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Synthesis of chiral water-soluble metalloporphyrins (Fe, Ru,): new catalysts for asymmetric carbene transfer in water

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ABSTRACT

The reaction of optically active Halterman porphyrin with sulfuric acid (95%) provided the expected water-soluble *para*-tetrasulfonated porphyrin in 82% yield. The metalloporphyrin complexes were prepared by metal insertion (iron) or direct sulfonation of the chiral ruthenium porphyrin. The asymmetric addition of diazoacetate to styrene to give optically active *trans* cyclopropyl ester (ee up to 86%) was carried out in water by using chiral iron or ruthenium porphyrins with a possible reuse due to the high solubility and stability in aqueous solution.

Water-soluble metalloporphyrins have a wide range of applications as oxidation and cyclopropanation catalysts, or as hosts for molecular recognition.[1] As a result of lipophilic nature of porphyrins, and consequently difficulty in preparation, however, only limited chiral water-soluble metalloporphyrins have been synthesized for chiral recognition,[2,3] and no asymmetric catalysis in aqueous solution has yet been reported. Recently, the possibility of using water as a solvent in organic reactions has been extensively investigated, especially for stereoselective reactions.[4] For example, the preparation of cyclopropanes from alkenes and diazo substrates in water has been reported,[5,6] but the products obtained are often *cis* and *trans* isomer mixtures.[6] Over the years, our group[1,7] and others[8] have been interested in the stereoselective preparation of multisubstituted cyclopropanes and high stereoselectivities and enantioselectivities have been obtained in organic solvents. Recently, we have engaged in a research program aimed at expanding the scope of water-based organic synthesis.[9] However, O–H insertion was observed when rhodium porphyrins were used as catalysts.[10,11] In contrast, during our studies, we observed the absence of O–H insertion with tetramesitylporphyrinruthenium carbon monoxide.[12] Futhermore, we reported the first X-ray structure of a ruthenium porphyrin carbene complex with a methanol as an axial ligand *trans* to the Ru-carbon bond.[13] Since the ruthenium carbene bond was found stable in the presence of hydrophilic solvent, such as methanol, we became interested in exploring the possibility that ruthenium porphyrins (and possibly iron porphyrins) may also catalyze cyclopropanation in water and alcohols. Accordingly, we report herein the preparation of optically active water-soluble metalloporphyrins and reveal that not only ruthenium porphyrins but also iron porphyrins are indeed catalysts for diastereoselective and asymmetric cyclopropanation of styrene in water.

The starting point of the work described here was the introduction of four sulfonate groups into an optically active porphyrin with the aim of preparing water soluble porphyrins. We choose a C2-symmetric group which contains two norbornane groups fused to the central benzene ring, previously reported by Halterman and Jan.[14] Initially we planned to introduce first the sulfonic acid in the porphyrin ring of **1** and then metallation. The sulfonation of Halterman porphyrin was performed with a modified Fleischer method.[15] To prevent the fragile optically active porphyrin to be damaged, the reaction in concentrated H_2SO_4 to give **2** (Scheme 1) was run at room temperature for 5 h. The confirmation that the sulfonations have taken place in the four para positions was done by ^1H NMR. The ^1H NMR of Halterman porphyrin shows in $CDCl_3$ a resonance due to the *para*-H of the phenyl rings at 7.36 ppm; this resonance completely disappears after sulfonation in compound **1**. Smaller reaction times yielded a partially water-soluble porphyrin mixture and, thus, the sulfonation of all four of the phenyl groups appears to be necessary for a well-behaved water-soluble porphyrin.

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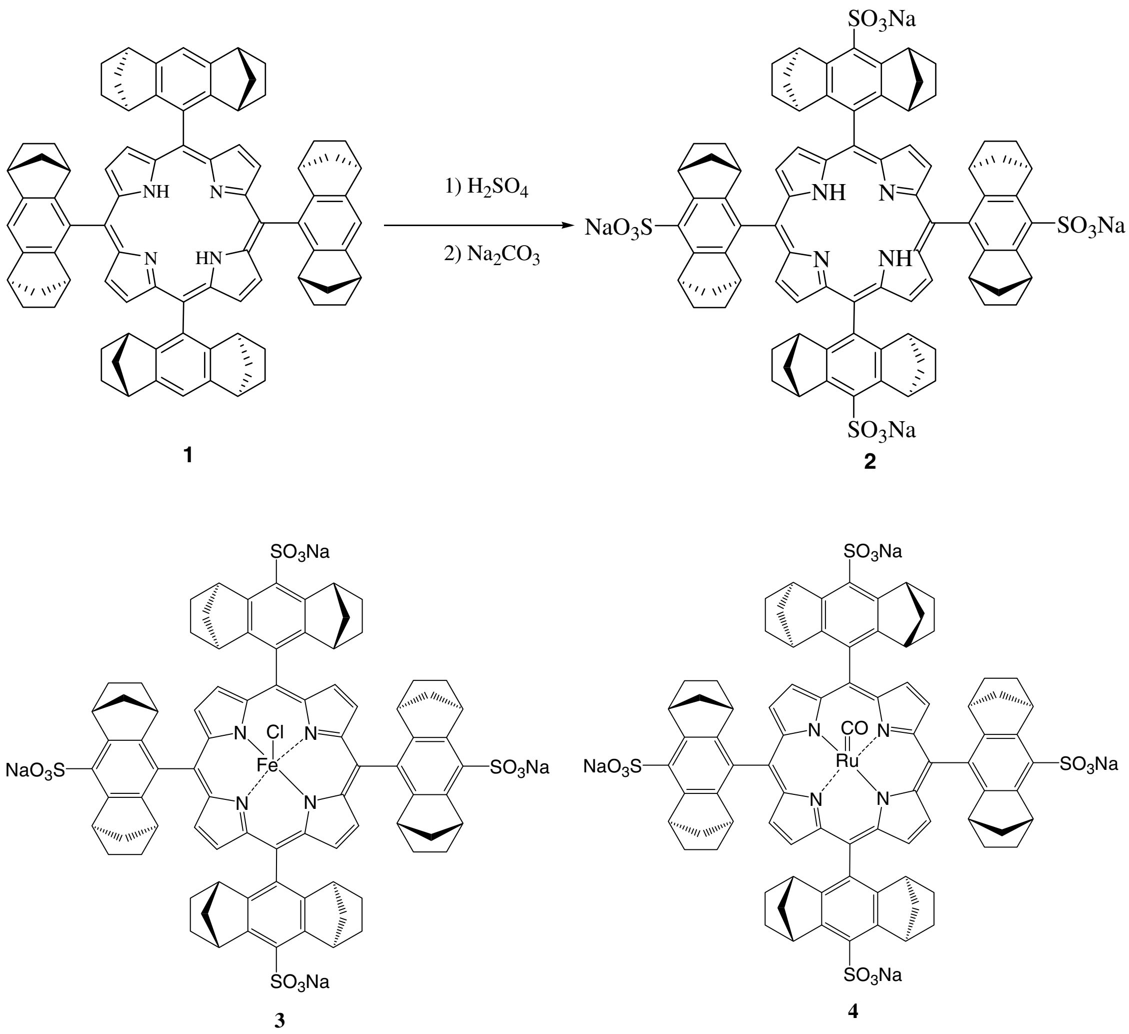
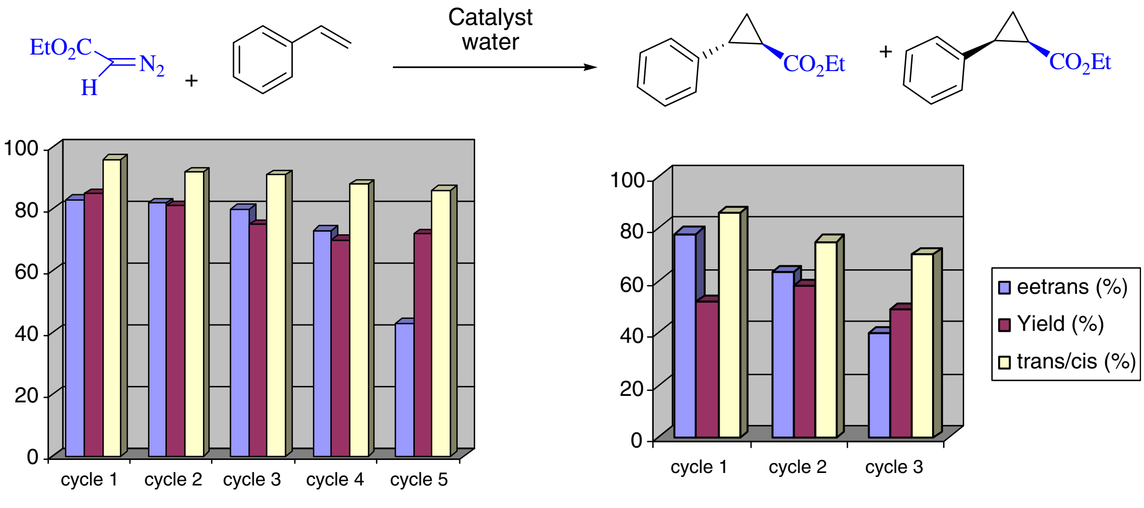


Scheme 1.



(A) Reuse of HaltSFe(Cl) **3** (B) Reuse of HaltSRu(CO) **4**

Figure 1. Reuse of: HaltSFe(Cl) **3** (A) and HaltSRu(CO) **4** (B) as catalysts for cyclopropanation of styrene with ethyl diazoacetate.

A fourfold excess of $FeCl_3$ was sufficient to get the expected metalloporphyrin **3** in a reasonable yield (51%). In contrast, all attempts to insert the ruthenium atom directly in the water-soluble porphyrin **2** failed. We then conceived an alternative strategy based on direct sulfonation of ruthenium porphyrin (Fig. 1). Starting from ruthenium Halterman porphyrin, the sulfonation was also performed in $H_2SO_4$to give **4** at room temperature for 4–5 h. All the porphyrins **2**, **3** and **4** were also characterized by ^{1}H NMR and MALDI-TOF.

The bench-mark reaction between styrene and ethyl diazoacetate to give cyclopropane esters (Scheme 1) was first tested with **3**. In all cases, the catalyst was fully dissolved in water and an additional quantity of substrate was added to the solution without any organic solvent. We chose these two reagents, extensively used molecules both in homogeneous and in heterogeneous processes, as suitable substrates to show difference in terms of enantioselectivity, diastereoselectivity and reactivity.[16] Using **3** as a chiral water-soluble catalyst, the cyclopropane was formed in good yield (85%) with high diastereoselectivity (*trans*/*cis*: 92/8) and good enantioselectivity for the *trans* isomer (83%) (Fig. 1A, cycle 1).

The recovery and recyclability of water-soluble**3** were also examined. The metalloporphyrin was tested for enantioselectivity and reactivity in the same cyclopropanation reaction leading four recycling steps with a weak progressive decrease of enantioselectivity (from 83% to 73%). As can be seen in Figure 1A, only after four cycles there was an erosion of the enantiomeric excess, whereas the chemical yield was maintained at 72% (Fig. 1A). Oxidation of the possible iron(II)-carbene complex as intermediate in the catalytic cycle with traces of oxygen may explain this latter result.

The water-soluble ruthenium porphyrin complex **4** was also tested for asymmetric cyclopropanation. The results are summarized in Figure 1B. As shown in the figure, high diastereoselectivity (*trans*/*cis*: 96/4) and good enantioselectivity for the *trans* isomer (83%) were also observed during the first cycle, but with a modest yield (52%). However, a progressive erosion in the enantiomeric excess was observed during the second (ee = 62%) and the third (ee = 40%) cycles.

In conclusion, we have successfully prepared new water-soluble metalloporphyrins[17] and demonstrated that asymmetric cyclopropanation can be efficiently performed in water for hydrophobic substrates.[18] These complexes will be applied in the near future in other catalytic asymmetric reactions and in chiral recognition of amino acids.

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17. All new compounds reported here gave spectral data consistent with the assigned structures. Reaction conditions and selected data: For **2.** Halterman porphyrin[14] (100 mg, 0.087 mmol) and sulphuric acid 95% (10 ml) were stirred for 5 h at room temperature. To the resulting solution, ice was added slowly to give a green mixture. Then water (30 ml) was added and the pH was adjusted to 7 with sodium carbonate. The solution was evaporated and the residue was treated with a mixture of acetone/methanol (7/3) in order to precipitate the salt. Then the salt was filtered off and the filtrate containing porphyrin was concentrated, dissolved in water and purified through a Sephadex columm (G25). The solution was then evaporated to give a purple powder. Yield = 82%. ^{1}H NMR (CD_3OD, 500 MHz): δ 8.78 (br, s, 8H, β pyrrole), 4.60 (s, 8H, CH), 2.72 (s, 8H, CH), 1.97 (m, 16H, CH_2), 1.58–0.90 (m, 32H, CH_2). ^{13}C NMR (MeOD, 125 MHz):170.42, 163.45–162.63 (br), 150.25, 142.61, 133.31, 131.18, 129.02–128.25 (br), 121.67, 119.30, 117.43, 117.01, 114.68, 45.02, 43.83, 27.65, 27.56. MALDI-TOF calcd $m/z = 1483.849$ $[M\text{-}3Na+2H]^-$ for $C_{84}H_{74}N_4NaO_{12}S_4$, found 1483.849 (425 ppm). UV (CH_3OH) λ_{max}, nm (ε cm^{-1} mM^{-1}): 416 (210), 515 (6.56), 551 (1.28), 579 (1.48), 631 (0.64). For **3.** Compound **2** (60 mg, 0.038 mmol) was dissolved under argon in DMF (10 ml) and the solution heated to reflux. $FeCl_2$, $6H_2O$ (46 mg, 0.23 mmol, 6 equiv) was then added to the solution. The reaction was followed by UV–vis. After refluxing for 5 h, the mixture was allowed to cool to room temperature and concentrated by vacuum evaporation. The crude product was dissolved in water, treated with a cationic exchange resin (Dowex 50) and the solution was evaporated under reduced pressure. Yield = 51%. MALDI-TOF: calcd $m/z = 1537.343$ $[M\text{-}3Na+H]^-$ for $C_{84}H_{74}FeN_4NaO_{12}S_4$, found 1537.671. UV ($CH_3OH$) λ_{max}, nm (ε cm^{-1} mM^{-1}): 395 (82.54), 528 (10.31). For **4:** Same procedure as H_2HaltS with HaltRuCO (100 mg, 0.078 mmol). Yield = 65%. ^{1}H NMR (CD_3OD, 500 MHz): δ 8.78 (br, s, 8H, β pyrrole), 4.60 (s, 8H, CH), 2.72 (s, 8H, CH), 1.97 (m, 16H, CH_2), 1.58–0.90 (m, 32H, CH_2).^{13}C NMR (CD_3OD, 125 MHz): δ 210.11, 178.20, 148.15, 149.36, 143.63, 140.99, 130.48, 69.21, 53.76, 47.96, 43.73, 42.52,28.15. MALDI-TOF: calcd $m/z = 1628.288$ $[M\text{-}Na+H]^{\cdot}$ for $C_{84}H_{73}N_4Na_3O_{12}RuS_4$, found 1628.820. UV ($CH_3OH$) λ_{max}, nm (ε cm^{-1} mM^{-1}): 412 (40.03), 528 (3.64). IR (KBr): 1940 (CO), 1637 cm^{-1}.
18. *Cyclopropanation of styrene in water*: The catalytic reactions were carried in Schlenk tube under argon and were magnetically stirred. The iron catalyst **3** (0.5%) and cobaltocene (5 μmol, 1 mg) were placed in an oven-dried Schenk tube. This Schlenk tube was evacuated and backfilled with argon. Water (0.5 mL) was added via syringe, followed by styrene (0.5 mmol). Then diazo derivative (13 mg, 0.1 mmol in 0.5 ml of water) was added slowly to the mixture over a period of 30 min. After 24 h, the resulting mixture was extracted two times with CH_2Cl_2, dried over $MgSO_4$. Then the reaction was reloaded with compound **3**. Catalytic reactions were controlled on a Varian CP-3380 Gas Chromatograph equipped with a CP-Chirasil-Dex Column for yield and ee and Perkin Elmer 341 polarimeter for optical rotation. The same procedure was used with ruthenium compound **4** but without cobaltocene.