Chemoenzymatic synthesis of chiral 4,4′-bipyridyls and their metal–organic frameworks†

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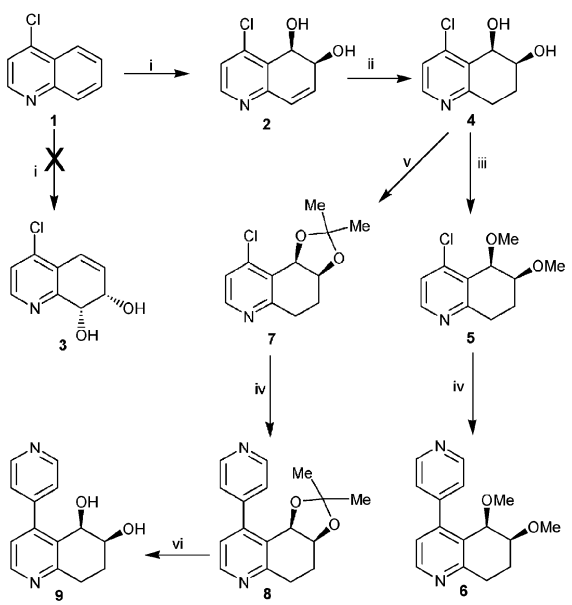
The first enantiopure 4,4′-bipyridyls, 6, 8, and 9 have been prepared in four or five steps *via* bacterial dioxygenase-catalysed *cis*-dihydroxylation of 4-chloroquinoline 1 and C–C coupling; ligands 6 and 9 are found to be effective building blocks for the preparation of chiral metal–organic frameworks as demonstrated with the rational synthesis of two pillared-grid structures $[Zn_2(fumarate)_2(L)]$, which exhibit interesting structural and dynamic aspects.

Engendering chirality in metal–organic frameworks (MOFs)[1] is currently of widespread interest because of the possibilities for such materials in enantioselective separation, sensing and catalysis.[2] Despite the fact that 4,4′-bipyridyl (bipy) is one of the most widely-used and topologically predictable building blocks for the synthesis of MOFs,[3] its chiral derivatisation has not yet been greatly explored.[4] Here we describe the synthesis of the first enantiopure 4,4′-bipyridyl derivatives followed by the rational synthesis of two chiral pillared-layer MOFs which exhibit interesting structural and dynamic aspects.

Dioxygenase-catalysed *cis*-dihydroxylation of polycyclic azaarenes, to yield the corresponding enantiopure *cis*-dihydrodiols, has been reported earlier.[5–7] Whole cell biotransformations of quinoline and 2-chloroquinoline were thus found to yield both 5,6- and 7,8-*cis*-dihydrodiols, using *Pseudomonas putida* UV4 as a source of toluene dioxygenase (TDO). As part of the current programme to evaluate the potential of azaarene *cis*-dihydrodiols as chiral ligands,[7b] 4-chloroquinoline **1** was used as a substrate for *P. putida* UV4; 4-chloro-5,6-dihydroquinoline-5,6-diol **2** was isolated in low yield (4%) with no evidence of the alternative isomer 4-chloro-7,8-dihydroquinoline-7,8-diol **3**. Using whole cells of *Sphingomonas yanoikuyae* B8/36, a source of biphenyl dioxygenase (BPDO), *cis*-dihydrodiol **2** was again obtained as the sole metabolite but in higher yield (33%). BPDO, having a larger active site than TDO, catalysed the *cis*-dihydroxylation of 4-chloroquinoline **1** more efficiently, and therefore provided sufficient *cis*-dihydrodiol **2** for further synthetic studies.

Catalytic hydrogenation of *cis*-dihydrodiol **2**, to give the *cis*-tetrahydrodiol **4**, was achieved in good yield (89%), without concomitant hydrogenolysis of the chlorine atom, using PtO_2/H_2 in EtOAc at normal temperature and pressure. Hydrogenation and hydrogenolysis of 4-chloro-5,6-dihydroquinoline-5,6-diol **2** occurred when Pd/C was used as catalyst and the resulting (5*R*,6*S*)-5,6,7,8-tetrahydroquinoline-5,6-diol was found to be enantiopure (>98% ee). A similar absolute configuration (5*R*,6*S*) and enantiopurity (>98% ee) was thus established for metabolite **2**.

Treatment of *cis*-diol **4** with methyl iodide and sodium hydride gave the dimethoxy derivative **5** (72%, see Scheme 1). This compound was in turn reacted with 4-pyridineboronic acid using a new catalyst system for Suzuki coupling, *i.e.* palladium



Reagents: i *S. yanoikuyae* B8/36 (33%); ii H_2, PtO_2, EtOAc (89%); iii MeI, NaH (72%); iv 4-pyridineboronic acid, $Pd_2(dba)_2$,$(C_6H_{11})_3P$ (57%); v DMP (86%); vi TFA (82%)

Scheme 1 Synthesis of chiral 4,4′-bipyridine derivates **6**, **8** and **9**

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† Electronic supplementary information (ESI) available: Synthesis and characterisation data, XRPD pattern, TGA and DSC plots, and variable temperature solid state ^{13}C NMR spectra for $[Zn_2(fumarate)_2(\mathbf{6})]\cdot 2DMF$. CCDC 695604–695606. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b812366g

dibenzylideneacetone [$Pd_2(dba)_3$], tricyclohexylphosphine (PCy_3) and aqueous K_3PO_4.[8] The required chiral dimethoxy-4,4′-bipyridine **6** was thus obtained (57%) in four steps from 4-chloroquinoline **1**. A similar coupling procedure of the acetonide derivative **7** was used to give protected 4,4′-bipyridine **8** (57%) which was then hydrolysed to give the *cis*-dihydroxy-4-chloroquinoline **9** (82%). Since each of **6**, **8** and **9** contains two chiral centres, they should be highly stable to racemisation.

For the synthesis of MOFs derived from **6** and **9**, pillared-layer structures based on dimetal paddlewheels were targeted. Based on the conditions employed by Hupp *et al.*[9] for the synthesis of [Zn_2(fumarate)$_2$(bipy)], $Zn(NO_3)_2$, fumaric acid and **6** were heated in DMF–ethanol–water for 48 h at 60 °C. On cooling, an initial batch of crystals obtained was determined to be Zn_5(fumarate)$_4$(DMF)$_2(OH)_2$ by single-crystal X-ray crystallography.‡ A second batch of crystals was obtained after addition of further ethanol and standing for 1 week, which had the target mixed ligand pillared-layer structure [Zn_2(fumarate)$_2$(**6**)] (Fig. 1a and b). It consists of a single network (in contrast to double interpenetration in the non-chiral analogue [Zn_2(fumarate)$_2$(bipy)]) with square grids based on Zn_2 nodes and fumarate linkers, pillared by **6**.

Compound **6** has two distinguishable pyridine rings, and the pillars are arranged in a non-centrosymmetric head-to-tail fashion. The XRPD pattern of the bulk matched well with the pattern predicted from the crystal structure confirming it to be phase pure (see ESI†). The pyridyl rings in each pillar are mutually orthogonal (in contrast to coplanar in [Zn_2(fumarate)$_2$(bipy)]). The pillars are also more strongly tilted from the normal to the layers than in [Zn_2(fumarate)$_2$(bipy)] (24° *versus* 15°, respectively). The methoxy groups form 'walls' between the fumarate groups of adjacent layers and therefore the widest continuous channels are orthogonal to the layers (Fig. 1b). The lack of interpenetration is most likely due to the greater steric bulk of **6** *versus* 4,4′-bipy. In this regard **6** is similar to triethylenediamine (TED) which gives analogous non-interpenetrated pillared-layer frameworks (although with smaller layer spacings).[10] Consequently, whereas [Zn_2(fumarate)$_2$(bipy)] has relatively little space for non-framework molecules (0.5 DMF per formula unit), [Zn_2(fumarate)$_2$(**6**)] possesses larger pores. It was not possible to model the disordered solvent in the crystal structure. It was therefore removed from the calculations using the SQUEEZE program[11] resulting in a calculated channel volume of 443.1 $Å^3$ (45%) per unit cell (or Zn_2 unit). Thermogravimetric analysis revealed a mass loss of 19.8% between 25 °C and 180 °C, corresponding closely to 2 molecules of DMF per Zn_2 unit (calc. 19.0%).

Under similar preparative conditions, [Zn_2(fumarate)$_2$(**9**)]·4DMF was obtained. To avoid the formation of phases analogous to Zn_5(fumarate)$_4$(DMF)$_2(OH)_2$, an excess of **9** was used and crystals of the target pillared-grid [Zn_2(fumarate)$_2$(**9**)] were indeed obtained directly. Again, a non-interpenetrated structure was adopted (see Fig. 1c). Compound **9** coordinates selectively *via* nitrogen despite the potentially reactive (and chelating) diol functionality. These chiral diol sites therefore remain available for derivatisation with further Lewis acids.[12] In contrast to [Zn_2(fumarate)$_2$(**6**)], included DMF is largely ordered, although some of the sites are not fully occupied.

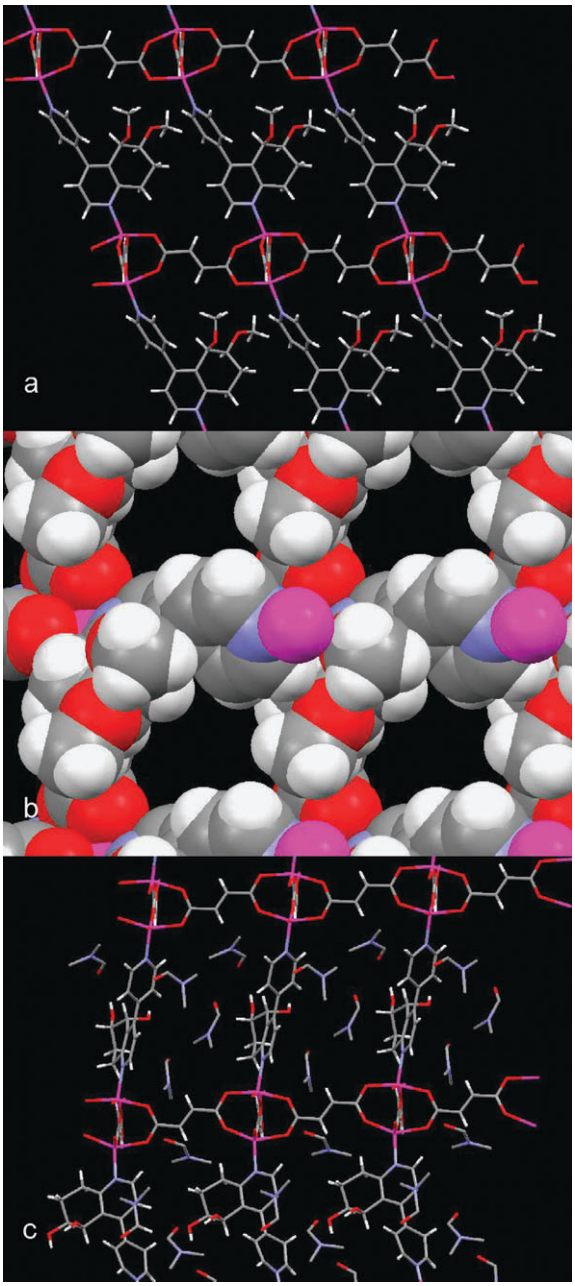

Fig. 1 (a) and (b) X-Ray crystal structure of [Zn_2(fumarate)$_2$(**6**)]; (c) [Zn_2(fumarate)$_2$(**9**)] (H-atoms in DMF molecules are omitted for clarity).

Specifically, O···O distances from the hydroxyls to four of the eight crystallographically independent DMF guest molecules suggest that hydrogen bonds are present (O···O = 2.73–2.87 Å). An interesting difference to [Zn_2(fumarate)$_2$(**6**)] is the centrosymmetric, head-to-head arrangement of the pillars in the $\{Zn_2(\mathbf{9})\}_\infty$ chains. Comparison of the two structures reveals no specific origin for this difference, but the presence of hydrogen bonding to positionally ordered DMF in [Zn_2(fumarate)$_2$(**9**)] suggests that solvent molecules may exert different templating influences in the two structures. There is a pronounced helical twist in the $\{Zn_2(\mathbf{9})\}_\infty$ chains with a repeating distance corresponding to four layers and resulting in a long *b* axis of 53.89 Å (Fig. 2).

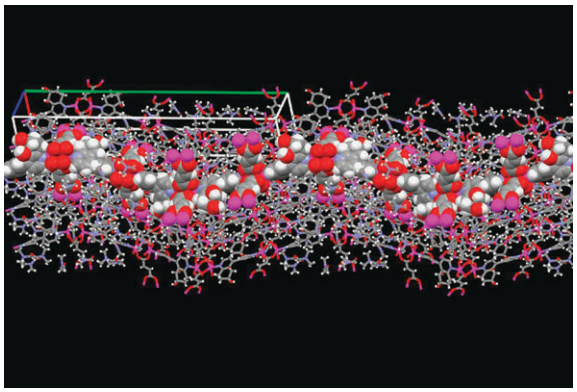

Fig. 2 Structure of [Zn_2(fumarate)$_2$(**9**)] with one $\{Zn_2(\mathbf{9})\}_\infty$ chain of pillars shown in space-filling mode to highlight the helical twist. The repeat distance corresponds to four layers (one unit cell *b* axis, 53.89 Å).

The lack of symmetry and bulky substituents present in **6** and **9** contrasts markedly with 4,4′-bipy and this raises issues of rotational isomerism and potentially disordered phases. The lack of interpenetration in these structures also leaves wide spacings between the pillars which may facilitate pillar rotation. To investigate these aspects a variable-temperature CPMAS ^{13}C NMR study was conducted on [Zn_2(fumarate)$_2$(**6**)] (see ESI for spectra†). At 25 °C the spectrum exhibits sharp lines for the framework carbon centres indicating a well-ordered structure consistent with the X-ray results (see spectrum 1). Signals due to included DMF are broader, indicating disorder, also as expected. A short (1 s) recycle direct polarisation (DP) experiment (spectrum 2) shows signals from the DMF and the O-methyls implying short *T*1 values, and suggesting also that these centres are relatively mobile. At 100 °C (spectrum 3) the signals due to DMF become sharper and exhibit greater intensity in the DP spectrum (spectrum 4), indicating increased mobility. Also, signals due to the pyridine group of **6** become broader, consistent with rotation of this part of the pillars. At 150 °C (spectrum 5), further signals due to **6** become broad and appear in the DP spectrum (spectrum 6), indicating general mobility and/or disorder of the pillars. The spectra therefore confirm the motional freedom of the pillars and show that the unsubstituted pyridine ring is able to rotate more freely than the bulkier substituted ring. Interestingly, on returning to 25 °C (spectrum 7), the signals are generally broader than in the initial spectra suggesting that the structure remains disordered after heating. Consistent with the TGA, only partial desolvation occurred under conditions of the NMR experiments as shown by signals due to remaining DMF.

In conclusion, enzymatic oxidation has been used to prepare the first enantiopure 4,4′-bipyridyl derivatives. This has further enabled chiral MOFs to be prepared in a rational manner based on pillared-layer topologies which are known for 4,4′-bipy. Unusual structural and dynamic aspects have resulted from the presence of bulky low-symmetry pillars. Further studies of sorption and associated aspects of these materials are under way.

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Notes and references

‡ Crystal structures were determined from data collected with rotating-anode MoKα radiation for Zn_5(fumarate)$_4$(DMF)$_2$(OH)$_2$ and [Zn_2(fumarate)$_2$(**6**)], and with synchrotron radiation for [Zn_2(fumarate)$_2$(**9**)]·4DMF. Structure solution and refinement included treatment of highly disordered solvent as described above, and free refinement of the occupancy of all DMF molecules for the synchrotron-derived structure. Non-framework volume was calculated using CALC VOID from within PLATON.[13] See CCDC 695604–695606 for full details. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b812366g

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