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Colorimetric enantioselective recognition of chiral secondary alcohols via hydrogen bonding to a chiral metallocene containing chemosensor

Both catalytically active and inactive diastereoisomers of a chiral metallocene-containing nucleophilic catalyst have been shown to function as sensors for chiral secondary alcohols. Since both diastereoisomers can use hydrogen bonding to recognise chiral secondary alcohols but only one diastereoisomer was previously found to be an active catalyst for secondary alcohol acylation points to divergent recognition mechanisms between the two systems and highlights the utility of investigating catalysis and sensing side by side.

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Colorimetric enantioselective recognition of chiral secondary alcohols *via* hydrogen bonding to a chiral metallocene containing chemosensor†

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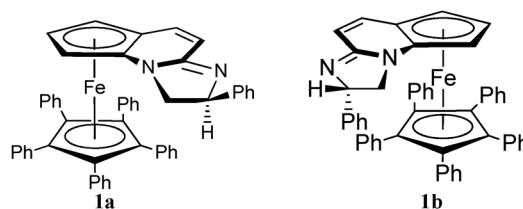
An operationally simple colorimetric method for enantioselective detection of chiral secondary alcohols *via* hydrogen bonding interactions using a chiral ferrocene derivative is reported.

This century has seen an increasing demand for determining the concentration and purity of enantiomers due to the importance of enantiopurity in the pharmaceutical industry.^{1,2} Chiral molecular recognition systems have been employed, to assess enantiopurity, which exploit both covalent interactions,^{3–8} and non-covalent interactions.⁹ Among non-covalent recognition systems reported ionic interactions, hydrogen bonding,^{10–12} π - π interactions,¹³ metal coordination^{14–16} and hydrophobic interactions have all been shown to be effective, and these interactions have attracted great interests as they are employed for many applications such as self-assembly^{17–19} and molecular recognition.^{20–30} The hydrogen bond is an important directional inter- or intra-molecular interaction, which is crucial for controlling molecular conformation and molecular aggregation.¹² In the area of molecular recognition, hydrogen bonding controls the strength of binding between ligands and receptors. For example, in biological systems, the binding between a substrate and an enzyme, as well as cell surface recognition, in great degree, depends on the hydrogen bond interactions.³¹

Steiner outlined the palette of hydrogen bonding patterns available including O-H...N and N-H...O/N interactions.¹² These interactions have been extensively explored in the crystal engineering of supramolecular structures,^{32,33} catalytic reactions and molecular recognition.^{23,34} Ghosh designed a series of pyridine

derivatives for distinguishing carboxylic acids from non-hydroxyl analogues through hydrogen bonding.^{23,34} Shinkai introduced chiral acids as templates to create enantiomerically pure aggregated structures using hydrogen bonding interactions, which have the potential for enantioselective sensing of chiral acids.²⁰ However, to the best of our knowledge, no one has yet used the nitrogen (N)-hydroxyl (C-OH) hydrogen bonding interaction for enantioselective detection of chiral alcohols. Herein, we report a strategy to enantioselectively detect alcohols through hydrogen bond interactions.

Compounds **1a** and **1b** were previously synthesised and tested as enantioselective catalysts for the kinetic resolution of secondary alcohols (Scheme 1 and S1, ESI†).^{35,36} It was especially noteworthy that whilst diastereoisomer **1b** functioned exquisitely as a catalyst for kinetic resolution by acylation diastereoisomer **1a** was completely inactive (an open top face was reasoned to be required for the acylated catalyst to be able to effectively deliver its cargo). The imidazole nitrogens on **1a** and **1b** are strongly Lewis basic and can themselves form a hydrogen bond with alcohols.^{37–39} Therefore, we decided to investigate whether **1a** and **1b** were able to enantioselectively recognise chiral alcohols. From the outset it was observed that the hydrogen bond interactions between **1a** and chiral alcohols are strongly dependent on the solvent, spectral changes in acetonitrile are the most pronounced (S2, ESI†). The binding between **1a** and a series of chiral alcohols was investigated using UV-vis spectroscopy. With dimethyl D/L-tartrates (D-DT and L-DT) the absorption peak was red-shifted from 516 nm to 576 nm (Fig. 1). Enantioselectivity was observed as dimethyl D-tartrate produced



Scheme 1 Structures of compounds **1a** and **1b**.

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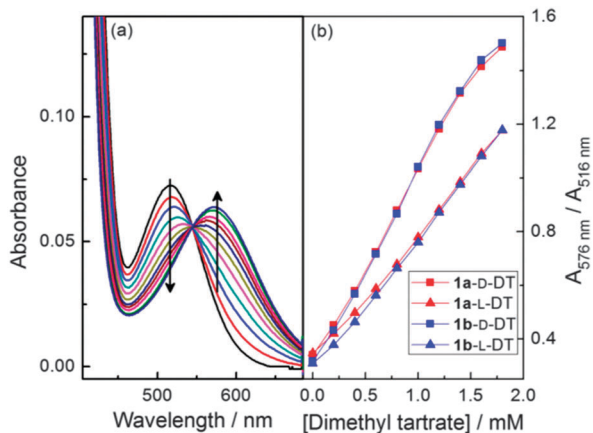


Fig. 1 (a) UV spectra changes of 0.1 mM **1a** in MeCN upon addition of dimethyl D-tartrate; (b) the ratio of absorbance at 576 nm to 516 nm versus concentration of D/L-tartrate for **1a** and **1b**.

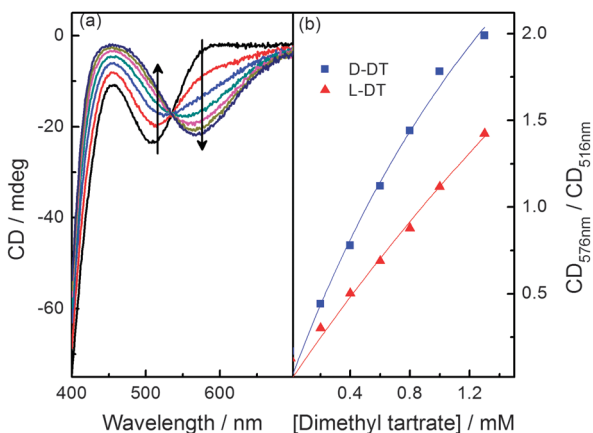


Fig. 2 (a) CD spectra changes of 0.1 mM **1a** in MeCN upon the addition of dimethyl D-tartrate; (b) the ratio of absorbance at 576 nm to 516 nm versus concentration of D/L-tartrate.

larger spectral shifts with **1a** and **1b** than that of dimethyl L-tartrate (Fig. 1 and 2). The observed binding constants for dimethyl D/L-tartrates with **1a** and **1b** are $392.5 \pm 63.2/112.5 \pm 29.3 \text{ dm}^3 \text{ mol}^{-1}$ and $298.3 \pm 84.7/141.4 \pm 26.1 \text{ dm}^3 \text{ mol}^{-1}$ respectively (S3, ESI†). Meanwhile enantioselective recognition could be observed colorimetrically, since after the addition of six equivalents of dimethyl D-tartrate to a solution of **1a**, a colour difference is observed as shown in (Fig. 3).

The sensing behaviours of the diastereoisomers **1a** and **1b** with dimethyl D/L-tartrates were identical, demonstrating a divergence between applications to alcohol recognition as opposed to acylation catalysis, *i.e.* the inactive catalyst, **1a**, works equally well as a sensor. As such we chose to make further use of the inactive catalyst and continued our investigations with compound **1a** only. A series of chiral ester containing secondary alcohols were studied and chiral alcohols with $pK_a \leq 12$ displayed higher chiral discrimination $\Delta \geq 0.1$ (Δ is the difference between $(A_{576\text{ nm}}/A_{516\text{ nm}})$ for each pair of enantiomers with 0.1 mM **1a** and 0.6 mM of the chiral alcohol)⁴⁰ (Table 1). D/L-Tartaric acids were also investigated and while pronounced spectral and colorimetric

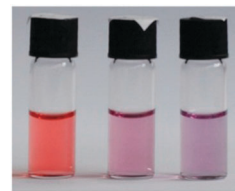


Fig. 3 From left to right: 0.1 mM **1a**, 6 eq. dimethyl L-tartrate, 6 eq. dimethyl D-tartrate in MeCN.

Table 1 Structures of the chiral secondary alcohols tested in this study and the ratio of absorption at 576 nm to 516 nm of compound **1a** after addition of 6 equivalents of each chiral alcohol

Chiral alcohols ($A_{576\text{ nm}}/A_{516\text{ nm}}$) ^a	Δ ^b	pK_a ⁴¹
 (-)-Dimethyl D-tartrate 0.982	 (+)-Dimethyl L-tartrate 0.742	0.240 11.44 ± 0.20
 (-)-Diisopropyl D-tartrate 0.641	 (+)-Diisopropyl L-tartrate 0.446	0.195 11.70 ± 0.20
 (2R,3S)-methyl 2,3-dihydroxy-3-phenylpropanoate 0.366	 (2S,3R)-methyl 2,3-dihydroxy-3-phenylpropanoate 0.350	0.016 12.33 ± 0.20
 (+)-Methyl D-lactate 0.626	 (-)-Methyl L-lactate 0.555	0.071 13.07 ± 0.20
 Methyl (R)-(-)-mandelate 0.580	 Methyl (S)-(+)-mandelate 0.457	0.123 12.19 ± 0.20
 (S)-1-phenylpropane-1,3-diol 0.334	 (R)-1-phenylpropane-1,3-diol 0.333	0.001 13.93 ± 0.20
 (1R,2R,3S,5R)-(-)-Pinanediol 0.348	 (1S,2S,3R,5S)-(+)-Pinanediol 0.333	0.015 14.68 ± 0.60

^a Ratio of absorption at 576 nm to 516 nm, [**1a**] = 0.1 mM, [chiral alcohols] = 0.6 mM. ^b Δ is the difference between $(A_{576\text{ nm}}/A_{516\text{ nm}})$ for each pair of enantiomers.



changes were observed, no enantioselectivity was detected (S4 and S5, ESI†). The observed binding constants for D/L-tartaric acid with **1a** are $3131 \pm 1157 \text{ dm}^3 \text{ mol}^{-1}$ and $4636 \pm 1755 \text{ dm}^3 \text{ mol}^{-1}$ respectively (S6, ESI†). ^1H NMR titrations of **1a** with dimethyl D-tartrate and D-tartaric acid indicate that similar hydrogen bonding species are responsible for the observed spectral changes (S7–S9, ESI†). We believe that enantioselectivity is controlled by steric demands within the hydrogen bonding complexes formed between the guest (acid or alcohol) and compound **1a** (S9, ESI†). Therefore, the increased distance between **1a** and the chiral centres for the hydrogen bonding complexes formed with the tartaric acid (3 bonds) over the alcohols (2 bonds) explains the lack of enantioselectivity observed between the D/L-tartaric acids.

A simple and enantioselective colorimetric sensing strategy for chiral secondary alcohols has been developed based on chiral chemosensor **1**. The hydrogen bond is crucial for the enantioselectivity with more acidic alcohols exhibiting greater enantio-differentiation upon interaction with **1**. Whilst the planar chirality in the sensors was not the overriding chiral recognition motif it is important to note that the metallocene fragment provides a coloured sensor that was vital in establishing a colorimetric assay and the potential to extend this work into the electrochemical arena in the future.

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