L-Prolinoyl chiral picket iron porphyrins evaluated for the enantioselective epoxidation of alkenes

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Four atropisomers of an L-prolinoyl picket porphyrin were synthesised from tetra-*o*-aminophenyl porphyrin (TAPP) and were evaluated as alkene epoxidation catalysts after incorporation of iron in the porphyrin core. In the case of the αααα atropisomer bearing the four amino groups on the same side, a bulky base was employed in order to suppress the eventual reaction on the non-functionalised side of the porphyrin. The resulting enantioselectivities were compared with either other chiral motifs or with the corresponding strapped porphyrins. The enantioselectivities obtained with picket porphyrins are as high as those for strapped porphryins, and in some cases, even higher.

Introduction

In the permanent quest for selective and efficient enantioselective porphyrinoid catalysts for the epoxidation of alkene, a very large number of different chiral superstructures has already been reported.[1–3] Unfortunately, and although some remarkable catalysts are known, systematic studies dealing with very subtle structural variations and leading to complete series of new catalysts are still lacking. So far, only rare illustrations of these studies have been reported and obviously, what has been realised for the salen type ligand[4] remains to be undertaken in the context of the porphyrin core.[5,6] Nevertheless, some examples of detailed studies have recently been published.[5–11] We have scrutinised the influence of different chiral straps in D_2- or C_2-symmetrical superstructures. Although the enantiomeric excesses (ee) were low (31% at best), we were able to reach two conclusions.[12] Firstly, no general structure-activity relationship was to be found between the steric hindrance and observed enantioselectivity. Secondly, the chiral strap, if not flexible enough or too close to the metal centre, has a negative effect on the enantioselectivity. An alternative to these too-congested chiral porphyrins could be illustrated by the analogous catalysts in which the straps do not exist. In this work, the corresponding—with the same chiral inducer—picket porphyrins have been studied in exactly the same conditions. Additionally, to compare with already described results, two other chiral amino acids have also been employed. To do so, we chose two amino acids with an alcohol function that can be easily protected with the tosyl group, thereby increasing the size of the lateral chain of the amino acid.

Results and discussion

Synthesis and characterisation of the free ligands

The picket porphyrins described in this work were synthesised as precursors of different strapped analogues that have been studied in solution by ^{1}H NMR spectroscopy and in the solid state.[10] In three previous reports, such picket porphyrins bearing chiral amino acids have been synthesised. In two of them, *N*-Boc-L-alanine and *N*-Boc-L-phenylalanine were condensed on the αβαβ atropisomer of tetra-*o*-aminophenyl porphyrin (TAPP) by the isobutyl chloroformate method, which allows no epimerisation during the synthesis.[13,14] In the third report, *N*-Boc-L-proline has been attached on the same porphyrin *via* the dicyclohexylcarbodiimide (DCC) procedure, yielding zinc porphyrins useful for the chiral recognition of amino esters.[15] Our own results with L-prolinoyl strapped porphyrins prepared from the αβαβ and ααββ atropisomers of TAPP prompted us to enlarge this investigation to the four analogous picket porphyrins based on the four atropisomers of TAPP.[16] Such a study has been carried out only once[9] in the case of the epoxidation of styrene. In this study, the chiral centre came from a binaphthyl aldehyde condensed with pyrrole and the ααββ atropisomer was shown to be the most enantioselective with 57% ee, a result consistent with the catalyst of Collman, Rose and coworkers.[17]

In our case, the four atropisomers of TAPP were primarily separated by low pressure silica gel chromatographies and then functionalised with the *N*-Boc amino acid (Fig. 1). For the αααα atropisomer, Lindsey's method for the equilibrium displacement was applied.[18] The typical coupling reaction was carried out using mixed anhydride activation, a classical procedure in peptide synthesis.[19] The formation of the amide bond between the porphyrin and the *N*-Boc-L-proline was accomplished in dry tetrahydrofuran (THF) in the presence of *N*-methylpiperidine at room temperature after activation of the carboxylic acid of the amino acid with isobutylchloroformate at −20 °C, in the same solvent.[20] An excess of *N*-protected amino acid (100 equiv.) was required. This coupling reaction proceeds with excellent yields of *ca* 85%.

The chiral integrity of the *N*-Boc-L-proline was conserved after the coupling reaction as shown by the ^{1}H NMR spectrum of the porphyrin in which the Boc group was removed with CF_3CO_2H–CH_2Cl_2 (1:10) at room temperature.[21] The resulting porphyrin exhibits a sharp and well-resolved ^{1}H NMR

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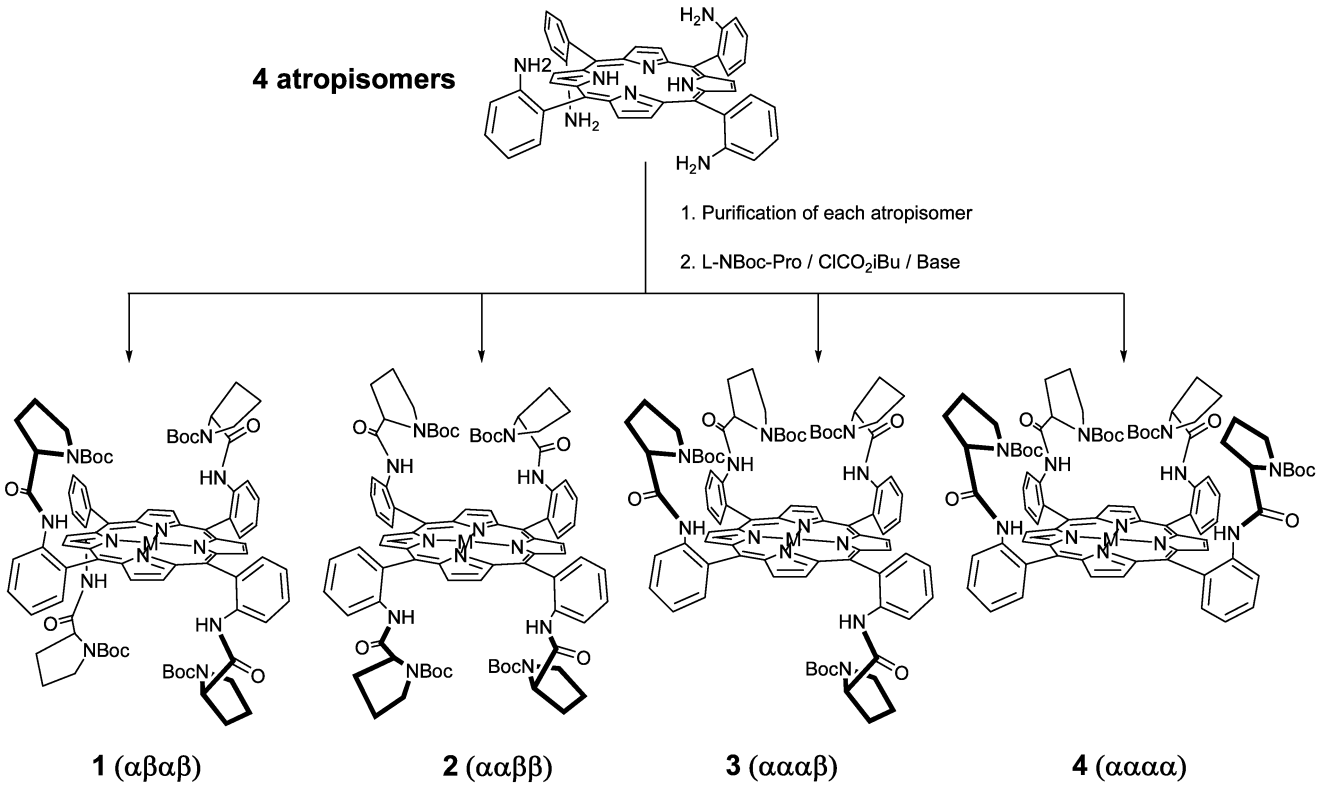

Fig. 1 Synthetic pathway for the preparation of the four L-prolinoyl chiral atropisomers (M = 2H or FeCl).

spectrum.† Particularly noteworthy are the protons bound to the β-pyrrolic and chiral carbons, which appear as 2 singlets (4H) at 8.76 and 8.83 ppm and a triplet (^3J = 6.8 Hz) at 3.16 ppm, respectively. Such an observation was not possible with picket porphyrins having Boc group, because of broad signals most certainly resulting from the rotation of the bulky Boc residue, as reported for the L-alanine[22] and L-phenylalanine analogues.[14,23]

Asymmetric epoxidation of olefins

The four L-prolinoyl iron(III) chloro derivatives **1**–**4** were evaluated for the epoxidation of two quite different olefins: *p*-chlorostyrene and 1,2-dihydronaphthalene. The former is a terminal olefin, the latter disubstituted and more encumbered. It has already been shown that the enantioselectivities obtained with these two olefins can be significantly different. Additionally, in the case of the αβαβ atropisomer, two other chiral amino acids were employed: *O*-*p*-toluenesulfonyl-L-*trans*-4-hydroxyproline (TsO-L-HOPro) and *O*-*p*-toluenesulfonyl-L-tyrosine (TsO-L-Tyr), which are structural analogues of the native amino acids but more sterically hindered (Fig. 2).

Iodosylbenzene was used as the single oxygen donor and a 1000:100:1 ratio was maintained for the substrate, oxidant and catalyst, respectively. These were dissolved in degassed CH_2Cl_2 in a Schlenk tube. The mixture was stirred at room temperature for 30 min and then quenched with 2% PPh_3 in CH_2Cl_2 to consume the excess iodosylbenzene. Enantiomeric excesses were determined by GC using a Chirasil-Dex CB column. The results are listed in Table 1. For comparison purposes, the ee obtained with two strapped porphyrins in the αβαβ and ααββ geometries are also reported in this table (entries 7 and 8).[12]

† In the L-prolinoyl series, and in opposition with the L-alanine and L-phenylalanine cases, the porphyrins bearing the deprotected amino acid, in our hands, were stable enough to allow NMR data to be recorded but not enough to allow further reactions after their purification.

Different observations must be underlined:

–For both olefins, it is striking that the ααββ isomer leads to the lowest ee. Surprisingly, it has been shown that this atropisomer, bearing binaphthyl residues, exhibits very high enantioselectivies.[17]

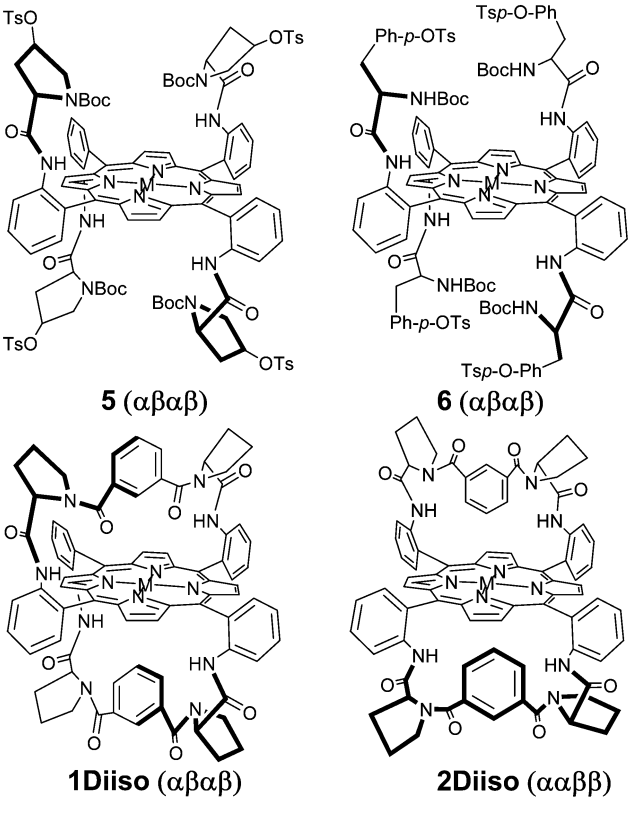

Fig. 2 Different picket and strapped chiral porphyrins (M = 2H or FeCl) built from L-proline, L-*trans*-4-*O*-tosylhydroxyproline or L-*O*-tosyltyrosine.

Table 1 Enantiomeric excesses (%) obtained with different L-amino acyl porphyrins for the epoxidation of *p*-chlorostyrene and 1,2-dihydronaphthalene

Compound	*p*-Chlorostyrene	1,2-Dihydronaphthalene
1Fe	16.5	34
2Fe	4	9
3Fe	10	14.5
4Fe[a]	22	10
5Fe	4	28
6Fe	1	7
1DiisoFe[b]	5	19
2DiisoFe[b]	28	14

[a] With 1-*tert*-butyl-5-phenylimidazole. [b] See ref. 12.

–The ee with the αβαβ atropisomer reaches 34% in the case of the disubstituted olefin, a better enantioselectivity than the one reported for the analogous strapped porphyrin **1**DiisoFe, for which only 19% was obtained.

–In the αααα geometry, although the enantiogenic face is sterically crowded, and provided a very bulky axial base is employed (Table 2), the best ee among the four atropisomers is obtained for the terminal olefin. Incidentally, it can be noted that the effect on the enantioselectivity of 1-*t*Bu-5-phenylimidazole[24] is significant in comparison with that of 4,5-diphenylimidazole.

–The substitution of L-Pro with either TsO-L-HOPro or TsO-L-Tyr does not improve the enantioselectivity. This confirms that, even in a flexible structure, too much hindrance implies a negative consequence on the selectivity of the epoxidation reaction.

The choice of a chiral inducer with a cyclic structure, namely L-proline, induces a significant increase in the ee in comparison with other motifs such as phenylalanine or related structures.[25] In the latter, although the ee does not reach 10%, an inverted structure-activity relation is found, according to the number of pickets. Additionally, an increase in the steric hindrance at the periphery of the cycle is totally vain in the case of the terminal olefin and has no effect for the disubstituted one, as shown with catalyst **5**Fe (Table 1).

The combined results obtained from both L-prolinoyl picket and L-prolinoyl strapped porphyrins show that the αβαβ-strapped structures are not very selective, independently of the nature of the olefin. In our case, the analogous picket catalyst leads to much better results. In the ααββ geometry, the opposite conclusion seems to be reached: the strapped structures are more selective than the picket moieties. This cannot be explained by the possible mobility of the pickets, which should be at least equivalent in the αβαβ conformation.

Finally, in light of our results, the αααβ conformation represents the most versatile catalyst with respect to the nature of the olefin. Indeed, the porphyrin **3**Fe is the only catalyst for which the ee obtained for both olefins are quite similar. We believe that, if the structural problem of the single picket on one side of the macrocycle can be solved, this conformation could deserve more investigation.

Table 2 Enantiomeric excesses (%) obtained with **4**Fe and different axial bases for the epoxidation of *p*-chlorostyrene and 1,2-dihydronaphthalene

Axial base	*p*-Chlorostyrene	1,2-Dihydronaphthalene
Pyridine	5	8
4,5-Diphenylimidazole	6	8
1-*t*Bu-5-phenylimidazole	22	10

Conclusion

With a common chiral moiety, we have investigated the enantioselectivities of the four possible atropisomers of a chiral picket porphyrin. The results are compared with those obtained for two strapped porphyrin geometries, prepared with the same chiral motif, evidently. Three clear conclusions can be drawn. (1) For the picket structures, the αβαβ conformation is the best one. (2) In the case of strapped porphyrins, the ααββ geometry is confirmed to lead to the best enantioselectivity. (3) Independently of the nature of the olefin, the correct balance between steric hindrance and chiral induction cannot be achieved with this type of porphyrin. New strategies targeting more versatile and efficient catalysts are under investigation in our laboratories.

Experimental

General considerations

The analytical facilities were provided by the Université de Bourgogne (C.S.M.) in Dijon. ^{1}H (500.13 MHz) and ^{13}C (125.05 MHz). NMR spectra were recorded on a Bruker Avance DRX 500 spectrometer and referenced to the residual protonated solvents. Mass spectra were acquired on a MS/MS ZABSpec TOF spectrometer at the Université de Rennes 1 (C.R.M.P.O.). UV-vis spectra were recorded on a Varian Cary 1E spectrometer. IR spectra were recorded on a Bruker IFS 66 spectrometer. All solvents (ACS for analysis) were purchased from Carlo Erba. THF was distilled from potassium metal. CH_2Cl_2 was used as received. Triethylamine and *N*-methylpiperidine were distilled on CaH_2. The starting materials were generally used as commercially available (Acros, Aldrich) without any further purification. All reactions were performed under an argon atmosphere and monitored by TLC (silica, CH_2Cl_2–CH_3OH). Column flash chromatographies were performed on silica gel (Merck TLC-Kieselgel 60H, 15 μm).

Synthesis of free ligands

α-5,15:β-10,20-Tetrakis[2-(*N*-*tert*-butoxycarbonyl-L-prolinoylamido)phenyl]porphyrin, 1. *N*-Boc-L-proline (19.46 g, 90.4 mmol, 100 equiv.) were dissolved in dry THF (120 mL) under an argon atmosphere, at −20 °C. *N*-methylpiperidine (16.5 mL, 135 mmol, 150 equiv.) and then isobutylchloroformate (11.15 mL, 85.9 mmol, 95 equiv.) were added. Immediately, a white precipitate appeared. Then a solution of 610 mg of αβαβ-TAPP (0.9 mmol) in 50 mL of THF, maintained at −20 °C, was added. The reaction mixture was stirred 3 h at this temperature and then was warmed to room temperature. The mixture was filtered and the precipitate washed with diethyl ether. The solution was evaporated under vacuum and the residue was chromatographed on silica gel (elution with a CH_2Cl_2–MeOH (98:2)). The pure product was obtained in 85% yield (1.15 g). ^{1}H NMR 500 MHz (δ ppm, $CDCl_3$, 300 K): −2.58 (s. 2H, NH_{pyr}), 0.35 (m, 12H, Pro), 0.95 (s, 36H, Boc), 1.28 (s, 8H, Pro), 1.53 (s, 4H, Pro), 3.56 (s, 4H, Pro*), 7.57 (s, 8H, aro), 7.88 (s, 4H, aro), 8.05 (s, 4H, NHCO), 8.69 (s, 4H, aro), 8.75 (s, 4H, β-pyr), 8.78 (s, 4H, β-pyr). ^{13}C NMR 125 MHz (δ ppm, $CDCl_3$, 300 K): 28.2, 30.7, 45.3, 46.4, 61.7, 79.5, 80.1, 115.3, 121.4, 122.3, 123.6, 130.4, 131.9, 132.0, 134.8, 138.7, 153.2, 154.6, 170.7, 171.3. UV-vis [CH_2Cl_2, λ/nm ($10^{-3}\cdot\varepsilon$/M^{-1} cm^{-1})]: 419 (357.2), 513 (22.3), 546 (5.2), 588 (6.3), 645 (1.9). MS (FAB): m/z = 1463.0 $[M]^{+\bullet}$. IR (KBr, υ/cm^{-1}): 3380 (NH), 1698 (CO).

α-5,10:β-15,20-Tetrakis[2-(*N*-*tert*-butoxycarbonyl-L-prolinoylamido)phenyl]porphyrin, 2. 2 was synthesised according to the above-mentioned procedure, fully described for compound **1**. The pure compound was obtained in 89% yield (1.18 g). ^{1}H

NMR 500 MHz (δ ppm, $CDCl_3$, 300 K): −2.68 (s, 2H, NH_{pyr}), −1.96 (s, 1H, Pro), −1.63 (m, 1H, Pro), −0.99 (m, 1H, Pro), −0.44 (m, 2H, Pro), −0.12 (m, 4H, Pro), 0.63 (m, 4H, Pro), 0.89 (m, 6H, Pro), 1.17 (m, 36H, Boc), 1.61 (s, 3H, Pro), 2.66 (m, 2H, Pro), 3.49 (m, 4H, Pro*), 7.18 (s, 2H), 7.64 (d, *Jo* = 7.0 Hz, 2H), 7.90 (m, 4H), 8.00 (d, *Jo* = 7.5 Hz, 4H), 8.10 (s, 2H), 8.16 (m, 4H), 8.61 (d, *Jo* = 6.5 Hz, 2H), 8.71 (s, 2H), 8.80 (s, 4H, NHCO), 8.87 (s, 2H). ^{13}C NMR 125 MHz (δ ppm, $CDCl_3$, 300 K): 28.7, 28.9, 30.1, 43.9, 46.4, 59.5, 61.7 114.5, 117.7, 120.6, 123.7, 124.6, 125.0, 127.3, 127.5, 130.2, 130.6, 131.8, 133.2, 134.0, 136.09, 139.1, 145.9, 152.9, 154.3, 170.5, 171.5. UV-vis [CH_2Cl_2, λ/nm ($10^{-3}\cdot\varepsilon/M^{-1}$ cm^{-1})]: 419 (308.2), 513 (16.8), 546 (3.9), 587 (4.9), 642 (1.7). HR-MS (LSI-MS): calcd. m/z = 1485.7012 $[M+Na]^+$ for $C_{84}H_{94}N_{12}NaO_{12}$, found 1485.6994. IR (KBr, υ/cm^{-1}): 3383 (NH), 1698 (CO).

α-5,10,15:β-20-Tetrakis[2-(*N-tert*-butoxycarbonyl-L-prolinoyl-amido)phenyl]porphyrin, 3. 3 was synthesised according to the above-mentioned procedure, fully described for compound **1**. The pure compound was obtained in 90% yield (1.19 g). ^{1}H NMR 500 MHz (δ ppm, $CDCl_3$, 300 K): −2.61 (s, 2H, NH_{pyr}), −0.88 (s, 2H, Pro), −0.75 (s, 2H, Pro), 0.55 (s, 10H, Pro), 1.13 (s, 6H, Pro), 1.30 (s, 27H, Boc), 1.45 (s, 9H, Boc), 1.58 (s, 4H, Pro), 3.53 (s, 4H, Pro*), 7.64 (s, 4H), 7.89 (s, 4H), 8.01 (s, 4H), 8.31 (s, 2H), 8.78 (m, 10H). ^{13}C NMR 125 MHz (δ ppm, $CDCl_3$, 300 K): 26.3, 28.0, 28.9, 30.1, 30.2, 40.9, 43.8, 45.8, 61.7, 79.8, 112.5, 114.4, 121.8, 123.7, 125.0, 130.4, 131.8, 133.6, 134.7, 138.9, 153.7, 154.5, 169.3, 170.5. UV-vis [CH_2Cl_2, λ/nm ($10^{-3}\cdot\varepsilon/M^{-1}$ cm^{-1})]: 419 (372.7), 513 (19.8), 547 (5.1), 588 (6.0), 644 (2.2). HR-MS (LSI-MS): calcd. m/z = 1485.7012 $[M+Na]^+$ for $C_{84}H_{94}N_{12}NaO_{12}$, found 1485.7015. IR (KBr, υ/cm^{-1}): 3382 (NH), 1698 (CO).

α-5,10,15,20-Tetrakis[2-(*N-tert*-butoxycarbonyl-L-prolinoyl-amido)phenyl]porphyrin, 4. 4 was synthesised according to the above-mentioned procedure, fully described for compound **1**. The pure compound was obtained in 79% yield (1.05 g). ^{1}H NMR 500 MHz (δ ppm, $CDCl_3$, 300 K): −2.63 (s, 2H, NH_{pyr}), 0.47 (m, 2H, Pro), 0.98 (m, 9H, Pro), 1.49 (m, 9H, Pro), 1.53 (m, 36H, Boc), 3.01 (m, 2H, Pro), 3.41 (m, 2H, Pro), 3.80 (m, 4H, Pro*), 7.44 (m, 2H), 7.54 (m, 4H), 7.64 (m, 2H), 7.84 (m, 2H), 7.89 (t, *Jo* = 7.5 Hz, 4H), 8.04 (s, 1H), 8.10 (m, 1H), 8.21 (m, 1H), 8.25 (d, *Jo* = 7.5 Hz, 2H), 8.64 (t, *Jo* = 7.5 Hz, 2H), 8.73 (m, 2H), 8.77 (d, *Jo* = 4.5 Hz, 2H, β-H), 8.79 (d, *Jo* = 4.5 Hz, 2H, β-H), 8.83 (m, 2H), 8.87 (m, 4H), 9.01 (d, *Jo* = 4.0 Hz, 2H, β-H), 9.05 (d, *Jo* = 4.0 Hz, 2H, β-H), 9.12 (m, 1H), 9.22 (m, 1H). ^{13}C NMR 125 MHz (δ ppm, $CDCl_3$, 300 K): 21.3, 21.5, 22.3, 23.2, 24.1, 28.9, 29.1, 29.7, 30.2, 30.7, 31.1, 43.9, 45.4, 46.7, 46.8, 59.4, 60.6, 61.6, 79.5, 79.9, 81.0, 81.9, 82.4, 114.8, 115.1, 117.7, 118.1, 120.7, 120.9, 124.1, 124.7, 125.0, 127.9, 128.4, 129.7, 130.2, 130.6, 131.9, 134.7, 135.0, 135.4, 135.6, 135.8, 136.1, 136.5, 137.6, 137.8, 138.2, 153.7, 154.2, 154.5, 170.1, 170.2, 171.1, 172.2. UV-vis [CH_2Cl_2, λ/nm ($10^{-3}\cdot\varepsilon/M^{-1}$ cm^{-1})]: 419 (443.1), 514 (20.1), 549 (5.6), 587 (6.3), 644 (4.4). HR-MS (LSI-MS): calcd. m/z = 1485.7012 $[M+Na]^+$ for $C_{84}H_{94}N_{12}NaO_{12}$, found 1485.7024. IR(KBr, υ/cm^{-1}): 3481 (NH), 1697 (CO).

α-5,15:β-10,20-Tetrakis[2-(*N-tert*-butoxycarbonyl-*O-para*-toluene-sulfonyl-L-*trans*-4-hydroxyprolinoylamido)phenyl]porphyrin, 5. 5 was synthesised according to the above-mentioned procedure, fully described for compound **1**, but with *N-tert*-butoxycarbonyl-*O-para*-toluenesulfonyl-L-*trans*-4-hydroxyproline (**10**) as the amino acid. The pure compound was obtained in 49% yield (0.95 g). ^{1}H NMR 500 MHz 0(δ ppm, $CDCl_3$, 300 K): −2.56 (s, 2H, NH_{pyr}), 0.13 (m, 18H, Boc), 0.43 (s, 8H, Pro), 0.84 (s, 8H, Boc), 0.91 (m, 10H, Boc), 1.41 (s, 2H, Pro), 1.65 (m, 4H, Pro), 2.33 (m, 12H, CH_{3Ts}), 2.83 (s, 2H, Pro), 3.04 (s, 2H, Pro), 3.45 (m, 4H, Pro), 4.72 (s, 2H, Pro), 7.17 (s, 8H, aro + aro_{Ts}), 7.41 (s, 4H, aro_{Ts}), 7.51 (s, 8H, aro), 7.87 (s, 8H, aro), 8.39 (s, 4H, NHCO), 8.63 (s, 4H, aro), 8.75 (s, 8H, β-pyr). ^{13}C NMR 125 MHz (δ ppm, $CDCl_3$, 300 K): 21.9, 27.4, 28.1, 34.2, 37.2, 52.1, 58.7, 59.9, 79.0, 80.6, 81.0, 115.1, 122.4, 124.1, 127.9, 130.3, 132.5, 133.6, 135.7, 138.4, 145.4, 152.9, 154.5, 169.3, 170.3. UV-vis [CH_2Cl_2, λ/nm ($10^{-3}\cdot\varepsilon/M^{-1}$ cm^{-1})]: 421 (392.4), 515 (20.0), 547 (4.9), 589 (6.5), 647 (1.8). MS (FAB): m/z = 2145.3 $[M+H]^+$. IR (KBr, υ/cm^{-1}): 3475 (NH), 1699 (CO).

α-5,15:β-10,20-Tetrakis[2-(*N-tert*-butoxycarbonyl-*O-para*-toluene-sulfonyl-L-tyrosinoylamido)phenyl]porphyrin, 6. 6 was synthesised according to the above-mentioned procedure, fully described for compound **1**, but with *N-tert*-butoxycarbonyl-*O-para*-toluenesulfonyl-L-tyrosine (**8**) as the amino acid. The pure compound was obtained in 29% yield (0.11 g). ^{1}H NMR 500 MHz (δ ppm, $CDCl_3$, 300 K): −2.50 (s, 2H, NH_{pyr}), 0.82 (m, 36H, Boc), 2.32 (m, 4H, CH_{2Tyr}), 2.37 (m, 12H, CH_{3Ts}), 2.46 (m, 4H, CH_{2Tyr}), 3.67 (m, 4H, H*), 4.70 (s, 4H, NH_{Tyr}), 5.76 (m, 4H, aro), 6.12 (s, 4H, aro), 6.25 (m, 4H, aro), 7.13 (m, 12H, aro), 7.26 (m, 4H, aro), 7.31 (m, 4H, aro), 7.42 (m, 4H, aro), 7.58 (m, 4H, aro), 7.69 (m, 4H, β-pyr), 7.83 (m, 4H, aro), 8.65 (m, 4H, aro), 8.69 (m, 8H, NHCO + β-pyr). ^{13}C NMR 125 MHz (δ ppm, $CDCl_3$, 300 K): 22.0, 28.0, 28.2, 28.6, 37.9, 51.2, 55.7, 79.9, 122.0, 122.3, 124.0, 128.6, 128.9, 130.0, 130.2, 132.1, 135.2, 136.1, 137.8, 145.6, 154.8, 169.9. UV-vis [CH_2Cl_2, λ/nm ($10^{-3}\cdot\varepsilon/M^{-1}$ cm^{-1})]: 422 (254.9), 516 (14.8), 549 (4.7), 591 (4.7), 649 (2.0). MS (EI): m/z = 2343.0 $[M]^{+\bullet}$. IR (KBr, υ/cm^{-1}): 3414 (NH), 1694 (CO).

***N-tert*-Butoxycarbonyl-L-tyrosine, 7.** In a 500 mL round-bottom flask equipped with a stir bar, an addition funnel, a thermometer and a reflux condenser, in an ice bath, 6.1 g (152.5 mmol) of NaOH were dissolved in 150 mL of water. L-Tyrosine (25.12 g, 138.6 mmol) in suspension in 100 mL of *tert*-butanol are added. Di-*tert*-butyl dicarbonate (30.26 g, 138.6 mmol) in solution in 50 mL of *tert*-butanol was carefully added dropwise (with control of temperature). After the addition period, the mixture was allowed to react overnight at room temperature. The two layers were separated in a separatory funnel and the aqueous layer washed twice with 35 mL of pentane. The resulting organic layer was extracted three times with 10 mL of a saturated solution of sodium bicarbonate. The aqueous layer was cooled down in an ice bath and acidified with 2 M HCl (around 110 mL) until pH 2 was reached. The resulting precipitate was dissolved in 100 ml of ethyl acetate, washed twice with 25 mL of water and dried over magnesium sulfate. Evaporation of the solvents yielded a yellow oil, from which white crystals were obtained by addition of hexane, overnight in a refrigerator. Yield (29.25 g, 75%). ^{1}H NMR 500 MHz (δ ppm, $CDCl_3$, 300 K): 1.42 (s, 9H, Boc), 3.04 (s, 2H, CH_2), 4.55 (d, 1H, CH), 6.73 (d, 2H, aro), 6.97 (d, 2H, aro). ^{13}C NMR 125 MHz (δ ppm, $CDCl_3$, 300 K): 28.7, 37.5, 54.9, 81.2, 116.1, 127.7, 130.5, 155.4, 156.3, 176.2. MS (FAB): m/z = 281 $[M]^{+\bullet}$. Anal. calcd for $C_{14}H_{19}NO_5$ (%): C, 59.78, H, 6.81, N, 4.98; found (%): C, 59.47, H, 7.13, N, 4.88. IR (KBr, υ/cm^{-1}): 3413 (OH), 1765 (CO), 1690 (CO).

***N-tert*-Butoxycarbonyl-*O-para*-toluenesulfonyl-L-tyrosine, 8.** In a 500 mL round-bottom flask equipped with a stir bar, an addition funnel, a thermometer and a reflux condenser, in an ice bath, 1.82 g (45.5 mmol) of NaOH were dissolved in 50 mL of water. **7** (11.64 g, 41.4 mmol) in solution in 50 mL of diethyl ether was added. One added dropwise 7.89 g (41.4 mmol) of tosyl chloride in solution in 50 mL of diethyl ether. After the addition period, the mixture was allowed to react overnight at room temperature. After separation of the two layers, the aqueous layer was washed twice with 35 mL of pentane.

The resulting organic layer was extracted three times with 10 mL of a saturated solution of sodium bicarbonate. The aqueous layer was cooled down in an ice bath and acidified with 2 M HCl (around 110 mL) until pH 1 was reached. The resulting precipitate was dissolved in 50 ml of ethyl acetate, washed twice with 25 mL of water and dried over magnesium sulfate. Evaporation of the solvents yielded a white solid, which was recrystallised from petroleum ether, overnight in a refrigerator. Yield (15.32 g, 85%). ^{1}H NMR 500 MHz (δ ppm, $CDCl_3$, 300 K): 1.44 (s, 9H, Boc), 2.47 (s, 3H, CH_{3Ts}), 3.06 (m, 1H, CH_2), 3.18 (m, 1H, CH_2), 4.58 (m, 1H, CH), 6.95 (d, 2H, $Jo = 8.5$ Hz, aro_{Tyr}), 7.13 (d, 2H, $Jo = 8.5$ Hz, aro_{Tyr}), 7.33 (d, 2H, $Jo = 8.1$ Hz, aro_{Ts}), 7.72 (d, 2H, $Jo = 8.1$ Hz, aro_{Ts}). ^{13}C NMR 125 MHz (δ ppm, $CDCl_3$, 300 K): 22.1, 28.7, 37.6, 54.5, 81.0, 122.9, 128.9, 130.2, 131.0, 132.7, 135.4, 145.8, 149.1, 155.7, 175.5. MS (EI): $m/z = 435$ $[M]^+$. Anal. calcd for $C_{21}H_{25}NO_7S$ (%): C, 57.92, H, 5.79, N, 3.22, S, 7.36; found (%): C, 57.82, H, 5.74, N, 3.10, S, 6.64. IR (KBr, υ/cm^{-1}): 1746 (CO), 1672 (CO).

***N-tert*-Butoxycarbonyl-L-*trans*-4-hydroxyproline, 9. 9** was synthesised according to the above-mentioned procedure, fully described for compound **7**. The pure compound was obtained in 79% yield (25.5 g). ^{1}H NMR 500 MHz (δ ppm, $CDCl_3$, 300K): 1.40 (s, 9H, Boc), 3.46 (m, 1H, Pro), 3.56 (m, 3H, Pro), 4.43 (m, 1H, Pro), 4.47 (m, 1H, Pro*), 6.98 (s, 1H, OH). ^{13}C NMR 125 MHz (δ ppm, $CDCl_3$, 300 K): 14.5, 21.4, 28.1, 28.6, 28.7, 38.2, 39.2, 54.7, 54.9, 58.0, 58.3, 60.9, 67.4, 69.5, 70.1. MS (EI): $m/z = 232$ $[M+H]^+$. Anal. calcd for $C_{10}H_{17}NO_5$ (%): C, 51.94, H, 7.41, N, 6.06; found (%): C, 51.41, H, 7.59, N, 6.15. IR (KBr, υ/cm^{-1}): 3412 (OH), 1734 (CO), 1663 (CO).

***N-tert*-Butoxycarbonyl-*O-para*-toluenesulfonyl-L-*trans*-4-hydroxyproline, 10. 10** was synthesised according to the above-mentioned procedure, fully described for compound **8**. The pure compound was obtained in 81% yield (4.5 g). ^{1}H NMR 500 MHz (δ ppm, $CDCl_3$, 300 K): 1.27 (s, 9H, Boc), 2.29 (s, 3H, CH_{3Ts}), 3.43 (m, 4H, Pro), 4.31 (m, 1H, Pro), 4.89 (m, 1H, Pro*), 7.22 (d, $Jo = 8.1$ Hz, 2H, aro_{Ts}), 7.62 (d, $Jo = 8.1$ Hz, 2H, aro_{Ts}). ^{13}C NMR 125 MHz (δ ppm, $CDCl_3$, 300 K): 22.1, 35.8, 39.3, 52.3, 55.0, 82.4, 128.2, 130.5, 145.8, 156.4, 178.3. MS (EI): $m/z = 386$ $[M]^+$. Anal. calcd for $C_{17}H_{23}NO_7S$ (%): C, 52.97, H, 6.01, N, 3.63, S, 8.32; found (%): C, 53.05, H, 6.08, N, 3.94, S, 7.93. IR (KBr, υ/cm^{-1}): 1754 (CO), 1636 (CO).

General procedure for iron insertion

Incorporation of iron in the free-base porphyrins was accomplished by the iron(II) bromide method under a controlled atmosphere. The free-base ligand was dissolved in THF inside a glove box maintained under 1 ppm of dioxygen. 2,6-Lutidine and an excess of $FeBr_2$ were added to the mixture. The solution was heated at 55 °C for 12 h until the reaction was completed as indicated by UV-vis spectroscopy. Temperature was carefully monitored so that no atropisomerisation was to occur. The product was oxidised by air for 1 h. The solvent was removed under vacuum and the residue dissolved in CH_2Cl_2 and washed with brine. The product was chromatographed on silica gel.

1Fe(Cl). Prepared from **1**, according to the above-mentioned iron insertion method. UV-vis [CH_2Cl_2, λ/nm ($10^{-3}\cdot\varepsilon$/M^{-1} cm^{-1})]: 417 (66.1), 572 (3.7). HR-MS (LSI-MS): calcd. $m/z = 1116.4210$ $[M-4Boc-Cl+4H]^+$ for $C_{64}H_{60}FeN_{12}O_4$, found 1116.4212. IR (KBr, υ/cm^{-1}): 3382 (NH), 1701 (CO).

2Fe(Cl). Prepared from **2**, according to the above-mentioned iron insertion method. UV-vis [CH_2Cl_2, λ/nm ($10^{-3}\cdot\varepsilon$/M^{-1} cm^{-1})]: 417 (102.1), 574 (6.1). MS (FAB): $m/z = 1514.3$ $[M-Cl-2H]^+$. IR (KBr, υ/cm^{-1}): 3387 (NH), 1699 (CO).

3Fe(Cl). Prepared from **3**, according to the above-mentioned iron insertion method. UV-vis [CH_2Cl_2, λ/nm ($10^{-3}\cdot\varepsilon$/M^{-1} cm^{-1})]: 418 (99.0), 575 (8.5). MS (FAB): $m/z = 1515.6$ $[M-Cl-H]^+$. IR (KBr, υ/cm^{-1}): 3383 (NH), 1699 (CO).

4Fe(Cl). Prepared from **4**, according to the above-mentioned iron insertion method. UV-vis [CH_2Cl_2, λ/nm ($10^{-3}\cdot\varepsilon$/M^{-1} cm^{-1})]: 417 (67.8), 572 (6.5). MS (FAB): $m/z = 1513.6$ $[M-Cl-3H]^+$. IR (KBr, υ/cm^{-1}): 3411 (NH), 1697 (CO).

5Fe(Cl). Prepared from **5**, according to the above-mentioned iron insertion method. UV-vis [CH_2Cl_2, λ/nm ($10^{-3}\cdot\varepsilon$/M^{-1} cm^{-1})]: 417 (101.6), 576 (7.5). MS (FAB): $m/z = 2198.0$ $[M-Cl+H]^+$. Anal. calcd for $C_{112}H_{116}ClFeN_{12}O_{24}S_4\cdot H_2O$ (%): C, 59.74, H, 5.28, N, 7.46, S, 5.70; found (%): C, 59.64, H, 5.38, N, 7.48, S, 5.31. IR (KBr, υ/cm^{-1}): 3476 (NH), 1701 (CO).

6Fe(Cl). Prepared from **6**, according to the above-mentioned iron insertion method. UV-vis [CH_2Cl_2, λ/nm ($10^{-3}\cdot\varepsilon$/M^{-1} cm^{-1})]: 418 (68.0), 578 (4.3). MS (FAB): $m/z = 2395.8$ $[M-Cl-H]^+$. Anal. calcd for $C_{128}H_{124}ClFeN_{12}O_{24}S_4\cdot CH_2Cl_2$-(%): C, 61.51, H, 5.04, N, 6.67, S, 5.09; found (%): C, 61.92, H, 5.45, N, 6.68, S, 4.78. IR (KBr, υ/cm^{-1}): 3417 (NH), 1692 (CO).

General procedure for asymmetric epoxidation

The catalyst (1 μmol) and the olefin (1000 μmol), as well as the base (250 μmol) with **4**Fe, were dissolved in degassed CH_2Cl_2 (2 mL) in a Schlenk tube. While stirring under N_2, PhIO (100 μmol) was added in one portion. The mixture was stirred at room temperature for 30 min and then quenched with 2% PPh_3 in CH_2Cl_2. The solvent was removed under reduced pressure. Pentane was added and the mixture was filtered. Dodecane (100 μL, GC standard) was added. Enantiomeric excesses were determined by GC on a Chirasil-Dex CB capillarity column. The GC conditions were as follows: (epoxide, oven temperature, retention time): *p*-chlorostyrene oxide, 120 °C, 22.5 and 24.3 min; 1,2-dihydronaphthalene oxide, 130 °C, 18.9 and 20.4 min.

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