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Noncovalent induced circular dichroism sensors based on a chiral metal–organic framework: chiral induction synthesis, quantitative enantioselective sensing and noncovalent sensing mechanism†

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As an important class of chiral optical sensors, chiral induced circular dichroism (ICD) sensors have received increasing attention. Herein, a series of monometallic and bimetallic centered metal–organic frameworks (MOFs) with the same crystal structure, namely $[\text{Cu}(\text{L})(2,2'\text{-bipy})]\cdot\text{H}_2\text{O}$ (**LNNU-2**), $[\text{Cd}(\text{L})(2,2'\text{-bipy})(\text{H}_2\text{O})]$ (**LNNU-3**) and $[\text{Zn}_x\text{Cu}_y(\text{L})(2,2'\text{-bipy})]\cdot\text{H}_2\text{O}$ ($x:y = 9.6:0.4\text{--}1.0:9.0$) ($\text{H}_2\text{L} = \text{HOCC}_6\text{H}_4\text{CH}_2\text{PO}(\text{OH})(\text{OC}_2\text{H}_5)$, $2,2'\text{-bipy} = 2,2'\text{-bipyridine}$), have been successfully synthesized for studying the non-covalent ICD sensing mechanism. **LNNU-2** shows excellent ICD sensing performance due to the strong metal coordination interaction between **LNNU-2** and chiral tryptophan (Trp). In contrast, there is no ICD effect between **LNNU-3** and chiral Trp due to the absence of metal coordination interaction. The results indicate that the metal coordination interaction plays a decisive role in generating and amplifying ICD signals in this sensing system. Compared to the previously reported **LNNU-1** ($[\text{Zn}(\text{L})(2,2'\text{-bipy})]\cdot\text{H}_2\text{O}$) sensor, **LNNU-2** is not only capable of quantifying the enantiomeric composition of chiral Trp samples at a lower concentration but also enables highly selective and accurate determination of L-Trp concentration in water, mixed natural amino acids and simulated blood plasma components by the circular dichroism (CD) titration method. **LNNU-2** also allows the accurate determination of the absolute configuration and enantiomeric excess (ee) values of two chiral aromatic amino alcohols in pure water. Additionally, the effects of different chiral amino acids as chiral inducers on the chiral induction synthesis of enantio-enriched **LNNU-2** were investigated. As a result, the enantioenriched (**P**)-**LNNU-2** and (**M**)-**LNNU-2** were successfully obtained using L-alanine (L-Ala) and D-alanine (D-Ala) as chiral inducers, respectively.

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Introduction

Chirality is fundamental in nature and vital in chemistry, biology, life sciences, materials sciences, and other fields.^{1–7} The enantiomers of chiral molecules often exhibit different pharmacological, metabolic, therapeutic or toxicological properties, but have the same physical and chemical properties in an achiral environment.^{8,9} Therefore, the rapid, highly selective and accurate determination of the enantiomeric composition of chiral analytes is extremely important. Over the past decades, the most commonly applied techniques have been

chromatography with chiral stationary phases and nuclear magnetic resonance (NMR) analysis with chiral solvating or derivatizing agents.^{10–15} However, these methods are not suitable for rapid analysis, due to expensive instrumentation, time-consuming steps, and sophisticated programs. In contrast, chiral optical sensing is considered to be a promising method due to the advantages of simple operation, rapid response, high sensitivity and low cost.^{16–25} Chiral optical sensing can allow the enantioselective recognition of chiral molecules by monitoring changes in the fluorescence/circular dichroism (CD) signals of chiral optical sensors. Thus, the rational design and construction of chiral optical sensors is of great importance for the determination of the enantiomeric composition of chiral analytes.

In recent years, chiral metal–organic frameworks (MOFs) have become an important class of chiral optical sensing materials due to their stable chiral structures, designable functional sites and specific porosity.^{26–39} Some optical sensors based on chiral MOFs have been reported for the enantio-

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selective sensing of amino acids, amino alcohols, drugs, etc.^{26–34} Despite the considerable progress in the design and application of optical sensors based on chiral MOFs, several challenges remain: (1) relying on a single optical signal change to achieve differentiation of target enantiomers, which is susceptible to interference from external factors and has poor resistance to background interference; (2) reports on the accurate determination of enantiomeric excess (ee) values for chiral analytes are rare. It is worth noting that the induced circular dichroism (ICD) technique may provide a feasible strategy for dealing with the above problems. Strong ICD signals could be generated through covalent or noncovalent interactions between the sensor and the chiral analyte.^{19,40–51} The generation of red-shifted ICD signals (above 300 nm) is likely to eliminate the interference from chiral impurities when quantitative analysis of ee values is performed. Recently, a reusable, highly selective and sensitive ICD sensor (**LNNU-1**) based on a chiral MOF was first reported by our group.⁵¹ This ICD sensor could accurately determine the absolute configuration and enantiomeric ratio of chiral tryptophan (Trp) in water, mixed natural amino acids, and simulated blood plasma components, respectively. However, there are three unresolved problems: (1) although it has been confirmed that the ICD effect between **LNNU-1** and chiral Trp is due to three simultaneous noncovalent interactions (metal coordination, hydrogen bonding and $\pi\cdots\pi$ interactions) in aqueous solution (Fig. S1†), it is necessary to further explore the effect of these noncovalent interactions on the generation and amplification of ICD signals; (2) **LNNU-1** was unable to determine the concentration of chiral Trp in water or mixed chiral amino acids when using the CD titration method; (3) **LNNU-1** was not capable of quantifying the enantiomeric composition of other chiral compounds by noncovalent ICD sensing. Among the above problems, the study of the noncovalent ICD sensing mechanism is very pivotal. It may provide a strategy for the targeted design and synthesis of highly sensitive ICD sensors based on chiral MOFs. Highly sensitive ICD sensors have the potential to determine the concentration of chiral Trp in water or mixed chiral amino acids, and to analyze the enantiomeric composition of other chiral compounds. Previous work has demonstrated that the $\pi\cdots\pi$ interaction is an indispensable noncovalent interaction for the ICD sensing of chiral aromatic amino acids (L-/D-Trp).⁵¹ Herein, only metal coordination and hydrogen bonding interactions in this ICD sensing system should be further investigated. Our idea is to synthesize new chiral MOFs that should be isomorphic to **LNNU-1** but have other unsaturated or saturated metal centers. By observing the differences in the ICD signals between these MOFs and chiral Trp/chiral Trp derivatives, it is possible to determine the effects of metal coordination and hydrogen bonding interactions on the generation and amplification of ICD signals.

Thus, a series of monometallic and bimetallic-centered MOFs with the same crystal structure, namely $[\text{Cu}(\text{L})(2,2'\text{-bipy})]\cdot\text{H}_2\text{O}$ (**LNNU-2**), $[\text{Cd}(\text{L})(2,2'\text{-bipy})](\text{H}_2\text{O})$ (**LNNU-3**) and $[\text{Zn}_x\text{Cu}_y(\text{L})(2,2'\text{-bipy})]\cdot\text{H}_2\text{O}$ ($x:y = 9.6:0.4\text{--}1.0:9.0$) ($\text{H}_2\text{L} = \text{HOOCCH}_6\text{H}_4\text{CH}_2\text{PO}(\text{OH})(\text{OC}_2\text{H}_5)$, 2,2'-bipy = 2,2'-bipyridine),

have been successfully synthesized. It is found that the metal coordination interaction is critical and indispensable to this ICD sensing system. The strength of ICD signals increased with the enhancement of Lewis acidity in the metal center of the above MOFs. Subsequently, **LNNU-2** interacted with L-Trp and three L-Trp derivatives containing different active sites, resulting in different ICD effects. These results further confirmed that the metal coordination interaction played a decisive role in the generation of ICD signals, while the hydrogen bonding interaction only affected the amplification degree of the ICD signal. Compared with **LNNU-1**, **LNNU-2** has a higher sensitivity for ICD sensing of chiral Trp. It allows the highly selective and accurate determination of L-Trp concentration in water, mixed natural amino acids and simulated blood plasma components by the CD titration method. Moreover, **LNNU-2** achieves the accurate determination of the absolute configuration and ee values of two chiral aromatic amino alcohols in water without the involvement of any organic solvent. Inspired by the results of the noncovalent ICD sensing mechanism, we investigated the effects of different chiral amino acids as chiral inducers on the chiral induction synthesis of enantioenriched **LNNU-2**. Surprisingly, the enantioenriched (*P*)-**LNNU-2** and (*M*)-**LNNU-2** were successfully obtained using L-alanine (L-Ala) and D-alanine (D-Ala) as chiral inducers, respectively.

Results and discussion

Synthesis, characterization and stability

A new chiral MOF, $[\text{Cu}(\text{L})(2,2'\text{-bipy})]\cdot\text{H}_2\text{O}$ (**LNNU-2**), was successfully synthesized by selecting the copper^{II} (Cu^{II}) ion with stronger Lewis acidity to replace the zinc^{II} (Zn^{II}) ion of **LNNU-1**. **LNNU-2** was isomorphic to **LNNU-1**, and the crystal structure and characterization of **LNNU-2** are provided in the ESI (Tables S1 and S2 and Fig. S2†). In addition, a series of Zn^{II} and Cu^{II} ion co-doped bimetallic MOFs isomorphic to **LNNU-1**, $[\text{Zn}_x\text{Cu}_y(\text{L})(2,2'\text{-bipy})]\cdot\text{H}_2\text{O}$ ($x:y = 9.6:0.4\text{--}1.0:9.0$), were also successfully obtained. All the above products were block crystals, and the color of these crystals gradually deepened with the increase in the amount of Cu^{II} ions (Fig. 1a). The powder X-ray diffraction (PXRD) patterns and Fourier transform infrared (FT-IR) spectra showed that the above bimetallic MOFs have the same crystal structure as **LNNU-1** (Fig. 1b and c). Additionally, the actual molar ratios of $\text{Zn}^{\text{II}}/\text{Cu}^{\text{II}}$ ions in the bimetallic MOFs were detected using an inductively coupled plasma emission spectrometer (ICP). As shown in Table S3,† the content of Cu^{II} ions in the products of bimetallic MOFs increased with the increase of the amount of the raw material $\text{Cu}(\text{CH}_3\text{COO})_2\cdot\text{H}_2\text{O}$, while the content of Zn^{II} ions decreased with the decrease of the amount of raw material $\text{Zn}(\text{CH}_3\text{COO})_2\cdot 2\text{H}_2\text{O}$.

Subsequently, the stabilities of **LNNU-2** and a series of bimetallic MOFs were investigated. **LNNU-2** and bimetallic MOFs have similar thermal gravimetric (TG) curves, and thus, **LNNU-2** was used as a representative (Fig. S3a and b†). Thermal gravimetric and differential thermal analysis

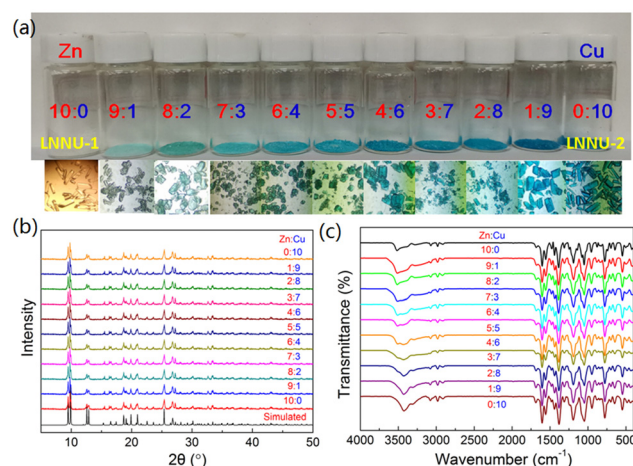


Fig. 1 (a) The images, (b) PXRD patterns and (c) FT-IR spectra of LNNU-1, LNNU-2 and the bimetallic MOFs.

(TG-DTA), PXRD patterns and FT-IR spectra of LNNU-2 showed that its framework structure could be stable up to 200 °C (Fig. S3a, c and d[†]). In addition, the PXRD patterns and FT-IR spectra of LNNU-2 after immersing in pure water and the aqueous solution of L-Trp (2.5×10^{-3} M) indicated that the framework structure of LNNU-2 remained stable (Fig. S4[†]). The above results indicated that LNNU-2 and a series of Zn^{II} and Cu^{II} ion co-doped bimetallic MOFs were successfully obtained, and they could be used to study the noncovalent ICD sensing mechanism.

The noncovalent ICD sensing mechanism

The suspensions of LNNU-1@L-Trp, LNNU-2@L-Trp and a series of bimetallic MOFs@L-Trp were analyzed by CD spectroscopy under identical conditions. As expected, the ICD signal intensities of the above suspensions increased with the increasing content of Cu^{II} ions in the MOFs, and the ICD signals were gradually red-shifted (Fig. 2a and Table S4[†]). In particular, the complete replacement of Zn^{II} ions with Cu^{II} ions caused a dramatic increase in the measured intensity. The crystal structures of the above MOFs were identical, and thus, the variation in the ICD signal could be mainly attributed to the different Lewis acidities of the metal centers in the MOFs. Since the Lewis acidity of the Cu^{II} ion was stronger than that of the Zn^{II} ion, it was more likely to interact with the nitrogen (N) atom of the amino group in Trp. This resulted in an amplification of the ICD signal. Then, if the coordination geometry of the metal center of the MOF is saturated, could it produce the ICD effect after interacting with chiral Trp? Inspired by the above idea, we tried to synthesize a new MOF with the saturated coordination mode of the metal center by replacing the Zn^{II} ion with the cadmium^{II} (Cd^{II}) ion having the same d¹⁰ electron configuration to self-assemble with H₂L and 2,2'-bipy. Fortunately, a new chiral MOF, [Cd(L)(2,2'-bipy)(H₂O)] (LNNU-3), was successfully synthesized. Single-crystal structural analysis indicated that a lattice water molecule (O1

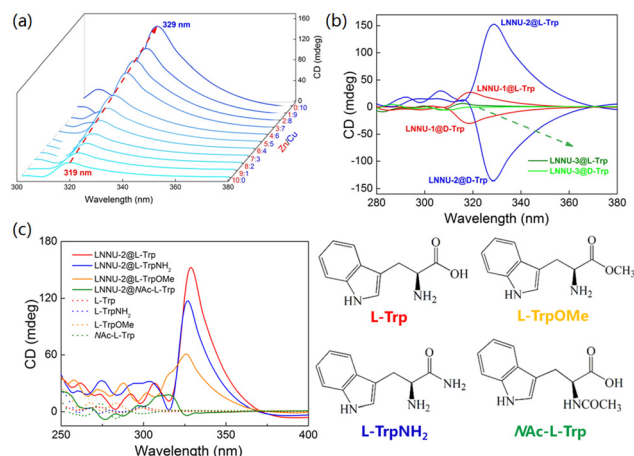


Fig. 2 (a) CD spectra of the suspensions of LNNU-1@L-Trp, LNNU-2@L-Trp and a series of bimetallic MOFs@L-Trp; (b) CD spectra of the suspensions of LNNU-1@D/L-Trp, LNNU-2@D/L-Trp and LNNU-3@D/L-Trp; (c) CD spectra of aqueous solutions of L-Trp and its derivatives, and the suspensions of LNNU-2@L-Trp, LNNU-2@L-TrpNH₂, LNNU-2@L-TrpOMe and LNNU-2@NAc-L-Trp.

W) in the crystal structure of LNNU-1 became a coordination water molecule (O6) in LNNU-3 (Fig. S5 and Tables S5, S6[†]). Thus, the metal center of LNNU-3 adopted a saturated coordination mode, while the framework of LNNU-3 was basically the same as that of LNNU-1. The chiral characterization and stability of LNNU-3 are provided in the ESI (Fig. S6[†]). Then, the suspensions of LNNU-1@D/L-Trp, LNNU-2@D/L-Trp and LNNU-3@D/L-Trp were analyzed by CD spectroscopy under the same conditions (Fig. 2b). The results showed that the suspensions of LNNU-3@D/L-Trp did not produce an ICD signal due to the absence of the unsaturated coordination metal center. In contrast, the suspensions of both LNNU-1@D/L-Trp and LNNU-2@D/L-Trp produced obvious enantiomeric ICD signals. The above results indicated that the metal coordination interaction was critical and indispensable in this sensing system. The strength of the ICD signal increased with the enhancement of the Lewis acidity of the metal center of the MOFs.

To further explore the effects of metal coordination and hydrogen bonding interactions on the generation and amplification of ICD signals, L-Trp and three L-Trp derivatives with different active sites were selected to interact with LNNU-2, respectively. As shown in Fig. 2c and Table S7,[†] the ICD signal intensity of the LNNU-2@analyte suspension followed the order LNNU-2@L-Trp > LNNU-2@L-TrpNH₂ > LNNU-2@L-TrpOMe > LNNU-2@NAc-L-Trp. This result showed that the ICD signal intensity of the LNNU-2@L-Trp suspension was the strongest, indicating that multiple noncovalent interactions facilitated the output and amplification of the ICD signal. L-TrpNH₂ could be regarded as a molecule formed by replacing the -COOH in L-Trp with -CONH₂. Although -CONH₂ could also participate in the formation of hydrogen bonding, the hydrogen bonding strength of N-H...O is weaker than that of O-H...O. Therefore, the ICD signal intensity of the LNNU-2@L-

TrpNH₂ suspension was slightly weaker than that of LNNU-2@L-Trp suspension. The main difference between L-TrpOMe and L-Trp was the substitution of –COOH by –COOCH₃, resulting in no hydrogen bonding interaction between L-TrpOMe and LNNU-2. Therefore, the ICD signal intensity of the LNNU-2@L-TrpOMe suspension was significantly weaker than that of LNNU-2@L-Trp and LNNU-2@L-TrpNH₂ suspensions. In contrast, when –NHCOCH₃ completely replaced –NH₂ in L-Trp, the metal coordination interaction disappeared in the sensing system, resulting in no ICD signal output in the LNNU-2@Nac-L-Trp suspension. The above results suggested that the metal coordination interaction played a decisive role in the generation of ICD signals, and the hydrogen bonding interaction only affected the amplification degree of the ICD signal.

Determination of L-Trp concentration

L-Trp is an essential amino acid that is very important for humans and animals, and its imbalance or deficiency may lead to several chronic diseases.^{52,53} Although LNNU-1 exhibited good enantioselective sensing of chiral Trp at a millimolar analytical concentration in the previous research,⁵¹ it was unable to detect the concentration of L-Trp based on the ICD response (Fig. S7†). As demonstrated in Fig. 2b and Table S4,† the ICD signal intensity of the LNNU-2@L-Trp suspension was about 5.8 times higher than that of the LNNU-1@L-Trp suspension. Therefore, LNNU-2 should have a higher sensitivity for ICD sensing of L-Trp. This result provided a possibility for achieving the accurate determination of L-Trp concentration in water using the CD titration method.

Subsequently, the CD spectra of the LNNU-2 suspension (2.0 mg LNNU-2 in 2.0 mL deionized water after treating by ultrasonication for 20 minutes) were measured *in situ* after incremental addition of freshly prepared L-Trp solution (2.5×10^{-3} M). After each addition, the CD spectrum of the suspension was monitored. As demonstrated in Fig. 3a, the intensity of the ICD signal appearing at 325 nm gradually increased with the increase of L-Trp concentration. The linear regression equation was derived from the calibration curve, ICD (mdeg) = 0.13218[C] (μM) – 0.18606 ($R^2 = 0.9990$), which was established based on the plot of the average value of the ICD signal intensities (325 nm) *versus* L-Trp concentrations in the range from 0 to 4.339×10^{-4} M (Fig. 3b). According to the limit of detection (LOD) equation⁵⁴ $LOD = 3\sigma/S$ (σ is the standard deviation of 10 blank measurements, and S is the slope between ICD signal intensity *versus* L-Trp concentration), the LOD was obtained as 2.00×10^{-5} M. A good linear relationship provided a chance to efficiently and accurately detect the concentration of L-Trp, as demonstrated by the quantitative detection results of L-Trp concentration discussed below.

Using LNNU-2 as an ICD sensor, 10 samples with different concentrations of L-Trp aqueous solutions were detected by CD spectroscopy in the range of 7.50×10^{-5} to 5.00×10^{-4} M, and the intensities of the ICD signals at 325 nm were recorded (Fig. S8 and Table S8†). By substituting the ICD signal intensity into the linear equation $ICD \text{ (mdeg)} = 0.13218[C] \text{ (}\mu\text{M)} -$

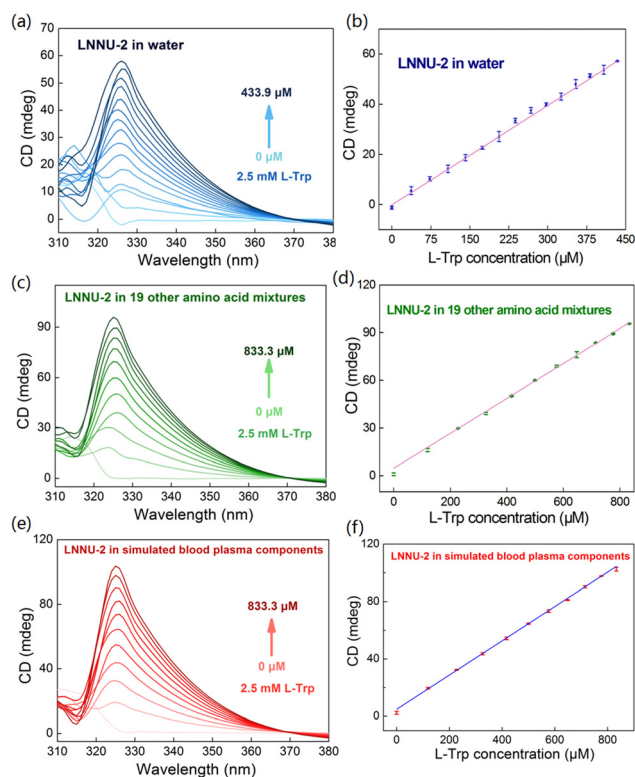


Fig. 3 CD spectra of LNNU-2 dispersed in water (a), the mixed aqueous solution of 19 other natural amino acids (c) and the simulated blood plasma components (e) upon incremental addition of the L-Trp aqueous solution (2.5×10^{-3} M); the linear relationship between ICD intensities at 325 nm and the concentrations of L-Trp in water (b), the mixed aqueous solution of 19 other natural amino acids (d) and the simulated blood plasma components (f).

0.18606, the calculated L-Trp concentration was the detected concentration, which was very close to the actual concentration of the sample. As shown in Table S8,† the actual concentration of the L-Trp sample was 2.78×10^{-4} M (entry 6), while the detected concentration was 2.79×10^{-4} M. Even for the L-Trp sample with a low concentration, it showed good detection results, that is, the actual concentration in the L-Trp aqueous solution was 7.50×10^{-5} M (entry 1), and the detected concentration was 7.83×10^{-5} M. The average relative error between the detected and actual concentrations of 10 L-Trp aqueous solution samples was only 2.6%, indicating that LNNU-2 could accurately and rapidly detect the concentration of L-Trp in water using the CD titration method.

The detection of the concentration of an individual chiral amino acid in a mixture of other chiral amino acids is challenging by using chiral optical sensing techniques due to the similar properties of chiral amino acid molecules. Since LNNU-2 had high sensitivity for the ICD sensing of L-Trp in water, we tried to determine the concentration of L-Trp in a mixed aqueous solution of 19 other natural amino acids. First, we assessed the selectivity of LNNU-2 toward natural amino acids. As illustrated in Fig. S9,† the CD spectrum of the LNNU-2@L-Trp suspension showed a strong ICD signal at

329 nm, while the CD spectra of pure aqueous solutions of all natural amino acids and the suspensions of **LNNU-2**@other natural amino acids exhibited no ICD signals. This result indicated that **LNNU-2** had a high selectivity for the ICD sensing of *L*-Trp in the presence of other natural amino acids and without interference from the co-existing species. Subsequently, using the same method as the above, a standard curve was established in the *L*-Trp concentration range from 0 to 8.333×10^{-4} M (Fig. 3c and d), and the linear equation was derived from the standard curve as $\text{ICD (mdeg)} = 0.1097[\text{C}] (\mu\text{M}) + 4.80784$ ($R^2 = 0.9996$). The LOD of *L*-Trp was calculated to be 2.28×10^{-5} M. The effectiveness of the *L*-Trp concentration analyses was demonstrated by analyzing 10 *L*-Trp samples at varying concentrations in the presence of 19 other natural amino acids (Table S8 and Fig. S10†). As shown in Table S8,† the actual concentrations of the *L*-Trp samples were 2.58×10^{-4} M (entry 1), 3.54×10^{-4} M (entry 3), 5.54×10^{-4} M (entry 8) and 6.82×10^{-4} M (entry 10), and the detected concentrations were 2.54×10^{-4} M, 3.55×10^{-4} M, 5.53×10^{-4} M and 6.80×10^{-4} M, respectively. The average value of the relative error between the detected and actual concentrations of the 10 samples was only 0.7%. The above results indicated that **LNNU-2** could be used as a highly selective ICD sensor for the accurate determination of *L*-Trp concentration in the presence of other natural amino acids.

Trp is the only amino acid that binds to plasma albumin and exists in a balance between albumin-bound and free forms in the peripheral circulation.⁵³ Therefore, it is of biological significance to detect the concentration of free *L*-Trp in blood plasma components. Fortunately, using **LNNU-2** as an ICD sensor, the determination of *L*-Trp concentration in simulated blood plasma components showed the same accuracy and high selectivity. A standard curve was established using the above same method, and the linear equation $\text{ICD (mdeg)} = 0.11957[\text{C}] (\mu\text{M}) + 4.83409$ ($R^2 = 0.9996$) was obtained (Fig. 3e and f). In addition, the LOD was calculated to be 1.97×10^{-5} M. Based on the measurement and analysis of 10 *L*-Trp samples at varying concentrations, it was concluded that the **LNNU-2** sensor could also be used to accurately determine the *L*-Trp concentration in simulated blood plasma components (Table S8 and Fig. S11†). For instance, the actual concentrations of three *L*-Trp samples were 1.85×10^{-4} M (entry 2), 6.06×10^{-4} M (entry 7) and 8.05×10^{-4} M (entry 10), and the detected concentrations were 1.85×10^{-4} M, 6.07×10^{-4} M and 8.06×10^{-4} M, respectively. The average relative error was only 0.8%. This result indicated that **LNNU-2** could accurately and efficiently determine the concentration of *L*-Trp in simulated blood plasma components without any interference from other coexisting species.

The recyclability of sensing materials is important for assessing their practicality. Therefore, the recycling performance of **LNNU-2** in water, mixed natural amino acids and simulated blood plasma components was investigated (Fig. S12a–c†). After performing the sensing experiments of **LNNU-2**, the suspensions of **LNNU-2**@*L*-Trp were centrifuged and washed with water several times, and then the ICD signal of the above sus-

pensions disappeared. Subsequently, an aqueous solution of *L*-Trp was added to the recycled samples. The results showed that the ICD signals of **LNNU-2**@*L*-Trp suspensions can be recovered and regenerated. After five continuous cycles, the ICD signal intensities of **LNNU-2**@*L*-Trp suspensions were basically the same as those of the initial suspensions. Meanwhile, the PXRD patterns of the recycled **LNNU-2** samples revealed that their crystal structure was intact after five cycles (Fig. S12d†). The experimental results indicated that **LNNU-2** has excellent recyclability.

Quantitative enantioselective sensing of chiral Trp

Using the CD titration method, **LNNU-2** achieved the accurate determination of *L*-Trp concentration at a submillimolar concentration. Compared to **LNNU-1**, **LNNU-2** was expected to serve as an ICD sensor for determining the absolute configuration and ee value of the chiral Trp sample at a lower concentration. As demonstrated in Fig. S13a,† a calibration curve was constructed using samples containing Trp (2.5×10^{-4} M) at varying ee values (+100, +80, +60, +40, +20, 0, −20, −40, −60, −80 and −100%). Notably, a good linear relationship between the average value of the ICD signal intensities (325 nm) and the ee values of Trp samples was observed at submillimolar concentrations. The linear regression equation was calculated from the calibration curve, $\text{ICD (mdeg)} = 0.32289 \text{ ee (\%)} + 1.8991$ ($R^2 = 0.9992$). Thus, the ICD signal intensity at 325 nm could be used for the determination of the ee values of chiral Trp samples. In addition, the absolute configuration of the sample could be correctly assigned based on the direction of the ICD signal. The validity of the ICD sensing assay was demonstrated by analyzing 10 Trp samples at varying enantiomeric compositions in water (Table 1 and Fig. S13b†). For instance, sensing a mixture containing Trp with an ee value of 96% (entry 1) gave an exact ee value of 95.9%, and it was also able to determine the enantiomeric ratio of the sample at the same time (Table 1). By comparing the reference spectra (Fig. 2b), the absolute configuration of the major enantiomer was determined to be the L configuration. Notably, the absolute configurations of the major enantiomers of the 10 Trp samples were correctly assigned, and the average absolute error between the detected and the actual ee value was only 0.9%.

Quantitative enantioselective sensing of chiral aromatic amino alcohols

The ICD sensing mechanism indicated that if the functional sites of **LNNU-2** highly matched with the active sites of the chiral analyte, multiple noncovalent interactions might be generated between **LNNU-2** and the chiral analyte. Then, the noncovalent interactions might result in the emergence of a strong ICD response, which could achieve the determination of the absolute configuration and ee value of the chiral analyte. Inspired by this work, two chiral aromatic amino alcohols, namely, 2-phenylglycinol (**1**) and (−)-*cis*-1-amino-2-indanol (**2**), were selected for the noncovalent ICD sensing study (Fig. 4a and b).

Table 1 Assignment of the absolute configuration and analysis of the enantiomeric composition of 10 Trp samples (2.5×10^{-4} M) in water

Sample composition				Sensing results			
Entry	Abs. config.	%ee	Ratio L/D	Abs. config. ^a	%ee ^b	Ratio L/D ^b	%ee absolute error
1	L	96.0	98.0 : 2.0	L	95.9	97.9 : 2.1	0.1
2	D	−96.0	2.0 : 98.0	D	−95.5	2.2 : 97.8	0.5
3	L	90.0	95.0 : 5.0	L	88.5	94.3 : 5.7	1.5
4	D	−55.0	22.5 : 77.5	D	−55.1	22.4 : 77.6	0.1
5	L	80.0	90.0 : 10.0	L	81.1	90.6 : 9.4	1.1
6	D	−40.0	30.0 : 70.0	D	−40.9	29.5 : 70.5	0.9
7	L	70.0	85.0 : 15.0	L	68.8	84.4 : 15.6	1.2
8	D	−30.0	35.0 : 65.0	D	−29.0	35.5 : 64.5	1.0
9	L	50.0	75.0 : 25.0	L	50.6	75.3 : 24.7	0.6
10	D	−20.0	40.0 : 60.0	D	−18.5	40.7 : 59.3	1.5

^a By comparison of the sign of the ICD with the reference spectra (Fig. 2b). ^b Based on ICD signal intensities at 325 nm.

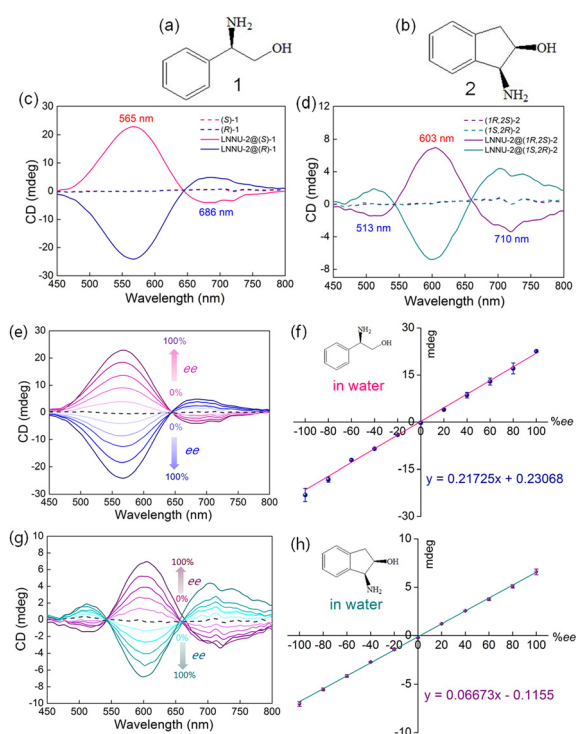


Fig. 4 Molecular structures of (a) 2-phenylglycinol (**1**) and (b) (−)-*cis*-1-amino-2-indanol (**2**); (c) CD spectra of LNNU-2@(*S*)-**1**/(*R*)-**1** suspensions and the pure aqueous solutions of (*S*)-**1** and (*R*)-**1**; (d) CD spectra of LNNU-2@(*1R,2S*)-**2**/(*1S,2R*)-**2** suspensions and the pure aqueous solutions of (*1R,2S*)-**2** and (*1S,2R*)-**2**; (e) CD spectra of LNNU-2 interacting with samples of **1** at varying enantiomeric compositions and (f) plot of the ICD signal intensities at 565 nm versus ee values of samples of **1** in water; (g) CD spectra of LNNU-2 interacting with samples of **2** at varying enantiomeric compositions and (h) plot of the ICD signal intensities at 603 nm versus ee values of samples of **2** in water.

LNNU-2 (2.0 mg) was dispersed in an aqueous solution (3.0 mL, 3.0×10^{-3} M) of each of the two chiral aromatic amino alcohol enantiomers and sonicated for 20 minutes before CD analysis. As expected, the ICD signals were detected

between LNNU-2 and two chiral aromatic amino alcohols, respectively. The CD spectrum of LNNU-2@(*S*)-**1** exhibited a strong positive ICD signal centered at 565 nm and a weak negative ICD signal at 686 nm, while the spectrum of LNNU-2@(*R*)-**1** exhibited opposite ICD signals (Fig. 4c). As demonstrated in Fig. 4d, the CD spectrum of LNNU-2@(*1R,2S*)-**2** showed a strong positive ICD signal at 603 nm and two weak negative ICD signals at 513 nm and 710 nm, respectively. As expected, the opposite ICD signals were observed in the spectrum of LNNU-2@(*1S,2R*)-**2**. Since multiple ICD signals were generated during the ICD sensing process, the strongest ICD signal was selected for the determination of the absolute configuration and ee value of the chiral aromatic amino alcohol sample. Thus, a calibration curve was established based on the plot of the average value of the ICD signal intensities (565 nm) versus ee values of samples of **1**, and then the linear regression equation, ICD (mdeg) = 0.21725 ee (%) + 0.23068 ($R^2 = 0.9978$) (Fig. 4e and f), was derived. Similarly, the linear regression equation ICD (mdeg) = 0.06673 ee (%) − 0.1155 ($R^2 = 0.9993$) was derived from the calibration curve based on the plot of the average value of the ICD signal intensities (603 nm) versus ee values of samples of **2** (Fig. 4g and h).

Based on the good linear relationship, the absolute configuration and ee analyses of the practical sample were further performed simultaneously using the LNNU-2 sensor. Six samples of **1** and **2** with different enantiomeric compositions were prepared in pure water, respectively. The absolute configuration was determined using the sign of the Cotton effect, and the ICD signal intensities at 565 nm for **1** and 603 nm for **2** were used to quantify ee values. As shown in Table 2 and Fig. S14,† the absolute configurations of the major enantiomers of the above samples could be correctly assigned, and the ee values were also accurately established. The average absolute error between the detected and the actual ee values of the six samples of both **1** and **2** was 1.2%. The results indicated that LNNU-2 could be used as an ICD sensor for the rapid and accurate quantification of the enantiomeric compositions of two chiral aromatic amino alcohols in water without the involvement of any organic solvent.

Table 2 Assignment of the absolute configuration and analysis of the enantiomeric composition of 2-phenylglycinol (**1**) and (–)-*cis*-1-amino-2-indanol (**2**) samples in pure water

Sample 1 composition				Sensing results			
Entry	Abs. config.	%ee	Ratio <i>R/S</i>	Abs. config. ^a	%ee ^b	Ratio <i>R/S</i> ^b	%ee absolute error
1	<i>R</i>	–88.0	94.0 : 6.0	<i>R</i>	–88.9	94.5 : 5.5	0.9
2	<i>S</i>	85.0	7.5 : 92.5	<i>S</i>	83.6	8.2 : 91.8	1.4
3	<i>R</i>	–48.0	74.0 : 26.0	<i>R</i>	–47.4	73.7 : 26.3	0.6
4	<i>S</i>	60.0	20.0 : 80.0	<i>S</i>	61.7	19.1 : 80.9	1.7
5	<i>R</i>	–32.0	66.0 : 34.0	<i>R</i>	–32.9	66.5 : 33.5	0.9
6	<i>S</i>	48.0	26.0 : 74.0	<i>S</i>	46.2	26.9 : 73.1	1.8

Sample 2 composition				Sensing results			
Entry	Abs. config.	%ee	Ratio 1 <i>R</i> ,2 <i>S</i> /1 <i>S</i> ,2 <i>R</i>	Abs. config. ^a	%ee ^b	Ratio 1 <i>R</i> ,2 <i>S</i> /1 <i>S</i> ,2 <i>R</i> ^b	%ee absolute error
1	1 <i>R</i> ,2 <i>S</i>	90.0	95.0 : 5.0	1 <i>R</i> ,2 <i>S</i>	88.2	94.1 : 5.9	1.8
2	1 <i>S</i> ,2 <i>R</i>	–92.0	4.0 : 96.0	1 <i>S</i> ,2 <i>R</i>	–91.5	4.2 : 95.8	0.5
3	1 <i>R</i> ,2 <i>S</i>	49.0	74.5 : 25.5	1 <i>R</i> ,2 <i>S</i>	47.4	73.7 : 26.3	1.6
4	1 <i>S</i> ,2 <i>R</i>	–66.0	17.0 : 83.0	1 <i>S</i> ,2 <i>R</i>	–64.7	17.6 : 82.4	1.3
5	1 <i>R</i> ,2 <i>S</i>	28.0	64.0 : 36.0	1 <i>R</i> ,2 <i>S</i>	27.4	63.7 : 36.3	0.6
6	1 <i>S</i> ,2 <i>R</i>	–40.0	30.0 : 70.0	1 <i>S</i> ,2 <i>R</i>	–38.4	30.8 : 69.2	1.6

^a By comparison of the sign of the ICD with the reference spectra (Fig. 4c and d). ^b Based on ICD signal intensities at 565 nm for **1** and 603 nm for **2**.

Chiral induction synthesis of enantioenriched LNNU-2

Single-crystal structural analysis revealed that LNNU-2 crystallized in a chiral space group of $P2_12_12_1$ with a Flack absolute configuration parameter of 0.029(4), indicating the enantiomeric purity of the single crystal (Table S1†).⁵⁵ Although the phosphonic acid ligand (H_2L) had a chiral phosphorus (P) center, the raw material used to synthesize H_2L was achiral, resulting in H_2L becoming a racemate. Therefore, the chirality of bulk samples of LNNU-2 should be random. To determine the chiral purity of LNNU-2, 20 single-crystal samples were randomly picked from the same batch and their solid-state CD spectra were recorded. Each single-crystal sample was found to be CD active, and 13 of them were in the *M*-configuration and 7 in the *P*-configuration (Fig. S15†). Apparently, two enantiomers (*M* and *P*) were present in the bulk LNNU-2 samples with a slight excess of the *M*-configuration.

Although many chiral MOFs with novel structures and excellent properties have been successfully obtained, the synthesis of homochiral or enantioenriched MOFs remains a challenge.

Chiral induction is an effective method for the synthesis of homochiral or enantioenriched MOFs, and the appropriate interactions between chiral inducers and achiral building blocks are very important for chiral induction synthesis.⁵⁶ Inspired by the results of the noncovalent ICD sensing mechanism, chiral Trp could be a candidate for chiral induction due to the existence of multiple noncovalent interactions between LNNU-2 and chiral Trp. Therefore, we attempted to split two enantiomers of LNNU-2 to obtain enantioenriched (*P*)-LNNU-2 and (*M*)-LNNU-2 using L-Trp and D-Trp as chiral inducers, respectively. The synthesis of enantioenriched LNNU-2 was carried out by replacing deionized water with an aqueous solu-

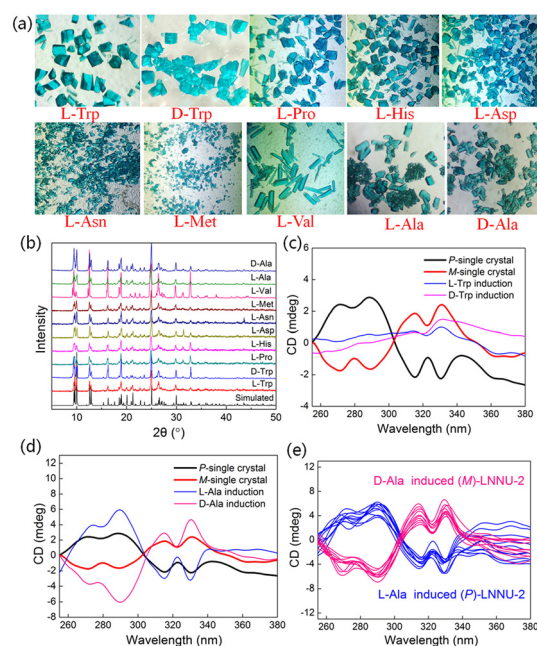


Fig. 5 (a) Images and (b) PXRD patterns of LNNU-2 products induced by chiral amino acids; (c) solid-state CD spectra of LNNU-2 products induced by L-Trp and D-Trp; (d) solid-state CD spectra of LNNU-2 products induced by L-Ala and D-Ala; (e) solid-state CD spectra of 10 randomly selected samples induced by L-Ala/D-Ala from the same batch.

tion of L-Trp (or D-Trp) at a concentration of 2.5×10^{-3} M, while the other original synthesis conditions of LNNU-2 remained unchanged. As a result, blue block crystals were obtained, and the PXRD patterns of products showed that they had the same framework structure as LNNU-2 (Fig. 5a and b).

However, solid-state CD spectra of the products showed that they had no CD activity either induced with L-Trp or D-Trp (Fig. 5c). This result indicated that the strong noncovalent interactions between LNNU-2 and chiral Trp were not favorable for the synthesis of enantioenriched LNNU-2. Therefore, using the same synthesis method, other different types of chiral amino acids were selected as chiral inducers for the chiral induction synthesis of LNNU-2 (Table S9†).

As shown in Fig. 5a, the LNNU-2 products induced by chiral amino acids were all blue block crystals, and the PXRD patterns of products confirmed that their framework structures were the same as that of LNNU-2 (Fig. 5b). Solid-state CD spectra showed that LNNU-2 bulk samples induced by L-proline (L-Pro), L-histidine (L-His) and L-aspartate (L-Asn) had Cotton effects similar to that of the single-crystal sample of (M)-LNNU-2 (Fig. S16a†). The only difference was that all CD spectra of these products had an additional positive CD signal near 260 nm. This suggested that the above products might not be enantioenriched but enantiomeric excess ($M > P$). In contrast, when L-aspartic acid (L-Asp), L-methionine (L-Met) and L-valine (L-Val) were selected as chiral inducers, the solid-state CD spectra of bulk samples of the products showed no CD activity, indicating that they were all racemates (Fig. S16b†). Surprisingly, the solid-state CD spectra of the products induced by L-Ala exhibited a Cotton effect opposite to that of the single-crystal sample of (M)-LNNU-2, suggesting the successful synthesis of (P)-LNNU-2 samples (Fig. 5d). Meanwhile, single-crystal structural analysis of the products revealed the presence of P-helical chains in the crystal structure, which had mirror symmetry with the M-configuration (Fig. S17†). A Flack parameter of 0.025(4) further verified that the P-configuration was determined correctly (Table S10†).⁵⁵ To determine the chiral purity of bulk samples of the products induced by L-Ala, the solid-state CD spectra of 10 bulk samples randomly picked from the same batch were measured (Fig. 5e). The results showed the same Cotton effects as that of the single-crystal sample of (P)-LNNU-2. The above results indicated that the enantioenriched (P)-LNNU-2 samples were successfully synthesized using L-Ala as a chiral inducer. Similarly, the enantioenriched (M)-LNNU-2 samples were also successfully obtained upon chiral induction of D-Ala. The solid-state CD spectra of 10 bulk samples randomly picked from the same batch had the same Cotton effect as that of the single-crystal sample with the M-configuration (Fig. 5e). Furthermore, two parallel syntheses of LNNU-2 were carried out using L-Ala and D-Ala as the chiral inducers, respectively. The solid-state CD spectra of 5 bulk samples randomly picked from each synthesis were the same as before (Fig. S18†). The results of crystal structure analyses and solid-state CD spectra demonstrated that two enantiomers of LNNU-2, (P)-[Cu(L)(2,2'-bipy)]·H₂O ((P)-LNNU-2) and (M)-[Cu(L)(2,2'-bipy)]·H₂O ((M)-LNNU-2), were successfully obtained by chiral induction, and L-Ala and D-Ala were suitable chiral inducers for the synthesis of enantioenriched LNNU-2 samples.

The above results suggested that using different chiral amino acids as chiral inducers resulted in products with the

same framework structure but different chiral features. Apparently, different amino acid inducers have different chiral induction effects on the synthesis of LNNU-2. It was found that the strong noncovalent interactions between LNNU-2 and chiral Trp reduced the degree of enantiomeric excess of LNNU-2, and the products changed from a slight enantiomeric excess to racemic. This suggested that too strong interactions between chiral inducers and building blocks were not conducive to the formation of enantioenriched products. Among the different types of chiral amino acids used as chiral inducers, only chiral Ala induced the enantioenriched LNNU-2. Compared with other chiral amino acids, chiral Ala is the simplest chiral amino acid in terms of the molecular structure and low positional resistance (Table S9†). Compared with chiral Trp, the molecular structure of chiral Ala lacked an aromatic group, so there was no $\pi \cdots \pi$ interaction between chiral Ala and LNNU-2. This weakened the degree of noncovalent interactions between the chiral inducer and the building blocks of LNNU-2. Instead, it is more favorable to generate the enantioenriched LNNU-2 in chiral induction synthesis. It could be seen that the rational control of the degree of noncovalent interactions between chiral inducers and framework building blocks might have a significant effect on the generation of enantioenriched products. Although we could not explain exactly why the enantioenriched LNNU-2 was successfully obtained upon chiral induction of L-Ala and D-Ala, the above-mentioned studies could provide ideas for screening suitable chiral inducers for the synthesis or splitting of chiral MOFs.

Conclusions

In summary, two new chiral MOFs, namely [Cu(L)(2,2'-bipy)]·H₂O (LNNU-2) and [Cd(L)(2,2'-bipy)(H₂O)] (LNNU-3), and a series of bimetallic MOFs, [Zn_xCu_y(L)(2,2'-bipy)]·H₂O ($x:y = 9.6:0.4-1.0:9.0$), were successfully designed and synthesized for the study of the noncovalent ICD sensing mechanism. By observing the differences in ICD signals between the above MOFs and L-Trp or between LNNU-2 and L-Trp and its derivatives, the effects of noncovalent interactions on the generation and amplification of ICD signals were investigated. The results indicated that multiple noncovalent interactions facilitated the output and amplification of the ICD signal. In this ICD sensing system, the metal coordination interaction played a decisive role in the generation of ICD signals, while the hydrogen bonding interaction only affected the amplification degree of the ICD signal. The strength of the ICD signal increased with the enhancement of the Lewis acidity of the metal center of the MOFs. Thus, LNNU-2 showed improved ICD sensing performance compared to the previously reported LNNU-1 sensor. LNNU-2 allowed the quantification of the enantiomeric composition of the chiral Trp sample at a lower concentration. More importantly, the amplified ICD signal of the LNNU-2@L-Trp suspension enabled highly selective and accurate determination of L-Trp concentration in water, mixed natural amino

acids and simulated blood plasma components, respectively. Based on the noncovalent ICD sensing mechanism, **LNNU-2** also achieved rapid and accurate determination of the absolute configuration and ee values of the chiral aromatic amino alcohols in pure water. In addition, different chiral amino acids were selected as chiral inducers for the chiral induction synthesis of enantioenriched **LNNU-2**. Remarkably, **LNNU-2** was successfully split into enantioenriched (*P*)-**LNNU-2** and (*M*)-**LNNU-2** upon chiral induction of *L*-Ala and *D*-Ala. This work provides new ideas for the rational design of MOF-based non-covalent ICD sensors and the screening of suitable chiral inducers for chiral induction synthesis.

Author contributions

Z. S. and C. J. conceived the concept and directed the project. Y. Z. designed the study, conducted most of the experiments, wrote the original draft and revised the manuscript. T. D. performed the experiments. X. Z., Y. Z., J. Y. and X. L. collected and analyzed the data. H. Z., C. J. and Z. S. modified the manuscript.

Conflicts of interest

There are no conflicts to declare.

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