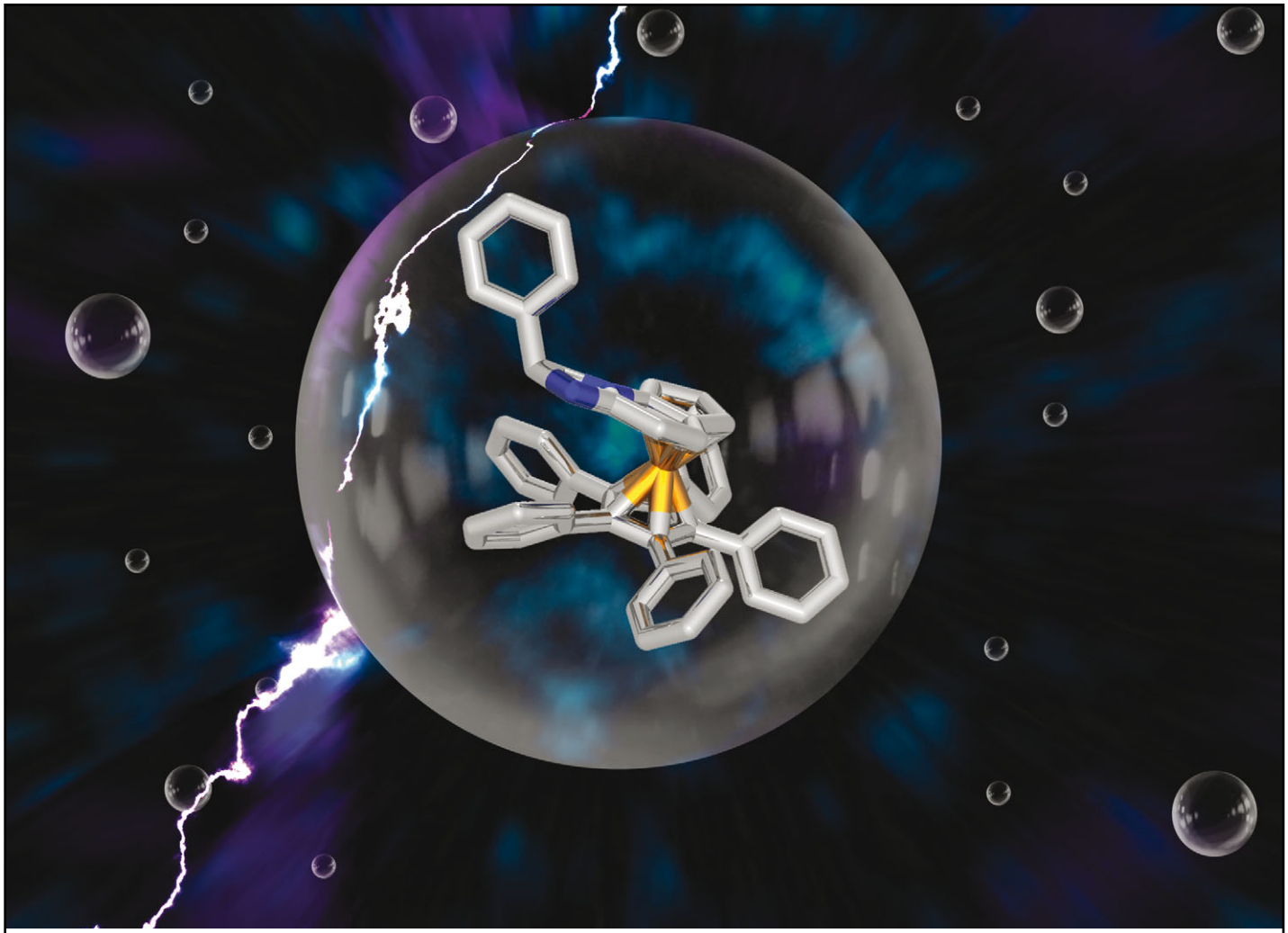

Featuring research from the CASE network in the UK and China. Prof. James, his team and collaborators including Prof. Deng and Dr Fossey describe a chiral metallocene-containing sensor for chiral secondary alcohols.

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.

Two articles in this issue of Chem. Commun. are authored by members of the CASE network, these papers feature as front and back cover articles.

As featured in:

See Wei-Ping Deng and Tony D. James *et al.*, *Chem. Commun.*, 2013, **49**, 8314.

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

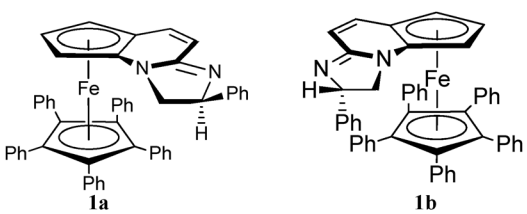
Su-Ying Xu,[a] Bin Hu,[b] Stephen E. Flower,[a] Yun-Bao Jiang,[c] John S. Fossey,[bd] Wei-Ping Deng*[b] and Tony D. James*[a]

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**.

[a] *Department of Chemistry, University of Bath, Bath BA2 7AY, UK. E-mail: t.d.james@bath.ac.uk*
[b] *Shanghai Key Laboratory of Functional Materials Chemistry & School of Pharmacy, East China University of Science and Technology, Shanghai, 20023, China*
[c] *Department of Chemistry, College of Chemistry and Chemical Engineering, and the MOE Key Laboratory of Analytical Sciences, Xiamen University, Xiamen 361005, China*
[d] *School of Chemistry, University of Birmingham, Edgbaston, Birmingham B15 2TT, UK*

† Electronic supplementary information (ESI) available: Solvent screen and investigations compound **1a**. See DOI: 10.1039/c3cc43083a

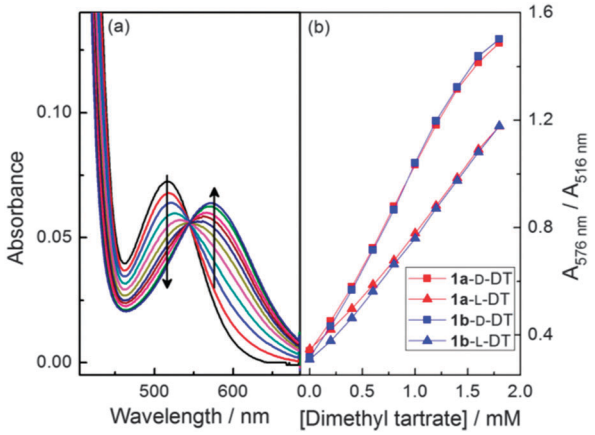


Fig. 1 (a) UV spectra changes of 0.1 mM **1a** in MeCN upon addition of dimethyl D-tartrate; (b) the ratio of absorbance at 576 nm to 516 nm *versus* concentration of D/L-tartrate for **1a** and **1b**.

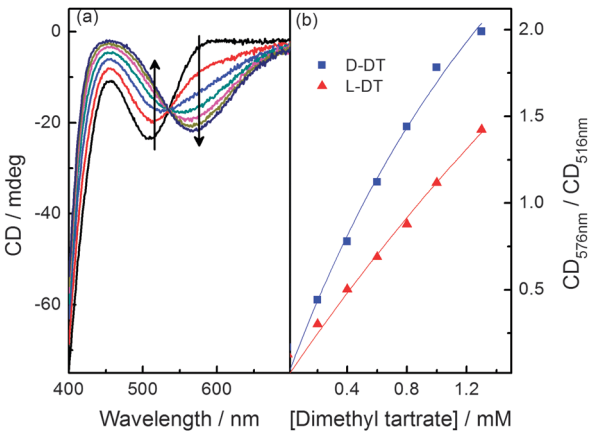


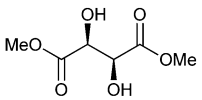
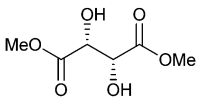
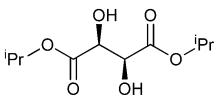
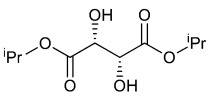
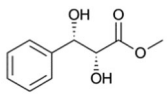
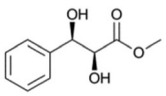
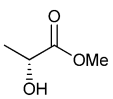
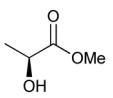
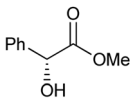
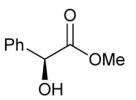
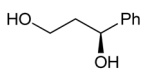
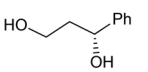
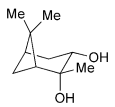
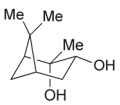
Fig. 2 (a) CD spectra changes of 0.1 mM **1a** in MeCN upon the addition of dimethyl D-tartrate; (b) the ratio of absorbance at 576 nm to 516 nm *versus* concentration of D/L-tartrate.

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 ± 63.2/112.5 ± 29.3 $dm^3\ mol^{-1}$ and 298.3 ± 84.7/141.4 ± 26.1 $dm^3\ mol^{-1}$ 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_{576nm}/A_{516nm}) 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_{576nm}/A_{516nm})[a]		Δ[b]	pK_a[41]
		0.240	11.44 ± 0.20
(-)-Dimethyl D-tartrate	(+)-Dimethyl L-tartrate		
0.982	0.742		
		0.195	11.70 ± 0.20
(-)-Diisopropyl D-tartrate	(+)-Diisopropyl L-tartrate		
0.641	0.446		
		0.016	12.33 ± 0.20
(2*R*,3*S*)-methyl 2,3-dihydroxy-3-phenylpropanoate	(2*S*,3*R*)-methyl 2,3-dihydroxy-3-phenylpropanoate		
0.366	0.350		
		0.071	13.07 ± 0.20
(+)-Methyl D-lactate	(-)-Methyl L-lactate		
0.626	0.555		
		0.123	12.19 ± 0.20
Methyl (R)-(-)-mandelate	Methyl (S)-(+)-mandelate		
0.580	0.457		
		0.001	13.93 ± 0.20
(*S*)-1-phenylpropane-1,3-diol	(*R*)-1-phenylpropane-1,3-diol		
0.334	0.333		
		0.015	14.68 ± 0.60
(1*R*,2*R*,3*S*,5*R*)-(-)-Pinanediol	(1*S*,2*S*,3*R*,5*S*)-(+)-Pinanediol		
0.348	0.333		

[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_{576nm}/A_{516nm}) 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 ± 1157 dm^3 mol^{-1} and 4636 ± 1755 dm^3 mol^{-1} respectively (S6, ESI†). ^{1}HNMR 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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