



# Mixed Multimetallic *tris*(2-pyridylmethyl)amine Based Complexes: Synthesis and Chiroptical Properties

Nadia Alessandra Carmo dos Santos,<sup>[a]</sup> Elena Badetti,<sup>[a]</sup> Federico Begato,<sup>[a]</sup> Klaus Wurst,<sup>[b]</sup> Giulia Licini,<sup>[a]</sup> and Cristiano Zonta\*<sup>[a]</sup>

Continuous intensification of reaction screening methodologies has required the development of novel high-throughput analytical technologies. This urge involves also chirality related fields where nowadays novel methods for reliable, fast and effective analysis are developed. Within this field, chiroptical spectroscopies have emerged as promising techniques, in particular when they are combined with stereodynamic probes for optical signal amplification. We report here the synthesis

and characterisation of a series of molecular architectures based on a modified *tris*(2-pyridylmethyl)amine (TPMA) complex which are able to amplify the electronic CD signal of phenylalanine. The study reports the synthesis of six novel TPMA based supramolecular architectures characterised by the presence of two different metals within the same molecule. Besides the synthesis, the study highlights how mixing metals influences the chiroptical properties of the formed compounds.

## Introduction

Within the field of chirality related technologies, there is a constant urge to develop effective methods to perform quantitative chiral analysis.<sup>[1–3]</sup> Commercial-scale production sites based on methods such as catalytic asymmetric synthesis, biocatalytic resolution, diastereomeric crystallization, and enantioselective absorption of enantiopure molecules must include facilities to verify and certify the optical purity of intermediates and end-products. Traditionally, chiral HPLC has been the preferred separation method in these industries<sup>[4]</sup> both for analytical and preparative purposes. However, in the market there is a strong demand for developing faster and cheaper stereochemical analysis methodologies. Chiroptical spectroscopies (CS) represent one of the most promising tools to reduce the cost and time of such stereochemical analyses. The main limitation of CS is the need to have a strong chromophore in the analyte.<sup>[5–7]</sup> However, in recent years, synthetic sensors have been developed to overcome this limitation by enhancing the strength of chiral absorption.<sup>[8–17]</sup>

Recently, we have been working in the application of *tris*(2-pyridylmethyl)amine (TPMA)<sup>[18]</sup> metal complexes both in catalysis<sup>[19–21]</sup> and supramolecular chemistry.<sup>[22–25]</sup> In particular, we exploited the sensor capabilities of a series of TPMA based molecular architectures in the determination of the enantiomeric excess of chiral molecules, using Circular Dichroism (CD),<sup>[26–31]</sup> Vibrational Circular Dichroism (VCD),<sup>[32]</sup> and Circular Polarised Luminescence (CPL).<sup>[30]</sup> In a typical experiment, mixing a modified TPMA zinc complex with one equivalent of the desired amino acid and half equivalent of zinc perchlorate resulted in the almost exclusive formation of a crystalline solid, corresponding to the trinuclear architecture **3-ZnZnZn** (Scheme 1).<sup>[33]</sup> The molecular structure has a C<sub>2</sub> symmetry, with the two metal ions at the two ends of the complex in a trigonal bipyramidal geometry and a typical propeller-shape formed by the three pyridine rings. The central metal ion is octahedral and coordinates two imine nitrogens, two carbonyls, and two extra *cis*-coordinated solvent molecules. Acetonitrile and methanol solutions of the complex displayed a strong CD signal, and TD-DFT studies have shown that CD signals arise by the helical arrangement of the ligand around the metal and by the exciton coupling of the atropisomeric biaryl systems. A similar

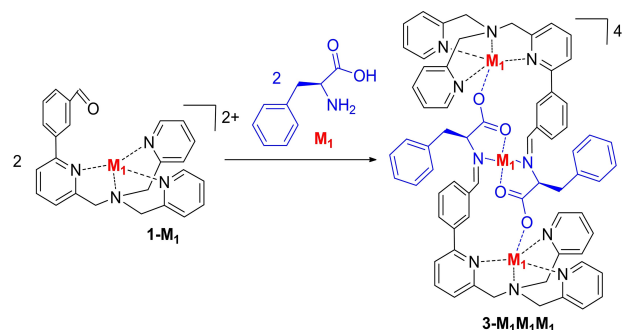
[a] Dr. N. A. Carmo dos Santos, Dr. E. Badetti, F. Begato, Prof. G. Licini, Prof. C. Zonta  
Department of Chemical Sciences  
University of Padova  
Via F. Marzolo 1, 35131 Padova, Italy  
E-mail: cristiano.zonta@unipd.it

[b] Prof. K. Wurst  
Institute of General, Inorganic and Theoretical Chemistry  
University of Innsbruck,  
6020 Innsbruck, Austria

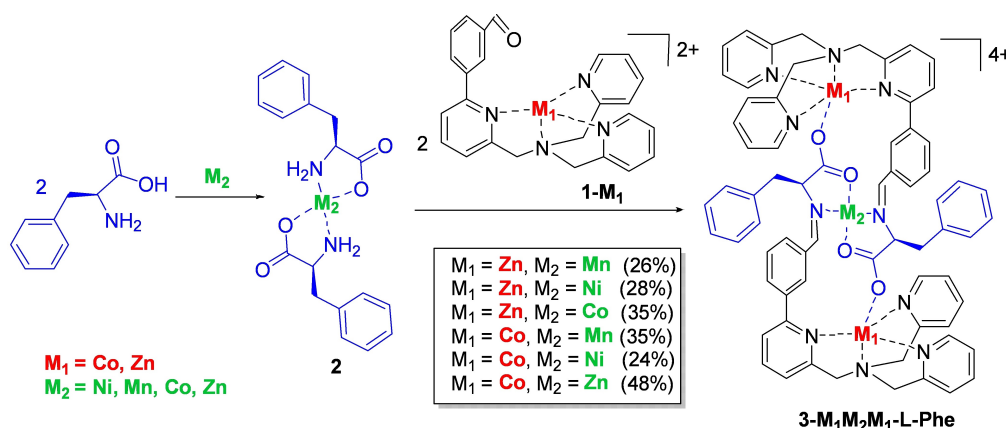
Supporting information for this article is available on the WWW under <https://doi.org/10.1002/ejic.202100392>

Part of the "44th ICCS Conference" Special Collection.

© 2021 The Authors. European Journal of Inorganic Chemistry published by Wiley-VCH GmbH. This is an open access article under the terms of the Creative Commons Attribution Non-Commercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.



Scheme 1. Synthetic scheme for the synthesis of the homo trimetallic system. Perchlorates anions have been removed for clarity.



**Scheme 2.** Synthesis of the hetero-metallic structure. Perchlorate anions have been removed for clarity.

synthetic approach was used for the preparation of the cobalt (II) analogue **3-CoCoCo**, which showed a strong enhancement of VCD signals.<sup>[32]</sup>

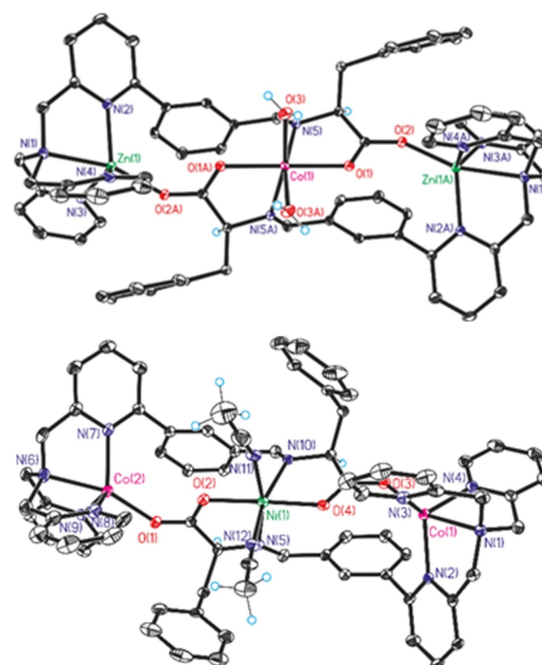
Starting from these results, our research was aimed to evaluate the possibility to substitute the central metal  $M_2$  to prepare mixed multimetallic architectures to see how these substitutions affect CD signal, thus the sensor capabilities. Herein, we report the evolution of our reported system, in which six different hetero-metallic complexes can be formed (Scheme 2). The reported synthesis, besides offering novel mixed multimetallic structures, has offered the possibility to study the CD properties of the novel systems.

## Results and Discussion

### Synthesis and Characterization

The initial aim of this work was to synthesize a heterometallic complex in which the central metal was different from the two metals coordinated by the two TPMA systems. To understand which metals are better suited to occupy the central position of the trimetallic structure, a survey on the database of crystallographic data (CCDC) has been performed. As already mentioned in the introduction, the central metal  $M_2$  atom adopts an octahedral geometry, coordinating two imine nitrogens, two carboxylates, and two solvent molecules. Structures with similar geometry were present within the database with Zn(II) and Co(II), as well as with Mn(II), Fe(II), and Ni(II).

Taking in consideration the results of the database search, a new synthetic procedure has been developed to insert one type of metal bound to the TPMA edges and a different metal within the cleft formed by the amino acids. This new synthetic route can be divided in three steps: the first is the formation of the metallic complex **1- $M_1$** , between the ligand and the metal  $M_1$ , which will form the edge of the structure. The second step is the formation of complex **2** by the complexation of the amino acids with the metal  $M_2$ , which will be the central core of the structure. The intermediate has been synthesized *in situ* by



**Figure 1.** XRD structure of the trinuclear **3-ZnCoZn** (top) and **3-CoNiCo** (bottom) complexes. Perchlorate anions have been removed for clarity.

the reaction between one equivalent of amino acid with 0.5 equivalents of metal salt  $M_2(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$  in anhydrous methanol, and the solution is stirred at 60 °C for ten minutes. In the final step, complex **1- $M_1$**  is added to the solution of **2** and the mixture is heated to 65 °C for twenty minutes (Scheme 1). The mixture is left at room temperature, furnishing the final product as a precipitate. The product is recovered by centrifugation and the wet solid is dried under reduced pressure. The developed synthetic protocol allowed to obtain mixed trinuclear structures with Co(II) or Zn(II) in the TPMA unit, and alternatively, Zn(II), Co(II), Mn(II) or Ni(II) in the central amino-acidic cleft. Since all metals used in this study are paramagnetic, except for zinc, NMR analyses did not furnish suitable analytical information. For this reason, the identity and purity of the recovered material

was confirmed by ESI-MS and elemental analysis. In particular, MS analysis has shown that self-assembly process does not allow the scrambling of the metals within different positions.<sup>[34]</sup>

While the synthesis of the molecular structures owning Fe(II) in the central cavity failed, it was possible to obtain crystals suitable for X-ray diffraction for both **3-ZnCoZn** and **3-CoNiCo** systems (Figure 1).

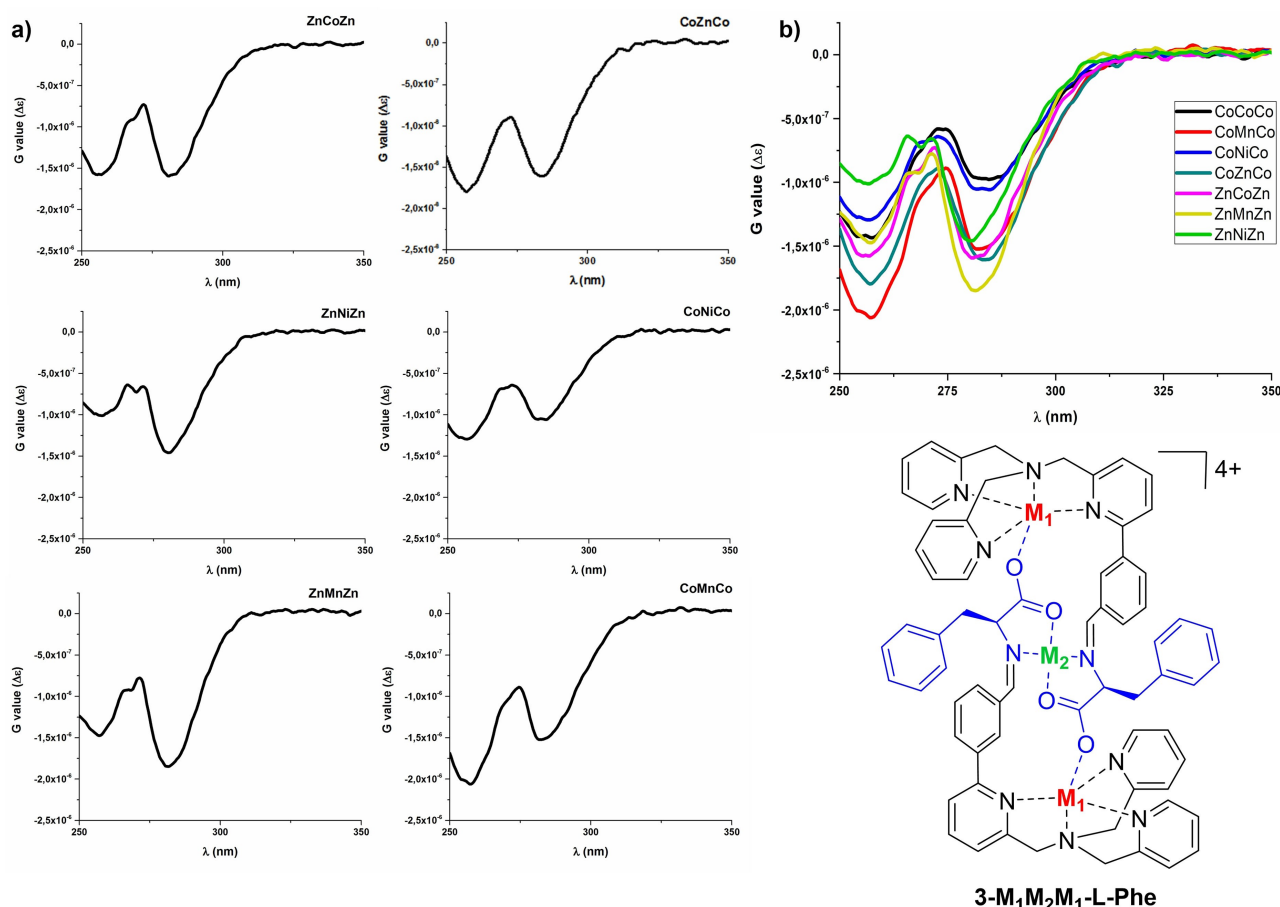
Moreover, in the reported structures, the molecular architectures are arranged with an overall  $C_2$  symmetry, with the two metal ions  $M_1$  at the two ends of the complex, in a trigonal bipyramidal geometry, and the central metal  $M_2$  with octahedral geometry. In the case of the Co(II) structure, two water molecules are coordinated to the metal centre, while in the case of Ni(II) structure two acetonitrile molecules are present.

### Optical studies

This study aimed to understand the effect that different metals can have on the chiroptical properties of this specific system, CD measurements on the six **3- $M_1M_2M_1$**  complexes have been performed. As it can be seen in Figure 2, the shape of the

dichroic signal is similar for all systems and, while the free amino acid L-Phe has a weak signal from 200 to 230 nm, all of these systems shows a remarkable enhancement of the CD signal. Two negative bands in the region before 300 nm are present for all systems with some variations on the intensity values. While it is difficult to find a clear-cut correlation between the metal and the observed CD signal, it can be seen that compounds **3-Co $M_2$ Co** generally show a higher absorption intensity in the wavelength region between 250 and 275 nm. On the other hand, the compounds **3-Zn $M_2$ Zn** show a higher absorption intensity in the wavelength region between 275 and 300 nm.

We can interpret the observed differences not in terms of “special” effect of the metals, but to small differences in the final structure of the complexes, which results in a changed chromophore orientation. Indeed, theoretical calculations performed by us in a previous study, revealed that the CD absorbances are mainly associated with exciton coupling of the aromatic chromophores within the system. We are faced with a phenomenon in which small variations in the geometry can have important effects on the final CD spectra.



**Figure 2.** a) Circular Dichroism spectra of **3- $M_1M_2M_1$**  compounds, b) comparison between the CD spectra of the different trinuclear complexes (**3-CoCoCo-L-Phe** has been synthesized according to a reported procedure).<sup>[35]</sup> CD measurements were performed diluting with anhydrous DMSO the synthesized cage to obtain a final concentration equal to  $1.0 \cdot 10^{-5} \text{ M}$  ( $0.1 \text{ cm}$  cuvette). The CD spectra were measured in millidegrees and reported in G value. For a spectra of L-Phe see ref [26].

## Conclusions

In this study, chiral multimetallic TPMA complexes bearing phenylalanine were synthesized and characterized. All systems have shown to work as stereodynamic sensors with strong CD signal in the region between 250 and 300 nm. The intensity and shape of the CD signal are affected by the metal characteristics. This suggests that the signal intensity in CD is only related to the orientation of the chromophores.

## Experimental Section

### General Remarks

Chemicals were purchased from Merck, Fluka, or Acros and used without further purification. ECD spectra were recorded on a Jasco J-715 or Jasco J-1500 instrument equipped with a Jasco MCB-100 circulation bath. ESI-MS spectra have been acquired in positive mode with an Agilent Technology LC/MSD Trap SL, interfaced to an Agilent 1100 binary pump. The samples were preventively diluted in acetonitrile and then injected via direct infusion with a syringe pump at a rate of 0.05 ml/min. Microanalyses were performed on a Flash 2000 Thermo Scientific Analyser. For the new compounds, satisfactory determinations were obtained: C  $\pm$  0.3, H  $\pm$  0.27.

### Synthesis of 3-M<sub>1</sub>M<sub>2</sub>M<sub>1</sub>-L-Phe

General Procedure: The amino acid L-Phe (0.033 mmol) was mixed with the desired perchlorate salt of the metal (M<sub>2</sub>) (0.017 mmol) in 1 mL of dry methanol. The mixture was heated and stirred at 60 °C for 10 minutes. To the resulting solution, the desired tris-(pyridylmethyl)-amine metal complex (1-M<sub>1</sub>) (0.031 mmol) was added, and the mixture was stirred at 65 °C for 20 minutes. The resulting precipitate was centrifuged and washed with dry methanol and diethyl ether. While <sup>1</sup>H NMR of 3-ZnZnZn has been reported previously,<sup>[33]</sup> in the case of Ni(II) complexes a paramagnetic behaviour is observed.

**3-CoMnCo-L-Phe** (M<sub>1</sub>=Co M<sub>2</sub>=Mn) Bright green (Yield 35%). ESI-MS(m/z): Calc. C<sub>68</sub>H<sub>60</sub>N<sub>10</sub>O<sub>4</sub>Co<sub>2</sub>Mn 3 ClO<sub>4</sub> 1550.1, Found 1550.2 (M<sup>+</sup>).

**3-CoNiCo-L-Phe** (M<sub>1</sub>=Co M<sub>2</sub>=Ni) Bright green (Yield 24%). ESI-MS(m/z): Calc. C<sub>68</sub>H<sub>60</sub>N<sub>10</sub>O<sub>4</sub>Co<sub>2</sub>Ni 3 ClO<sub>4</sub> 1553.1, Found 1553.2 (M<sup>+</sup>).

**3-CoZnCo-L-Phe** (M<sub>1</sub>=Co M<sub>2</sub>=Zn) Bright green (Yield 48%). ESI-MS(m/z): Calc. C<sub>68</sub>H<sub>60</sub>N<sub>10</sub>O<sub>4</sub>Co<sub>2</sub>Zn 3 ClO<sub>4</sub> 1559.1, Found 1559.1 (M<sup>+</sup>).

**3-ZnCoZn-L-Phe** (M<sub>1</sub>=Zn M<sub>2</sub>=Co) Light green (Yield 35%). ESI-MS(m/z): Calc. C<sub>68</sub>H<sub>60</sub>N<sub>10</sub>O<sub>4</sub>Zn<sub>2</sub>Co 3 ClO<sub>4</sub> 1564.2, Found 1564.5 (M<sup>+</sup>).

**3-ZnMnZn-L-Phe** (M<sub>1</sub>=Zn M<sub>2</sub>=Mn) Light gray (Yield 26%). ESI-MS(m/z): Calc. C<sub>68</sub>H<sub>60</sub>N<sub>10</sub>O<sub>4</sub>Zn<sub>2</sub>Mn 3 ClO<sub>4</sub> 1560.2, Found 1560.5 (M<sup>+</sup>).

**3-ZnNiZn-L-Phe** (M<sub>1</sub>=Zn M<sub>2</sub>=Ni) Pale green (Yield 28%). ESI-MS(m/z): Calc. C<sub>68</sub>H<sub>60</sub>N<sub>10</sub>O<sub>4</sub>Zn<sub>2</sub>Ni 3 ClO<sub>4</sub> 1563.1, Found 1563.2 (M<sup>+</sup>).

### X-Ray Analysis

All data sets were collected on a Bruker D8 Quest diffractometer (Photon 100) equipped with an Incoatec Microfocus source generator (multi layered optics monochromatized Mo-K $\alpha$  radiation,  $\lambda$  = 71.073 pm). The supplementary crystallographic data were deposited.

Deposition Numbers 1896150 (for 3-ZnCoZn-L-Phe) and 1896151 (for 3-CoNiCo-L-Phe) 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.

## Acknowledgements

Financial support from the University of Padova (P-DISC#10-BIRD2020-UNIPD), Fondazione Cassa di Risparmio Padova e Rovigo (CARIPARO).

## Conflict of Interest

The authors declare no conflict of interest.

**Keywords:** CD · Multimetallic structure · Self-assembly · Supramolecular chemistry

- [1] B. T. Herrera, S. R. Moor, M. McVeigh, E. K. Roesner, F. Marini, E. V. Anslyn, *J. Am. Chem. Soc.* **2019**, *141*, 11151–11160.
- [2] H. H. Jo, X. Gao, L. You, E. V. Anslyn, M. J. Krische, *Chem. Sci.* **2015**, *6*, 6747–6753.
- [3] B. T. Herrera, S. L. Pilicer, E. V. Anslyn, L. A. Joyce, C. Wolf, *J. Am. Chem. Soc.* **2018**, *140*, 10385–10401.
- [4] A. Ciogli, O. H. Ismail, G. Mazzocanti, C. Villani, F. Gasparrini, *J. Sep. Sci.* **2018**, *41*, 1307–1318.
- [5] G. Pescitelli, L. Di Bari, N. Berova, *Chem. Soc. Rev.* **2014**, *43*, 5211–5233.
- [6] D. Leung, S. O. Kang, E. V. Anslyn, *Chem. Soc. Rev.* **2012**, *41*, 448–479.
- [7] C. Wolf, K. W. Bentley, *Chem. Soc. Rev.* **2013**, *42*, 5408–5424.
- [8] C.-Y. Lin, S. Lim, E. V. Anslyn, *J. Am. Chem. Soc.* **2016**, *138*, 8045–8047.
- [9] Z. A. De Los Santos, C. Wolf, *J. Am. Chem. Soc.* **2016**, *138*, 13517–13520.
- [10] K. W. Bentley, Y. G. Nam, J. M. Murphy, C. Wolf, *J. Am. Chem. Soc.* **2013**, *135*, 18052–18055.
- [11] M. Anyika, H. Gholami, K. D. Ashtekar, R. Acho, B. Borhan, *J. Am. Chem. Soc.* **2014**, *136*, 550–553.
- [12] B. Li, J. Zhang, L. Li, G. Chen, *Chem. Sci.* **2021**, *12*, 2504–2508.
- [13] S. L. Pilicer, J. M. Dragna, A. Garland, C. J. Welch, E. V. Anslyn, C. Wolf, *J. Org. Chem.* **2020**, *85*, 10858–10864.
- [14] F. Y. Thanzeel, A. Sripada, C. Wolf, *J. Am. Chem. Soc.* **2019**, *141*, 16382–16387.
- [15] Z. A. De los Santos, C. C. Lynch, C. Wolf, *Angew. Chem. Int. Ed.* **2019**, *58*, 1198–1202; *Angew. Chem.* **2019**, *131*, 1211–1215.
- [16] D. T. Payne, M. K. Chahal, V. Březina, W. A. Webber, K. Ariga, F. D'Souza, J. Labuta, J. P. Hill, *Front. Chem.* **2020**, *14*, 28–40.
- [17] L.-L. Wang, M. Quan, T.-L. Yang, Z. Chen, W. Jiang, *Angew. Chem. Int. Ed.* **2020**, *59*, 23817–23824; *Angew. Chem.* **2020**, *132*, 24025–24032.
- [18] C. Bravin, E. Badetti, G. Licini, C. Zonta, *Coord. Chem. Rev.* **2021**, *427*, DOI 10.1016/j.ccr.2020.213558.
- [19] N. A. Carmo dos Santos, F. Lorandi, E. Badetti, K. Wurst, A. A. Isse, A. Gennaro, G. Licini, C. Zonta, *Polymer* **2017**, *128*, 169–176.
- [20] M. Natali, E. Badetti, E. Deponti, M. Gamberoni, F. A. Scaramuzza, A. Sartorel, C. Zonta, *Dalton Trans.* **2016**, *45*, 14764–14773.
- [21] N. A. Carmo dos Santos, M. Natali, E. Badetti, K. Wurst, G. Licini, C. Zonta, *Dalton Trans.* **2017**, *46*, 16455–16464.
- [22] C. Bravin, E. Badetti, F. A. Scaramuzza, G. Licini, C. Zonta, *J. Am. Chem. Soc.* **2017**, *139*, 6456–6460.
- [23] C. Bravin, G. Licini, C. A. Hunter, C. Zonta, *Chem. Sci.* **2019**, *10*, 1466–1471.
- [24] C. Bravin, G. Mason, G. Licini, C. Zonta, *J. Am. Chem. Soc.* **2019**, *141*, 11963–11969.
- [25] C. Bravin, G. Licini, C. A. Hunter, C. Zonta, *Chem. Eur. J.* **2020**, *26*, 9454–9458.

- [26] F. A. Scaramuzzo, G. Licini, C. Zonta, *Chem. Eur. J.* **2013**, *19*, 16809–16813.
- [27] F. A. Scaramuzzo, E. Badetti, G. Licini, C. Zonta, *Chirality* **2019**, *31*, 375–383.
- [28] F. A. Scaramuzzo, E. Badetti, G. Licini, C. Zonta, *Eur. J. Org. Chem.* **2017**, *2017*, 1438–1442.
- [29] E. Badetti, N. Alessandra Carmo dos Santos, F. A. Scaramuzzo, C. Bravin, K. Wurst, G. Licini, C. Zonta, *RSC Adv.* **2018**, *8*, 19494–19498.
- [30] N. A. Carmo dos Santos, E. Badetti, G. Licini, S. Abbate, G. Longhi, C. Zonta, *Chirality* **2018**, *30*, 65–73.
- [31] E. Badetti, V. Lloveras, F. Romano, R. Di Lorenzo, J. Veciana, J. Vidal-Gancedo, C. Zonta, G. Licini, *Eur. J. Inorg. Chem.* **2016**, *2016*, 4968–4973.
- [32] R. Berardozi, E. Badetti, N. A. Carmo Dos Santos, K. Wurst, G. Licini, G. Pescitelli, C. Zonta, L. Di Bari, *Chem. Commun.* **2016**, *52*, 8428–8431.
- [33] E. Badetti, K. Wurst, G. Licini, C. Zonta, *Chem. Eur. J.* **2016**, *22*, 6515–6518.
- [34] It should be noted that in the case of the synthesis of **3-ZnCoZn–L–Phe**, partial scrambling of the metals can occur as shown by ESI-MS in supporting info. However, simple recrystallization furnished the pure compound.
- [35] R. Berardozi, E. Badetti, N. A. Carmo dos Santos, K. Wurst, G. Licini, G. Pescitelli, C. Zonta, L. Di Bari, *Chem. Commun.* **2016**, *52*, 8428–8431.

---

Manuscript received: May 10, 2021  
Revised manuscript received: June 14, 2021  
Accepted manuscript online: June 17, 2021