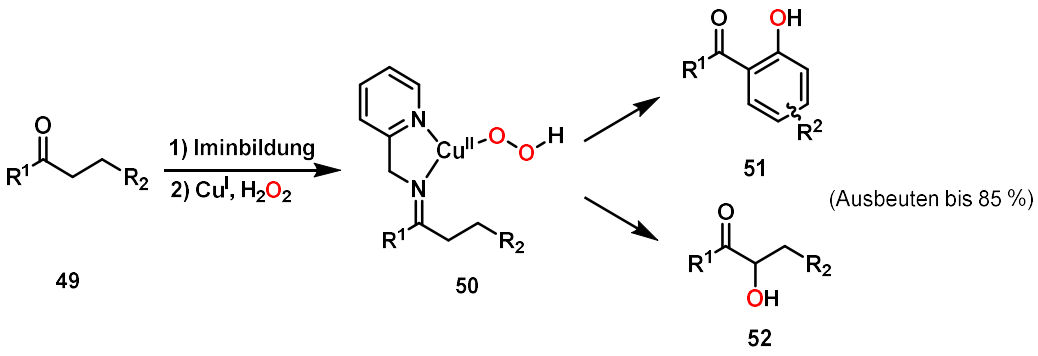


Abbildung 20: Selektive Hydroxylierung von sp^2- und sp^3-Zentren mittels Kupfer(II)-Hydroperoxido-Komplexen.[65]

Bei den von *Baran* beschriebenen stereoselektiven Hydroxylierungen von Steroidsystemen wird die Stereoinformation durch das Substrat induziert. Dementsprechend könnte ein Ansatzpunkt bieten, diese auch über asymmetrische Ligandensysteme zu übertragen. Der Einsatz von enantiomerenreinen Stoffen aus der Natur, die den sogenannten „Chiral Pool“ bilden, ist eine Vorgehensweise in der synthetischen und auch industriellen Chemie (Abschnitt 1.5).

1.5 Ligandensysteme ausgehend von Camphersäure

Chirale Naturstoffe werden unter anderem als Edukte enantiomerenreiner Folgeverbindungen oder auch als Organokatalysatoren für enantioselektive Synthesen eingesetzt.[66] Ein Stoff aus dem „Chiral Pool“ ist das Terpen Campher, das in enantioselektiven Synthesen mittels chiraler Auxiliare oder chiraler Liganden Verwendung findet.[67] Durch Oxidation von Campher ist Camphersäure **53** zugänglich,[68] welche mittels einer Schmidt-Reaktion in ein asymmetrisches Diamin **54** überführt werden kann.[69] Aufgrund der unterschiedlichen Reaktivität der beiden Aminfunktionen kann dieses als Ausgangssubstanz für asymmetrische Ligandensysteme eingesetzt werden.[42,70] In vorangegangenen Arbeiten wurden Ligandensysteme ausgehend von Camphersäure für enantioselektive Alkylierungen oder auch asymmetrische Silylcyanierungen von Aldehyden erfolgreich genutzt.[70] In der Arbeitsgruppe *Schindler* wurden ausgehend des Diamins **54** unter Verwendung des Vilsmeier-Salzes Tetramethylchloroformamidiniumchlorid (TMG-VS) zwei guanidinhaltige Ligandensysteme **55** und **56** synthetisiert (Abbildung 21).[42]

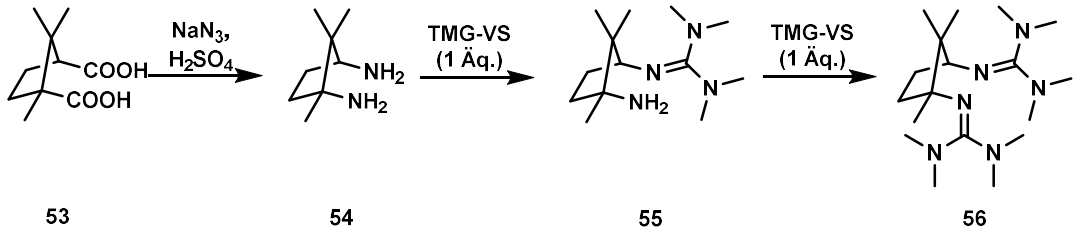


Abbildung 21: Die im Arbeitskreis *Schindler* synthetisierten guanidinhaltigen Ligandensysteme.[42]

Die Ligandensysteme **55** und **56** wurden mit $[Cu(CH_3CN)_4]OTf$ zu den Kupfer(I)-Komplexen umgesetzt und die Reaktion mit Sauerstoff in Propionitril mit Tieftemperatur-Stopped-Flow-Technik untersucht. Dabei konnte spektroskopisch die Ausbildung von kurzlebigen Bis(μ-oxido)dikupfer(III)-Komplexen beobachtet werden. Auf Grund des chiralen Ligandensystems werden diese als potentiell nützliche Systeme für asymmetrische Oxidationsreaktionen in Aussicht gestellt, erfolgreiche Oxidationsversuche werden jedoch nicht beschrieben.[42] Aus der einfachen Verfügbarkeit von Camphersäure und den derzeit Literatur unbekannten Untersuchungen von anderen Derivaten des Diamins **54** für Kupfer(I)-Komplexe zur Aktivierung von Sauerstoff erscheint es sinnvoll, eine systematische Variation der Restgruppen der Aminfunktionen des Diamins **54** durchzuführen, um Oxidationen von Substraten zu ermöglichen (Abschnitt 2).

2. Forschungsziele

Begründet aus dem Interesse an nachhaltigen chemischen Prozessen wurden in der Vergangenheit Kupfer(I)-Komplexe entwickelt, die molekularen Sauerstoff aktivieren und eine niederenergetische Möglichkeit für Oxidationsreaktionen bieten. Dabei zeigten sich jedoch Limitierungen im Substratbereich, was zur Darstellung neuartiger Kupfer(I)-Komplexe und zur Untersuchung von deren Reaktivitäten motiviert. Ein geeignetes Strukturmotiv für die Liganden wurde in der leicht zugänglichen Camphersäure **53** identifiziert.

Für den Aufbau der Kupfer(I)-Komplexe wurden zunächst Syntheseprotokolle für die Liganden **57**-**59** mit variierender Dentizität erarbeitet (Abbildung 22, Mitte), um geeignete Koordinationssphären zur Stabilisierung von Kupfer(I)-Ionen zu untersuchen. Durch Charakterisierungen des Aufbaus der Kupfer(I)-Komplexe wurden erste Hinweise über deren Reaktivität erwartet. Die Anbindung von Sauerstoff wurde aufgrund der in der Literatur beschriebenen, teilweise auftretenden Kurzlebigkeit der Adduktkomplexe mittels Tieftemperatur-Stopped-Flow-Technik verfolgt. Dies erlaubt die Aufnahme zeitabhängiger UV/Vis-Spektren im Millisekundenbereich. Ein besonderer Fokus wurde auf die Kristallisation eines Kupfer-Sauerstoff-Intermediates gelegt, da Röntgenstrukturanalysen dieser Verbindungsklasse relativ selten sind, aber zur Abschätzung der Reaktivität zum Beispiel gegenüber Substraten äußerste Wichtigkeit besitzen.

53

57: R^1, R^2, R^3, R^4 = Me
58: R^1 = 2-Methylpyridin; R^2, R^3, R^4 = Me
59: R^1, R^3 = 2-Methylpyridin; R^2, R^4 = Me

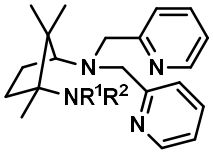
60: R^1, R^2 = Me
61: R^1 = Me, R^2 = Et
62: R^1, R^2 = Et

Abbildung 22: Die im Zuge dieser Arbeit synthetisierten Ligandensysteme, welche aus Camphersäure zugänglich sind.

Basierend auf den beobachteten Reaktivitäten der Kupfer(I)-Komplexe mit Sauerstoff wurde das Ligandensystem so modifiziert, dass es für synthetisch wertvolle intramolekulare Hydroxylierungen verwendet werden kann. Dabei konnte gezeigt werden, dass geringe sterische Veränderungen der Liganden **60**-**62** (Abbildung 22, Rechts) einen großen Einfluss auf den

Umsatz der Hydroxylierungen aufweisen. Die Ergebnisse dazu wurden im *European Journal of Inorganic Chemistry* veröffentlicht (**Abschnitt 3.1**).

Darauf aufbauend wurde das tripodale tetradentate Ligandensystem **63** (Abbildung 23) entwickelt, um mit dem resultierenden Kupfer(I)-Komplex stereoselektive Oxidationen von externen Substraten zu untersuchen. Zunächst wurde bei der Umsetzung des Kupfer(I)-Komplexes mit Sauerstoff die Bildung eines Bis(μ-oxido)dikupfer(III)-Adduktes spektroskopisch nachgewiesen. Da kleinste sterische Änderungen der Ligandensysteme in der vorangegangenen Arbeit zu einer signifikanten Änderung der Reaktivität geführt haben, wurde dies ebenfalls bei den gezielt synthetisierten Derivaten **64**-**66** erwartet. Die Ursache dafür lieferten detaillierte kinetische Untersuchungen zur Anbindung von Sauerstoff an das Kupfer(I)-Zentrum.



63: R^1, R^2 = Me
64: R^1 = Me, R^2 = Et
65: R^1, R^2 = Et
66: R^1 = Me, R^2 = ^{I}Prop

Abbildung 23: Tripodale tetradentate Ligandensysteme, welche aus Camphersäure synthetisiert wurden.

Erste Oxidationsversuche mit den neuartigen Kupfer(I)-Komplexen lieferten vielversprechende Ergebnisse bezüglich der Übertragung von Stereoinformation auf Substrate. Die Ergebnisse dazu wurden in der *Zeitschrift für anorganische und allgemeine Chemie* veröffentlicht (**Abschnitt 3.2**).

3. Veröffentlichte wissenschaftliche Artikel

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

Fabian Stöhr, Niclas Kulhanek, Jonathan Becker, Richard Göttlich, und Siegfried Schindler

Diese Arbeit wurde in der Fachzeitschrift *European Journal of Inorganic Chemistry* veröffentlicht.

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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-

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Supporting information for this article is available on the WWW under https://doi.org/10.1002/ejic.202100187

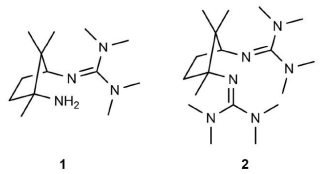
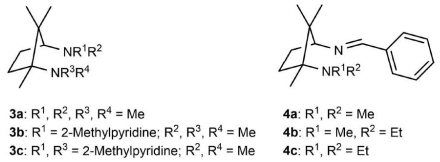


Figure 1. Camphor-like ligands used in previous work.[27] Complexation with Cu(I) and reaction with dioxygen resulting in a bis-(μ-oxido) copper complex.



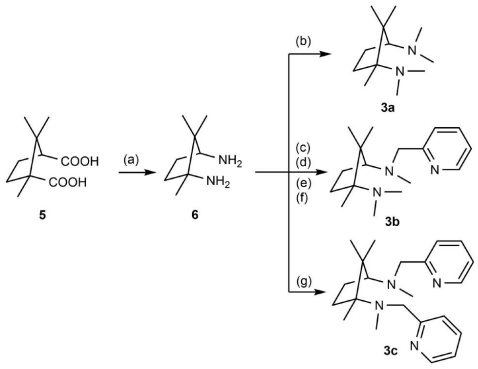
Scheme 1. Camphor-like ligands used in this work.

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

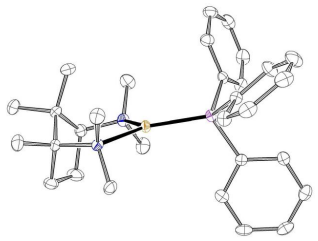


Figure 2. Molecular Structure of $[Cu(3a)(PPh_3)]^+$. Hydrogen atoms and the triflate anion are omitted for clarity. Ellipsoids are drawn at 50 % probability.

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

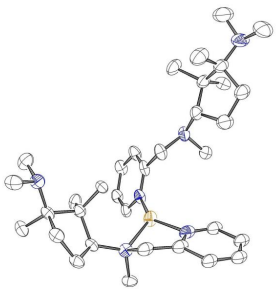


Figure 3. Molecular Structure of $[Cu(3b)_2]^+$. Hydrogen atoms and perchlorate anion are omitted for clarity. Ellipsoids are drawn at 50% probability.

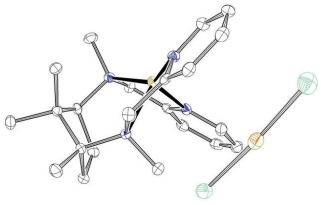
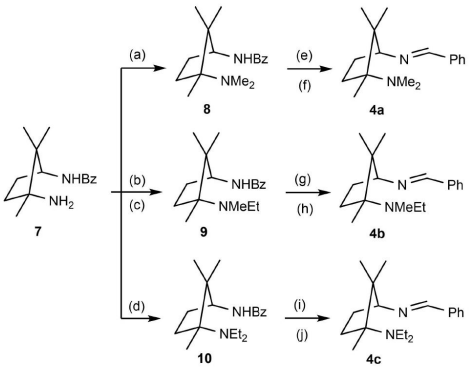


Figure 4. Molecular Structure of $[Cu(3c)]$ $[CuCl_2]$. Hydrogen atoms are omitted for clarity. Ellipsoids are drawn at 50% probability.



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%.

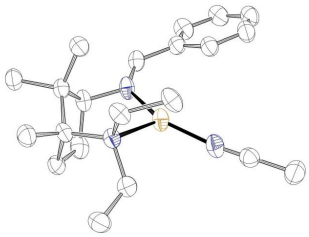


Figure 5. Molecular Structure of $[Cu(4c)(CH_3CN)]^+$. Hydrogen atoms and triflate anion are omitted for clarity. Ellipsoids are drawn at 50% probability.

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]

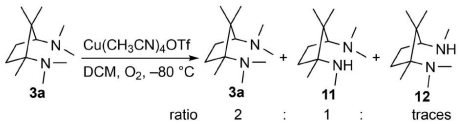
The absorbance vs. time trace at 414 nm can be fitted with a one exponential function and a rate constant of $k_{obs} = 0.13\ s^{-1}$ could be calculated, in line with our results for the reaction of dioxygen with the complexes $[Cu(TMGdmap)]^+$ and $[Cu(btmgp)]^+$. Therefore, no further kinetic measurements 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 4. Observed oxidation products after the reaction at −80 °C.

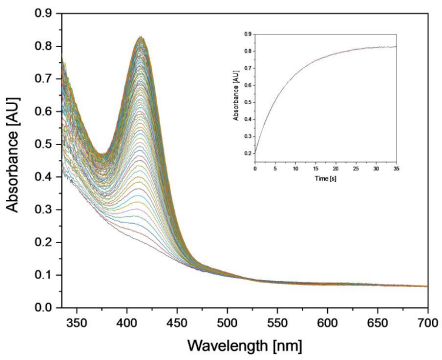
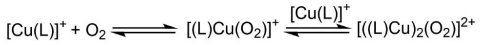
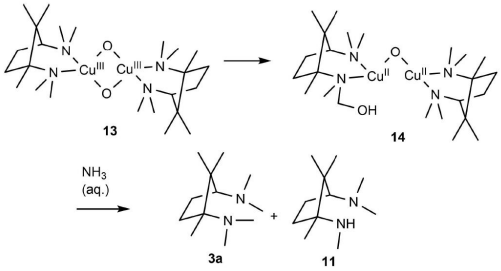


Figure 6. Time-resolved UV/Vis spectra of the reaction of [Cu(3a)]OTf ($c = 0.5 \times 10^{-3}$ M) with dioxygen ($c = 2.15 \times 10^{-3}$ M) in DCM at −89 °C for 35 s. The inset shows the absorbance vs time at $\lambda = 414$ nm.



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.

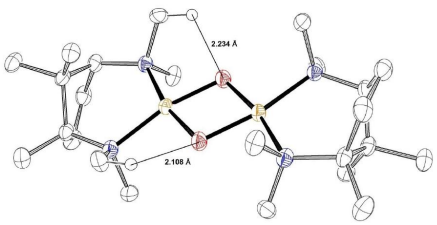


Figure 7. Molecular structure of $[Cu_2(3ad_{12})_2O_2]^{2+}$. Hydrogen atoms (except the nearest C–H's to O), the PF_6 anions and solvent molecules are omitted for clarity. Ellipsoids are drawn at 50% probability.

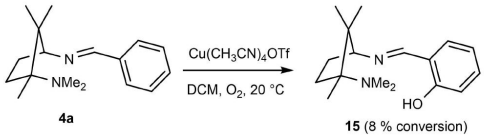
The reactivity of copper(I) complexes with the ligands **3a**–**3c** was investigated especially to detect dioxygen adduct complexes as intermediates. This was important prior to the investigations with ligands **4a**–**4c** that were chosen for possible intramolecular hydroxylation reactions because 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



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

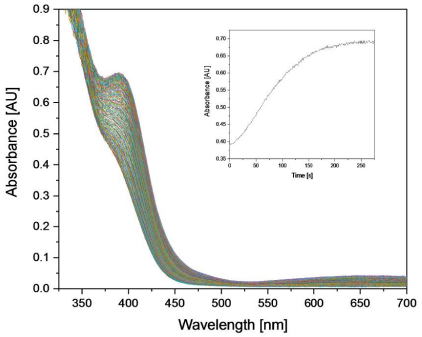


Figure 8. Time-resolved UV/Vis spectra of the reaction of **4a** and $[Cu(CH_3CN)_4]Otf$ ($c = 2\times10^{-3}$ M) with Dioxygen ($c = 2.15\times10^{-3}$ M) in DCM at −89 °C.

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 (3b) : The amine (obtained by Scheme 2e or **3e**) (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 (3c): 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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3.2 Reactivity of Copper Complexes with Tripodal Tetradentate Ligands based on Camphoric Acid towards Dioxygen

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Reactivity of Copper Complexes with Tripodal Tetradentate Ligands based on Camphoric Acid towards Dioxygen

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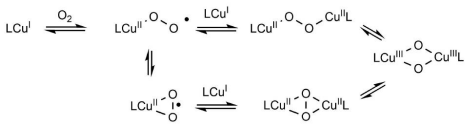
The reaction of dioxygen with copper(I) complexes containing camphor-derived ligands was investigated. Stopped-flow measurements revealed the formation of bis(μ-oxido) copper complexes at low temperatures. However, these intermediates were not stable enough to be isolated and decomposed quickly. Sterically more demanding alkyl groups slowed the formation of the bis(μ-oxido) copper complexes. A kinetic analysis was performed and showed - in line with previous reports - that the rate-determining step could be assigned to forming a mononuclear superoxido copper complex. For one of the reactions investigated, a product could be structurally characterized and turned out to be a copper(II) complex with an additional hydroxide as a ligand (most likely caused by a C–H abstraction from the solvent acetone). One of the complexes oxidized thioanisole to the corresponding sulfoxide (conversion of 34% according to GC-MS) with no byproducts. Chiral GC gave an enantiomeric excess of 14%.

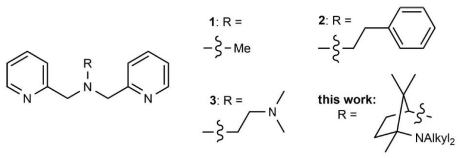
Introduction

Activation of molecular dioxygen is an essential topic in bioinorganic chemistry for possible applications in synthetic chemistry, the selective oxygenation of organic substrates.[1,2–4] For example, the copper enzyme tyrosinase, a monooxygenase, can hydroxylate the amino acid tyrosine leading to consecutive reactions to L-DOPA.[5] Furthermore, methane monooxygenase, based on either iron or copper ions in the active site, catalyzes methane oxidation to methanol.[6] So far, many model complexes containing copper(I) ions have been synthesized with different ligand systems to activate dioxygen.[3,4] In the reaction with O_2, a wide variety of so-called "copper-oxygen-adduct complexes" were characterized.[2,3,7] Several of these, often highly reactive species, can be used to oxidize diverse substrates with dioxygen as the oxidant.[8,9,10–13] The dioxygen binding mode depends on the ligands' geometric/steric and electronic properties. Some of the possible reactions leading to their formation of different intermediates are presented in Scheme 1.[2–4,14,15]

Astner et al. showed that the copper(I) complexes of the ligand Me-bpa **1** (Scheme 2) did not show an observable formation of an oxygen species.[16] In contrast, *Itoh* and co-workers reported a copper(I) complex with ligand **2** (Scheme 2), where the methyl group is exchanged for a phenethyl group.[17] This ligand can stabilize copper(I) by d-π interaction of the phenyl residue to the copper center. This copper(I) complex's reaction with dioxygen led to a bis(μ-oxido) copper complex in acetone. However, this oxygen intermediate decomposed even at low temperatures and led to an intramolecular hydroxylation of the phenylethyl sidearm.[17]



Scheme 1. Possible reaction pathways of the reaction of copper(I) complexes with dioxygen.[15]



Scheme 2. Derivatives of bispicolylamine (R = H), the ligands Me-bpa **1**, $^{Phe}L^{Pym2}$ **2**, and Me_2-uns-penp **3** used in previous work and the new ligands described herein.

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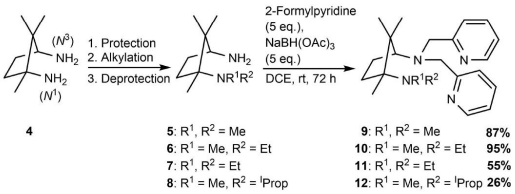
With an aminoethyl group for R (Scheme 2), the tripodal ligand uns-penp[18] was obtained, and derivatives of this ligand were applied successfully for stabilizing copper oxygen intermediates. For example, the ligand Me_2-uns-penp (**3**) formed a dimeric copper (*trans*-1,2-peroxido) complex.[13,19] With tetraphenylborate as an anion, it was possible to stabilize this usually unstable intermediate even at room temperature. With this peroxido species, the oxidation of toluene could be achieved.[13] More recently, we described the immobilization of a copper(I) complex with derivatives of uns-penp on silica for the oxidation of toluene.[20] The results of this work could become important for future applications of oxygenation reactions in a flow reactor.

As we were interested in enantioselective oxygenations, we started investigating the reactions of copper(I) complexes containing camphor-derived ligands[21] with dioxygen.[11,15] Camphor-based systems have also been reported previously by Garcia-Bosch and co-workers.[22] As a precursor, we applied camphor related bisamine **4** (Scheme 3), which can be easily prepared from camphoric acid.[23] The ligands could be easily modified, and the resulting copper(I) complexes showed good properties in stabilizing oxygen intermediates. Thus we could obtain a bis(μ-oxido) copper complex that was structurally characterized.[11] We decided to further functionalize the bpa system by introducing a camphor derivative as the R group with different alkyl residues (Schemes 2 and 3).

Results and Discussion

Synthesis and Characterization of Ligands and Copper Complexes

The educts **5**–**7** (Scheme 3) of the final ligand systems were prepared by literature procedures.[11] The synthesis of amine **8** is described in the supporting information. However, the alkylation of the nitrogen N^1 with more bulky groups (for example, R_1=^{i}Prop, R_2=Et) was not successful, presumably because of the high steric hindrance in this position (details are given in the supporting information). The ligands **9**–**12** were synthesized by adapting the reaction conditions with slight modifications of the synthesis of the ligand acetyl-uns-penp.[18] After purification using column chromatography, the pure ligands were obtained.



Scheme 3. Synthesis of the ligand systems using reductive amination conditions.

Crystallographic data for ligands **9** and **10** are given in the supporting information.

Attempts to crystallize copper(I) complexes of these ligands failed. In all cases, only yellow-colored oils were obtained. Therefore, copper(I) complexes obtained in an in situ 1:1 mixture of $[Cu(CH_3CN)_4]OTf$ and the corresponding ligand in deuterated acetone were characterized by NMR (acetone was used because the reactivity with dioxygen was only observed in acetone, *vide infra*; NMR data are reported in the supporting information).

In contrast to copper(I) complexes, it was possible to structurally characterize copper(II) complexes of the ligands **9**, **10**, and **11**. To understand if the alkylated nitrogens N^1 of the ligands can also coordinate with copper ions, we decided to use a mixture of $CuCl_2$ and $Cu(ClO_4)_2$ in a 0.5 to 0.5 ratio for the complexation reaction. With $Cu(ClO_4)_2$ alone, no crystals could be obtained. In the case of ligand **9** (R^1, R^2=Me) and **11** (R^1, R^2=Et), blue-colored crystals were obtained, which could be structurally characterized (Figure 1). For both complexes, [Cu(**9**-H)Cl]$(ClO_4)_2$ and [Cu(**11**-H)Cl]$(ClO_4)_2$, the alkylated nitrogen got protonated, presumably caused by the solvent methanol. Using aprotic solvents, the crystallization failed.

The implementation of the ligands **10** (R^1=Me, R^2=Et) and **11** (R^1, R^2=Et) with $CuCl_2$ led to the formation of green-colored crystals, which were structurally characterized. In both cases, only the bpa unit binds to the copper center in a square pyramidal fashion (Figure 2). Chloride effectively competes with

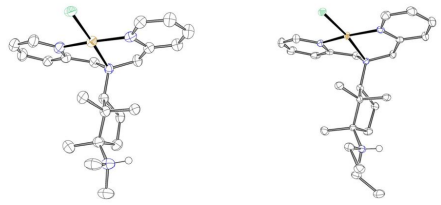


Figure 1. Molecular structures of [Cu(**9**-H)Cl]$(ClO_4)_2$ (left) and [Cu(**11**-H)Cl]$(ClO_4)_2$ (right). Hydrogen atoms (except N–H), solvent molecules, and perchlorate anions are omitted for clarity. Anisotropic displacement ellipsoids are set to 50% probability.

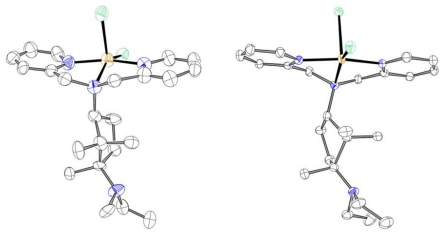


Figure 2. Molecular structures of [Cu(**10**)Cl_2] (left) and [Cu(**11**)Cl_2] (right). Hydrogen atoms are omitted for clarity. Anisotropic displacement ellipsoids are set to 50% probability.

coordinating the alkylated nitrogen that can bind to the copper(II) ions, as described below.

Reactivity of the Copper(I) Complexes with Dioxygen and Kinetic Investigations

The first benchtop experiments with the complex solutions of the ligands **9**–**12** with $[Cu(CH_3CN)_4]OTf$ were performed in DCM at −80 °C. A slow color change from yellow to green was observed when bubbling dry oxygen through this solution. This could be caused by the oxidation of Cu(I) to Cu(II). When the reaction was monitored with stopped-flow techniques, no intermediate, e.g. an oxido/peroxido species, was observed. This indicates that in DCM, a possible oxygen intermediate cannot sufficiently be stabilized, and the color change indicates the oxidation of copper(I) to copper(II). However, in contrast to the related complexes reported by *Itoh* and co-workers (described above),[17] no disproportionation reactions were observed.

However, when the reactions of the different complex solutions were performed in acetone at −80 °C, a color change to a dark brown color occurred (Figure 3). In the case of the complex solution with the double methylated ligand **9**, the occurrence was much faster (instantaneously) in contrast to the other ligands and the brown color switched to green after approximately one minute. When using the other ligands **10**–**12**, the brown color appeared much slower (minute range) and stayed much longer. After warming to room temperature, the color changed to green in all cases. We previously observed similar color changes when a copper(I) complex with a tetramethylated diamine ligand reacted with dioxygen.[11]

The reaction was monitored with low-temperature stopped-flow techniques to verify the occurrence of an "oxygen adduct" complex. While investigating the double methylated ligand **9**, the formation of a band at 389 nm was observed, which indicates the formation of the postulated bis(μ-oxido) copper complex (Figure 4).[2,11,25] The typical appearance of the band near 300 nm cannot be observed because of the limitation of our detector for measurements lower than 330 nm and the absorbance of the solvent acetone in that region. A decrease of the absorbance maximum at 389 nm could be detected after approximately one minute, completely in line with our observation in the benchtop experiment.

The absorbance vs. time trace measured under pseudo first order conditions (dioxygen concentration in excess) can be

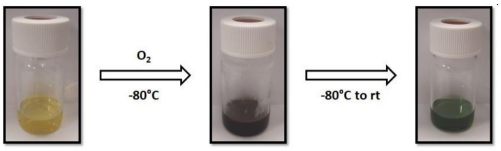


Figure 3. The copper(I) complex solutions react with dioxygen at −80 °C.

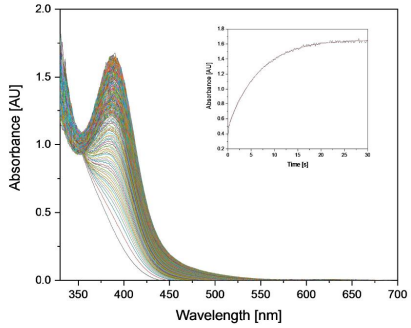


Figure 4. Time-resolved UV/Vis spectra of the reaction of $[Cu(CH_3CN)_4]OTf$ and **9** ($c = 0.6 \times 10^{-3}$ mol/L) with dioxygen ($c = 5.7 \times 10^{-3}$ mol/L) in acetone at −75 °C over 30 s. The inset shows the absorbance vs. time at $\lambda = 389$ nm.

fitted to a single exponential function. Therefore, the copper complex's concentration is first order in the rate law. The plot of k_{obs} vs. the concentration of dioxygen yielded a linear correlation (Figure 5) with an intercept. This shows that the consumption of O_2 is also first order in the rate law. The intercept indicates a reversible reaction in the rate-determining step, the dioxygen binding. This was observed previously in a related study on the formation of a copper peroxido complex by *Lerch et al.* using the ligand Pim^{iPr2}. A detailed description of the kinetic analysis is described herein.[24]

In line with this publication and previous work on forming other bis(μ-oxido) copper complexes[12,15,25], a proposed mechanism for the overall reaction is presented in Scheme 4. The rate-limiting step is assigned to the formation of a superoxido complex (eq. 1). However, as described previously through extensive DFT calculations using guanidine-containing ligands, it is not possible to spectroscopically detect this intermediate

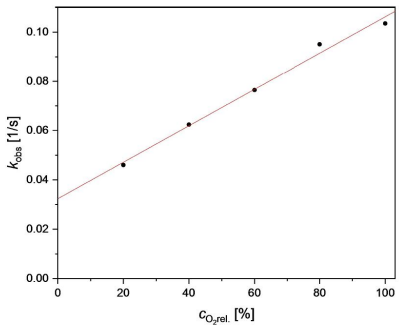
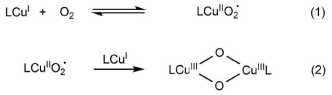


Figure 5. Plot k_{obs} *vs.* relative concentration of dioxygen using the double methylated ligand **9**. The measurements were done in acetone at −75 °C with the copper salt $[Cu(CH_3CN)_4]OTf$.



Scheme 4. Proposed formation of the bis(μ-oxido) copper complexes.

due to the much faster formation of the observed bis(μ-oxido) copper complex (eq. 2).[25]

Additionally, a temperature-dependent series of measurements allowed to calculate the activation parameters ($\Delta H^{\ddagger} =$ 18.5 kJ/mol; $\Delta S^{\ddagger} = -165$ J/(mol·K) from an Eyring plot (see supporting information). The highly negative value for the activation entropy has been observed by us previously for a related complex system[15] and indicates an associative mechanism. This supports the coordination of the alkylated nitrogen of the ligand system, as discussed below. Dioxygen binds at the copper ion while the alkylated nitrogen atom is still coordinated, followed by the formation of the bis(μ-oxido) copper complex in a consecutive reaction while breaking the bond to the alkylated nitrogen atom with the bulky group. Thus leading to a bis(μ-oxido) copper complex similar to the copper(II) complexes in Figure 2, with the two chloride ions replaced by the two bridging oxido anions.

Due to the intermediates' short lifetime, obtaining them as solids (crystals) for complete characterization was impossible. Therefore, it was tried to crystallize one of the products after the reaction. From the oxidation of $[Cu(CH_3CN)_4]PF_6$ and the ligand **9**, a few blue-colored crystals were obtained that could be picked and structurally characterized. The molecular structure of this complex is presented in Figure 6 (crystallographic data are reported in the supporting information).

The molecular structure of the copper(II) complex clearly shows that the amine nitrogen atom N^1 can be coordinated as well. This is what we assume for the copper(I) complexes with this ligand series. The coordinated hydroxide ion most likely is caused by a C–H abstraction from the solvent acetone. The decomposition of bis(μ-oxido) copper complex to copper hydroxido complexes is well known by us and others.[8,26,27]

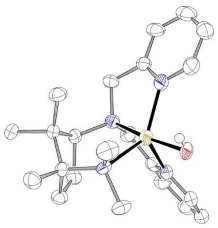


Figure 6. Molecular structure of the copper-hydroxido complex with ligand **9**. Hydrogen atoms (except O–H) and PF_6 anion are omitted for clarity. Anisotropic displacement ellipsoids are set to 50 % probability.

However, these complexes are potentially helpful for the oxidation of substrates.[26,27] Unfortunately, we failed in selectively synthesizing this complex for applications in oxidation reactions.

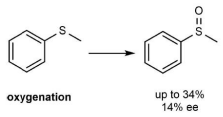
As described above, copper(I) complexes with the ligands **10**, **11**, and **12** reacted nearly the same way as with ligand **9**; however, by a factor of about ten slower (data for the kinetic investigations with these complexes are reported in the supporting information). From the comparison of the activation parameters (Table 1), it is clear that the activation enthalpies cause differences in reaction rates.

Oxidation of external substrates

The oxidation of external substrates with bis(μ-oxido) copper complexes is well known, - e.g., Herres-Pawlis and co-workers described the oxidation of 2-naphthol to the corresponding *ortho* quinone.[28] Trials to oxidize this substrate with the copper complexes reported herein only led to the formation of BINOL. This was not surprising because the oxidative coupling reaction is already described in the literature using copper(II) amine complexes.[29] Attempts to oxidize the non-activated substrate cyclohexane failed. The oxidation of toluene, described by Karlin[10] using a bis(μ-oxido) copper species, did not lead to the formation of benzyl alcohol or benzaldehyde. Only the oxidation of thioanisole to the corresponding sulfoxide (Scheme 5) could be detected. While using the double methylated ligand **9**, the sulfoxide was detected with a conversion of 34% using GC-MS with no visible byproducts. Chiral GC gave an enantiomeric excess of 14%. Using the complex solutions of the other ligands, the corresponding sulfoxide could be detected only in traces. Most likely, this is a consequence of the sterically more demanding alkyl groups in ligands **10**–**12** suppressing a close approach of the substrate molecule. Casella and co-workers also performed asymmetric oxidation of thioanisole. Using a binuclear copper complex containing a chiral diamino-

Table 1. Activation parameters for the reaction of dioxygen with all copper(I) complexes described herein.

Cu(I)L	$\Delta H^{\ddagger}$/kJ/mol	$\Delta S^{\ddagger}$/J/(mol K)	$k_{(obs)}$ at -73 ± 1 °C/ 1 s^{-1}
9	$+18.5 \pm 0.3$	-165 ± 1	0.146
10	$+24.7 \pm 0.6$	-153 ± 3	0.015
11	$+25.7 \pm 0.1$	-148 ± 1	0.016
12	$+24.9 \pm 0.1$	-154 ± 2	0.013



Scheme 5. Oxygenation of thioanisole to the corresponding sulfoxide.

m-xylene tetra(benzimidazole) ligand, a comparable enantiomeric excess of 12% of the corresponding sulfoxide was observed.[30] Furthermore, *Gamba et al.* described catalytic sulfoxidation. A dicopper peroxido complex was assigned as the reactive intermediate.[31] In our previous work, we also showed that bis(μ-hydroxido) dicopper complexes can oxidize thioanisole.[26] However, only small *ee*'s up to 4 % were detected. Due to the high interest in chiral sulfoxides, for example, in drug research, these results could play a role in future synthetic concepts.[32]

Summary and Conclusion

A series of camphor-derived ligands had been prepared, and copper(II) complexes with some of these ligands were structurally characterized. The reaction of dioxygen with the copper(I) complexes led to the formation of bis(μ-oxido) copper complexes as reactive intermediates that could be detected spectroscopically. A kinetic analysis, applying low temperature stopped-flow measurements allowed us to postulate a reaction mechanism that was in line with previous investigations by us and others. In contrast to previous work, it was not possible to isolate and structurally characterize one of the bis(μ-oxido) copper complexes formed due to the instability of these compounds, even at low temperatures. One of the complexes turned out to oxidize thioanisole (in a low conversion) selectively to the corresponding sulfoxide with an enantiomeric excess of 14%, a promising result for future work in this area. Detecting a copper(II) complex with an additional hydroxide as a ligand could indicate the involvement of hydroxido complexes as possible oxidants.

Experimental Section

General: Chemicals and solvents were purchased from commercial sources (AcrosOrganics, Alfa Aesar, Merck, and Sigma Aldrich). The solvents were distilled and, if necessary, dried using standard procedures. Oxygen-free solvents were obtained by redistillation under argon. Preparation under anaerobic conditions was carried out in a glovebox (MBraun) under Argon atmosphere. Column chromatography was performed using Silica 60, 0.04–0.063 mm (MACHEREY-NAGEL). ^{1}H and ^{13}C spectra were measured on a Bruker Avance II 400 MHz and Bruker Avance III HD 400 MHz spectrometer. Complex solutions were measured on a Bruker Avance III HD 600 MHz spectrometer. The ^{1}H- and ^{13}C-NMR spectra were calibrated against the residual proton and carbon signals of chloroform ($\delta = 7.26$ and $\delta = 77.2$) and acetone ($\delta = 2.05$ and $\delta = 29.8$).[33] HRMS(ESI) was measured with an ESI-MS Bruker Micro-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. Chiral GC was performed with a HP 5890 SERIES II GAS CHROMATOGRAPH with Hydrodex ß-TBDAc column.

Stopped-Flow measurements: The copper(I) complex solutions were prepared in a glove box by adding the copper salt solution to the ligand solution under stirring and were filled in glass syringes. Saturated solutions of dioxygen were prepared by bubbling dry oxygen through dry acetone in a syringe for 10 minutes. The saturated dioxygen concentration in acetone is 11.4×10^{-3} mol/L at 25 °C.[34] The measurements were performed by a commercial HI-TECH SF-61SX2 instrument (TgK Scientific, Bradford-on-Avon, UK) at different temperatures. Detailed descriptions of the stopped-flow measurements and fitting of the kinetic data have been described previously.[24,25,35]

Ligand synthesis: The amines **5**–**7** were synthesized using literature procedures.[11] The synthesis of amine **8** is described in the supporting information. The final ligands were obtained by reductive amination reactions:

(1*R*,3*S*)-*N*^{1}-Dimethyl-*N*^{3}-bis(2-pyridinylmethyl)-1,2,2-trimethylcyclopentane-1,3-diamine (9): Amine **5** (0.76 g; 4.5 mmol) was dissolved in 30 ml DCE. Pyridine-2-carbaldehyde (2.13 ml, 22.4 mmol) and $NaBH(OAc)_3$ (4.75 g, 22.4 mmol) were added. The mixture was stirred under nitrogen over three days. The mixture was made basic with 50 ml NaOH solution (~15 wt.%) and extracted with DCM (3x50 ml). The organic phases were combined and the solvent was removed. The residue was purified by flash column chromatography (DCM:MeOH 9/1 (to remove the impurities), then diethyl ether, 2% NEt_3; silica). The product was obtained as a colorless solid (1.37 g; 3.90 mmol; 87%). Crystals suitable for SC-XRD were obtained by dissolving the solid in a minimal amount of DCM followed by diethylether diffusion at −20 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm] 8.54–8.49 (m, 2H), 7.66 (td, $J = 7.6$, 1.8 Hz, 2H), 7.62–7.56 (m, 2H), 7.18–7.10 (m, 2H), 3.96 (d, $J = 14.7$ Hz, 2H), 3.76 (d, $J = 14.7$ Hz, 2H), 3.21 (t, $J = 9.4$ Hz, 1H), 2.17 (s, 6H), 1.89–1.59 (m, 3H), 1.57–1.48 (m, 1H), 0.95 (s, 3H), 0.83 (s, 3H), 0.78 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm] 160.7, 149.1, 136.4, 123.3, 122.0, 68.3, 66.2, 59.6, 48.6, 40.2, 37.0, 23.7, 18.5, 18.4, 11.3. HRMS (ESI): calcd. for $C_{22}H_{32}N_4$ [M+H$^+$] 353.2700, found 353.2703. $C_{22}H_{32}N_4$: calcd. C 74.96, H 9.15, N 15.89; found C 74.75, H 9.37, N 15.55.

(1*R*,3*S*)-*N*^{1}-Ethyl-*N*^{1}-methyl-*N*^{3}-bis(2-pyridinylmethyl)-1,2,2-trimethylcyclopentane-1,3-diamine (10): Amine **6** (0.71 g; 3.9 mmol) was dissolved in 30 ml DCE. Pyridine-2-carbaldehyde (1.80 ml, 18.9 mmol) and $NaBH(OAc)_3$ (4.10 g, 19.3 mmol) were added. The mixture was stirred under nitrogen over three days. The mixture was made basic with 50 ml NaOH solution (~15 wt.%) and extracted with DCM (3×50 ml). The organic phases were combined and the solvent was removed. The residue was purified by flash column chromatography (DCM:MeOH 9/1 (to remove the impurities), then diethyl ether, 2% NEt_3; silica). The product was obtained as a light yellowish oil (1.36 g; 3.70 mmol; 95%) which crystallized after some time. The crystals were suitable for SC-XRD. ^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm] 8.54–8.47 (m, 2H), 7.66 (td, $J = 7.6$, 1.8 Hz, 2H), 7.62–7.55 (m, 2H), 7.17–7.09 (m, 2H), 3.96 (d, $J = 14.7$ Hz, 2H), 3.75 (d, $J = 14.7$ Hz, 2H), 3.14 (t, $J = 9.4$ Hz, 1H), 2.50–2.37 (m, 1H), 2.22–2.10 (m, 1H), 2.08 (s, 3H), 1.85–1.56 (m, 3H), 1.55–1.45 (m, 1H), 0.95 (t, $J = 7.1$ Hz, 3H), 0.89 (s, 3H), 0.84 (s, 3H), 0.77 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm] 160.8, 149.0, 136.3, 123.3, 121.9, 68.2, 66.8, 59.6, 48.7, 45.9, 36.9, 35.6, 24.2, 18.8, 18.3, 14.3, 12.9. HRMS (ESI): calcd. for $C_{23}H_{34}N_4$ [M+H$^+$] 367.2856, found 367.2861. $C_{23}H_{34}N_4$: calcd. C 75.37, H 9.35, N 15.29; found C 75.29, H 9.41, N 15.52.

(1*R*,3*S*)-*N*^{1}-Diethyl-*N*^{3}-bis(2-pyridinylmethyl)-1,2,2-trimethyl-cyclopentane-1,3-diamine (11): Amine **7** (1.30 g; 6.55 mmol) was dissolved in 40 ml DCE. Pyridine-2-carbaldehyde (3.10 ml, 32.6 mmol) and $NaBH(OAc)_3$ (6.96 g, 32.8 mmol) were added. The mixture was stirred under nitrogen over three days. The mixture was made basic with 50 ml NaOH solution (~15 wt.%) and extracted with DCM (3×50 ml). The organic phases were combined and the solvent was removed. The residue was purified by flash column chromatography (DCM:MeOH 9/1 (to remove the impurities), then diethyl ether, 2% NEt_3; silica). The product was obtained as a yellowish oil (1.37 g; 3.60 mmol; 55%). ^{1}H NMR (400 MHz,

$CDCl_3$) δ [ppm] 8.55–8.48 (m, 2H), 7.66 (td, J=7.6, 1.8 Hz, 2H), 7.60 (dt, J=7.9, 1.2 Hz, 2H), 7.18–7.10 (m, 2H), 3.96 (d, J=14.7 Hz, 2H), 3.76 (d, J=14.7 Hz, 2H), 3.09 (t, J=9.5 Hz, 1H), 2.55–2.34 (m, 4H), 1.93–1.80 (m, 1H), 1.79–1.55 (m, 2H), 1.50–1.41 (m, 1H), 0.96 (t, J=7.1 Hz, 6H), 0.89 (s, 3H), 0.86–0.81 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm] 160.9, 149.1, 136.3, 123.3, 121.9, 68.2, 67.7, 59.6, 49.1, 45.0, 36.0, 24.3, 19.2, 18.6, 17.0, 16.5. HRMS (ESI): calcd. for $C_{24}H_{36}N_4$ [M+H$^+$] 381.3013, found 381.3014. $C_{24}H_{36}N_4$: calcd. C 75.74, H 9.53, N 14.72; found C 75.41, H 9.25, N 14.38.

(1*R*,3*S*)-*N*^{1}-Isopropyl-*N*^{1}-methyl-*N*^{3}-bis(2-pyridinylmethyl)-1,2,2-trimethylcyclopentane-1,3-diamine (12): Amine **8** (0.44 g; 2.22 mmol) was dissolved in 30 ml DCE. Pyridine-2-carbaldehyde (0.85 ml, 8.9 mmol) and $NaBH(OAc)_3$ (1.89 g, 8.89 mmol) were added. The mixture was stirred under nitrogen over three days. The mixture was made basic with 70 ml NaOH solution (~15 wt.%) and extracted with DCM (3x70 ml). The organic phases were combined and the solvent was removed. The residue was purified by flash column chromatography (DCM:MeOH 19/1 (to remove the impurities), then diethyl ether, 1% NEt_3; silica). The product was obtained as a yellowish oil (0.22 g; 0.58 mmol; 26%). ^1H NMR (400 MHz, $CDCl_3$) δ [ppm] 8.54–8.47 (m, 2H), 7.65 (td, J=7.6, 1.8 Hz, 2H), 7.62–7.56 (m, 2H), 7.17–7.09 (m, 2H), 3.95 (d, J=14.8 Hz, 2H), 3.75 (d, J=14.8 Hz, 2H), 3.19–3.06 (m, 2H), 2.05 (s, 3H), 1.88–1.44 (m, 4H), 0.96–0.82 (m, 15H). ^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm] 160.8, 149.0, 136.3, 123.2, 121.9, 68.2, 67.4, 59.6, 49.3, 47.5, 36.5, 28.5, 24.2, 21.2, 21.0, 19.0, 18.3, 16.3. HRMS (ESI): calcd. for $C_{24}H_{38}N_4$ [M+H$^+$] 381.3013, found 381.3011.

[Cu(9-H)Cl](ClO$_4$)$_2$: Ligand **9** (50.0 mg; 0.142 mmol) was dissolved in approx. 2 ml MeOH. The solution was added to a mixture of $CuCl_2$ (9.5 mg, 0.071 mmol) and $Cu(ClO_4)_2x6H_2O$ (26.3 mg; 0.0710 mmol). A blue solid was formed which was filtered off. Slow evaporation of the solvent led to the formation of some crystals, which were structurally characterized.

[Cu(11-H)Cl](ClO$_4$)$_2$: Ligand **11** (55.9 mg; 0.147 mmol) was dissolved in approx. 2 ml MeOH. The solution was added to a mixture of $CuCl_2$ (9.9 mg, 0.074 mmol) and $Cu(ClO_4)_2x6H_2O$ (27.2 mg; 0.0734 mmol). A blue solid was formed which was filtered off. Slow evaporation of the solvent led to the formation of some crystals, which were structurally characterized.

[Cu(10)Cl$_2$]: Diethyl ether diffusion to a solution of ligand **10** (32.4 mg; 0.0884 mmol) and $CuCl_2$ (11.8 mg; 0.0878 mmol) in approx. 1 ml MeOH led to the formation of green crystals (suitable for SC-XRD). The crystals were filtered off, washed with diethyl ether (3x~5 ml) and dried in vacuum. The complex was obtained as green powder (20.6 mg; 0.0411 mmol; 47%). $C_{23}H_{34}N_4CuCl_2$: calcd. C 55.14, H 6.84, N 11.18; found C 55.13, H 6.84, N 11.09.

[Cu(11)Cl$_2$]: Diethyl ether diffusion to a solution of ligand **11** (34.8 mg; 0.0914 mmol) and $CuCl_2$ (12.0 mg; 0.0893 mmol) in approx. 1 ml MeOH led to the formation of green crystals (suitable for SC-XRD). The crystals were filtered off, washed with diethyl ether (3x~5 ml) and dried in vacuum. The complex was obtained as green powder (11.9 mg; 0.0231 mmol; 26%). $C_{24}H_{36}N_4CuCl_2$: calcd. C 55.97, H 7.05, N 10.88; found C 55.99, H 6.96, N 10.65.

[Cu(9)OH](PF$_6$): In a glove box $[Cu(CH_3CN)_4](PF_6)$ (23.8 mg; 0.0639 mmol) in approx. 0.5 ml acetone was added to Ligand **9** (22.1 mg; 0.0627 mmol) in approx. 0.5 ml acetone. Dry dioxygen was bubbled through the solution at −80 °C for two minutes. After warming to rt, diethyl ether diffusion led to the formation of a small amount of blue colored crystals, which were suitable for SC-XRD.

General Procedure for the Oxidation Experiments: $[Cu(CH_3CN)_4]OTf$ (0.05 mmol) dissolved in approx. 1 ml acetone was added to the ligand (0.05 mmol) in approx. 1 ml acetone under stirring. The substrate (0.05 mmol) dissolved in approx. 0.1 ml acetone was added. Dry dioxygen was bubbled through the solution for 10 min at −80 °C. After 24 h the solution was warmed to rt and diluted with aqueous ammonia (~20 ml) and was extracted with DCM (~20 ml). The organic phase was concentrated in vacuum and analyzed using GC-MS and chiral GC (in the case of thioanisole oxidation).

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

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

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