Iron(III) Complexes of Chiral Bipyridine Macrocycles as Novel Metallo-catalysts

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We have prepared a novel series of chiral macrocycles based on amino acid-linked bipyridines; the iron(III) complexes of these ligands act as catalysts for alkene epoxidation.

The remarkable stereoselectivity of many metalloenzyme-catalysed reactions is due, in large part, to the chiral environment surrounding the metal. Synthetic macrocyclic ligands offer an attractive way of holding chiral groups in similar proximity to a metal centre in such a way that they can interact with an approaching substrate.[1] In designing potential ligands for catalytically active transition metals we sought to incorporate the following features: (i) a π-acceptor ligand capable of sustaining a range of metal oxidation states, (ii) readily available and modifiable chiral residues close to the metal and capable of influencing the approach of a substrate, (iii) a readily variable cavity size for the control of substrate selectivity, (iv) sufficient chemical stability to withstand multiple turnovers under a range of catalytic reaction conditions.

In this paper the preparation, complexation, and catalytic properties of a new macrocyclic ligand containing a bipyridine unit linked to two amino acid residues (**1**) are reported.[2] The iron(III) complex of this compound has been prepared and shown to be capable of catalysing the epoxidation of alkenes.

The synthesis of (**1**) is outlined in Scheme 1. Reaction of *N*-benzyloxycarbonyl-L-valine (2 equiv.) and 1,5-diaminopentane with 2-chloro-*N*-methylpyridinium iodide gave the diamide (**2**)† in 79% yield. Deprotection by catalytic hydrogenation (10% Pd–C, MeOH) afforded the diamine (**3**)† in 98% yield. High-dilution coupling of (**3**) and 6,6′-bis(chlorocarbonyl)-2,2′-bipyridine (**4**)[3] ($<10^{-3}$ M, CH_2Cl_2, Et_3N) followed by alumina chromatography (CH_2Cl_2–MeOH, 100:1) and crystallization from acetonitrile provided (**1**) in 67% yield {m.p. 289—91 °C, $[\alpha]_D^{25}$ 107.8° (*c* 1, CH_2Cl_2)}, ^{1}H n.m.r. ($CDCl_3$) δ 8.66 (d, *J* 9.1 Hz, 2H, N*H*CH), 8.29 (d, *J* 7.5 Hz, 2H, bipy 5-H), 8.04 (t, *J* 7.5 Hz, 2H, bipy 4-H), 7.82 (d, *J* 7.5 Hz, 2H, bipy 3-H), 7.20 (m, 2H, N*H*CH_2), 4.63 (dd, *J* 5.1 and 9.1 Hz, CHCO), 3.63, 3.08 (m, 4H, CH_2N), 2.39 (m, 2H, C*H*Me), 1.60 (m, 4H, C$H_2$$CH_2N$), 1.45 (m, 2H, C$H_2$$CH_2$$CH_2N$), 0.97 (d, *J* 6.6 Hz, 3H, Me), and 0.95 (d, *J* 6.6 Hz, 3H, Me)}. By replacing L-valine with L-proline in Scheme 1, the analogous bipyridine (bipy)–proline macrocycle was prepared in similar overall yields.

Inspection of CPK (Corey–Pauling–Koltun) molecular models suggested a preferred conformation for (**1**) in which both valine carbonyl groups are turned inward and capable of binding to the complexed metal. In this form the isopropyl

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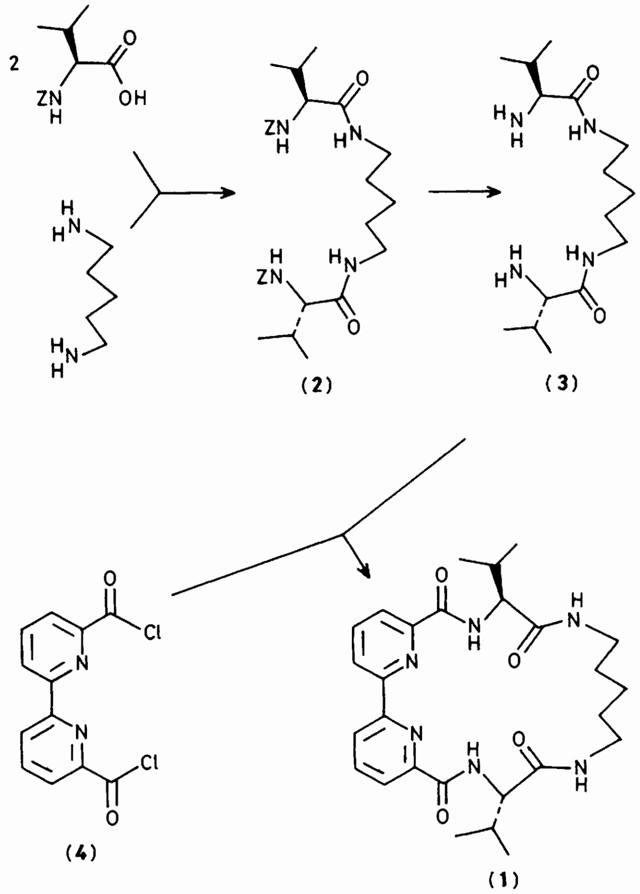
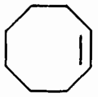
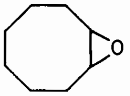
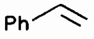
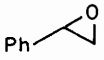
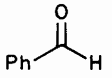
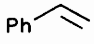
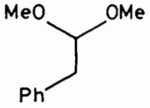
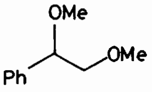
† All new compounds gave satisfactory spectroscopic and combustion and/or mass spectral data.



Scheme 1. Z = $PhCH_2OC(:O)$–.

Table 1. Epoxidation studies with complex (**1**) and iodosylbenzene.[a]

Solvent	Substrate	Product (% yield)
MeCN		 (55)
MeCN		 (10)  (20)
CH_2Cl_2-MeOH		 (39)  (6)

[a] Typical experiment: the complex (2×10^{-5} mol) was dissolved in the solvent (3 ml) and treated with substrate (9×10^{-4} mol) under argon. Solid iodosylbenzene (3.5×10^{-4} mol) was added during 4 h with stirring with the formation of an orange complex. After stirring overnight the red colour reappeared and the mixture was worked up by column chromatography (silica; hexane–Et_2O). Products were identified by gas chromatography and ^1H n.m.r. spectroscopy. [b] Yields calculated relative to iodosylbenzene consumed.

substituents should be perpendicular to the plane of the ring in a good position to interact with an incoming substrate.

As expected (**1**) forms complexes with a range of transition metals. For example addition of (**1**) to a solution of $Fe(ClO_4)_3$ in acetonitrile formed an air-stable, deep red complex, with a characteristic metal–bipyridine charge transfer band at 537 nm[4] [$\lambda_{max.}$ ($\varepsilon \times 10^{-3}$) 254 (103), 298 (55), and 537 nm (6.7)], which could be isolated as a red powder from methylene chloride–hexane (m.p. 210 °C, decomp.).‡ The proline macrocycle did not form a complex with $Fe(ClO_4)_3$. This is presumably due to the more rigid proline residues forcing the macrocycle to take up a conformation which does not allow access to the bipyridine. Ligands of type (**1**) should be applicable to a range of metal–bipyridine-catalysed processes, *e.g.* epoxidation, cyclopropanation, 1,2-hydroxylation, *etc.* We have initially investigated the catalytic reactivity of Fe^{III}–(**1**) towards alkene epoxidation. A number of metal complexes, particularly derived from porphyrins,[5] have been shown to be effective catalysts for the epoxidation of alkenes by various oxidants (iodosylbenzene, hydroperoxides, peracids, *etc.*) *via* metal–oxo species. Treatment of a deep red solution of Fe^{III}–(**1**) in acetonitrile with iodosylbenzene generated a pale orange species ($\lambda_{max.}$ 465 nm; ε 5.7×10^{-3}) which was capable of epoxidizing alkenes. The nature of the products and their yields are shown in Table 1. Cyclo-octene gave exclusively epoxidized product in reasonable yield while styrene formed its epoxide and benzaldehyde.§ Analysis of the stereoselectivity of styrene epoxide formation using the chiral shift reagent $Eu(hfs)_3$[6] {tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorato]europium(III)} showed essentially racemic product. This is understandable as the least hindered approach of the alkene to a metal-bound oxidizing agent will be from the side opposite the isopropyl groups with only minimal chiral interaction. Interestingly the oxidation of styrene in methylene chloride–methanol (4 : 1) resulted in two new products, (1,2-dimethoxyethyl)benzene (DMEB) and phenylacetaldehyde dimethylacetal (PADA) in fair overall yield. These products may arise from direct methanol trapping (for DMEB) or rearrangement followed by reaction with methanol (for PADA) of the proposed β-cation[6] or β-radical[7] intermediates in metal–oxo-catalysed epoxidations. We are further investigating the mechanistic implications of these findings. In each of the above cases after multiple turnovers of the catalyst (>10) the deep red colour of Fe^{III}–(**1**) returned when all the iodosylbenzene had been consumed.

In summary we have developed routes to transition metal complexes of chiral bipyridine macrocycles and shown them to be effective catalysts for alkene epoxidation under strongly oxidizing conditions. We are presently making rational changes to (**1**) to increase the steric bulk around the metal centre in order to improve the enantiofacial selectivity of approach of the substrate.

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‡ The valine carbonyl stretching frequency (ν_{CO}) diminishes by 40 cm^{-1} on complexation, indicating participation of the carbonyl groups in metal binding.

§ This reactivity is dependent on the macrocyclic structure of (**1**). The acyclic derivative [formed from (**4**) and L-valine methyl ester] did not complex $Fe(ClO_4)_3$.

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