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Metallopeptide Design Hot Paper

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Conformationally Constrained Cyclic Peptides: Powerful Scaffolds for Asymmetric Catalysis**

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Abstract: *Cyclic peptides containing a disulfide bridge were identified as a simple and versatile coordination sphere for asymmetric catalysis. Upon complexation with Cu^{2+} ions they catalyze Diels–Alder and Friedel–Crafts reactions with high enantioselectivities of up to 99 % ee and 86 % ee, respectively. Moreover, the peptides ligands were systematically optimized with the assistance of "Alanine Scanning". This biomolecular design could greatly expand the choice of peptide scaffolds for artificial metallopeptide catalysts.*

Tremendous efforts have been devoted to the design of asymmetric artificial metalloenzymes that are capable of introducing an achiral transition-metal complex into an existing protein scaffold through covalent or supramolecular interactions.[1] Such catalytic systems have been constructed from different host proteins, metals, and ligands and they have proven to be efficient for catalyzing several reactions with excellent enantioselectivities.[2] However, this approach still faces some limitations. The host proteins are either costly compared to small chiral ligands or they need to be produced by recombinant expression, which is associated with the difficult task of generating large libraries.[3] In this respect, chiral polypeptide ligands are a suitable alternative since they are readily accessible by standard solid-phase synthesis. Miller and co-workers reported a number of non-metal-containing peptide catalysts that often exhibit excellent enantioselectivities, reaching enantiomeric excess (*ee*) above 90 %.[4] On the other hand, oligo- and polypeptides with natural aspartic acid side chains and nonnatural amino acids with phosphine or pyridine functions were complexed with metal ions to act as catalysts in enantioselective organic transformations.[5] The peptide scaffolds included metal-chelating helical[5a] or β-turn structures,[5b] oriented β-turns,[5c] self-assembled β-sheet motifs,[5d] and natural polypeptide folds.[5e,f] However, peptide scaffolds with little sequence constriction and flexibility in the amino acid composition remain elusive. Moreover, most artificial metallopeptides require significant synthetic efforts.

Herein, we introduce a novel metallopeptide design based on a stable cyclic peptide scaffold that is obtained by an intramolecular disulfide linkage. In addition, our peptide ligand contains only natural amino acids, thus allowing us to avoid any nonnatural building blocks and elaborate post-modification protocols for metal coordination. Moreover, we show that "alanine scanning", a method usually employed to characterizethe structure and function of proteins, is an efficient tool to rationally improve the performance of metallopeptide catalysts for the Diels–Alder (D-A) and Friedel–Crafts (F-C) reactions.

Our metallopeptide design strategy started with the generation of a peptide scaffold with a confined structure. Inspired by the widespread occurrence of disulfide bridges in proteins[6] and the fact that disulfide linkages stabilize specific peptide conformations,[7] we decided to use this structural element to fabricate cyclic peptides and evaluate their suitability for asymmetric catalysis. In the next step, anchoring sites for the metal ion were defined. Two types of binding modes were considered. In one scenario, the metal ion interacts with the amino group of the N-terminus, whereas in the other, the metal species complexes with a histidine side chain. To achieve a well-defined interaction between the metal and the peptide scaffold, the C-terminus was blocked by amidation to avoid competitive metal coordination.[8] In the case of the histidine-containing peptides the N-terminus was not protected because of the well-known preferential binding to the aromatic heterocycle.[9] With these considerations in mind, we synthesized a small library of 15 cyclic nonapeptides of which nine contained an internal histidine metal anchoring point. The amino acid sequence between the two terminal cysteines was random; only sequences known to form secondary structures were avoided. The peptides were prepared by solid-phase peptide synthesis, purified by C18 reversed-phase HPLC, and characterized by MALDI-TOF mass spectrometry.[10]

With these peptides the Cu^{2+}-catalyzed D-A reaction of aza-chalcone (**1**) with cyclopentadiene (**2**) in aqueous medium[2d,5e,11] was pursued since this particular transformation is a good model to evaluate the selectivity of the potential metallopeptide catalysts (Figure 1 a). Remarkably, out of our small library two sequences yielded an enantiomeric excess of more than 60 % underlining the potency of our selected scaffold for asymmetric catalysis. The top-performing peptides, **L5** and **L12**, achieved *ee* values of 62 % and 85 %, respectively (Figure 1 b).

Encouraged by the results of the first round of random screening, we took a more rational approach to the second

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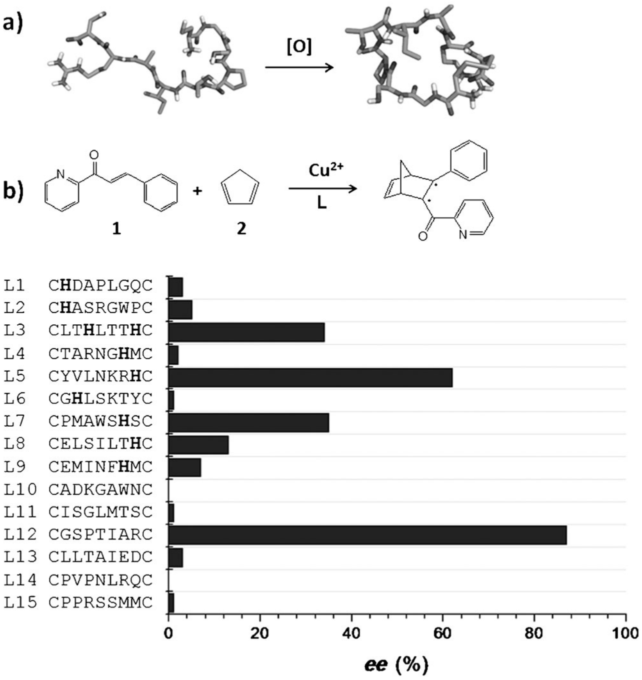


Figure 1. a) Schematic representation of the proposed cyclic peptide ligand with constrained conformation through an intramolecular disulfide bridge. b) Screening of a cyclic peptide ligand library for the D-A reaction shown. General conditions : **1** (0.6 μmol), **2** (24 μmol), $Cu(NO_3)_2$ (15% mol), **L** (30% mol) in 20 mM 3-(*N*-morpholine)propane sulfonic acid buffer (MOPS) with pH 6.5, for 3 days at 6°C. All peptides are C-terminal NH_2 amides.

round of peptide optimization. For this purpose, "alanine scanning" was performed with **L5** and **L12** to elucidate the contribution of each amino acid to the stereochemical outcome of the D-A reaction.[12] "Alanine scanning" is a method often used by molecular biologists to determine the importance of a particular residue within a given protein with regard to protein stability or biological activity.[13] Here, the systematic replacement of non-cysteine amino acids within **L5** and **L12** by alanine was carried out and the role of each of the seven amino acids in the catalytic process was examined.

A set of alanine-scanning peptides generated from **L5** (**L16–L22**) was evaluated in the D-A model reaction under optimized conditions (Table 1). Notably, for peptide **L22**, where the histidine residue is replaced by alanine, only 3% *ee* was detected. The loss of enantioselectivity clearly underlines the importance of the histidine residue for chiral induction. At the same time, all other alanine mutants generally induced lower enantioselectivities than **L5**. Of note, we observed that peptides **L17** and **L18** yielded especially low selectivities (13% *ee* and 15% *ee*, respectively). It is tempting to suggest that residues at positions $i+1$ and $i+2$ (Table 1) make major contributions to the enantioselectivity of **L5**. Therefore, it is reasonable to expect that insertion of large aromatic residues at these positions might result in improved ligands in terms of enantioselectivity. To this end, mutant **L23** was prepared. Two tryptophans were placed in the "sensitive" positions, the other residues of **L5** were retained. Significantly increased enantiomeric excess was observed with **L23** in the model Cu^{2+}-catalyzed D-A reaction (90% *ee*).

Table 1: Alanine scanning data for **L5**.[a]

Ligand	Sequence[b]	Alanine position	*ee* (*endo*) [%]
L16	C**A**VLNKRHC	*i*	29
L17	CY**A**LNKRHC	$i+1$	13
L18	CYV**A**NKRHC	$i+2$	15
L19	CYVL**A**KRHC	$i+3$	31
L20	CYVLN**A**RHC	$i+4$	50
L21	CYVLNK**A**HC	$i+5$	29
L22	CYVLNKR**A**C	$i+6$	3
L23	CY**WW**NKRHC		90

[a] Reaction conditions are the same as those applied in the first round of screening. [b] All peptides are C-terminal NH_2 amides.

Next, alanine scanning was performed for **L12** with peptides **L24–L29** (Table 2). To our surprise, when glycine at position *i* was replaced by alanine, no enantioselectivity was observed. Although at present the origin of this decrease is still unclear, it proves the important role of glycine at this position for the stereoselective outcome of the conversion. Since this residue is next to the N-terminal cysteine, which is presumed to be the primary binding site for Cu^{2+}, glycine might be required for the specific binding of Cu^{2+}. In contrast to **L24**, exchanging the other residues with alanine only caused a slight drop of selectivities. With these hints from alanine scanning, we did not introduce mutations containing larger residues, as for **L5**, but instead systematically shortened **L12** while maintaining the circular constraint and the key glycine residue. Eight new sequences **L30–l37** were synthesized and again applied in the D-A reaction (Table 3). For **L32** and **L36** high *ee* values were determined (94% *ee* and 96% *ee*, respectively). These results proved that alanine scanning is an important tool to determine the role of different residues within cyclic peptides for asymmetric catalysis. The alanine scanning results are an excellent starting point for the improvement of the peptide-based catalysts by rational design.

Table 2: Alanine scanning data for **L12**.[a]

Ligand	Sequence[b]	Alanine position	*ee* (*endo*) [%]
L24	C**A**SPTIARC	*i*	0
L25	CG**A**PTIARC	$i+1$	81
L26	CGS**A**TIARC	$i+2$	75
L27	CGSP**A**IARC	$i+3$	77
L28	CGSPT**A**ARC	$i+4$	85
L29	CGSPTIA**A**C	$i+6$	83

[a] Reaction conditions are the same as those applied in the first round of screening. [b] All peptides are C-terminal NH_2 amides.

Besides alanine scanning, other efforts were undertaken to investigate the structural requirements for asymmetric catalysis employing cyclic metallopeptides. As such, the D-A reaction was carried out in the presence of tris-(2-carboxyethyl)phosphine (TCEP),[14] a reagent that reduces the disulfide bridge, resulting in peptide linearization. In the

Table 3: Results of D-A reactions based on shortened **L12**.[a]

Ligand	Sequence[b]	*ee* (*endo*) [%]	Ligand	Sequence[b]	*ee* (*endo*) [%]
L30	`CGSPTIAC`	80	**L34**	`CGPTIARC`	2
L31	`CGSPTIC`	30	**L35**	`CGTIARC`	22
L32	`CGSPTC`	94	**L36**	`CGIARC`	96
L33	`CGSPC`	72	**L37**	`CGARC`	0

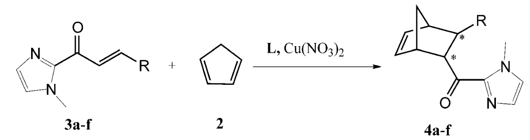
[a] Reaction conditions are the same as those applied in the first round of screening. [b] All peptides are C-terminal NH_2 amides.

presence of TCEP, racemic products were obtained with **L5**, **L12**, **L23**, **L32**, and **L36**, indicating the crucial role of the intramolecular disulfide bond for providing a stable peptide scaffold and the importance of the rigid scaffold for the observed high enantioselectivities. At this stage, the location of the Cu^{2+} ion is still unclear and is the subject of future studies.

To further elucidate the catalytic activity, the initial rate (V_{init}) of the D-A reaction, mediated by Cu^{2+}, **L5**-Cu^{2+}, **L12**-Cu^{2+}, **L23**-Cu^{2+}, **L32**-Cu^{2+}, and **L36**-Cu^{2+}, was measured from the initial decrease in absorption of **1** (see the Supporting Information). Taking V_{init} into account, the apparent second-order rate constants (k_{app}) were determined.[11a,b] The reactions catalyzed by complexes with **L5**, **L12**, and **L23** reacted more slowly than those with the free $Cu(NO_3)_2$, while those with **L32**-Cu^{2+} and **L36**-Cu^{2+} reacted slightly faster, which indicates that the peptides only act as source of chirality for the reaction (Table S1). It is noteworthy that, **L5**-Cu^{2+} provided only a slight rate increase over the uncatalyzed reaction. In this case, a background reaction might proceed in parallel with the metal-complex-mediated reaction, which can explain the lower *ee* values of the product obtained from the reaction catalyzed by **L5**-Cu^{2+}.

The scope of the D-A reaction was investigated by employing the two best performing peptides, **L32** and **L36**. Since the pyridyl moiety could not be removed readily or transformed after the reaction, it limits the synthetic potential of the catalytic system. Therefore, we replaced the pyridine group by a imidazole auxiliary, which still allows for efficient copper binding and at the same time greatly increases the practical applicability of our novel metallopeptide catalyst.[15] Under optimized conditions, α,β-unsaturated 2-acyl imidazoles **3a**–**f** underwent efficient D-A reactions with cyclopentadiene. Good conversions and diastereoselectivities, as well as excellent enantioselectivities, ranging from 90–95% *ee* for **L32** and 92–96% *ee* for **L36**, were achieved (Table 4). The catalyst loading can be lowered from 10 to 3 mol% without a significant effect on the enantioselectivity (entry 2). Improved *ee* values (97% and 99%) can be realized by decreasing the reaction temperature but this is at the expense of conversion efficiency (entry 3). When the scale of the reaction was increased by a factor of 400 (50 mg of **3a**) with **L36**, product **4a** was obtained with 91% *ee* and a yield of 89% (entry 4). Neither the electronic nature nor the position of the substituent on the aryl ring had significant influence on the *ee* values. In the case of **3c**, only moderate conversions were observed, most likely due to the lower solubility of this substrate (entry 6).

Table 4: Results of D-A reactions based on **L32** and **L36**.[a]



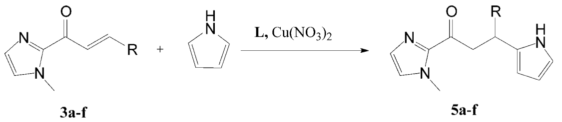
3a=C_6H_5 **3b**: R=*p*-$CH_3OC_6H_5$ **3c**: R=*p*-ClC_6H_5
3d: R=*o*-BrC_6H_5 **3e**:R=*m*-$CH_3OC_6H_5$ **3f**: R=*p*-$CH_3C_6H_5$

Entry	Substrate	Conv. [%] **L32/L36**	*endo*:*exo* **L32/L36**	*ee* (endo) [%] **L32/L36**
1	**3a**	full/96	95:5/95:5	93/94
2[b]	**3a**	95/90	96:4/95:5	88/87
3[c]	**3a**	55/40	96:4/95:5	97/99
4[d]	**3a**	–/89[e]	–/95:5	–/91
5	**3b**	97/96	96:4/97:3	94/95
6	**3c**	44/45	94:6/95:5	90/92
7	**3d**	90/70	95:5/94:6	94/92
8	**3e**	80/85	93:7./96:4	95/96
9	**3f**	95/90	95:5/94:6	94/95

[a] See the Experimental Section for typical reaction conditions. Data were obtained from the crude product by HPLC analysis on a chiral stationary phase. The *ee* values are averaged over two experiments and are reproducible within ±2%. [b] 3 mol% Cu^{2+} and 4.5 mol% peptide. [c] Reactions were carried out at −17°C. [d] Reaction was scaled up by a factor of 400 (50 mg of **3a**) at 6°C. [e] Yield of isolated product.

Encouraged by these results, we attempted to broaden the reaction scope to another kind of Lewis acid catalyzed reaction. The F-C reaction was employed since it is a powerful carbon–carbon bond-forming process in modern organic chemistry.[15a,b,16] Here, the transformation was performed using pyrrole as the nucleophile. Substrates **3a**–**f** exhibited good conversions but lower enantioslectivities (Table 5). However, decreasing the reaction temperature again led to high *ee* values (80% *ee* and 86% *ee* for **L32** and **L36**, respectively) (entry 2). When the scale of the reaction was increased to 50 mg of **3a** and with **L36** as the ligand, 73% *ee* was achieved (93% yield of isolated product **5a**, entry 3). In

Table 5: Results of F-C reactions based on **L32** and **L36**.[a]



Entry	Substrate	Conv. [%] **L32/L36**	*ee* (*endo*) [%] **L32/L36**
1	**3a**	99/99	71/75
2[b]	**3a**	88/87	80/86
3[c]	**3a**	–/93[d]	–/73
4	**3b**	99/99	56/59
5	**3c**	91/89	71/75
6	**3d**	96/93	76/79
7	**3e**	95/93	72/75
8	**3f**	98/96	64/68

[a] See the Experimental Section for typical reaction conditions. Data were obtained from the crude product by HPLC analysis on a chiral stationary phase. The *ee* values are averaged over two experiments and are reproducible within ±2%. [b] Reactions were carried out at −17°C. [c] Reaction was scaled up by a factor of 400 (50 mg of **3a**) at 6°C. [d] Yield of isolated product.

contrast to the D-A reaction, an electronic effect of the substituent was shown in the F-C reaction. In the case of **3b** and **3f** (entries 4 and 8), substitution of the phenyl ring with an electron-donating group at the *para* position afforded decreased *ee* values. In contrast, substrates with an electron-donating group at the *meta* positon (entry 7) or an electron-withdrawing group at the *ortho* (entry 6) or *para* position (entry 4) provided reacted with selectivities similar to that of the reaction of **3a** (entry 1).

The copper-catalyzed D-A reaction described in our work was previously carried out in the presence of proteins and polypeptides. These hybrid catalytic systems generally contain large scaffolds, including serum albumins(ca. 580 amino acids),[2d] bovine pancreatic polypeptide (31 amino acids),[5e] and *Lactococcal* multidrug resistance regulator (ca. 120 amino acids).[17] High enantioselectivities have been achieved with α,β-unsaturated 2-acyl pyridines as dienophiles. However, in the case of α,β-unsaturated 2-acyl imidazoles as a more practical class of dienophiles, the highest *ee* value reported to date is only 65%.[5e] In this context, we have significantly reduced the size of the peptide scaffold to only six amino acids while attaining excellent enantioselectivities with the practical substrates, which are potentially useful from a synthetic point of view. Although comparable results for this reaction were shown in other catalytic systems,[18] we wish to emphasize that we present the highest selectivities for these substrates within the field of protein- and peptide-based catalysis.

In conclusion, we have shown a novel and versatile small-peptide scaffold for Lewis acid catalyzed reactions. The peptide scaffold can be fabricated very easily by standard solid-phase synthesis without the necessity of additional modifications or incorporation of nonnatural amino acids. These attractive features are accompanied by high enantioselectivities in the copper-catalyzed D-A reaction and the aqueous F-C reaction, that is, up to 99% *ee* and 86% *ee*, respectively. Furthermore, the high hit rate of randomly chosen sequences, along with the loss of enantioselectivity that accompanies peptide linearization, provides evidence that a confined fold achieves significantly higher enantiomeric enrichment than that obtained from scaffolds exhibiting more structural flexibility. An additional strength of the present study is the convenient application of the alanine scanning technique. This method provides important mechanistic insights for the stereoselective outcome of the catalyzed reaction and allows rapid improvement of the catalytic performance by systematic re-design of the peptide ligands.

Experimental Section

Standard procedure for reactions catalyzed by **L32**- and **L36**-Cu^{2+} complexes: A catalyst solution composed of 450 μL of 200 μM of the peptide ligand and 60 μL of 1 mM $Cu(NO_3)_2$ was shaken for 30 min. An aliquot of a stock solution of dienophile in CH_3CN (20 μL of 0.03 M solution) was added and the mixture was cooled to 6 °C. The reaction was started by addition of the freshly distilled cyclopentadiene (2 μL, 24 μmol) or pyrrole (2 μL, 29 μmol), and the mixture was shaken for 3 days at 6 °C, followed by extraction with diethyl ether (3 × 1 mL). After removal of the solvent, the *ee* values of crude products were directly determined by HPLC on a chiral stationary phase.

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