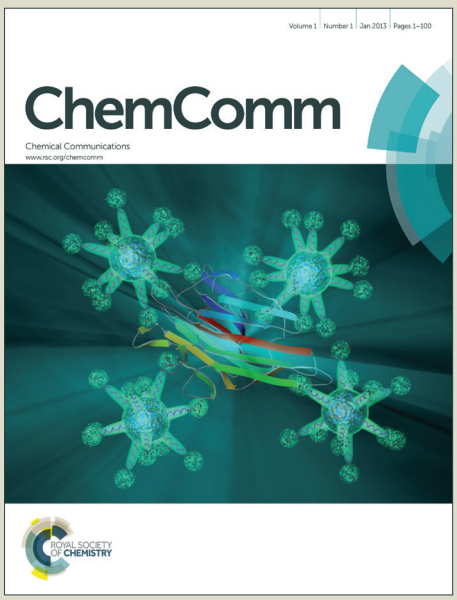
ChemComm

Accepted Manuscript



ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/chemcomm

Chemical Communications

COMMUNICATION

Self-Selecting Homochiral Quadruple-Stranded Helicates and Control of Supramolecular Chirality

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

Stephanie A. Boer[a] and David R. Turner*[a]

Enantiomeric M_4L_4 helical cages have been prepared whose supramolecular chirality is induced by the chemical chirality of the self-sorting amino acid-derived ligands that are used. Using scrambled diastereomeric ligands or achiral glycine-derived ligands yields analogous complexes yet 'turns off' the supramolecular chirality by producing centrosymmetric cages.

In the past few decades the field of supramolecular coordination container complexes has attracted considerable attention due to the potential applications of these materials in a wide variety of fields, particularly as reaction vessels, selective host species and in the stabilisation of reactive molecules.[1] The synthesis of cage complexes under self-assembly conditions from simple components can be achieved with a semblance of predictability using coordination bonds by combining multiple bridging ligands, with the coordinating groups appropriately positioned to promote a discrete structure, with metals of appropriate coordination preferences.[2]

The incorporation of chirality into coordination cages imparts the potential for applications in enantioselective processes such as sensing,[3] catalysis[4] and separation.[5] It is possible to incorporate chirality into coordination cages by spontaneous resolution using achiral ligands by generating chiral centres around tris(chelate) metal centres which may interconvert in solution.[6] However, from both of these strategies the challenge then arises of forming the complexes in an enantiomerically pure form. A more reliable method for the synthesis of chiral coordination cages is the use of enantiomerically pure ligands. A variety of strategies have been adopted, including appending chiral groups to the exterior or interior of ligands known to form cages, effectively adding chiral groups to achiral frames.[7] More recently, induction of supramolecular chirality has been achieved by the use of enantiopure ligands in tetrahedral architectures with the chirality of the ligand reflected in the handedness (Λ/Δ) around the metal centre.[8]

Chiral coordination cages can also be constructed in the form of helicates, typically generated as racemic mixtures, exploiting the presence of a twist within the ligands which imparts a helical sense in the complex.[9] The use of a chiral ligand will ensure the formation of a helicate, while the use of achiral ligands can form either helicates or mesocates.[10] A convenient synthetic route for the formation of chiral ligands is the incorporation of amino acids. Recently enantiomeric homochiral, quadruple-stranded helicate using amino acid-derived ligands with a bicyclooctene core were reported,[11] and control of chirality in tetrahedral cages by virtue of the ligands is known.[12]

Herein we report homochiral helicates and analogous mesocates constructed using 3,3',4,4'-biphenylsulfonediimides (BPSD) substituted with amino acids. The chiral M_4L_4 cages have supramolecular homochirality based on the handedness of the ligands employed. Reaction of a D/L ligand mixture results in the self-selective formation of the enantiomeric cages.

We have previously reported naphthalene- and perylene-diimides appended with amino acids that have been incorporated into homochiral coordination polymers with interesting interpenetration topologies including two materials capable of enantiomeric resolution of small analytes.[13] Whilst the planar aromatic core groups lent themselves to the formation of extended networks we have more recently turned our attention to non-planar core groups that are anticipated to form discrete cage complexes due to their internal angle, with the sulfone unit previously reported to be amenable.[9d]

The enantiopure dicarboxylic acids L-H_2LeuBPSD and D-H_2LeuBPSD were synthesised from 3,3'4,4'-biphenylsulfonetetracarboxylic dianhydride and the respective leucine isomer under microwave irradiation in acetic acid (Figure 1). The achiral glycine analogue, H_2GlyBPSD, was

[a] School of Chemistry, Monash University, Clayton, VIC 3800, Australia.
† Footnotes relating to the title and/or authors should appear here.
Electronic Supplementary Information (ESI) available: Full experimental details and synthetic procedures; crystallographic data (in CIF format, CCDC 1422157-1422162) and refinement details. See DOI: 10.1039/x0xx00000x

synthesised by a similar route under reflux in DMF (see Supporting Information).

Reaction of enantiopure L-H_2LeuBPSD or D-H_2LeuBPSD with copper nitrate in methanol/dimethylacetamide and a small amount of triethylamine yields crystalline material containing the helical cages $[Cu_4(LeuBPSD)_4(Solv)_4]$, **1** (Figure 1, see Supporting Information for full experimental details).[‡] Structural determination by single-crystal X-ray diffraction reveals that the two materials are enantiomers of each other with both crystallising in the non-centrosymmetric space group *P*1 (only the L-LeuBPSD derivative is discussed here).

Crystals of $[Cu_4(L\text{-}LeuBPSD)_4(OH_2)_4]$, Λ-[**1**$(H_2O)_4$], contain one complex in the asymmetric unit alongside partially-ordered non-coordinated solvent. The Λ-**1** cage contains $\{Cu_2(O_2C)_4\}$ paddlewheel motifs at either end of the helical complex, connected by the four L-LeuBPSD ligands, with aqua ligands coordinated to both the inner- and outer-facing apical sites of the paddlewheel. The internal Cu^{II} atoms are separated by 7.2 Å with an internal volume of *ca.* 300 $Å^3$ in the absence of coordinating solvent. When viewed along the vector passing through the four copper atoms the paddlewheel motifs have a negligible rotational offset with regards to each other. The ligands do not bridge between sites on the paddlewheels that lie immediately above/below, rather they bridge between sites related by a torsion angle of *ca.* 90° generating a helical sense around the central Cu_4 rotation axis of the complex.

The arrangement of four leucine residues around the paddlewheel motif is such that the substituents must form a propeller motif thereby inducing helicity, presumably driven in part by the relative steric bulk of the substituents (Figure 2A). The helicity of the cages containing L- and D-leucine is Λ and Δ, respectively. These complexes demonstrate that supramolecular chirality, *viz.* the directionality of the helix, can be induced by the molecular chirality of the ligands used forcing a preferred geometry around the coordination sites. Circular dichroism (CD) conducted on acetonitrile solutions of Λ-**1** and Δ-**1** show opposing Cotton effects that are slightly shifted and greatly enhanced compared to the spectra for the ligands alone indicating that the cages persist in solution (Figure 3). The solution stability of the cages is also observed by the presence of *m/z* peaks corresponding to $[\mathbf{1}+H]^+$ and $[\mathbf{1}+Na]^+$ in the ESI-MS spectra (see Supporting Information) although no peaks are observed in which solvent is associated.

The coordinated solvent is difficult to assign crystallographically, due to apparent rotational disorder along the Cu-O bond and/or disorder of the nature of the solvent within individual cages, and is not observed by mass spectrometry. In the X-ray structure of Λ-**1** the coordinated solvents all appear to be water, whilst in the structure of Δ-**1** the solvent is best modelled as four methanol molecules. A serendipitous crystalline sample was obtained from a d_6-DMSO solution of Λ-[**1**$(OH_2)_4$] and subsequently replicated on a larger scale (see Supporting Information). This material was found to contain the complex $[Cu_4(L\text{-}LeuBPSD)_4(DMSO)_2(OH_2)_2]$ with the DMSO ligands coordinated on the interior of the cages, thereby demonstrating that the solvent within the cages can be exchanged in solution. Crystallography reveals that there are areas of diffuse electron density, *i.e.* guest solvent, within the cages that cannot be resolved (except in the case of compound **3**, *vide infra*).

In order to explore the supramolecular self-selectivity of the Λ-**1** and Δ-**1** complexes, a reaction of a 50:50 mixture of L-H_2LeuBPSD and D-H_2LeuBPSD with copper nitrate was conducted. As with the individual reactions, a crystalline material was able to be isolated and structurally characterised. Analysis of the X-ray diffraction data revealed the crystals to be centrosymmetric (space group *C*2/*c*) with the asymmetric unit containing one cage complex in which all of the amino acid groups are of the same handedness (Figure 2B). The enantiomeric ligands only form complexes with ligands of like handedness, demonstrating that the mixed-ligand system displays narcissistic self-selection to form the helical complexes.[§] Powder X-ray diffraction (PXRD) reveals that the bulk material comprises both the centrosymmetric crystals containing Λ-**1**/Δ-**1** and chiral crystals of pure Λ-**1** and Δ-**1** (see Supporting Information). Circular dichroism of the bulk solid dissolved in acetonitrile shows a small Cotton effect indicating a slight excess of Δ-**1**. A CD spectrum taken of the reaction solution soon after mixing and on one isolated crystal shows the expected lack of response, suggesting that the response observed from the bulk solid is likely due to a seeding effect in the bulk sample during crystallisation.

The control of supramolecular chirality by the handedness of the ligand prompted exploration of analogous systems in which the chirality is removed in one of two ways. Firstly the chirality can be removed by using an achiral ligand, H_2GlyBPSD, derived from glycine rather than a chiral amino acid. Secondly a racemic ligand, *rac*-H_2LeuBPSD, in which the terminal groups are of opposite handedness, can be used.

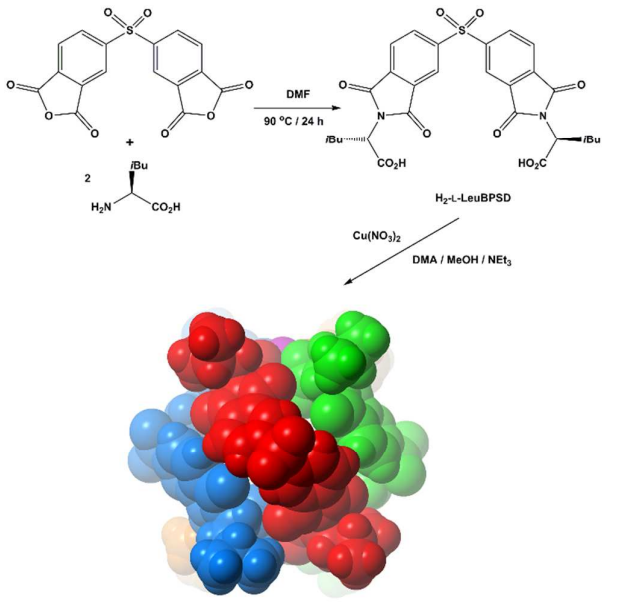


Figure 1: A representative synthesis of the L-leucine derived ligand (L-H_2LeuBPSD) and the helicate cage $[Cu_4(L\text{-}LeuBPSD)_4]$, Λ-**1** (coordinated solvent displayed only by the donor atom for clarity)

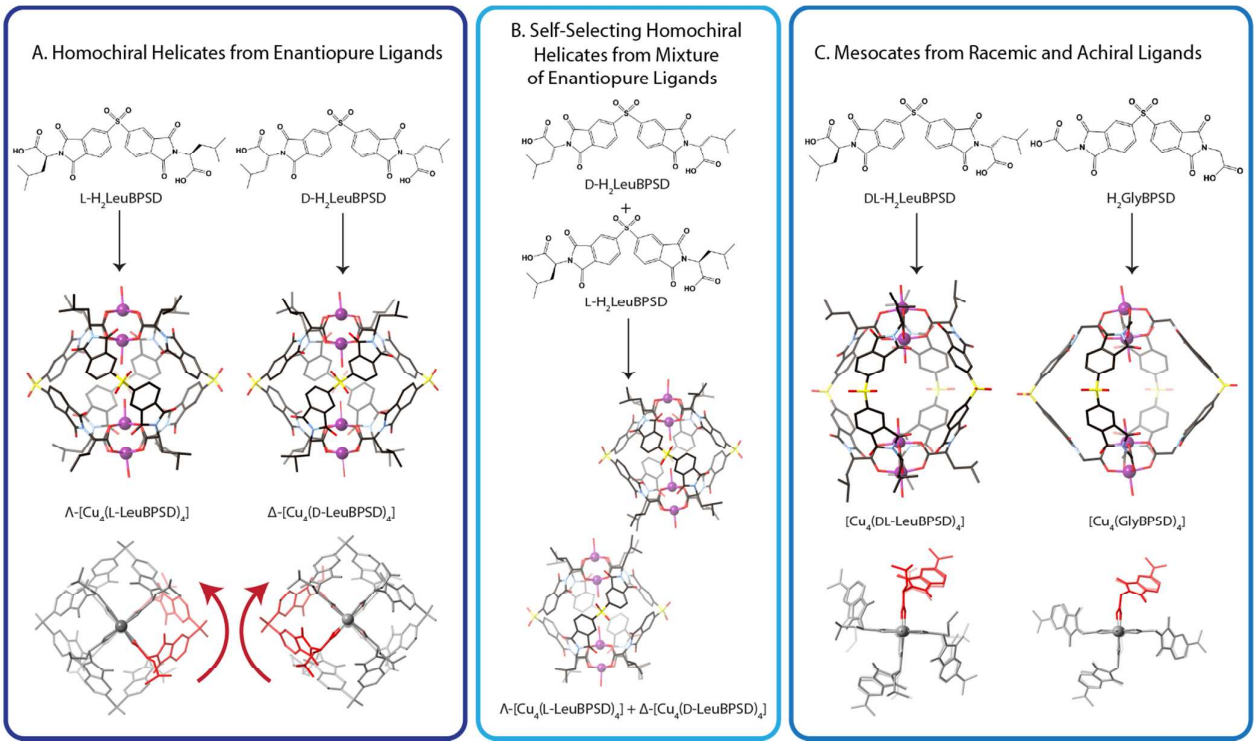


Figure 2: The chirality at the stereocentres in the ligands determines the supramolecular chirality (i.e. helicity) of the complex formed. (a) The use of enantiomerically pure ligands, D-H_2LeuBPSD and L-H_2LeuBPSD, exclusively yields Δ- and Λ-helical complexes, respectively. (b) 'Self-selection' occurs from a mixture of D-H_2LeuBPSD and L-H_2LeuBPSD to form the helical complexes rather than a mixed-ligand analogue. (c) Analogous centrosymmetric capsules can be formed by using the achiral ligand H_2-GlyBPSD or by using the DL-H_2LeuBPSD ligand (containing mixed D- and L-leucine terminal groups) with helicate formation prevented in the absence of enantiopure ligands.

rac-H_2LeuBPSD was prepared by reacting a 50:50 mixture of D- and L-leucine with 3,3'4,4'-biphenylsulfonetetracarboxylic dianhydride which is expected to yield a statistical mixture of the R,R-, S,S-, and R,S-substituted isomers (1:1:2). Given the statistical prevalence of the desired R,S isomer (DL-H_2LeuBPSD) the racemic dicarboxylic acid was reacted without purification with $Cu(NO_3)_2$ to form a crystalline material under analogous conditions to the enantiomerically pure Λ-**1** and Δ-**1**. Single crystal X-ray diffraction allowed structural characterisation of the achiral complex $[Cu_4$(DL-LeuBPSD)$_4(MeOH)_2(OH_2)_2]$ (**2**) with PXRD showing the that other possible products (*viz.* the enantiopure complexes Λ-**1** and Δ-**1** in both their homochiral and centrosymmetric co-crystalline forms) were also present in the bulk as expected using a mixture of ligands in the synthesis (see ESI). Complex **2** crystallises in the centrosymmetric setting *P*-1 with half of the complex in the asymmetric unit. Complex **2** is analogous to **1**, with copper paddlewheels bridged by four DL-LeuBPSD dicarboxylate ligands (Figure 2c). The ligands are arranged such that one of the paddlewheels is exclusively coordinated to the R terminal groups and the other exclusively by S terminal groups with these coordination environments therefore being identical to those in **1** and further demonstrating the self-selection of the enantiomers. Due to the orientation that is required at each paddlewheel the ligands cannot be oriented in a helical arrangement and instead bridge between coordination sites on the paddlewheels that are directly in line with each other. The difference in geometry leads to the interior of the capsule being elongated compared Λ-**1** and Δ-**1** with an internal Cu···Cu distance of 9.0 Å (*c.f.* 7.2 Å).

Using the achiral H_2GlyBPSD ligand the complex $[Cu_4$(GlyBPSD)$_4(MeOH)_3(OH_2)]$ (**3**) was isolated as a phase-pure crystalline material (Figure 2c). The cage is very similar in structure to **2** with a non-helical arrangement of ligands between the two paddlewheels. Although there are no stereocentres in the ligand the arrangement around one paddlewheel is such that the imide groups are orientated in a similar propeller motif, presumably due to the steric requirements of the ligand. These propeller motifs are of opposite directions at each end of the centrosymmetric cage and therefore the overall arrangement is analogous to **2**. The internal Cu···Cu distance in **3** is slightly larger than in **2** (9.3 Å vs. 9.0 Å) due to a subtle difference in the arrangement of the ligands. In **2** the ligands are approximately evenly spaced around the central Cu_4 axis as can be seen in the N···N separations between neighbouring imide groups which lies in the range 6.2-6.9 Å. In **3** the complex is 'pinched' in one direction with two N···N distances of 6.0 Å and two of 7.1 Å demonstrating that these cages have some flexibility. The crystal structure of **3** also reveals well-ordered, partial occupancy dimethylacetamide within the cage with two

positions partially protruding through the larger windows in the side of the cage.

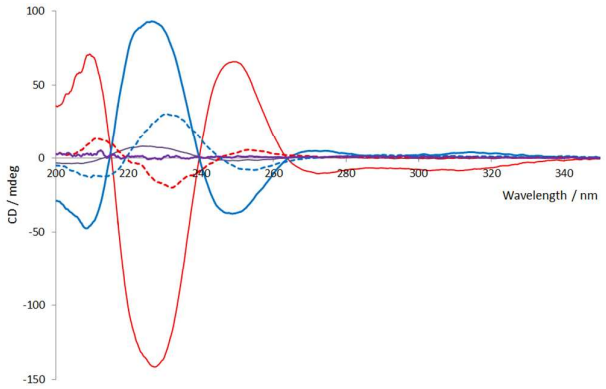


Figure 3: Circular dichroism spectra for Λ-**1** (solid red); L-H_2LeuBPSD (dashed red); Δ-**1** (solid blue); D-H_2LeuBPSD (dashed blue); bulk Λ-**1**/Δ-**1** product (grey); Λ-**1**/Δ-**1** single crystal (purple).

In conclusion, we have demonstrated that the supramolecular chirality of cage complexes can be controlled by the helical sense imparted through the use of enantiopure dicarboxylate ligands surrounding copper paddlewheel motifs. The two enantiomeric ligands display self-selection when simultaneously reacted with $Cu(NO_3)_2$ to form Λ- and Δ-helical cages. Using the R,S analogue of the LeuBPSD ligand gives a centrosymmetric cage in which a degree of self-selectivity is retained with each paddlewheel exclusively bound to either the R or the S terminal group is a complex that closely resembles that containing the achiral GlyBPSD ligand. These complexes demonstrate that the supramolecular chirality of cages can be controlled by stereocentres around paddlewheel motifs thereby offering new synthetic routes to enantiopure container species.

DRT acknowledges the Australian Research Council for a Future Fellowship (FT120100300). Part of this work was undertaken on the MX1 beamline at the Australian Synchrotron, Victoria, Australia.[14]

Notes and references

‡ The cages all crystallise with coordinated and non-coordinated solvent which differs between complexes/structures (see Supporting Information for full details).

§ We note that although the term 'narcissistic self-sorting' is often used in the literature, the phrase suffers in this instance when referring to enantiomeric ligands as Narcissus fell in love with his reflection which, by definition, would have been of the opposite handedness.

1 (a) T.R. Cook and P.J. Stang, *Chem. Rev*., 2015, **115**, 7001-7045. (b) M.M.J. Smulders, I.A. Riddell, C. Browne and J.R. Nitschke, *Chem. Soc. Rev.,* 2013, **42**, 1728. (c) H. Amouri, C. Desmarets and J. Moussa, *Chem. Rev.*, 2012, **112**, 2015. (d) D.R. Turner, A. Pastor, M. Alajarín and J.W. Steed*, Struc. Bond.*, **108**, 97.

2 (a) M.D. Ward, *Chem. Commun*., 2009, 4487. (b) J. Bunzen, J. Iwasa, P. Bonakdarzadeh, E. Numata, K. Rissanen, S. Sato and M. Fujita, *Angew. Chem. Int. Ed.*, **51**, 3161. (c) S. Mukherjee, P.S. Mukherjee, Chem. Commun. 2014, 50, 2239. (d) T.R. Cook, Y.-R. Zheng and P.J. Stang, *Chem. Rev.*, 2013, **113**, 734. (e) T.K. Ronson, S. Zarra, S.P. Black, J.R. Nitschke, *Chem. Commun.*, 2013, **49**, 2476. (f) N.L. Netzer, F.-R. Dai, Z. Wang and C. Jiang, *Angew. Chem. Int. Ed.*, **53**, 10965. (g) J.J. Yang, M. Bhadbhade, W.A. Donald, H. Iranmanesh, E.G. Moore, H. Yan and J.E. Beves, *Chem. Commun.*, 2015, **51**, 4465.

3 J. Dong, Y. Zhou, F. Zhang, Y. Cui, *Chem. Eur. J.*, 2014, **20**, 6455.

4 (a) C. Garcia-Simon, R. Gramage-Doria, S. Raoufmoghaddam, T. Parella, M. Costas, X. Ribas and J.N.H. Reek, *J. Am. Chem. Soc.*, 2015, **137**, 2680. (b) S.J. Lee, S.-H. Cho, K.L. Mulfort, D.M. Tiede, J.T. Hupp and S.T. Nguyen, *J. Am. Chem. Soc.*, 2008, **130**, 16828. (c) T. Murase, S. Peschard, S. Horiuchi, Y. Nishioka and M. Fujita, *Supramol. Chem.*, 2011, **23**, 199.

5 D. Fiedler, D.H. Leung, R.G. Bergman and K.N. Raymond, *J. Am. Chem. Soc.*, 2004, **126**, 3674.

6 (a) D. Fiedler, D.H. Leung, R.G. Bergman and K.N. Raymond, *J. Am. Chem. Soc.*, 2004, **126**, 3674. (b) A.M. Castilla, W.J. Ramsay and J.R. Nitschke, *Chem. Lett.*, 2014, **43**, 256.

7 (a) M. Schweiger, S.R. Seidel, M. Schmitz and P.J. Stang, *Org. Lett.*, 2000, **2**, 1255. (b) M. Ikemi, T. Kikuchi, S. Matsumura, K. Shiba, S. Sato, M. Fujita, *Chem. Sci.*, 2010, **1**, 68.

8 (a) S.P. Argent, T. Riis-Johannessen, J.C. Jeffery, L.P. Harding and M.D. Ward, *Chem. Commun.*, 2005, 4647. (b) M. Albrecht, S. Burk and P. Weis, *Synthesis*, 2008, 2963. (c) A.M. Castilla, N. Ousaka, R.A. Bilbeisi, E. Valeri, T K. Ronson and J.R. Nitschke, *J. Am. Chem. Soc.*, 2013, **135**, 17999. (d) N. Ousaka, J.K. Clegg and J.R. Nitschke, 2012, *Angew. Chem. Int. Ed.*, **51**, 1464. (e) T. Liu, Y. Liu, W. Xuan and Y. Cui, *Angew. Chem. Int. Ed.,* 2010, **49**, 4121.

9 (a) C. Piguet, G. Bernardinelli and G. Hopfgartner, *Chem. Rev.*, 1997, **97**, 2005. (b) S. Goetz and P.E. Kruger, *Dalton Trans.*, 2006, 1277. (c) Z. Zhang and D. Dolphin, *Chem. Commun.,* 2009, 6931. (d) W. Xuan, M. Zhang, Y. Liu, Z. Chen and Y. Cui, *J. Am. Chem. Soc.*, 2012, **134**, 6904.

10 (a) M. Scherer, D.L. Caulder, D.W. Johnson and K.N. Raymond, *Angew. Chem. Int. Ed*., 1999, **38**, 1588. (b) D. Wu, P. Huang, Y. Shui and G. Wu, *Inorg. Chem. Commun*., 2013, **29**, 205. (c) F. Cui, S. Li, C. Jia, J.S. Mathieson, L. Cronin, X.J. Yang and B. Wu, *Inorg. Chem*., 2012, **51**, 179. (d) J. Xu, T.N. Parac and K.N. Raymond, *Angew. Chem. Int. Ed*., 1999, **38**, 2878.

11 L. Chen, J. Kang, H. Cui, Y. Wang, L. Liu, L. Zhang and C.Y. Su, *Dalton Trans*., 2015, **44**, 12180.

12 (a) S.P. Argent, T. Riis-Johannessen, J.C. Jeffery, L.P. Harding and M.D. Ward, *Chem. Commun.*, 2005, 4647. (b) M. Albrecht, S. Burk and P. Weis, *Synthesis*, 2007, 2963. (c) T. Liu, Y. Liu, W. Xuan and Y. Cui, *Angew. Chem. Int. Ed.*, 2010, **49**, 4121. (d) N. Ousaka, J.K. Clegg and J.R. Nitschke, *Angew. Chem. Int. Ed.*, 2012, **51**, 1464.

13 (a) S.A. Boer, Y. Nolvachai, C. Kulsing, L.J. McCormick, C.S. Hawes, P.J. Marriott and D.R. Turner, *Chem. Eur. J*., 2014, **20**, 11308-11312. (b) S.A. Boer, C.S. Hawes and D.R. Turner, *Chem. Commun.*, 2014, **50**, 1125-1127. (c) L.J. McCormick and D.R. Turner, *CrystEngComm*, 2013, **15**, 8234-8236.

14 N.P. Cowieson, D. Aragao, M. Clift, D.J. Ericsson, C. Gee, S.J. Harrop, N. Mudie, S. Panjikar, J.R. Price, A. Riboldi-Tunnicliffe, R. Williamson and T. Caradoc-Davies, *J. Synchrotron Rad.*, 2015, **22**, 187.