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Determination of the absolute configuration and identity of chiral carboxylic acids using a Cu(II) complex of pyridine–benzimidazole-based ligand

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ABSTRACT

We report a new achiral Cu host [Cu(bmb–bpy)(H_2O)($OTf)_2$] (bmb–bpy = 6,6′-bis[((1-methylbenzimidazol-2-yl)thio)methyl]-2,2′-bipyridine) for the enantioselective and chemoselective recognition of chiral carboxylic acids. The binding of chiral carboxylic acids to [Cu(bmb–bpy)(H_2O)($OTf)_2$] produced an exciton-coupled circular dichroism signal; the linear discriminant analysis allowed the assignment of the absolute configuration, enantiomeric excess, and identity of chiral carboxylic acids.

In drug development and natural product synthesis, chiral carboxylic acids are important intermediates. The development of a time-efficient and cost-effective stereoselective assay is essential for the assignment of enantiomeric purity of chiral carboxylic acids.[1] High-throughput screening (HTS) has been used for the drug discovery in pharmaceutical industry[2] and the discovery of efficient catalysts for asymmetric reactions.[3] Most commonly, HTS is performed by high-performance liquid chromatography (HPLC) or gas chromatography (GC).[4] However, HPLC or GC is not an optimal method for HTS because of the low-efficiency and time-consuming requirements when a large number of samples are analyzed. The exciton-coupled circular dichroism (ECCD) is a valuable tool for determining the absolute configurations of chiral compounds.[5] Recently, ECCD signals were used along with the linear discriminant analysis (LDA), allowing both enantioselective and chemoselective recognition, to determine the absolute configuration and identity of chiral molecules.[6] In this method, the host molecules should contain two chromophores and a chiral recognition site for the guest molecules. Herein, we report the Cu(II) complex of a pyridine–benzimidazole-based ligand containing two benzimidazole units as chromophores and a vacant coordination site on the Cu(II) and its application for the determination of the absolute configuration and identity of chiral carboxylic acids.

The synthesis of the ligand, 6,6′-bis[((1-methylbenzimidazol-2-yl)thio)methyl]-2,2′-bipyridine (bmb–bpy), was achieved by the coupling of 6,6′-bis(bromomethyl)-2,2′-bipyridine **2** with 2-benzimidazolethiol **3** in the presence of potassium hydroxide in toluene to afford thioether **4**, followed by the methylation of **4** with methyl iodide and anhydrous potassium carbonate in acetonitrile to afford bmb–bpy (Scheme 1). Starting material **2**, which is one of the widely used materials for the fabrication of bipyridine-based supramolecular architecture, was prepared by the bromination of 6,6′-dimethyl-2,2′-bipyridine **1** under heating or irradiation conditions.[7] However, the reaction yields were moderate and the purification was difficult because of the uncontrollable formation of brominated by-products. In this study, we improved this reaction procedure using a dichloromethane (CH_2Cl_2)/water mixture as the solvent and irradiation under a 150-W halogen lamp. The use of water/organic solvent mixtures in photobromination has been reported for different pyridines.[8]

The Cu(II) complex, Cu(bmb–bpy)(H_2O)($OTf)_2$, was prepared by the reaction of Cu(II) trifluoromethanesulfonate ($Cu(OTf)_2$) with bmb–bpy in an equimolar ratio (Scheme 2). The crystal structure showed that bmb–bpy acted as a tetradentate ligand, coordinating through the nitrogen atom of the bipyridine group and two benzimidazoles (Fig. 1).[9] Notably, bmb–bpy ligand was helically twisted, which is a preferable feature for the ECCD procedure; in addition, one water molecule existed at the vacant coordination site on the Cu(II), which is expected to behave as a recognition site for the target chiral molecules. The UV–visible spectra for the

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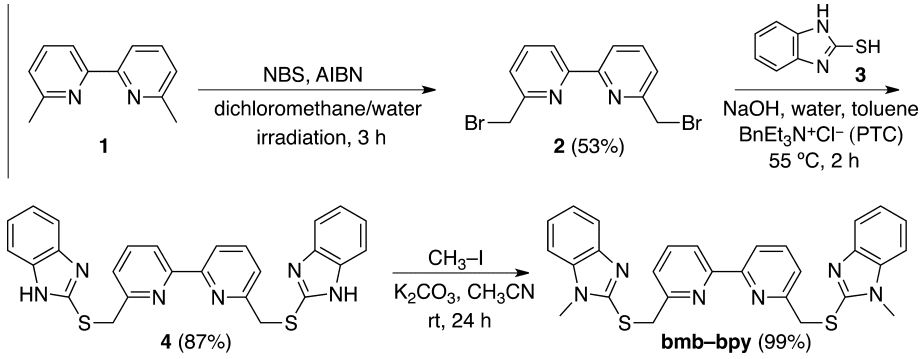
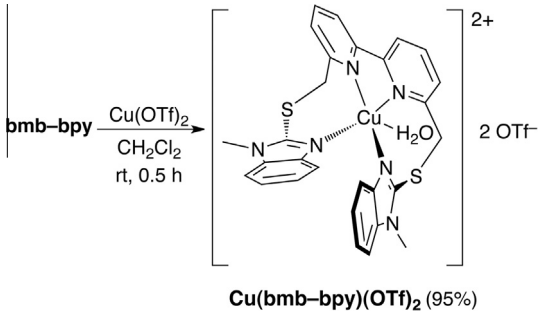


Scheme 1. Synthesis of 6,6′-bis[((1-methylbenzimidazol-2-yl)thio)methyl]-2,2′- bipyridine (bmb–bpy).



Scheme 2. Synthesis of Cu(bmb–bpy)(H_2O)($OTf)_2$.

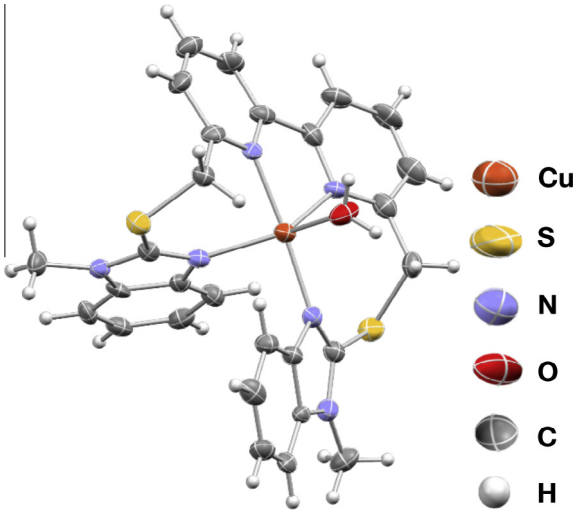


Figure 1. ORTEP drawing of Cu(bmb–bpy)(H_2O)($OTf)_2$ (50% probability). The triflate and solvent molecules are omitted for clarity.

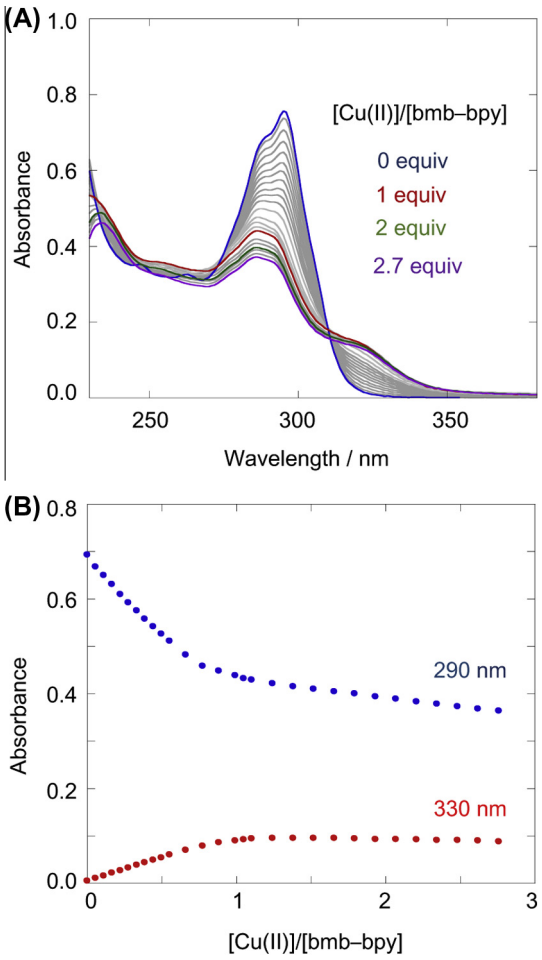


Figure 2. UV–visible absorption spectra: (A) Titration was carried out by adding $Cu(OTf)_2$ [1.0×10^{-4} M in CH_2Cl_2/CH_3CN = 1/1] to bmb–bpy [1.8×10^{-6} M in CH_2Cl_2]. (B) Determination of the stoichiometry of the complexation of Cu(II) to bmb–bpy using the molar ratio method.

titration of bmb–bpy with Cu(II) in CH_2Cl_2 showed that on adding Cu(II) ion, the absorbance intensity of the band at λ_{max} = 290 nm decreased, whereas that at λ_{max} = 330 nm increased, and an isosbestic point occurred at 310 nm (Fig. 2A). The titration curve for this system reveals that the stoichiometry is also 1:1 (Fig. 2B).

Four chiral carboxylic acids were used: 2-phenylbutyric acid (PBA), 2-phenylpropionic acid (PPA), 2-bromopropionic acid (BPA), and *N*-boc-2-piperidinecarboxylic acid (PCA), as reported in the literature for investigating the chiral recognition using the ECCD spectra and LDA plot (Fig. 3).[6a] These chiral carboxylic acids do not absorb above 230 nm. The association study of Cu(bmb–bpy)(H_2O)($OTf)_2$ with PBA was carried out in CH_2Cl_2 and 0.02 wt % CH_3OH, and all the circular dichroism (CD) spectra were measured at −10 °C owing to their low intensity at room temperature (see the Supplementary data, General Procedure, Fig. S15). The CD analysis results are shown in Figure 4. The achiral host [Cu(bmb–bpy)(H_2O)($OTf)_2$] itself displayed no signal in the CD spectra. The binding of (*R*)-PBA to the achiral host produced an ECCD signal that showed the positive first Cotton effect and negative second Cotton effect at the wavelength range of 300–360 nm and 260–300 nm, respectively (Fig. 4A). These results may be

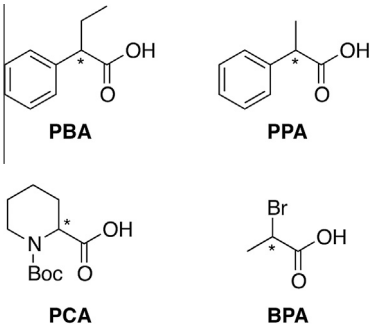


Figure 3. Chiral guest: 2-phenylbutyric acid (PBA), 2-phenylpropionic acid (PPA), *N*-boc-2-piperidinecarboxylic acid (PCA), and 2-bromopropionic acid (BPA).

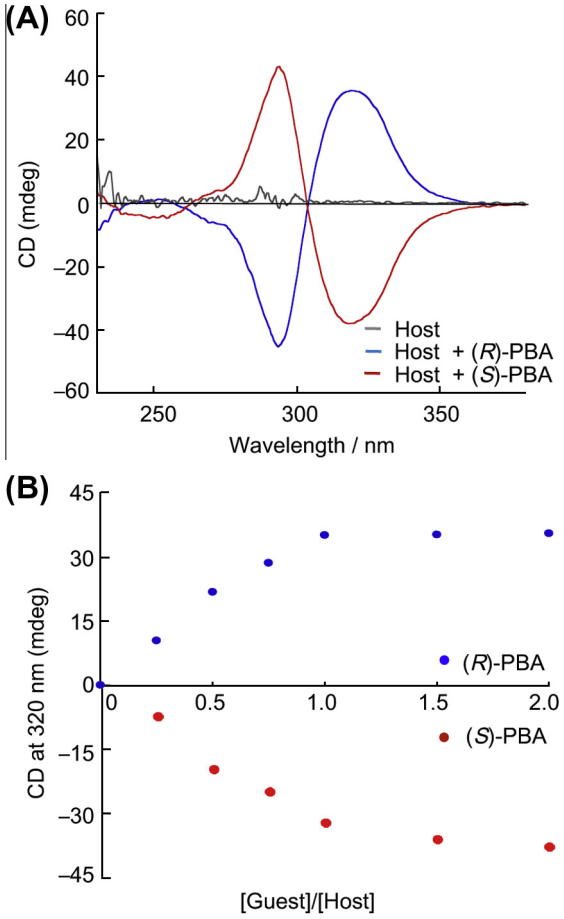


Figure 4. (A) CD spectra of Cu(bmb–bpy)(H_2O)($OTf)_2$ without and with 2.0 equiv of each enantiomer of PBA [0.5 mM, in CH_2Cl_2 and 0.02 wt % CH_3OH]. (B) Titration of (*R*)- and (*S*)-PBA [0–2.0 equiv] with Cu(bmb–bpy)(H_2O)($OTf)_2$.

ascribed to the two transition electric dipole moments of each benzimidazole unit that are oriented in a clockwise direction. The CD spectrum was completely inverted and resulted in a mirror image when the opposite enantiomer, (*S*)-PBA, was used as the chiral carboxylic acid. The theoretical calculation result of the ECCD spectra was in excellent agreement with that of the experimentally obtained CD curve (see the Supplementary data, molecular orbital (MO) calculations). The CD spectra obtained from the titration of each enantiomer of PBA with Cu(bmb–bpy)(H_2O)($OTf)_2$ showed saturation when 1.0 equiv of PBA was added, and the intensity did not change with increasing concentration of PBA (Fig. 4B). Therefore, we decided to use 2.0 equiv PBA in the ECCD–LDA study (*vide infra*). The single crystal X-ray analysis of a (*R*)-PPA recognition complex revealed that 1:1 stoichiometric complex was formed and the water molecule was replaced by the chiral carboxylate anion on the metal center (Fig. 5).[9]

The LDA was applied to analyze the CD data and determine the identity of the chiral carboxylic acids (Fig. 6). LDA is a supervised pattern recognition protocol that is used for the classification of data or the assignment of new analytes to their appropriate classes.[10] Five replicates were prepared for each enantiomer of each chiral carboxylic acid, and the data were analyzed at four different wavelengths (333, 313, 295, and 285 nm) and subjected to the LDA. These wavelengths were selected because they represent the amount of variance in the CD data. The LDA plot showed a good discrimination between the chiral carboxylic acid guests. F1-axis shows the difference in the absolute configuration between each enantiomer of the chiral carboxylic acids. The plots of the chiral carboxylic acids with a positive first Cotton effect appear at a negative position on F1-axis, whereas the plots of the negative first Cotton effect appear at a positive position. A stronger CD intensity shows a larger absolute value of F1, whereas a weaker CD intensity shows a smaller absolute value. Each enantiomer exists symmetrically with respect to the original point 0 in the LDA plot. F2-axis shows a small difference in the CD profile for each sample. The resulting LDA plot was proved to be 100% reliable by the jack-knife analysis, indicating that this method can be applied for assigning the identity of the chiral carboxylic acids successfully.

To apply the ECCD system using Cu(bmb–bpy)(H_2O)($OTf)_2$ for the determination of the enantiomeric excess (*ee*) of the chiral carboxylic acids, calibration lines were constructed. Eight unknown samples were prepared with *ee* values in the range −100% (*S*) to 100% (*R*) and measured them by CD spectroscopy. Then, calibration lines were constructed for each guest from the intensity at 320 nm wavelength in the CD spectrum; their corresponding actual *ee* values were also calculated using this calibration line (Fig. 7). The resulting calibration line fitted a linear regression with $R^2 = 0.99$, indicating that the ECCD system using Cu(bmb–bpy)(H_2O)($OTf)_2$ can be applied for the determination of the *ee* of the chiral carboxylic acids.

In this study, we report a new achiral Cu host [Cu(bmb–bpy)(H_2O)($OTf)_2$] for assigning the absolute configuration, identity, and *ee* of chiral carboxylic acids. This system has an advantage over the achiral hosts reported previously[6] owing to the workable proposition at the longer wavelengths. When the host is bound to a chiral guest in the Cu center, the CD signals were observed above 320 nm. From the treatment of the CD data by the LDA, the absolute configuration and identity of the chiral carboxylic acids were

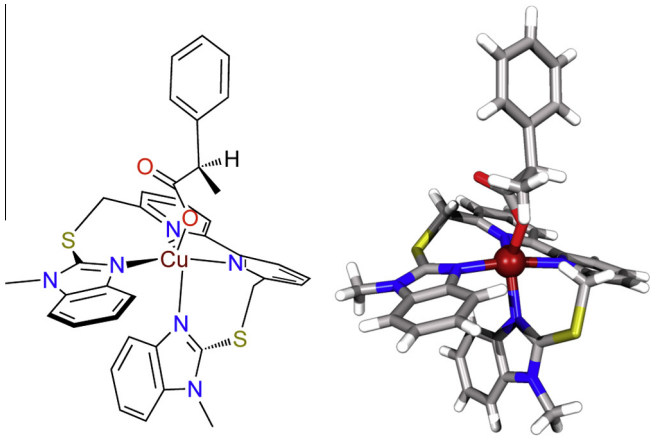


Figure 5. Chemical and crystal structure of a host–guest complex between Cu(bmb–bpy)(H_2O)($OTf)_2$ and (*R*)-PPA. The triflate and solvent molecules are omitted for clarity.

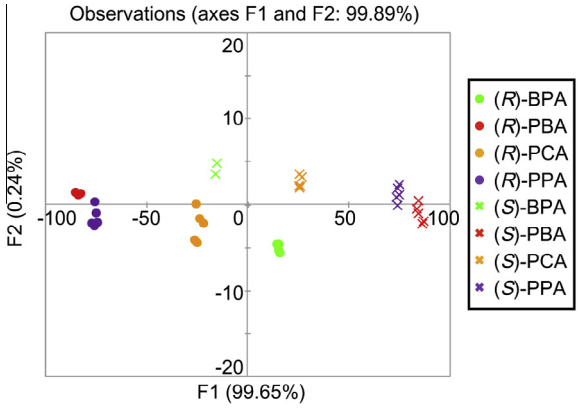


Figure 6. LDA plot of four enantiomeric pair guests with Cu(bmb–bpy)(H_2O)($OTf)_2$ [0.5 mM, in CH_2Cl_2 and 0.02 wt % CH_3OH].

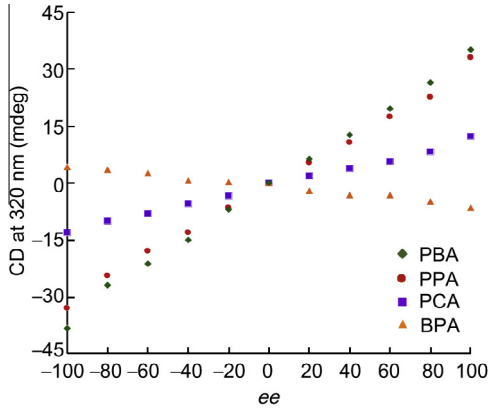


Figure 7. CD signal at 320 nm with varying ee values for the solution of four chiral carboxylic acids and Cu(bmb–bpy)(H_2O)($OTf)_2$ [0.5 mM, in CH_2Cl_2 and 0.02 wt % CH_3OH].

determined. Moreover, in the *ee* measurements of the eight samples, a good calibration line for the *ee* values was obtained. The ECCD–LDA system requires an obvious change in the profile of the CD spectra, and the host fulfills this requirement by the induced-fit adjustment to chiral guest binding. We believe that this system can be applied for the HTS of chiral compounds.

Acknowledgments

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Supplementary data

Supplementary data (details of the synthesis and characterization data for all the new compounds, X-ray crystallography, and MO calculation data for Cu(bmb–bpy)(H_2O)($OTf)_2$, CD titration experiments, and calibration lines for determining *ee*) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.02.032.

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9. Crystallographic data (excluding structure factors) for the structure in this Letter has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 978953 and 984710. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1 EZ, UK [fax:+44 (0) 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].
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