Azaarene *cis*-dihydrodiol-derived 2,2′-bipyridine ligands for asymmetric allylic oxidation and cyclopropanation†

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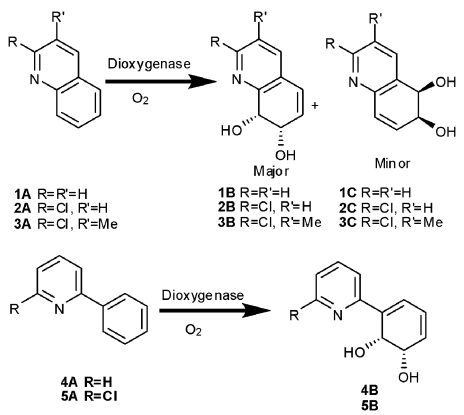
Biphenyl dioxygenase-catalysed *cis*-dihydroxylation of 2-chloroquinoline, 2-chloro-3-methylquinoline and 2-chloro-6-phenylpyridine substrates yielded the corresponding enantiopure *cis*-dihydrodiols; enantiopure 2,2′-bipyridines, synthesised in four steps from 2-chloroquinoline, proved to be efficient chiral ligands in catalytic asymmetric allylic oxidation and cyclopropanation reactions of alkenes.

The dioxygenase-catalysed dihydroxylation of carbocyclic arenes, to yield the corresponding enantiopure *cis*-dihydrodiol metabolites, has provided a new pool of chiral compounds for use in chemoenzymatic synthesis. Recent reviews[1a–d] list many examples of their applications in the synthesis of natural products, *e.g.* alkaloids and sugars, and non-natural products, *e.g.* carbasugars and isomeric dihydrodiols. The corresponding *cis*-dihydrodiol metabolites, derived from bicyclic azaarenes, *e.g.* **1A** → (7*S*,8*R*)-**1B** and (5*R*,6*S*)-**1C**,[2a,b] and, more recently, monocyclic azaarenes, *e.g.* **4A** → (1*S*,2*R*)-**4B**, are also now available.[3,4] It is noteworthy that both toluene dioxygenase (TDO) and biphenyl dioxygenase (BPDO) enzymes strongly favour catalytic *cis*-dihydroxylation of the carbocyclic rings rather than the pyridine rings in azaarenes **1A** and **4A**. Although an increasing range of *cis*-dihydrodiol metabolites derived from mono-,[3,4] di-,[2a,b] tri-[4–6] and tetracyclic[7] azaarenes have been reported, up to the present, few have been used as synthetic precursors.[4]

Using whole cells of the bacterium *Pseudomonas putida* UV4 (expressing TDO), the enantiopure (>98% *ee*) *cis*-dihydrodiols (7*S*,8*R*)-**2B** (major) and (5*R*,6*S*)-**2C** (minor) were previously isolated as the main metabolites of 2-chloroquinoline **2A** (Scheme 1).[2b] *cis*-Dihydrodiol (7*S*,8*R*)-**2B** (>98% *ee*), also obtained using *Sphingomonas yanoikuyae* B8/36 (expressing BPDO),[2b] was of particular interest, since the chlorine atom at C-2 could, in principle, provide entry into a new range of chiral 2,2′-bipyridines *via* an established homocoupling procedure.[8] The major objectives of the current study were: (i) the biocatalytic synthesis and stereochemical assignment of the new *cis*-dihydrodiols **3B** and **5B**, derived from the corresponding azaarenes 2-chloro-3-methylquinoline (**3A**) and 2-chloro-6-phenylpyridine (**5A**) (ii) the utilization of azaarene *cis*-diols **2B**, **3B** and **5B** in the chemical synthesis of enantiopure 2,2′-bipyridine ligands **2F**, **3F**, **5F–8F** and (iii) evaluation of the potential of the chiral 2,2′-bipyridines **2F**, **6F–8F** as ligands for catalytic asymmetric allylic hydroxylation and cyclopropanation reactions (Scheme 2).

While the TDO-catalysed biotransformation of azaarene **2A** yielded mainly metabolite (7*S*,8*R*)-**2B**, the bulkier substrates **3A** and **5A** unfortunately proved unacceptable to this enzyme. When the alternative enzyme, BPDO, present in *S. yanoikuyae* B8/36 and having a larger active site, was used with substrate **3A**, a PLC separable (5% MeOH–$CHCl_3$) mixture of *cis*-dihydrodiols **3B** (35%) and **3C** (25%) metabolites was obtained; under similar conditions *cis*-dihydrodiol **5B** was the sole metabolite of azaarene **5A**, albeit in lower yield (14%). The absolute configurations of the new bioproducts (7*S*,8*R*)-**3B** and (1*S*,2*R*)-**5B** were firmly established by circular dichroism spectroscopy (CD). Enantiopurity values in each case were determined to be >98% *ee* by formation of the corresponding (−)-(*S*)- and (+)-(*R*)-2-(1-methoxyethyl)benzeneboronic acid (MEBBA) derivatives followed by ^{1}H-NMR analysis, using methods similar to those recently reported for other *cis*-dihydrodiols.[9a–d]

The metabolites **2B**, **3B** and **5B** were partially hydrogenated to give the corresponding *cis*-tetrahydrodiols **2D**, **3D** and **5D** (>95% yield) under conditions that avoided hydrogenolysis of the chlorine atoms (PtO_2/H_2, EtOAc, Scheme 2). *cis*-Tetrahydrodiols **2D**, **3D** and **5D** were protected as the



Scheme 1 Enzyme-catalysed synthesis of azaarene *cis*-dihydrodiols **1B–5B** and **1C–3C**.

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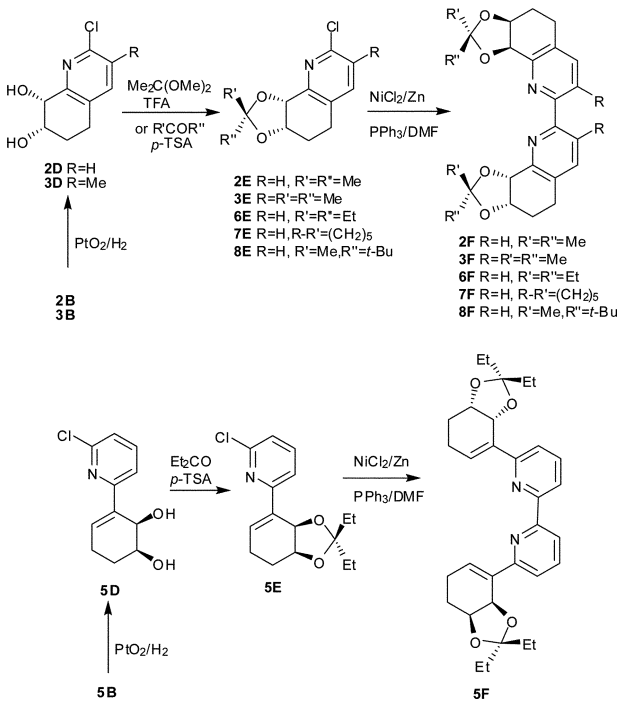


Scheme 2 Synthesis of 2,2′-bipyridines **2F**, **3F** and **5F–8F**.

corresponding acetal derivatives **2E**, **3E**, **5E–8E** (60–96% yield). Compound **8E**, the major (90%) of two diastereoisomers formed, was purified by chromatography. It was found to have the bulky R′ group (*t*-Bu) in a *syn* relationship with the proximate carbocyclic ring based on strong NOE interactions between: (i) the Me group and the H-7, H-8 atoms, (ii) the *t*-Bu group and the H-3, H-4 atoms.

The stoichiometric, nickel(0)-mediated homocoupling of acetals **2E**, **3E** and **5E–8E** yielded the corresponding enantiopure substituted 2,2′-bipyridines **2F**, **3F** and **5F–8F** (34–96% yield). X-ray crystallographic analysis of bipyridine **2F**, derived from the *cis*-dihydrodiol (7*S*,8*R*)-**2B**, confirmed both its structure and *transoid*-conformation in the solid state, with respect to the pyridine nitrogen atoms (Fig. 1).†

A large scale TDO-catalysed biotransformation of the commercially available 2-chloroquinoline produced a sufficient quantity of *cis*-dihydrodiol **2B** (30% yield) for the synthesis of a range of 2,2′-bipyridines, *e.g.* **2F**, **6F**, **7F**, and **8F**, and an evaluation of their potential as chiral ligands. The Kharasch–Sosnosky allylic hydroxylation reaction[11] of cyclohexene **9** and cycloheptene **11** was used to test ligands **2F**, **6F**, **7F** and **8F** (Scheme 3); a summary of the results obtained is shown in Table 1. The ability of ligand **2F** to complex with Cu(I) was confirmed by reacting it with $Cu(MeCN)_4ClO_4$ in MeOH solvent. The red complex **2G** was fully characterised by

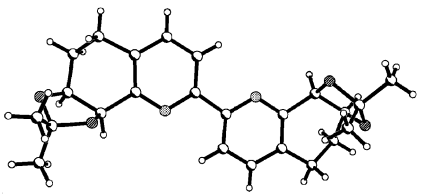
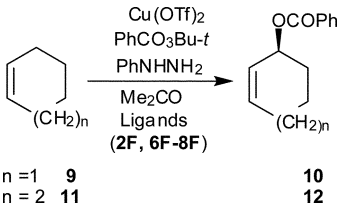


Fig. 1 X-ray crystal structure of 2,2′-bipyridine **2F**.[10]



Scheme 3 Asymmetric allylic oxidation of alkenes **9** and **11**.

Table 1 Isolated yields and % *ee* values of products **10** and **12** obtained by asymmetric allylic oxidation of alkenes **9** and **11**

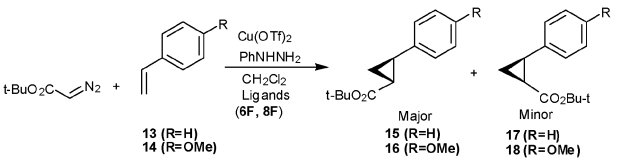
		Product		
Ligand	Alkene		Yield (%)	% *ee*
2F	**9**	**10**	89	73
	11	**12**	50	85
6F	**9**	**10**	92	82
	11	**12**	43	91
7F	**9**	**10**	55	85
	11	**12**	72	92
8F	**9**	**10**	91	90
	11	**12**	89	97

elemental microanalysis, NMR and mass spectrometry and was found to have two molecules of ligand **2F** complexed as a Cu(I) perchlorate. The data obtained are consistent with the chelated nitrogen atoms of ligand **2F** adopting a *cisoid* conformation coordinated in a distorted tetrahedron around the copper(I) ion.

The Cu(I) catalyst required in allylic hydroxylation reactions was generated *in situ* by reduction of the complex of Cu(II) triflate with bipyridine ligands **2F**, **6F–8F** (6 mol%) using phenylhydrazine in acetone solvent.[11]

The benzoate products **10** and **12** were obtained with a strong preference (73–97% *ee*) for the (*S*) configuration (Table 1). The optimal *ee* values in both the cyclohexene benzoate **10** (90%) and cycloheptene benzoates **12** (97%) were obtained using 2,2′-bipyridine ligand **8F**, where the bulky *tert*-butyl group appeared to have a strong directing effect. These results are comparable to the best achieved using various pyridine bis(diphenyloxazoline) ligands (up to 98% *ee*)[12a,b] and better than those obtained using other chiral 2,2′-bipyridine ligands (up to 91%).[12c–e]

The potential of 2,2′-bipyridines **6F** and **8F** as chiral ligands (1.5 mol%) during the asymmetric cyclopropanation of styrene substrates **13** and **14** was evaluated using $Cu(OTf)_2$, phenylhydrazine and *tert*-butyl diazoacetate (Scheme 4). The major *trans* substituted cyclopropanes **15** and **16** (90–97%) were readily separated from *cis* isomers **17** and **18** by PLC, with combined yields of *ca.* 50–70% (Table 2). The Cu(I) complexes of ligands **6F** and **8F** catalysed asymmetric



Scheme 4 Asymmetric cyclopropanation of alkenes **13** and **14**.

Table 2 Relative yields and *ee* values of products **15** and **16** from asymmetric cyclopropanation of alkenes **13** and **14**

		Product		
Ligand	Alkene		Yield (%)	% *ee*
6F	**13**	**15**	91[a]	88
6F	**14**	**16**	90[b]	91
8F	**13**	**15**	95[a]	92
8F	**14**	**16**	97[b]	95

[a] Relative to product **17**. [b] Relative to product **18**.

cyclopropanation of alkenes **13** and **14**, to give products **15** and **16** with high *de* (80–94%) and *ee* (88–95%) values. These results are comparable to the best reported using other types of chiral 2,2′-bipyridines obtained by alternative synthetic methods.[13]

The results in Tables 1 and 2 show that the new chiral 2,2′-bipyridines **2F**, **6F**, **7F** and **8F** obtained by the chemoenzymatic route are particularly useful in Cu(I)-catalysed reactions of alkenes to yield benzoate esters of chiral allylic alcohols and cyclopropanes with *ee* values up to 95–97%. This new route to chiral ligands has the additional advantage of synthetic versatility. Thus, for example, the addition of further chiral centres is possible *via* epoxidation or *cis*-dihydroxylation of the remaining alkene bonds in *cis*-dihydrodiols **2B**, **3B**, **5B** and bipyridine **5F**.

The potential of the 2,2′-bipyridines **3F** and **5F**, obtained using the same chemoenzymatic method, and the corresponding mono- and di-*N*-oxide derivatives of 2,2′-bipyridines **2F**, **3F**, **5F–8F** as chiral ligands for these and other types of catalytic asymmetric synthesis is currently under investigation.

In conclusion, this preliminary study has demonstrated that enantiopure *cis*-dihydrodiol bioproducts derived from azaarene substrates containing several functionalities can be converted in three steps to a new range of 2,2′-bipyridines. Several new 2,2′-bipyridines have already proved to be useful ligands for asymmetric allylic oxidation and cyclopropanation of alkenes. The synthetic versatility of these and other *cis*-dihydrodiol metabolites from mono- and polycyclic azaarenes should generate many new 2,2′-bipyridine ligands with applications to a much wider range of catalytic asymmetric synthesis reactions.

4-Chloroquinoline has similarly been found to yield a useful *cis*-dihydrodiol metabolite. This has in turn been used as an enantiopure building block in the production of chiral metal–organic frameworks (MOFs).[14]

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10 **Crystal data for 2F**: $C_{24}H_{28}N_2O_4$, M = 408.5, monoclinic, a = 10.103(4), b = 7.746(2), c = 13.929(4) Å, β = 93.59(2)°, U = 1088.0(6) Å^3, space group $P2_1$ (no. 4), Z = 2, T = 293(2) K, Mo-Kα radiation, λ = 0.71073 Å, $F(000)$ = 436, D_x = 1.247 g cm^{-3}, μ = 0.085 mm^{-1}, Bruker P4 diffractometer, ω scans, 4.0° < 2θ < 60.0°, measured/independent reflections: 4399/3383, R_{int} = 0.031, direct methods solution, full-matrix least squares refinement on F_o^2, anisotropic displacement parameters for non-hydrogen atoms; all hydrogen atoms located in a difference Fourier synthesis but included at positions calculated from the geometry of the molecule using the riding model, with isotropic vibration parameters. R_1 = 0.058 for 2058 data with $I > 2\sigma(I)$, 276 parameters, ωR_2 = 0.168 (all data), GoF = 1.02, $\Delta\rho_{min,max}$ = −0.20/0.30 e Å^{-3}. CCDC reference number 698751. The molecule has a *transoid*-conformation with respect to the pyridine rings. The N–C–C–N torsion angle is −176.5°. Data can be obtained from ESI or free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

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