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ARTICLE

Synthesis and characterization of copper complexes with tripodal ligands bearing amino acid groups

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Dedicated to Professor Dr. Peter Klüfers on the Occasion of his 70th Birthday

The tripodal ligand (2-aminoethyl)*bis*(2-pyridylmethyl)amine (uns-penp), known for its Cu/O_2 intermediates, was modified at one side arm by a selection of amino acids. With L-Tyrosine (Tyr), L-Histidine (His) and L-Lysine (Lys) it was possible to introduce chirality into the tripodal ligand system and to investigate the corresponding copper(I) complexes [Cu{L-His(BPh_3)uns-penp}], [Cu(L-Lys)uns-penp]OTf and [Cu(L-Tyr)uns-penp]OTf. [Cu{L-His(BPh_3)uns-penp}] could be structurally characterized and represents the first example of a copper(I) complex with a coordinated imidazole ring of the histidine ligand. Furthermore, these complexes demonstrated catalytic activity for the oxygenation of thioanisole with hydrogen peroxide as an oxidant.

Introduction

Copper/dioxygen intermediates play a significant role in oxygenation reactions in nature and in industrial applications.[1,2] Complexes of this type are observed for example in the active site of the oxygen carrier copper protein hemocyanin (Hc) in arthropods and mollusks. Copper enzymes such as tyrosinase or superoxide dismutase, are responsible for the *ortho* hydroxylation of phenol or the reduction of superoxide and are common in almost every lifeform.[1] Copper complexes with tripodal ligands based on *tris*(2-pyridylmethyl)-amine (tmpa), *tris*(2-aminoethyl)amine (tren) and (2-aminoethyl)*bis*(2-pyridylmethyl) amine (uns-penp) proved to be quite useful in the study of reversible dioxygen binding (Figure 1).[3–8]

Examining these compact model systems and their spectral features makes it possible to gain information about the geometric/electronic structures of the active species of the catalytic metal centers. Especially the ligand uns-penp is interesting because of the increased stability towards copper(I) ions. Furthermore, it obtains a primary amino group that allows easy modifications of the ligand itself. Those modifications can include the attachment of a side arm that introduces stereo chemical information to the ligand system, which in turn is of great importance in the catalytic synthesis of products with an enantiomeric excess in pharmaceutical industry.[9] For this purpose, the use of amino acids is a promising approach to create chirality and at the same time to obtain realistic models close to the natural copper complexes in proteins. This furthermore can provide an opportunity to connect oxygen sensitive copper complexes to peptide chains. Related Approaches have been reported in the past where amino acids have been attached to the original ligand by amide bonds.[10–14] However, the complexes described therein showed coordination of the amide oxygen to the respective metal centers of Cu(II), Zn(II) or Ni(II), which is not representative of the framework of metal-containing proteins in nature. We wanted to avoid this type of coordination and instead create a direct bond between the metal center and the chiral side arm of the attached amino acid of the chelate ligand. In recent research, the group of Shinobu Itoh *et al.* developed a model for the active-site of the lytic polysaccharide monooxygenase. In this example imidazole rings of the used ligand could form a direct coordination with the central copper ion.[15] We wanted to pursue this approach but through the direct use of amino acids.

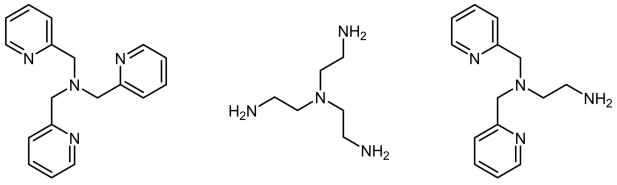

Figure 1. Tripodal ligands tmpa (left), tren (middle) and uns-penp (right).

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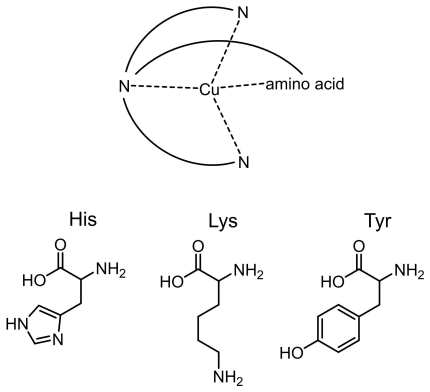


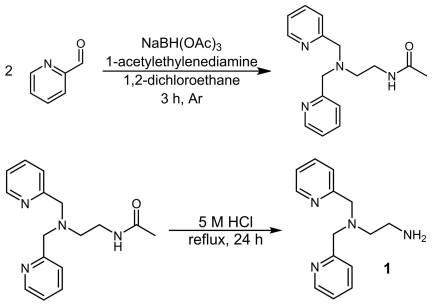
Figure 2. Simplified drawing of *uns-penp* with attached amino acid groups forming corresponding copper(I) complexes.

For the selection of the amino acids, histidine, lysine and tyrosine were chosen for the attachment to the ligand uns-penp with regard to their natural occurrence of the complexing amino acid ligands in copper-containing proteins. A simplified view of the model complexes described herein is presented in Figure 2. The coupling of the chiral side arm with *uns-penp* was performed via *Liquid Phase Peptide Coupling* (*LPPC*), which relies on the protection of the amine function of the amino acid with a *tert*-butyloxycarbonyl (*Boc*) group to prevent the coupling of two equal substrates or the formation of polymer side products. Common coupling reagents are the combination of a carbodiimide (e.g. *DCC*, *DIC*, *EDC*) and 1-hydroxybenzotriazol (HOBt).[16,17]

Results and Discussion

Synthesis and characterization of the ligands

The tripodal ligand uns-penp (**1**) was first synthesized and characterized in 1987 by Mandel *et al.*[18] Copper(I) and copper (II) complexes of this ligand as well as of the methyl derivative (Me_2-uns-penp) have been described previously.[19] There are different synthetic approaches to obtain this ligand, however, so far we obtained the best yields by the reaction of 2-pyridinecarboxaldehyde and 1-acetylethlyene diamine followed by a reduction of the tertiary amine with $Na(AcO)_3BH$. In the last step, the acetyl protection group was cleaved under acetic conditions with 5 M HCl solution (Scheme 1).

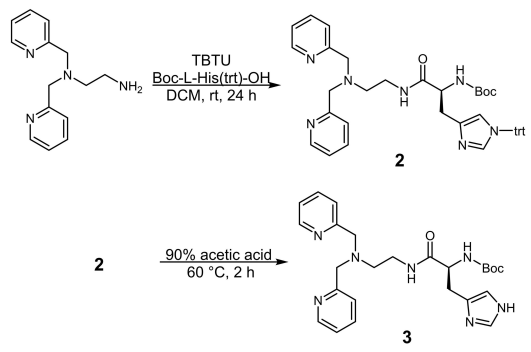


Scheme 1. Synthesis of acetyl uns-penp and uns-penp (**1**).

Boc-L-His-uns-penp

Histidine is one of the most common amino acids found in the active sit of Type I, II and III copper enzymes such as e.g. tyrosinase. This natural occurrence as a ligand offers a promising candidate for a successful complexation of copper combined with uns-penp (**1**). The synthesis was carried out according to a general procedure for the preparation of peptides via LPPC with **1** and Boc-L-His-OH. As coupling reagents, 1-hydroxybenzotriazol (HOBt) and 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimid (EDC) were replaced by a combined reagent **O**-(Benzotriazoyl)tetramethyluronium-tetrafluoroborat (TBTU), as a higher yield could be obtained with these. The mixture was stirred at room temperature in DCM for 24 hours. However, analysis via mass spectrometry showed that most of the conversion had caused the formation of unidentified side products while only a very small amount of the desired product was obtained. This is mainly caused by the participation of the imidazole ring of histidine in the coupling process, forming polymeric side products with the carboxylic groups of other histidine molecules. To prevent this, it is necessary to introduce a protection group for the N^{Im} of histidine. It turned out that a trityl group ($-CPh_3$) was best suited for its protection, because it is stable in neutral and alkaline media and furthermore, towards nucleophiles, which is required for the conditions of a LPPC. This approach allowed obtaining compound **2** in a good yield (Scheme 2).

The trityl protective group, like the Boc group, is labile in acidic conditions and therefore, a selective cleavage is necessary to remove the trityl group while leaving the Boc group intact. By applying a common method for the cleavage,[20] stirring **2** in a 90% acidic acid solution at 60 °C for two hours, Boc-L-His-uns-penp (**3**, Scheme 2) was obtained in excellent yields and no cleavage of the Boc protection group was observed.



Scheme 2. Synthesis of Boc-L-His(trt)-uns-penp (**2**) and Boc-His-uns-penp (**3**).

Boc-L-Lys-uns-penp

The coupling of **1** with L–Lysine was performed under the same reaction conditions as with L-Histidine (Scheme 3)

As with Histidine, it is necessary to use an additional protection group with Lysine, which has an additional primary amino group at its side arm that can interfere in the coupling process with **1**. The benzyl carbamate group (Cbz) is providing a good option for a selective cleavage via hydrogenation, while leaving the Boc group intact. By using 5 mol% Pd/C with hydrogen gas at room temperature successful cleavage was achieved and **4** could be obtained in good yields (74%).

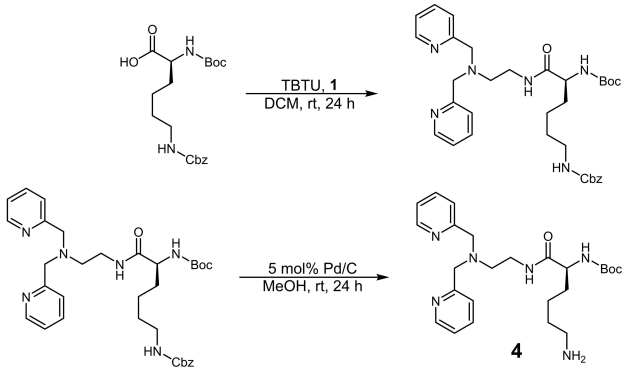
Boc-L-Tyr-uns-penp

The synthesis of Boc-L-Tyr-uns-penp (**5**) with **1** and L-Tyrosine was also performed with TBTU as a coupling reagent in DCM. An additional protective group for the hydroxyl group is not necessary. No major side products could be observed by ESI-MS (Scheme 4).

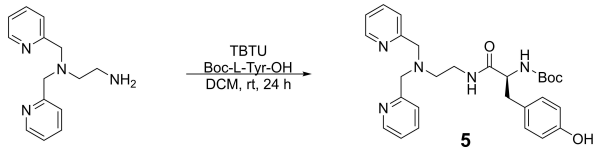
Synthesis and characterization of copper(I) complexes

The copper(I) complexes of all ligands were prepared under inert conditions in an argon atmosphere. Copper(I) salts [Cu(MeCN$_4$)]X (X = OTf, ClO$_4$) were used for complexation. By using **3** it was not possible to synthesize a stable copper(I)-complex. After an initial formation of the complex, indicated by a color change of the solution to yellow, a green/brown color developed after about 20–30 minutes and furthermore, a reddish precipitate (elemental copper) formed. All attempts to avoid this disproportionation reaction failed. However, by using [Cu(MeCN)$_4$]PF$_6$ followed by an anion exchange with NaBPh$_4$, it was possible to isolate a stable copper(I)-complex (Scheme 5).

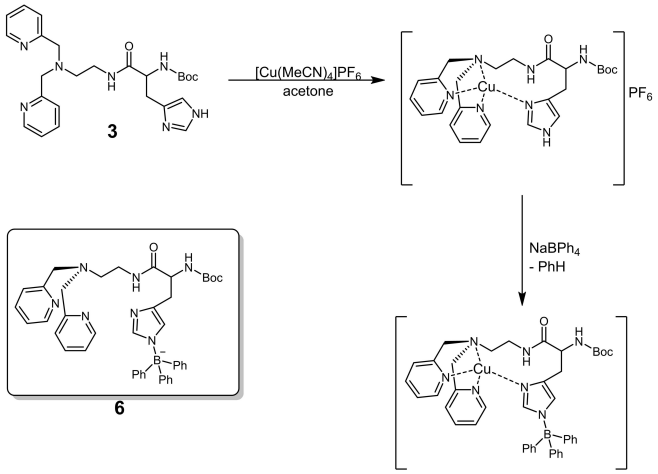
In contrast to our expectations, analytics via mass spectrometry and infrared spectroscopy revealed that our ligand underwent a chemical transformation during the anion exchange. Cleavage of one of the phenyl rings of the BPh$_4$ anion and the formation of a bond with the imidazole nitrogen N$^{\delta}$ was observed leading to the new ligand **6**. This was furthermore confirmed by obtaining crystals of the corresponding copper(I) complex, [Cu(**6**)] (Scheme 5) that were suitable for crystallographic characterization. The molecular structure of [Cu(**6**)] is presented in Figure 3, crystallographic data are reported in the Supporting Information. The copper(I) ion is coordinated in a distorted tetrahedral manner. Besides coordination of the two pyridyl nitrogen atoms and the amine nitrogen atom of the uns-penp molecule the copper(I) ion is furthermore bonded to the nitrogen atom of the imidazole ring. Due to the fact that histidine-with coordination through the imidazole unit-is quite common in copper proteins it could be expected that a large



Scheme 3. Synthesis of Boc-L-Lys-uns-penp (**4**).



Scheme 4. Synthesis of Boc-L-Tyr-uns-penp (**5**).



Scheme 5. Formation of Boc-L-His(BPh$_3$)-uns-penp (**6**) and copper complex [Cu{Boc-L-His(BPh$_3$)-uns-penp}].

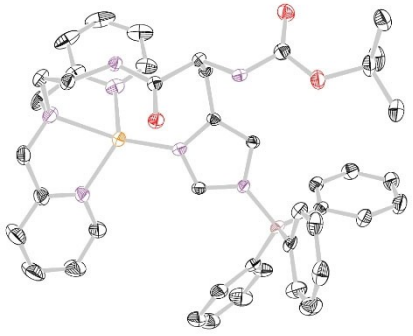


Figure 3. Molecular structure of [Cu{Boc-L-His(BPh$_3$)-uns-penp}] ([Cu(**6**)]) with a distorted tetrahedral coordination geometry and coordinated imidazole ring of L-histidine. Ellipsoids are set to 50% probability level.

number of structurally characterized copper complexes with this amino acid should be known. However, the opposite is true and with only a few exceptions of copper(II) histidine complexes[13,14,21–23] most of the few crystal structures reported (according to a search in the Cambridge Crystallographic Data Base) show no coordination to the imidazole ring. To the best of our knowledge, complex [Cu{Boc-L-His(BPh_3)-uns-penp}] is the first example of a structurally characterized copper(I) complex with a coordinated imidazole ring of L-histidine. The presence of the BPh_3 group seems to have favored the crystallization process, because this compound was the only copper(I) complex of our ligand series of amino acids for which it was possible to obtain a crystalline sample suitable for crystallographic characterization. Another positive side effect of the triphenyl boron group attached to the ligand is the increased stability of the copper(I)-complex itself. In contrast to our attempts (that failed as described above) to obtain a complex with ligand **3**, [Cu(**6**)] did not show signs of decomposition for a longer period of time. Most likely, this is caused by the substituted proton of the imidazole ring in **3**. Trials to remove protons by adding triethylamine or diisopropylethylamine prior to adding the copper salt were not successful either and again only enforced disproportionation/decomposition. Our hypothesis is also supported by a test that showed when using ligand **2** with [$Cu(MeCN)_4$]OTf, a stable copper(I) complex could be obtained. Due to the trityl group on the imidazole ring, analogous to the BPh_3 group from compound **6**, there is no longer a proton that can impair the stability of the complex.

Syntheses of the copper(I)-complexes with ligands **4** and **5** were carried out under similar conditions as described above. For the preparation of the copper(I) complex of **5** a stoichiometric amount of triethylamine was added additionally due to the acidic nature of the phenol side arm. It was possible to obtain yellow solids of both complexes. No crystals were obtained for structural analysis via SC-XRD. A conformational search applying the **C**onformer-**R**otamer **E**nsemble **S**ampling **T**ool (CREST) at an extended tight-binding semiempirical level of theory based on the analytical data and subsequent DFT (PBE, cc-pVDZ) calculations allow to suggest structural models for both complexes, [Cu(**4**)(MeCN)]OTf and [Cu(**5**)(MeCN)]OTf (Figure 4). The calculated bond lengths of the atoms of the ligands to the metal centre are presented in Table 1. The calculations within this study serve to obtain a structural guess of the complexes, rather than representing a full theoretical consideration.

It is interesting to note that in both cases calculations suggest the amide oxygen is coordinated to the copper(I) ion. We are not aware that this has been reported previously for copper(I) complexes, however, the amide oxygen atom coordination has been observed for a very similar copper(II) complex.[24] The structural assignment was furthermore supported by IR measurements and elemental analysis. Unfortunately, we did not succeed to record decent NMR spectra for the complexes with ligands **4**, **5** and **6** due to the instability of the complexes (paramagnetic Cu(II) formed in the samples).

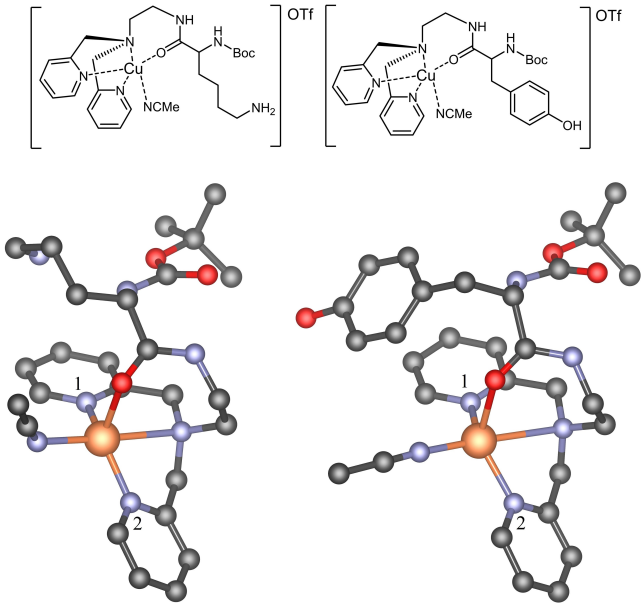


Figure 4. Molecular structures obtained by CREST//DFT calculations for the cations of [Cu(**4**)(MeCN)]OTf and [Cu(**5**)(MeCN)]OTf based on the analytical data. For clarity, the hydrogen atoms have been removed. CPK coloring scheme: black-carbon, red-oxygen, blue-nitrogen, orange-copper.

Table 1. Bond length of the coordination complex of the cations of [Cu(**4**)(MeCN)]OTf and [Cu(**5**)(MeCN)]OTf.

Bond length [Å]	$[Cu(4)(MeCN)]^+$	$[Cu(5)(MeCN)]^+$
Cu-N (Amine)	2.533	2.644
Cu-N (Pyridine-1)	1.996	2.031
Cu-N (Pyridine-2)	1.984	2.039
Cu-N (Nitrile)	2.091	1.941
Cu-O	2.214	2.267

Cyclic voltammetry

The electrochemical properties of [Cu(Me_2-uns-penp)]OTf, [Cu-(acetyl-uns-penp]OTf, [Cu(**4**)MeCN]OTf, [Cu(**5**)(MeCN)]OTf, [Cu-(**6**)] were examined by cyclic voltammetry in acetonitrile. With the exception of [Cu(**6**)] all complexes showed a reversible redox reaction. As an example, the cyclic voltammogram of [Cu(**4**)(MeCN)]OTf is presented in Figure 5 (ferrocene has been used as an internal standard). The $E_{1/2}$ values do not differ too much for all complexes (except for [Cu(**6**)]) investigated and all electrochemical data are reported in the Supporting Information.

Copper(II) complexes

Efforts to prepare copper(II) complexes were carried out with **3** and **4**. $Cu(ClO_4)_2 \cdot 6\ H_2O$ as well as $Cu(OTf)_2$ were used as copper salts for the complexation. Unfortunately, it was not possible to obtain crystalline samples for molecular structure determina-

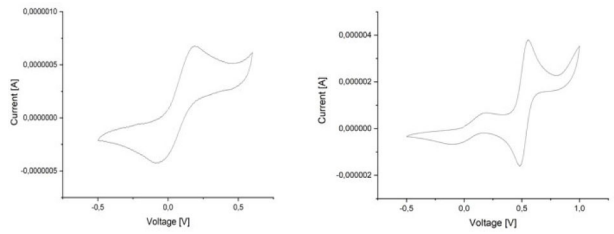


Figure 5. Cyclic voltammogram of [Cu(**4**)(MeCN)]OTf, left without and right with ferrocene added (298 K, scan rate: 100 mVs^{-1}, c[Cu(**4**)(MeCN)]OTf = 1 mM, electrolyte (NBu_4)BF_4: 0.1 M).

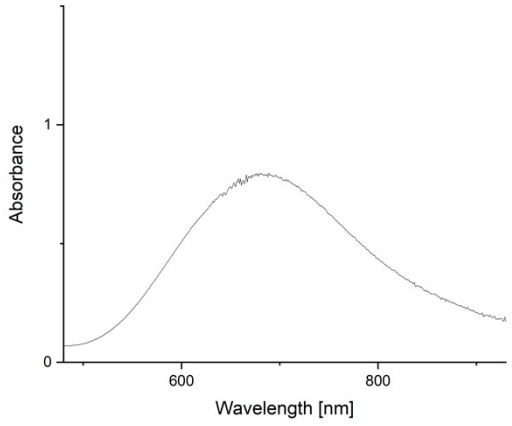


Figure 6. UV/Vis spectrum of [Cu(**4**)]$(OTf)_2$ with a λ_{max} = 690 nm.

tion. Solid samples furthermore showed impurities that hampered further characterization. However, mixing stoichiometric amounts of $Cu(ClO_4)_2 \cdot 6\ H_2O$ with ligands **3** and **5** allowed UV-vis measurements in methanol. Maxima of λ_{max} = 690 nm for both complexes support a complexation of copper(II) in a distorted square planar geometry in solution (Figure 6).[25]

Reactivity of copper(I) complexes towards dioxygen and hydrogen peroxide

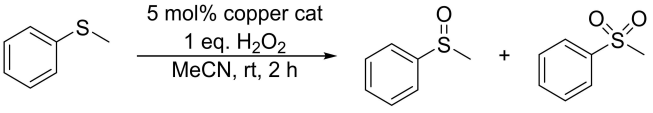
As described in the introduction it is well known that a large number of copper(I) complexes with tripodal ligands including as [Cu(Me_2-uns-penp]X react with dioxygen to form dinuclear end-on-peroxido complexes. However, reacting all our copper(I) complexes [Cu(**4**)(MeCN)]OTf, [Cu(**5**)(MeCN)]OTf and [Cu(**6**)] as well as [Cu(acetyl-uns-penp]OTf and [Cu{L-His(trt)uns-penp}]OTf in a benchtop test with dioxygen in solution at low temperatures (−80 °C) only showed a slow color change to a green colored solutions indicating oxidation to copper(II) without a detectable intermediate. This was furthermore confirmed by low temperature stopped-flow measurements as described previously.[19] Reactions of all complexes including [Cu(Me_2-uns-penp)]OTf with hydrogen peroxide only led to green solutions with more or less gas bubbles (dioxygen from decomposition of hydrogen peroxide).

Catalytic oxygenation of thioanisole

Despite the fact that no "dioxygen adduct" complexes were formed as intermediates it seemed worthwhile to test their properties with regard to catalytic oxidations. As a substrate thioanisole was used and its oxygenation to sulfoxide and/or sulfone was investigated using the copper complexes with the ligands **4**, **5**, **6** and [Cu(Boc-L-His(trt)uns-penp}] in comparison with uns-penp, [Cu{acetyl-uns-penp]OTf, [Cu(Me_2-uns-penp)]OTf in combination with dioxygen or hydrogen peroxide according to Scheme 6.

Especially the sulfoxide as a product is of interest, because of its widespread application in pharmaceutical chemistry. This and the simple analysis of the two oxidation products methyl phenyl sulfoxide and methyl phenyl sulfone make thioanisole a popular substrate for catalytic oxygenation of sulfides.[26,27] Another interesting property of the sulfoxide is its chirality. By examining the reaction with a chiral gas chromatography column, it is possible to determine if a catalyst can form an enantiomeric excess of a specific enantiomer. The reaction shown in Scheme 6 was carried out at room temperature with a reaction time of 2 hours. After several attempts applying molecular oxygen as the sole oxidant in a temperature range between −80 °C and room temperature, it became clear that no conversion had taken place. For that reason, hydrogen peroxide was used for further experiments. All reactions were analyzed and quantified via GC/MS. The results are presented in Table 2.

Using just hydrogen peroxide without adding a copper complex no oxidation was observed (Table 2, entry a). Furthermore, applying only CuCl as a copper source negligible conversion was observed (Table 2, entry b). Furthermore, [Cu-(uns-penp)]OTf showed nearly no reactivity at all. In contrast, using [Cu(Me_2-uns-penp)]OTf conversion to 40 % sulfoxide and 8 % sulfone was observed (entry d). However, when [Cu(acetyl-uns-penp]OTf was applied conversion went down to only 12 % for the sulfoxide and 3 % sulfone (entry e). All copper(I) complexes with the ligands **4**, **5**, **6** and [Cu{Boc-L-His(trt)uns-penp}]OTf applied as suspensions did lead to the oxygenation of thioanisole (Table 2, entries f, g, h and i). However, it was not possible to gain an enantiomeric excess by any of the three catalysts. In all cases, the sulfoxide is the main product, with the highest conversion of 84 % with catalyst [Cu(Boc-L–Lys-uns-penp)(MeCN)]OTf (**4**) (entry f). A further oxidation to the sulfone distinguishes between the reactions, with the highest conversion of 13 % with [Cu{Boc-L-His(BPh_3)-uns-penp}] (**6**). Compared to CuCl (entry b) with only 2 % of the sulfoxide and traces of the sulfone and, the amino acid uns-penp catalysts show a significant higher catalytic activity with maximum conversions of 97 % (entry f). Besides, in case of the oxygenation with



Scheme 6. Oxygenation of thioanisole with hydrogen peroxide.

Table 2. Oxygenation of thioanisole with copper(I) catalysts and H_2O_2.

#	Catalyst	Sulfoxide [%]	Sulfone [%]	Total conversion [%]	TON
a	–	0	0	0	0
b	CuCl	2	traces	3	0.6
c	[Cu(uns-penp)]OTf	4	traces	5	1
d	[Cu(Me_2-uns-penp)]OTf	40	8	48	3
e	[Cu(Ac-uns-penp)]OTf	12	3	15	11
f	[Cu(**4**)MeCN)]OTf	84	13	97	19
g	[Cu(**5**)(MeCN)]OTf	6	2	8	2
h	[Cu(**6**)]	23	10	34	13
i	[Cu{Boc-LHis(trt)uns-penp}]OTf	8	2	10	3

0.5 mol% catalyst, 2 h, 1 eq. H_2O_2, MeCN, room temperature.

catalyst [Cu(**4**)(MeCN)]OTf, the sulfoxide was synthesized and isolated. After purification by column chromatography a yield of 69% was determined. From the results it is obvious that we do not see an effect of redox potential or the ability to form a peroxido complex as an intermediate species. We suspect a Fenton-like mechanism due to the gas development that occurs after adding hydrogen peroxide to the reaction solution.[28]

Conclusions

Our results showed that it is possible to synthesize amino acid derivatives based on the tripodal ligand uns-penp. These modified flexible ligand frameworks are able to adapt to the coordination sphere geometry of copper(I) metal ions. Furthermore, they provide an opportunity to connect these complex units to peptide chains. In the case of L-Lysine, L-Histidine and L-Tyrosine, copper(I) complexes were isolated, however, it was not possible to obtain the corresponding copper(II) complexes. We could determine the molecular structure of [Cu{L-His(BPh_3) uns-penp}] by using single crystal X-ray diffraction. This is the first example of a structurally characterized copper(I) complex with coordination to the nitrogen atom of the imidazole ring of histidine. However, in contrast to our previous findings (applying copper(I) complexes with related ligands) it was not possible to detect a "dioxygen adduct" intermediate in bench-top experiments (or stopped-flow measurements) when dioxygen was reacted with the described copper(I) complexes herein. In addition, the influence of the chirality introduced with the amino acid groups in the uns-penp ligand system was investigated for the catalytic oxygenation of thioanisole to 1-methyl phenyl sulfoxide, which bears a stereo center at its sulfur atom. While no enantiomeric excess could be detected all the catalysts could oxidize thioanisole to the sulfoxide, with the highest conversion of 97%.

Experimental Section

Materials and Methods. All chemicals used were of p.a. quality and were purchased from either Acros Organics, ACS or Sigma Aldrich. Dry purchased solvents for air sensitive synthesis were redistilled under argon. The preparation and handling of air sensitive compounds were performed in a glovebox or under standard Schlenk techniques. Electrospray-ionization MS (ESI-MS) measurements were performed on a Bruker microTOF mass spectrometer. The conversions of the catalytic reactions were determined with a Hewlett Packard 5890 gas chromatograph (GC) and an Agilent Technologies 7820 A GC-System coupled with an Agilent Technologies 5977B MSD EI mass spectrometer (GC/MS). For NMR measurements a Bruker Avance II 400 MHz (AV II 400) was used for all samples. IR spectroscopy was performed on a Jasco FT/IR 4100 and all samples were measured as KBR-pellets. UV-vis spectra were obtained using an Agilent 8453 spectrophotometer. Diffraction data were collected on a BRUKER D8 Venture system.

Synthesis of *N*-acetyl-uns-penp.[19] Under Schlenk conditions, 2-pyridinecarbaldehyde (4.3 g, 40 mmol) and *N*-acetylethylenediamine (2.0 g, 20 mmol) were dissolved in 100 mL 1,2-dichoroethane. $Na(AcO)_3BH$ (12.1 g, 57.1 mmol) was added and the solution was stirred for 4 hours at room temperature. After that, 100 mL of 2 M aqueous NaOH solution were added and the organic layer was extracted with 2×50 mL DCM. Furthermore, the combined organic solution was washed with brine (2×50 mL), dried over anhydrous Na_2SO_4, and the solvent evaporated *in vacuo*. The crude product is a yellowish oil (4.11 g, 14.4 mmol, 85%) and was used without further purification in the next step to remove the acetyl protecting group.

Synthesis of uns-penp (1).[19] The crude *N*-Acetyl-uns-penp (4.11 g, 14.4 mmol) was dissolved in 40 mL of a 5 M hydrochloric acid solution and refluxed for 24 hours. The pH of the cooled solution was increased to 10 by the addition of NaOH. The crude product was extracted with 3x50 mL DCM, dried over Na_2SO_4 and the solvent was evaporated. The obtained oil was purified by Kugelrohr distillation *in vacuo* (0.2 mbar) and at 150 °C. The yellowish-colorless oil (2.7 g, 11 mmol, 77%) was stored under argon. ^{1}H-NMR (400 MHz, $CDCl_3$): $\delta = 8.53$ (ddd, 2H), 7.65 (td, 2H), 7.50 (dt, 2H), 7.14 (dd, 2H), 3.85 (s, 4H), 2.85–2.72 (m, 2H), 2.66 (t, 2H). ^{13}C-NMR (101 MHz, $CDCl_3$): $\delta = 159.6$, 149.0, 136.3, 122.9, 122.8, 121.9, 77.5, 77.1, 76.8, 60.7, 57.4, 39.6.

Synthesis of Boc-L-His(trt)-uns-penp (2). In a 100 mL Schlenk flask and under inert conditions, uns-penp (0.24 g, 1.0 mmol), Boc-L-His (trt)-OH (0.50 g, 1.0 mmol), TBTU (0.35 g, 1.1 mmol) and TEA (0.12 g, 1.2 mmol) was mixed with 30 mL of dry DCM. The mixture was stirred for 24 hours at room temperature. After that, the reaction was quenched with 250 mL of EtOAc and washed with 3×50 mL 0.5 M citric acid, 3×50 mL sat. $NaHCO_3$ solution and 3×50 mL brine. The combined organic layers again were acidified to pH 2 with conc. HCl. The aqueous phase was separated and NaOH was added till pH 12 was reached, followed by an extraction with DCM. The solution was dried with $MgSO_4$ and the solvent was evaporated. A

greenish colored product (0.58 g, 0.80 mmol, 80%) was obtained (ESI-MS: $[M+H]^+ = 722.36$, $[M+Na]^+ = 744.36$)

^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.58 −8.43 (m, 2H), 7.76 (s, 1H), 7.63 (d, 2H), 7.40 (d, 2H), 7.37 −7.21 (m, 11H), 7.14 −7.00 (m, 9H), 6.60 (d, 1H), 4.48 (s, 1H), 4.12 (q, 1H), 3.85 (d, 2H), 3.77 (d, 2H), 3.34 (dt, 1H), 3.26 −3.03 (m, 2H), 2.92 (dd, 1H), 2.74 −2.58 (m, 2H), 1.41 (s, 9H). ^{13}C-NMR (101 MHz, $CDCl_3$) δ 171.1, 159.2, 155.7, 149.1, 142.4, 138.3, 137.0, 136.7, 129.7, 128.0, 123.0, 122.1, 119.6, 79.5, 75.2, 60.1, 53.4, 52.4, 38.6, 28.4, 21.1.

Synthesis of Boc-L-His-uns-penp (3). Boc-L-His(trt)-uns-penp (0.58 g, 0.80 mmol) was mixed with 90% acetic acid and stirred for two hours at 60 °C. After the reaction was allowed to cool, the acetic acid / water was evaporated. The oily remains were solved in 40 mL DCM and washed with 3×40 mL sat. $NaHCO_3$ solution and brine. The combined organic layers were acidified to pH 2 with conc. HCl. The aqueous phase was separated and again basified to pH 12 with NaOH, followed by an extraction with DCM. The solution was dried with $MgSO_4$ and the solvent was evaporated. The yellowish-colorless oil was obtained in a yield of 90% (0.35 g, 0.72 mmol). ESI-MS: $[M+H]^+ = 480.26$, $[M+Na]^+ = 502.25$; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.43 (dt, 2H), 7.77 (s, 1H), 7.56 (td, 2H), 7.31 (d, 1H), 7.29–7.23 (m, 5H), 7.08 (dd, 2H), 6.72 (s, 1H), 5.81 (d, 1H), 3.71 (s, 4H), 3.24 (s, 1H), 3.07 (d, 1H), 2.94 (dd, 1H), 2.64–2.55 (m, 2H), 1.35 (s, 9H). ^{13}C-NMR (101 MHz, $CDCl_3$): δ 170.6, 157.8, 148.1, 145.9, 135.7, 133.9, 126.9, 126.2, 122.3, 121.3, 81.0, 76.3, 76.0, 75.7, 58.8, 52.4, 51.5, 37.6, 36.4, 27.3.

Synthesis of Boc-L–Lys(Z)-uns-penp. In an 100 mL flask, uns-penp (0.50 g, 1.9 mmol), Boc-L-Lys(Z)-OH (0.72 g, 1.9 mmol), TBTU (0.67 g, 2.1 mmol) and TEA (0.12 g, 2.1 mmol) was mixed with 30 mL of dry DCM. The mixture was stirred for 24 hours at room temperature. 250 mL of EtOAc was added. The solution was washed with (3× 50 mL) 0.5 M citric acid, (3×50 mL) sat. $NaHCO_3$ and (3×50 mL) brine. After that, the organic layer was dried over $MgSO_4$ and the solvent evaporated. A reddish oil (73%, 0.84 g, 1.4 mmol) was obtained. The following cleavage of the cbz protective group was carried out without further purification.

Synthesis of Boc-L-Lys-uns-penp (4). 0.84 g (1.4 mmol) Boc-L-Lys (Z)-uns-penp was dissolved in methanol in a 100 mL flask. One spate tip of the Pd/C was added to the solution and a balloon filled with hydrogen gas was attached to the flask. The suspension was vigorously stirred at room temperature for 24 hours. The solution was filtered and the solvent evaporated. The remaining oil was dissolved in 100 mL EtOAc and extracted three times with 2 M HCl solution. The pH of the aqueous phase then was adjusted to 12 by a slow addition of NaOH solution. After that, the solution was again extracted with (3×50 mL) EtOAc. The combined organic phases were dried over $MgSO_4$ and the solvent was evaporated. The yield of the grass green solid is 78% (0.514 g, 1.5 mmol). ESI-MS: $[M+H]^+ = 471.29$, $[M+Na]^+ = 493.30$;

^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.58 (dd, 2H), 7.33 (dt, 2H), 7.17 (dd, 2H), 5.47 (d, 1H), 4.25 (d, 1H), 3.87 (s, 4H), 3.38 (d, 1H), 3.01 (s, 1H), 2.77 (t, 2H), 2.71 (t, 2H), 1.44 (m, 13H). ^{13}C-NMR (101 MHz, $CDCl_3$): δ 171.8, 159.0, 155.6, 149.1, 136.6, 123.2, 122.2, 79.5, 77.3, 77.0, 76.7, 59.9, 54.3, 52.5, 41.6, 38.6, 33.4, 32.6, 28.4, 22.6.

Synthesis of Boc-L-Tyr-uns-penp (5). 0.464 g (1.64 mmol) Boc-L-Tyrosine, 0.436 g uns-penp, 0.372 g (1.80 mmol) DCC, 0.276 g (1.80 mmol) HOBt and 0.250 mL (1.80 mmol) TEA were dissolved in 50 mL DCM. The reaction was stirred for 24 hours at room temperature. 200 mL EtOAc was added and the solution washed with 3× 50 mL sat. $NaHCO_3$, 3×50 mL 0.05 M citric acid solution and 3x50 mL brine. The solution was dried over Na_2SO_4 and the solvent evaporated. The light-yellow solid was cleaned via column chromatography. The yield was 32% (0,291 g, 0.576 mmol). ESI-MS: $[M+H]^+ = 506.27$, $[M+Na]^+ = 528.25$

^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.50 – 8.43 (m, 2H), 7.62 (s, 1H), 7.55 (td, 2H), 7.22 (d, 3H), 7.09 (dd, 2H), 6.96–6.89 (m, 2H), 6.64 – 6.55 (m, 2H), 5.34 (d, 1H), 4.33 (d, 1H), 3.67 (s, 4H), 3.19 (q, 2H), 2.58 – 2.53 (m, 2H), 1.39 (d, 12H), 1.20 (d, 1H). ^{13}C-NMR (101 MHz, $CDCl_3$): δ 170.2, 157.8, 154.5, 154.3, 148.0, 135.8, 129.4, 127.1, 122.4, 121.4, 114.9, 76.3, 76.0, 75.7, 58.6, 55.1, 52.4, 51.6, 37.7, 36.4, 27.3.

Synthesis of [Cu{Boc-L-His(trt)-uns-penp}] (6). Under inert conditions, 100 mg (0.139 mmol) Boc-L-His(trt)-uns-penp were dissolved in 4 mL acetone. In another vial, 51.8 mg (0.139 mmol) of $[Cu(MeCN)_4]PF_6$ was dissolved in 2 mL acetone and was added dropwise to the stirred solution of Boc-L-His(BPh_3)-uns-penp. A yellow suspension forms. For anion exchange, 47.6 mg $NaBPh_4$ (0.139 mmol) were added and the suspension became a clear yellow solution. For precipitation, the solution was added dropwise to an excess of diethyl ether and the resulting yellow solid complex (132 mg, 86%) was filtered and washed again with ether. IR-(KBr-disc)/cm^{-1}: 3411 (w), 3057 (m), 2988 (m), 1708 (m), 1588 (m), 1478 (m),1427 (m), 1153 (m), 1031 (m), 853 (s), 745 (s), 711 (s), 605 (m), 561 (w), 510 (w).

Synthesis of [Cu{Boc-L-His(BPh_3)-uns-penp}] (6). Under inert conditions, 200 mg (0.417 mmol) Boc-L-His-uns-penp was dissolved in 4 mL acetone. In another vial, 155 mg (0.417 mmol) of $[Cu(MeCN)_4]PF_6$ was dissolved in 2 mL acetone and was added dropwise to the stirred solution of Boc-L-His(BPh_3)-uns-penp. A yellow suspension forms. For anion exchange, 143 mg $NaBPh_4$ (0.417 mmol) was added and the suspension became a clear yellow solution. For precipitation, the solution was added dropwise to an excess of diethyl ether and the resulting yellow solid complex (130 mg, 40%) was filtered and washed again with ether. Crystals were obtained by evaporation of the complex solution in acetone. (CCDC deposition number 2025303) IR-(KBr disc)/cm^{-1}: 3401 (m), 3311 (m), 3060 (m), 1715 (m), 1570 (m), 1361 (s), 1321 (m), 1277 (s), 1153 (s), 1029 (s), 1134 (s), 1088 (m), 1005 (m), 704 (m), 636 (m), 570 (w), 514 (m).

Synthesis of [Cu(Boc-L-Lys-uns-penp)(MeCN)]OTf. Under inert conditions, 50 mg (0.10 mmol) of **4** was dissolved in 2 mL of acetone with the addition of 15 µL (0.11 mmol) triethylamine. In a second vial, 37 mg (0.10 mmol) of $[Cu(MeCN)_4]OTf$ was dissolved in 1 mL acetone which was added dropwise to the Boc-L-Tyr-uns-penp solution. The solvent of the solution was evaporated and a yellow solid was obtained in a quantitative yield. IR-(KBr disc)/cm^{-1}: 3325 (m), 3073 (m), 2939 (m), 2864 (m), 1711 (s), 1668 (s), 1516 (m), 1366 (m), 1268 (s), 1160 (s), 1036 (s), 762 (m), 638 (s), 570 (m), 518 (m). Elemental analysis: found: C, 48.4%; H, 6.4%; N, 11.4%; $C_{28}H_{41}CuF_3N_7O_8S$ x 2 acetone requires: C, 48.0%; H, 6.2%; N, 11.9%.

Synthesis of [Cu(Boc-L-Tyr-uns-penp)(MeCN)]OTf. Under inert conditions, 50 mg (0.10 mmol) of **5** was dissolved in 2 mL of acetone with the addition of 15 µL (0.11 mmol) triethylamine. In a second vial, 37 mg (0.10 mmol) of $[Cu(MeCN)_4]OTf$ was dissolved in 1 mL acetone which was added dropwise to the Boc-L-Tyr-uns-penp solution. The solvent of the solution was evaporated and a yellow solid was obtained in a quantitative yield. IR-(KBr disc)/cm^{-1}: 3340 (m), 2977 (m), 2928 (m), 2851 (w), 1712 (s), 1602 (m), 1518 (s), 1442 (m), 1367 (m), 1253 (s), 1159 (s), 1029 (s), 827 (w), 760 (m), 637 (s), 570 (w), 515 (w). Elemental analysis: found: C, 51.0%; H, 5.9%; N, 9.8%; $C_{31}H_{38}CuF_3N_6O_8S$ x 2 acetone requires: C, 50.8%; H, 5.8%; N, 9.6%.

Synthesis of [Cu(uns-penp)]OTf, [Cu(Me_2-uns-penp)]OTf [Cu(Ac-uns-penp)]OTf and complexes.[19] Under inert conditions, 1 eq. of the ligand was dissolved in 2 mL of acetone with the addition of 1.1 eq. of triethylamine. In a second vial, 1 eq. of $[Cu(MeCN)_4]OTf$

was dissolved in 1 mL acetone which was added dropwise to the ligand solution. The complexes were precipitated in n-pentane and yellow solids were obtained in a quantitative yield.

Catalytic oxygenation of thioanisole. 1.1 mL thioanisole (1.24 g, 10 mmol) and 5 mol% of catalyst [Cu(**4**)(MeCN)]OTf, [Cu(**5**)(MeCN)]OTf or [Cu(**6**)] were suspended in 10 mL acetonitrile. After that, a hydrogen peroxide solution (50 %, 560 µL, 10 mmol) was added dropwise in the stirred solution. To prevent the evaporation of the substrate the flask was sealed and the cap was equipped with a cannula which was plugged through a septum for pressure equalizing. The solution was stirred until the gas formation subsided and was then examined via GC/MS.

Isolation of 1-Methylphenylsulfoxide. The reaction solution was filtered and the solvent evaporated *in vacuo*. The resulting brownish crude solid was purified via column chromatography (1 : 1 EtOAc/n-Hex, R_f: 0.32). A pure white solid was obtained with a yield of 950 mg (69 %).

^{1}H-NMR (400 MHz, Chloroform-*d*): δ 7.71–7.60 (m, 2H), 7.60 – 7.46 (m, 3H), 2.73 (s, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ 145.7, 131.0, 129.4, 123.5, 77.4, 77.1, 76.8, 44.0.

Computational Details

The composition of the complexes [Cu(**4**)MeCN)]$^+$ and [Cu(**5**)MeCN)]$^+$ was derived from the IR and elemental analysis. The creation and analyzation of the geometric structures have been performed using the program CREST[29] with the iMTD-GC algorithm and the semiempirical method GFN2-xTB[30] to obtain the energetical most favourable conformation. For the five conformers with the lowest total energy at GFN2-xTB level of theory DFT calculations have been conducted employing the program Turbomole,[31–33] version 6.6. The PBE[34] exchange-correlation functional with RI approximation[35–37] and D3 (BJ)[38,39] dispersion correction have been chosen for the structural optimization and the calculation of the energies. The Dunning basis sets cc-pVDZ[40] for the elements C, H, O and N has been applied. For the copper atom the pseudopotential ECP10MDF[41] and the corresponding basis set cc-pVDZ-PP[42] has been used. Unrestricted KS-DFT calculations considering a singlet state have been employed for the single positively charged complexes. The electronic convergence criterion has been set to 10^{-7} E_H, the convergence of the structural relaxation to 10^{-6} E_H. Frequency calculations confirm the calculated structures as minima. The complex structures with the lowest total energy according to the semiempirical and DFT methods are presented within this study and the structural data are given in the SI.

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