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Determination of Amino Acid Enantiopurity and Absolute Configuration: Synergism between Configurationally Labile Metal-Based Receptors and Dynamic Covalent Interactions

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Abstract: Reliable determination of the enantiomeric excess of free amino acids can be obtained by measuring the induced circular dichroism of a multicomponent assembly formed by a modified tris(2-pyridylmethyl)amine ligand, a zinc salt, and the amino acid of interest. The systems furnish reliable information for all natural amino acids.

Keywords: amino acids · configuration determination · circular dichroism · chirality · ligands · molecular recognition

Introduction

Ever growing interest in new and efficient stereoselective reactions requires the development of effective methods that allow accurate determination of the enantiomeric excess (*ee*) of reagents and products.[1] For this purpose, the use of supramolecular sensors is increasing and is usually combined with optical signaling techniques because they are rapid and often inexpensive.[2] In this context, particular interest has been directed toward the use of circular dichroism (CD).[3] This is due to the high information content conveyed by this technique and to the wide availability of sensitive CD instruments. Because, in several cases, the chiral compounds of unknown enantiopurity lack strong chromophores, intermolecular interactions with stereodynamic chromophoric probes are used to generate distinct Cotton effects.[4] Moreover, the induced CD can allow determination of the absolute configuration of the compound of interest. The molecular recognition event is ruled by interactions such as inclusion complexes,[5] chiral ion pairs,[6] imine bond formation,[7] or metal–ligand interactions.[8] The latter have been extensively examined in tetradentate metal complexes that are characterized by a propeller-like arrangement of the ligand around the metal (Figure 1).[9–15]

Such peculiar geometry gives raise to the formation of two enantiomeric complexes in solution that are characterized by a clockwise (P) or counter-clockwise (M) arrangement of the ligand. The handedness of the molecular system can be controlled by the presence of a stereogenic center in the backbone ligand, or by a chiral guest carrying a stereogenic element. This particular feature has been extensively studied by the group of Canary.[9] In particular, tripodal ligands derived from quinoline or pyridine that are able to form propeller-like complexes with Zn^{II} and Cu^{II} ions have been used as molecular sensors or as redox-triggered chiroptical molecular switches.[10] More recently, Anslyn and Canary reported that the association between achiral quinoline-based metal complexes and chiral carboxylate, or *N*-Boc protected amino acids,[11] resulted in exciton-coupled CD, as well as the association between tris(2-pyridylmethyl)-amine (Tpy) metal complexes and chiral secondary alcohols.[12]

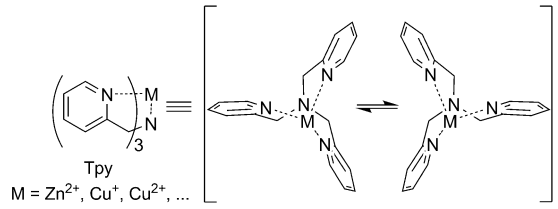

Figure 1. Clockwise (P) and counter-clockwise (M) arrangement of tris(2-pyridylmethyl)amine (Tpy) complexes.

In the past years, we have been interested in the synthesis of tripodal ligands and their relative metal complexes for their application in catalysis and in supramolecular chemistry.[13–15] As an example, enantiopure Ti^{IV} complexes bearing pseudo-C_3 amino triphenolate ligands have been shown to act as NMR chiral solvating agents for the stereochemical analysis of a series of sulfoxides,[14] or to control the dimerization process to the corresponding μ-oxo dinuclear species.[15] More recently, we have extended our interest to Tpy ligands and, in this article, we describe the synthesis and application of a new Tpy derivative, bearing an aldehydic moiety on one of the three arms, and its corresponding zinc complex. We envisioned that this new system could offer the possibility of combining the recognition capability of a configurationally labile Tpy complex, which has already been

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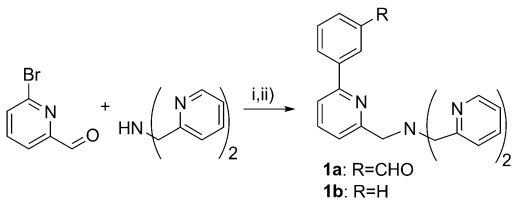
shown to be efficient for the coordination of carboxylate functionalities, with imine condensation chemistry, which is, in our case, directed to amine functions. This synergism is efficiently used for the determination of the *ee* of all natural α-amino acids.

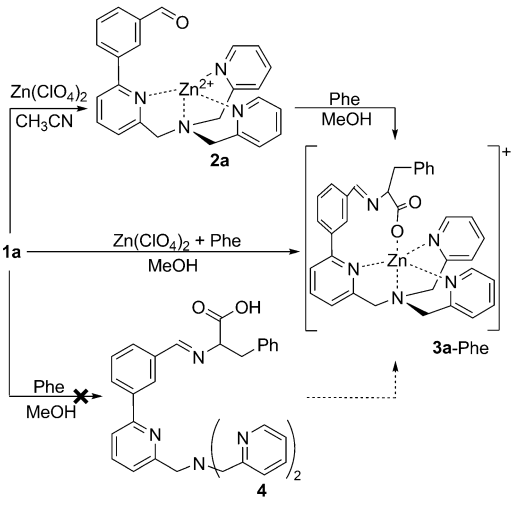
Results and Discussion

We first synthesized the new Tpy derivative **1a**, consisting of the Tpy core bearing a 3-formyl-phenyl substituent on one of the three arms (Scheme 1). Compound **1a** was obtained in two steps from reductive amination of commercially available 6-bromo-2-pyridinecarboxaldehyde and di(2-picolyl)amine, followed by Suzuki coupling with 3-formylphenyl boronic acid.[16–17] The synthesis was optimized to prepare ligand **1a** on a gram scale without requiring chromatographic purification. The corresponding zinc complex **2a** was synthesized by addition of $Zn(ClO_4)_2\,6H_2O$ to ligand **1a** in acetonitrile (Scheme 2). Condensation of **2a** with an amino acid could be monitored by ^{1}H NMR, UV and IR spectroscopy (Scheme 2).



Scheme 1. Synthesis of the ligands **1a** and **1b**. Reagents and conditions: i) $NaBH(OAc)_3$, THF, 12 h, RT (92%); ii) 3-formylphenylboronic acid or phenylboronic acid, $Pd(PPh_3)_4$, Na_2CO_3, H_2O/toluene/MeOH 1:1:0.5, 12 h, 90 °C (97%).

As an example, upon mixing **2a** and D-phenylalanine (D-Phe) in deuteromethanol solution, ^{1}H NMR indicated the disappearance of the formyl proton at 10.03 ppm. The formation of imine **3a**-D-Phe was also confirmed by FTIR measurements by the disappearance of the characteristic carbonyl stretching of the aldehyde (1700 cm^{-1}) and by the appearance of the stretching peak of the C=N bond (1635 cm^{-1}). In the UV/Vis spectra, the new species was characterized by the appearance of two peaks at 260 and 287 nm, respectively, which are negligible in the parent complex **2a** under the same experimental conditions. Interestingly, the complex **3a**-D-Phe shows a strong positive Cotton effect in the region between 220 and 320 nm (Figure 2). No meaningful CD signals were observed in this region by using compound **2a**, whereas the free amino acid D-Phe gave a weaker signal from 200 to 230 nm. Moreover, the presence of an excess of a single component did not affect the intensity of the signal. As expected, the specular CD spectrum was observed when L-Phe was used. On the basis of similar systems previously studied by other groups, we can hypothesize that the enhancement of the dichroic signal could originate from the preferential formation of a single propeller-like arrangement of the pseudo-C_3 metal complex. The simultane-



Scheme 2. Different routes for the preparation of the multiassembly **3a**-Phe.

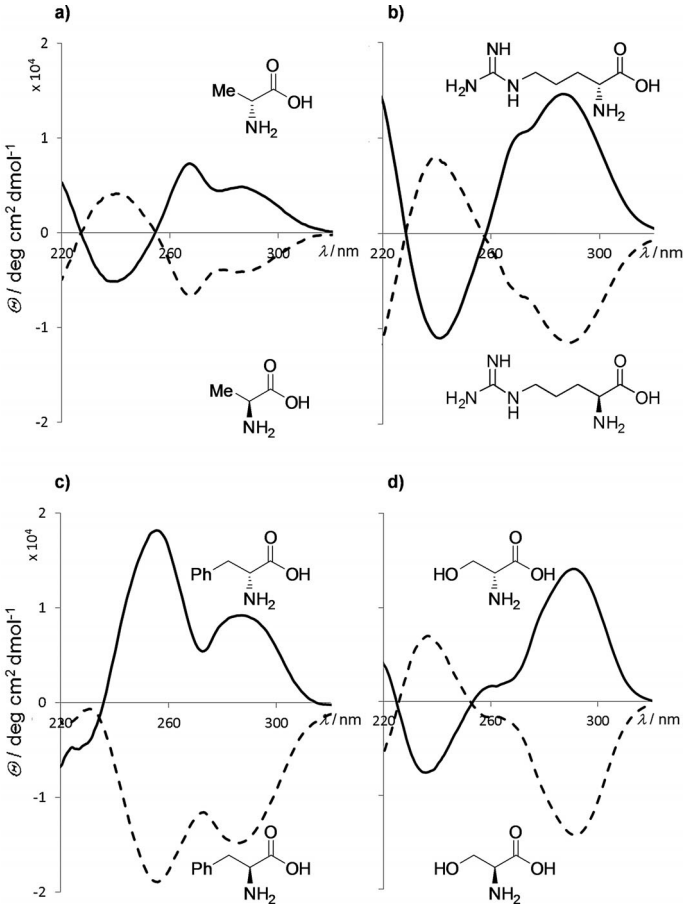


Figure 2. Comparison between the CD spectra obtained upon reaction of **2a** respectively with: a) Ala, b) Arg, c) Phe, and d) Ser. Curves obtained with D-form are in solid lines, whereas those obtained with L-form are in dashed lines.

ous coordination of the carboxylate to the metal center and the condensation reaction play a major role in fixing the handedness of the complex.

To confirm the crucial role of the aldehyde–amine condensation, we synthesized compound **1b**, an analogue of **1a** lacking the formyl group, which, in presence of $Zn(ClO_4)_2$ and D-Phe, did not show any meaningful dichroic signal. To test whether the observed behavior was general and could be used as a probe for *ee* determination, we built a calibration curve by using the CD molar ellipticity values at 256 nm for a series of samples of known enantiopurity. A good linear fit was observed, and reproducibility was confirmed employing four replicates for each data point. This demonstrated that **2a** could be used for the analysis and determination of unknown enantiopurity of Phe (Figure 3).

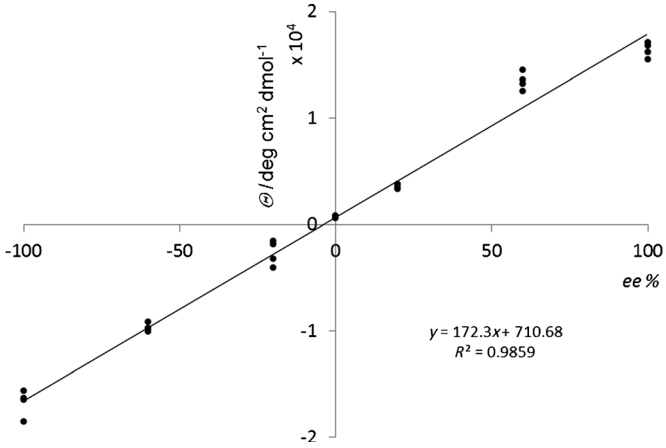


Figure 3. Values of Θ at 256 nm for samples at different *ee* of Phe. The calibration curve was built using four independent measurements.

The particular features of this recognition system also offer the possibility of using multicomponent assemblies of the species through one-pot reaction between ligand **1a**, $Zn(ClO_4)_2$, and amino acid D-Phe (Scheme 2). A mixture of the three components in methanol at 50 °C underwent complete conversion in five hours, as shown by the CD spectrum which was superimposable on that resulting from stepwise assembly. It is interesting to note that the situation was different in case of imine formation prior to metallation (Scheme 2). In this case the formation of imine **4** was extremely slow and did not allow its use as a probe for *ee* determination. All of these observations, in addition to the capability of using **1a** in a multicomponent assembly, point to the fact that the zinc is acting as a catalyst for the condensation reaction.

To test the generality of the protocol, the system was examined with the other 18 couples of proteogenic amino acids and phenylglycine with both enantiopure forms. As for Phe, all of the D-enantiomers showed a positive first Cotton effect, with the only variance being the magnitude and shape of the curve, whereas all of the L-enantiomers showed a negative first Cotton effect that was the mirror image of the plot of the corresponding D-amino acid. The configuration of the stereocenter could be assigned based on the sign of the first Cotton effect, because all L-stereocenters gave a negative signal and the D-stereocenters a positive signal. Having obtained CD spectra that differed in shape and intensity depending on the amino acid used, we wanted to discriminate between them on the basis of their identities and absolute configuration. For this purpose, we employed Principal Component Analysis (PCA), an unsupervised technique used to reduce the dimensionality of data space.[18] Such a chemiometric tool allowed a new set of variables to be created, named principal components (PC), to explain the variance of the system. A set of five duplicate samples were collected for each amino acid, and the CD spectra were recorded in duplicate for each sample. In our system, the different amino acids showed effective separation, allowing for discrimination based on the absolute configuration (Figure 4). The first principal component PC1, which accounts for almost 62% of the whole variance, is mainly connected to the amino acid configuration; all the D-amino acids were located on the negative projection of PC1, whereas all the L-amino acids were located on the positive projection of PC1, with the only exception being aspartic acid. Within a certain configuration, PC2 is mainly connected to the aliphatic or aromatic nature of the backbone, that is, in the plot PC2 versus PC1, D-Phe, D-Phg, D-Trp and D-Tyr are on the positive projection of PC2 and all the other D-amino acids are on the negative projection, whereas L-Phe, L-Phg, L-Trp and L-Tyr are on the negative projection and all the other L-amino acids on the positive projection, with the only exception again being aspartic acid. In this way, a global visualization could be obtained of the differences among the spectra and, as a consequence, among the behavior of the different amino acids on the base of their chemical features. The behavior of the system in the presence of aspartic acid is unclear; it is probably due to the presence of two carboxylate groups, which can compete in the binding to Zn^{II}, lowering the overall dichroic signal.

Conclusion

We have demonstrated that by combining the features of Tpy metal complexes and the presence of a highly reactive aldehyde group it is possible to obtain an extremely versatile system that can be used to determine the enantiopurity of simple proteogenic amino acids. The new Tpy system shows a remarkable enhancement of the CD signal upon binding with α-amino acids, allowing quantitative *ee* analysis with great accuracy. The ligand is easy to synthesize and the system undergoes rapid self-assembly under mild conditions, so that no further purification steps are required. Moreover, an accurate chemiometric analysis showed that the self-assembled systems can be used to discriminate among different amino acids, thus opening new perspectives for a fast screening of the nature and absolute configuration of a different class of molecules.

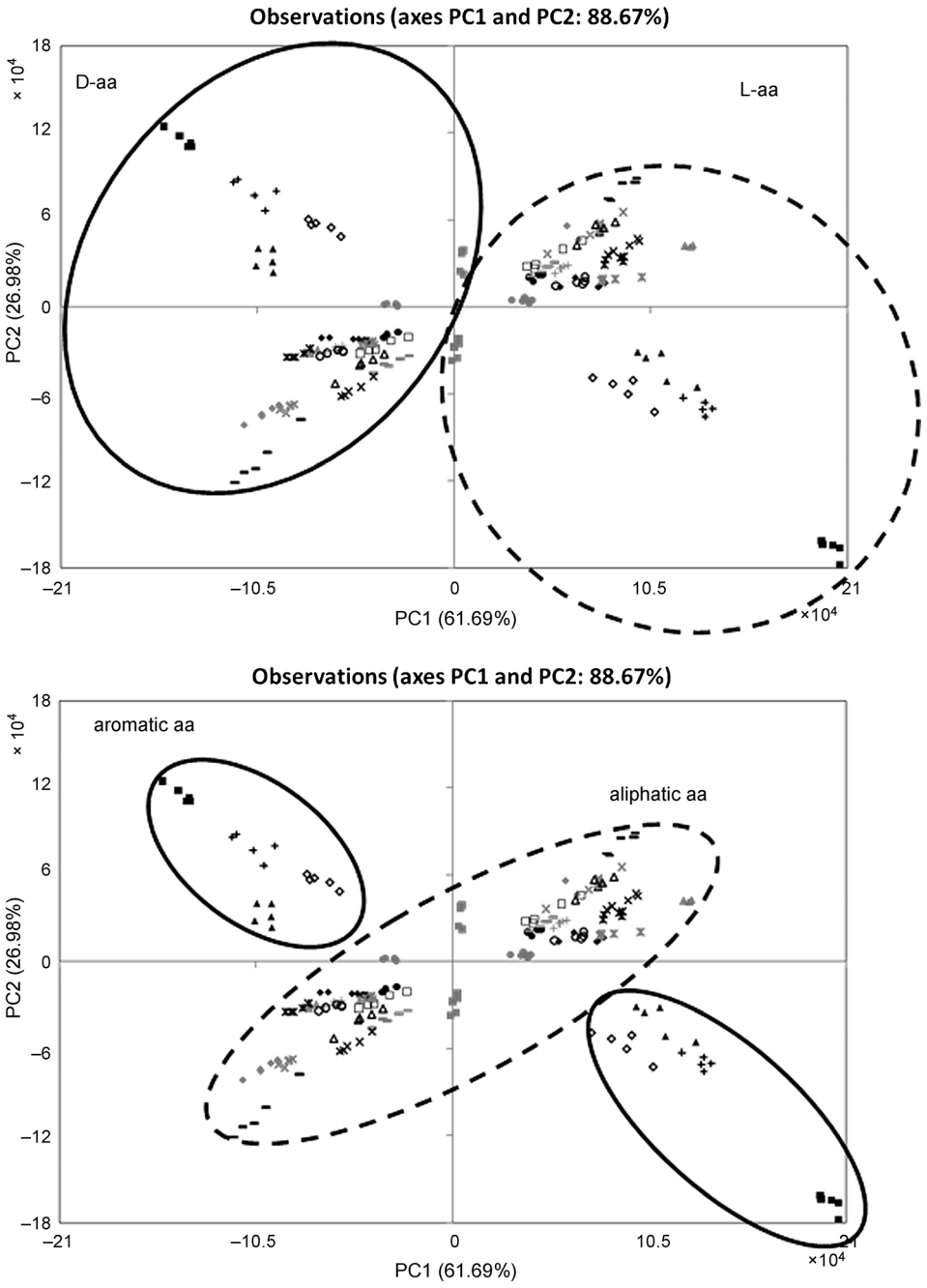


Figure 4. PCA: PC1 versus PC2 plot. In the upper panel, D-amino acids are all within the solid ellipse, L-amino acids are all within the dashed ellipse. In the bottom panel, aromatic amino acids are all within the solid ellipses, aliphatic amino acids are all within the dashed ellipse. Legend: ● Ala, ◆ Arg, ● Asn, ■ Asp, + Cys, ▲ Gln, □ Glu, ◆ His, × Ile, ○ Leu, – Lys, * Met, + Phe, ◇ Phg, – Pro, * Ser, △ Thr, ▲ Trp, ■ Tyr, × Val.

Experimental Section

General remarks: Chemicals were purchased from Aldrich, Fluka or Acros and used without further purification. CD spectra were recorded with a Jasco J-715 instrument. IR spectra were recorded with a Perkin–Elmer FTIR 1650. ^{1}H and $^{13}C\{1H\}$ NMR spectra (referenced to the solvent residual peak) were recorded at 301 K with Bruker AC-300 or 250 MHz instruments. ESI-MS experiments were carried out in positive mode with an Agilent Technologies LC/MSD Trap SL AGILENT instrument (mobile phase methanol). HRMS (ESI-TOF) analyses were performed with an Applied Biosystems ESI-TOF Mariner Biospectrometry Workstation (methanol as mobile phase with internal standards). MALDI-TOF analyses were carried out with an AB-SCIEX TOF-TOF 4800 instrument. Microanalyses were performed with a Flash 2000 Thermo Scientific Analyser. For new compounds, satisfactory determinations were obtained: C ± 0.3, H ± 0.27.

1-(6-Bromopyridin-2-yl)-*N*,*N*-bis(pyridin-2-ylmethyl)methanamine: 6-Bromopyridine-2-carboxyaldehyde (1 g, 5.4 mmol) and 2-dipicolylamine (968 μL, 5.4 mmol) were stirred in anhydrous THF (40 mL) under an N_2 atmosphere. After 1 h, sodium triacetoxy borohydride (1.14 g, 5.4 mmol) was added and the mixture was stirred under an N_2 atmosphere overnight at RT. The mixture was washed three times with saturated $NaHCO_3$ solution and the organic phase was dried over Na_2SO_4. Evaporation of the solvent under reduced pressure gave the pure product (1.82 g, 4.9 mmol, 92%) as a brownish solid. ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 8.53$ (d, $J = 4.9$ Hz, 2H; PyrH), 7.59 (m, 6H; PyrH), 7.30 (d, $J = 7.5$ Hz, 1H; PyrH), 7.15 (dd, $J = 7.1$, 4.9 Hz, 2H; PyrH), 3.90 ppm (s, 6H; CH_2); ^{13}C NMR (62 MHz, $CDCl_3$): $\delta = 161.10$, 158.90, 149.02, 141.20, 138.71, 136.46, 126.16, 122.99, 122.06, 121.55, 60.04, 59.38 ppm; MS (ESI): *m/z* calcd for $C_{18}H_{17}BrN_4$: 368.06; found: 369.2 $[M+H]^+$; MALDI-TOF: *m/z* calcd for $C_{18}H_{17}BrN_4$: 368.0637; found: 369.0016.

[6-(3-Formylphenyl)-2-pyridylmethyl]-bis(2-pyridylmethyl)amine (1a): 1-(6-Bromopyridin-2-yl)-*N*,*N*-bis(pyridin-2-ylmethyl)methanamine (1.8 g, 4.9 mmol), 3-formyl-phenyl boronic acid (1.1 g, 7.3 mmol), Na_2CO_3 (1.3 g, 12.2 mmol), and $Pd(PPh_3)_4$ (564 mg, 0.49 mmol) were dissolved in degassed H_2O/toluene/CH_3OH (1:1:0.5, 50 mL) under an N_2 atmosphere. The mixture was stirred for 10 h at 90 °C, then the solvent was evaporated under reduced pressure and the solid obtained was dissolved in $CHCl_3$. The organic phase was extracted three times with 5% aq. HCl solution. The aqueous phase was then basified with NaOH and extracted three times with $CHCl_3$. The organic phase was dried over Na_2SO_4 and then evaporated under reduced pressure and gave the pure product (1.87 g, 4.7 mmol, 97%) as a brownish oil. ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 10.03$ (s, 1H; CHO), 8.47 (m, 3H; PyrH + ArH), 8.23 (d, $J = 7.8$ Hz, 1H; ArH), 7.83 (d, $J = 7.6$ Hz, 1H; Ar H), 7.61 (m, 8H; PyrH + ArH), 7.08 (dd, $J = 7.0$, 4.9 Hz, 2H; PyrH), 3.93 (s, 2H; CH_2), 3.90 ppm (s, 4H; CH_2); ^{13}C NMR (62 MHz, $CDCl_3$): $\delta =$ 191.96, 159.11, 159.04, 154.58, 148.71, 139.95, 137.05, 136.44, 136.18, 132.39, 129.39, 129.07, 127.95, 122.60, 121.73, 121.65, 118.37, 59.88, 59.73 ppm; MS (ESI): *m/z* calcd for $C_{25}H_{22}N_4O$: 394.2; found: 395.4 $[M+H]^+$.

(6-Phenyl-2-pyridylmethyl)bis(2-pyridylmethyl)amine (1b): The reaction was conducted by following the procedure described for **1a**, but using phenylboronic acid instead of 3-formyl-phenyl boronic acid. The final yield was 97%. ^{1}H NMR, ^{13}C NMR and ESI+MS data corresponded to those reported in the literature.[19]

Complex 2a: Compound **1a** (200 mg, 0.5 mmol) was dissolved in the minimum amount of anhydrous acetonitrile and $Zn(ClO_4)_2{\cdot}6H_2O$ (1 equiv) was added. The solution was allowed to stand at RT for 5 min and then the solvent was evaporated under reduced pressure, giving the desired products as a yellow solid in 80% yield. *Caution!* Perchlorate salts of metal complexes with organic ligands are potentially explosive. They should be handled in small quantities and with caution. ^{1}H NMR (200 MHz, CD_3CN): $\delta = 4.33$ (m, 6H; CH_2), 7.62 (m, 5H; PyrH+ArH), 7.81 (m, 4H; PyrH+ArH), 8.17 (m, 4H; PyrH+ArH), 8.45 (d, $J = 6.0$ Hz, 2H; PyrH), 10.03 ppm (s, 1H; CHO); ^{13}C NMR (62 MHz, CD_3CN): $\delta = 57.23$, 57.45, 124.75, 126.01, 126.51, 127.06, 129.60, 131.40, 133.11, 135.49, 140.62, 142.87, 142.96, 149.31, 155.77, 157.55, 159.88, 192.79 ppm; MS (ESI): m/z calcd for $C_{25}H_{22}N_4OZn$: 458.11; found: 229.1 [$M^{2+}/2$]; MALDI-TOF: m/z calcd for $C_{25}H_{22}N_4OZn(ClO_4)$: 557.0565; found: 556.8926.

General procedure for CD measurements: For amino acids that were soluble in methanol, a solution of **2a** in methanol (0.0075 M) and a solution of amino acid in methanol (0.01 M) were mixed in ratio 1:1 (v/v) and kept overnight at 50 °C in presence of molecular sieves. For amino acids that were moderately soluble in methanol, a solution of **2a** in methanol (0.0075 M) and a solution of amino acid in methanol (0.001 M) were mixed in ratio 0.1:1 (v/v) and kept overnight at 50 °C in the presence of molecular sieves. For all other amino acids, a solution of **2a** in methanol (0.0075 M) and amino acid (1.25 equiv) were kept overnight at 50 °C in the presence of molecular sieves. The compounds were used without further purification. For CD measurements, suitable dilutions were performed, to obtain a final concentration in the cuvette of imine equal to $0.75{\cdot}10^{-4}$ M.

Acknowledgements

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