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Communication

A New Mn-Salen Micellar Nanoreactor for Enantioselective Epoxidation of Alkenes in Water

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Dedicated to Prof. Gaetano A. Tomaselli in occasion of his retirement

Abstract: A new chiral Mn-salen catalyst, functionalized with a long aliphatic chain and a choline group, able to act as surfactant catalyst for green epoxidation in water, is here described. This catalyst was employed with a commercial surfactant (CTABr) leading to a nanoreactor for the enantioselective epoxidation of some selected alkenes in water, using NaClO as oxidant. This is the first example of nanoreactor for enantioselective epoxidation of non-functionalized alkenes in water.

Keywords: epoxidation; water; enantioselectivity; nanoreactor; Mn-salen

1. Introduction

Water is one of the most abundant molecule in Nature and, due to its diffusion, cost, no-toxicity, and environmental compatibility, is probably one of the most desirable solvent for a reaction. In fact, organic solvents are commonly used in the pharmaceutical and chemical industries as reaction media but, for toxicological and environmental pollution reasons [1], manufacturers aspire to reduce the number and amount of solvents applied in a drug or chemical production. However, the use of water as solvent for organic synthesis is limited by the low solubility of organic compounds and the facile decomposition of many active species in water. This drawback was recently resolved by the use of nanocapsular systems [2] and micelles [3], which dissolved and stabilized organic substrates in water and, in some examples, act as molecular reactors for organic synthesis [4].

Olefin epoxidation is one of the most important and useful reaction because it leads to a wide range of organic compounds with significant applications in several technological fields [5]. In particular, chiral Mn(III)-salen complexes have been used as catalysts to obtain chiral epoxides, which represent an essential target due to the importance of enantiomerically pure compounds in industry and pharmaceuticals [6]. In this context, many efforts have been addressed to leave the "poor eco-friendly conditions" (e.g. the use of organic solvent and reaction with strong conditions), moving towards more efficient and eco compatible reactions, by using efficient heterogeneous catalysts [7] and/or reactions in aqueous media [3]. However, few examples of enantioselective epoxidation in water are reported in Literature [8]. A possible solution can be found in the self-assembly process, in order to obtain amphiphilic or self-assembled nanostructures [9], able to solubilize organic substrates in water.

Recently, our research group have developed new protocols to obtain epoxides with high enantioselectivity in water exploiting micelles, in which the surfactant act as co-ligand for a chiral

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Mn(III)-salen catalyst [8a,b]. In these systems, the micellar catalyst plays as a nanoreactor for the epoxidation reaction.

Here we present the design, synthesis and catalytic application of a new nanoreactor, in which chiral Mn(III)-salen catalyst **1-Mn** is itself a surfactant. Micellar nanoreactor consists in catalyst **1-Mn** and Cetyltrimethylammonium bromide (CTABr), mixed in an appropriate ratio (see Figure 1). Epoxidation results obtained with selected alkenes confirm the ability of our system to act as enantioselective catalyst in water. To the best of our knowledge, this is the first example of chiral nanoreactor able to efficiently catalyze enantioselective epoxidation in pure water.

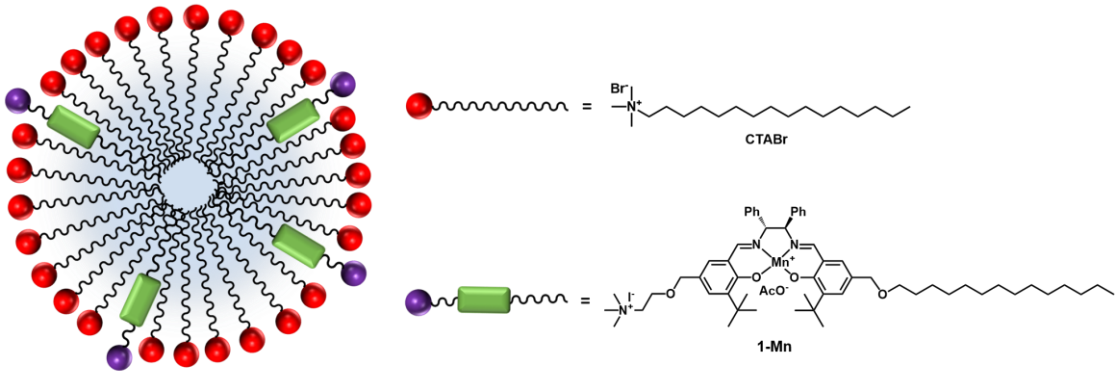

Figure 1. Schematic representation of the micellar nanoreactor and chemical structure of the catalyst **1-Mn** and CTABr.

2. Results and Discussion

Surfactant catalyst **1-Mn** was synthesized in the multi-step pathway showed in Scheme 1.

In the first step, 3-(tert-butyl)-2-hydroxybenzaldehyde was reacted with aqueous paraformaldehyde and HCl, leading to the 5-chloromethylated compound **2** in high yield (95%) [10]. Reaction of **2** with stoichiometric amount of tetradecanol in the presence of sodium hydroxide allowed to the selective introduction in 5-position of the long aliphatic chain, fundamental for the surfactant activity, (compound **3**, yield 32%). Ethanolamine was hypermethylated by reaction with a large excess of methyl iodide, in the presence of potassium carbonate, thus obtaining choline iodide **4** in almost quantitative yield. Choline derivative **4** was covalently bounded to aldehyde **2** following the same procedure used to prepare aliphatic aldehyde **3**. Thus, using an equimolar ratio of **2** and **4** in basic conditions, water soluble choline-aldehyde **5** was synthesized in 31 % yield. Salen moiety was assembled by using (*1R,2R*)-diphenyl-ethylendiamino-monochloride 6 [11], which in the presence of aldehyde **3** afforded to the mono-imino-amine-monochloride compound **7** in quantitative yield. Finally, surfactant chiral salen ligand **1** was obtained by condensation of **5** and **7**, in the presence of triethylamine (yield 67%). This strategy is the most viable way to obtain "non-simmetrical salen ligand" in high yield [12]. Water soluble manganese catalyst **1-Mn** was obtained in quantitative yield by addition of manganese acetate to the corresponding chiral ligand **1**. Compounds were fully characterized by NMR and ESI-MS (see Supplementary Materials).

Micellar nanoreactor has been assembled by using **1-Mn** and Cetyltrimethylammonium bromide (CTABr) as co-surfactant in a different molar ratio (see Table 1). We selected a cationic surfactant to obtain a micellar surface fully covered by the same positive charges. In addition, catalyst was designed in order to confine the catalytic metal center inside the hydrophobic region of nanoreactor (see Figure 1), in contrast respect our previously works where it laid on the Stern layer [8a,b]. In our opinion, the catalytic site sequestered in the interior of micelles should lead to a higher reaction rates, due to a proximity effect with the alkene inside the core of a micelle.

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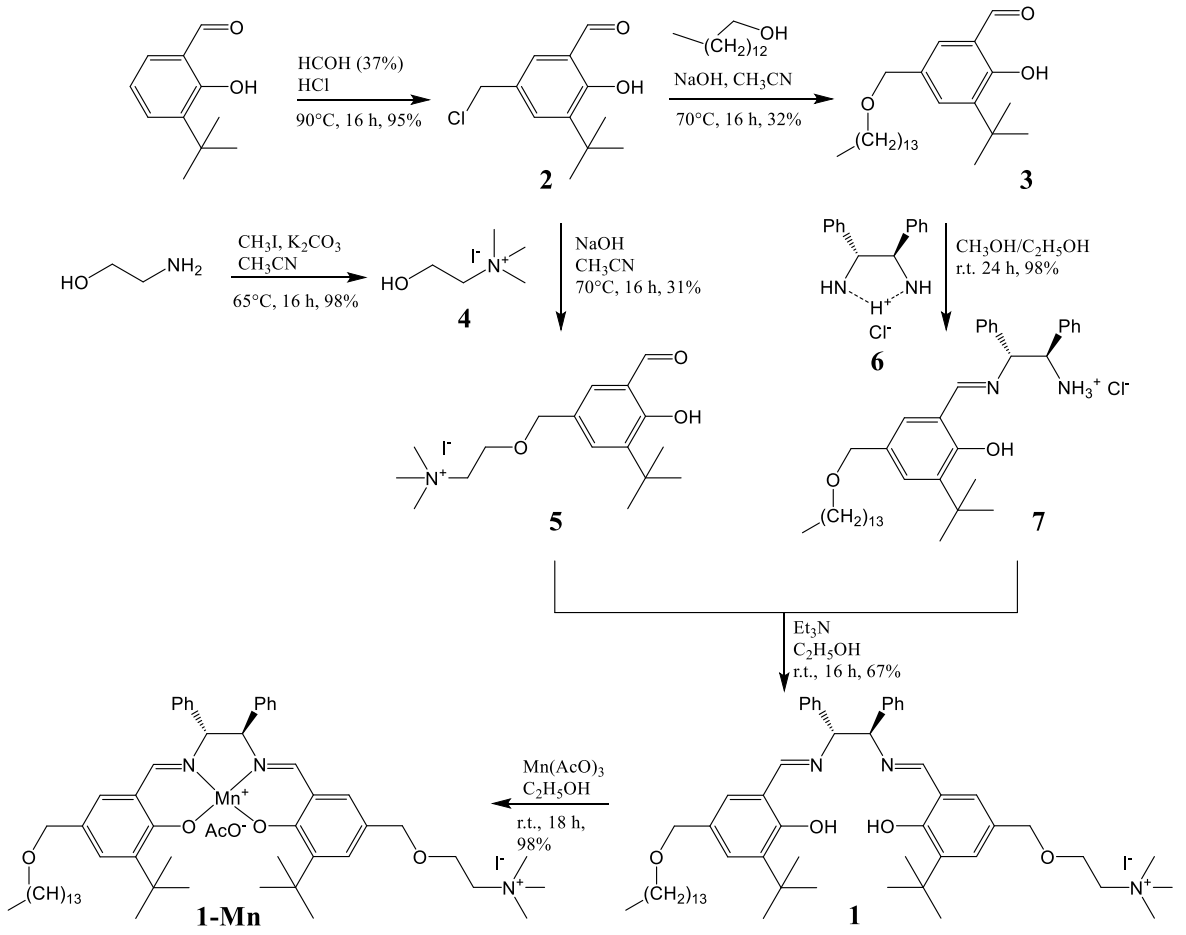

Scheme 1. Synthesis of catalyst **1-Mn**.

Micellar nanoreactor was characterized by DOSY measurements. In particular, diffusion coefficient data allowed us to calculate the hydrodynamic radius of the micelle [13]. Diffusion coefficient of a solution 0.03 M of CTABr in D_2O (the same concentration used in the epoxidation reaction) is 1.20 x 10^{-10} m^2 sec^{-1}, corresponding to a hydrodynamic radius of ca. 2.15 nm (see Materials and Methods), thus in according with the formation of a micelle (c.m.c. of CTABr is 8.6 x 10^{-4} M). The same measurements were performed with a solution 0.03 M of CTABr and 1 mM of **1-Mn** in D_2O, and a diffusion coefficient of 1.17 x 10^{-10} m^2 sec^{-1} was found (hydrodynamic radius of ca. 2.21 nm, see Materials and Methods), thus confirming that the presence of our catalyst does not modify the dimensions of the micelle.

Once confirmed the presence of micellar systems also with the addition of **1-Mn**, we tested our system as nanoreactor in the enantioselective epoxidation of 6-cyano-2,2-dimethylchromene, 1,2-dihydronaphthalene and *cis*-β-ethylstyrene in pure water, using NaClO as the oxidant. Results are summarized in Table 1.

Due to the high reactivity of 6-cyano-2,2-dimethylchromene in the oxidation reactions [14], using CTABr 0.03 M and 5 % of catalyst, total conversion in epoxide is complete in 3 hours, with an enantiomeric excess of ca. 83% (entries 1-2). The increase of concentration of CTABr, from 0.03 to 0.06 M, does not affect enantioselectivity and conversion values (entries 3-4). Enantiomeric excess values with 1,2-dihydronaphthalene were also in the range of 80-84%, confirming the ability of nanoreactor to give enantioselectivity. As showed in our previously works [8a,b], 1,2-dihydronaphthalene presents lower reaction rates compared to 6-cyano-2,2-dimethylchromene.

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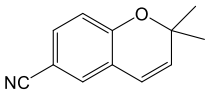
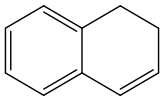
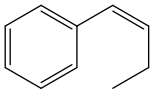
Table 1. Enantioselective epoxidation of 6-CN-2,2-dimethylchromene, 1,2-dihydronaphthalene and *cis*-β-ethylstyrene with NaClO catalyzed by micellar nanoreactor containing **1-Mn** and CTABr in H_2O at 25 °C.[a]

Alkene	Entry	[CTABr] (M)	1-Mn (%)[b]	Time (h)	e.e. (%)[c]	Conv. (%)[c]
	1	0.03	5	1	83[e]	85
	2	0.03	5	3	82[e]	100
	3	0.06	5	1	83[e]	87
	4	0.06	5	3	83[e]	100
	5	0.03	5	1	83[f]	17
	6	0.03	5	8	82[f]	46
	7	0.03	10	8	84[f]	64
	8	0.06	10	1	80[f]	76
	9	0.06	10	3	83[f]	100
	10	0.03	5	1	50[g]	73
	11	0.03	5	2	51[g]	100
	12[d]	0.015	10	1	56[g]	88
	13[d]	0.015	10	4	57[g]	100
	14[d]	0.03	10	1	56[g]	86
	15[d]	0.03	10	4	58[g]	100
	16[d]	0.06	10	1	58[g]	85
	17[d]	0.06	10	4	57[g]	100

[a] In all experiments [alkene] = [NaClO] =1.17 x 10^{-2} M, buffered with 1 mL of 0.05 M Na_2HPO_4 at pH 11.2 in a total volume of 2 mL; [b] referred to the alkene concentration; [c] determined by GC analysis using a chiral column (see Materials and Methods) and *n*-dodecane as internal standard; [d] NaClO was added dropwise in 1 h; [e] config. (*3R,4S*) determined by measuring the optical rotation; [f] config. (*1R,2S*) determined by measuring the optical rotation; [g] Enantiomeric excess (e.e.) value is referred to the to the major *cis* epoxide (*cis*/*trans* = 4)

In fact, at the same conditions, after 1 hours of reaction only 17% of conversion was obtained (entry 1 vs. entry 5). After 8 hours of reaction, 46% of conversion value was observed (entry 6). The increase of concentration of catalyst **1-Mn** (10% respect to substrate) was not sufficient to reach the full conversion, affording a conversion of 64% (entry 7). While, with 0.06 M of CTABr, conversions increased to 76% after 1 hour and 100% after 3 hours (entries 8 and 9, respectively). These results suggest a strong contribute of the nature of substrate in the reaction rate.

This hypothesis was confirmed considering *cis*-β-ethylstyrene: using 0.03 M of CTABr and 5% of catalyst, conversion reach 73% in 1 h and 100% after 2 h. However, the enantioselectivity value observed was 51% (entries 10-11).

In order to increase enantioselectivity with this alkene, we evaluated the effect of CTABr surfactant concentration, performing epoxidation reactions at 0.015, 0.03 and 0.06 M of CTABr, using 10% of catalyst (entries 12-17). We noted that the 10% of catalyst amount leaded to a slight improvement of enantioselectivity (56-58%), while the reaction rates remained quite similar.

Noteworthy, the simple CTABr micelle containing selected alkenes in water, after addition of NaClO, leads to a racemic mixture of epoxides, while in the classic biphasic system (CH_2Cl_2/H_2O) this reaction was never been observed [6,15]. Thus, the presence of the chiral catalyst is essential to catalyzed the enantioselective epoxidation of alkenes.

3. Materials and Methods

3.1. General

The NMR experiments were carried out at 27° C on a Varian UNITY Inova 500 MHz spectrometer (^{1}H at 499.88 MHz, ^{13}C-NMR at 125.7 MHz) equipped with pulse field gradient module (Z axis) and a tunable 5 mm Varian inverse detection probe (ID-PFG). ESI mass spectra were acquired on a API 2000™ AB Sciex using MeOH (positive ion mode). All chemicals were reagent grade and

were used without further purification. Enantiomeric excesses were determined by GC analysis with a Perkin Elmer Capillary (Perkin Elmer, Waltham, MA, USA) using dimethylpentyl-beta (DIMEPEBETA-086) chiral column (25 m × 0.25 mm ID, 0.25 μm film) for 6-cyano-2,2-dimethylchromene; DiAcTBuSiliBETA-ov-1701 chiral column (25 m × 0.25 mm ID, 0.25 μm film) for *cis*-β-ethylstyrene and dimethyl-pentyl-beta (DMePeBETACDX) chiral column (25 m × 0.25 mm ID, 0.25 μm film) for 1,2-dihydronaphthalene. The absolute configuration of the obtained epoxides were determined by measuring the optical rotation with a polarimeter. Absolute configurations were assigned by comparison of the measured $[\alpha]_D^{20}$ values with those reported in the literature [16]. ^{1}H NMR characterizations of compounds **2** and **4** are in according those reported in literature [7c].

3.2. DOSY measurements

The DOSY technique provides information about the size of the molecular aggregate in solution. In fact, by means of the Stokes–Einstein equation, the diffusion coefficient of the CTABr can be converted into its hydrodynamic radius R_h and this value can be compared with the calculated radius obtained by Hyperchem-minimized structure of the surfactant (in the maximum extension, CTABr is ca. 2 nm, leading a micellar aggregates of ca. 4 nm of diameter). Thus, combining the diffusion coefficient of the CTABr (D = 1.20 x 10^{-10} m^2 sec^{-1}) with the viscosity of D_2O at 298 K in the Stokes–Einstein equation ($R = k_BT/6\pi\eta D$; where k_B is the Boltzmann constant, T is the absolute temperature, and η is the viscosity of D_2O at 298 K (0.85 cP)), a hydrodynamic radius R_h(exp) = 2.15 nm was obtained. The same treatment for the nanoreactor containing CTABr and **1-Mn** give a R_h(exp) = 2.21 nm.

3.3. Synthesis and characterization

Synthesis of aldehyde ***2***. 0.720 mL (8.6 mmol) of aqueous formaldehyde and 9 mL of HCl conc. were added to 1 g (5.61 mmol) of the 3-*t*But-salicylaldehyde. The mixture was stirred at 90°C for 16 h. Reaction was cooled to room temperature obtaining a precipitate. Diethyl ether was added to the aqueous solution, extracted and dried with Na_2SO_4. Evaporation of solvent affords to compound **2** (yield 95%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.85 (s, 1H, OH), 9.87 (s, 1H, CHO), 7.53 (d, *J* = 2.5 Hz, 1H, ArH), 7.44 (d, *J* = 2.5 Hz, 1H, ArH), 4.59 (s, 2H, -CH_2Cl), 1.43 (s, 9H, Ar-CH_3). Anal. Calcd. For $C_{12}H_{15}ClO_2$: C, 63.58; H, 6.67; Cl, 15.64. Found C, 63.51; H, 6.62; Cl, 15.58.

Synthesis of aldehyde ***3***. Tetradecanol (629 mg, 2.95 mmol) was dissolved in 25 mL of acetonitrile dry and 118 mg (2.95 mmol) of NaOH was added. The mixture was heated at 70 °C for 4 hours, then 700 mg (3.10 mmol) of aldehyde **2**, dissolved in 15 mL of acetonitrile dry, was added dropwise in 1 hour. Reaction was stirred at 70 °C overnight under nitrogen. Then, solvent was removed under reduced pressure, the crude product was dissolved in CH_2Cl_2 and washed with water. Organic phase was dried with Na_2SO_4 and purified by column chromatography (*n*-hexane/EtOAc 98/2) affording pure compound **3** as oil (yield 32%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.76 (s, 1H, OH), 9.87 (s, 1H, CHO), 7.49 (d, *J* = 2.0 Hz, 1H, ArH), 7.37 (d, *J* = 2.0 Hz, 1H, ArH), 4.44 (s, 2H, Ar-CH_2-O), 3.48 (t, *J* = 6.5 Hz, 2H, O-*CH_2*-CH_2-), 1.62 (m, 2H, O-CH_2-*CH_2*-), 1.42 (s, 9H, Ar-CH_3), 1.25-1.30 (m, 22H, O-CH_2-CH_2-*$(CH_2)_{11}$*-CH_3), 0.88 (t, *J* = 7.5 Hz, 3H, O-CH_2-CH_2-$(CH_2)_{11}$-*CH_3*). ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.0, 160.7, 138.3, 133.9, 130.9, 129.3, 120.3, 72.2, 70.7, 34.8, 31.9, 29.7, 29.66, 29.61, 29.47, 26.34, 29.2. ESI-MS *m*/*z* 405.3 $[M+H]^+$. Anal. Calcd. For $C_{26}H_{44}O_3$: C, 77.18; H, 10.96. Found C, 77.09; H, 10.89.

Synthesis of choline iodide ***4***. A suspension containing 2 g (32.7 mmol) of ethanolamine, 9 g (65.4 mmol) of K_2CO_3 anhydrous and 23.11 g (163 mmol) of CH_3I in 25 mL of acetonitrile dry was stirred vigorously overnight at 65°C under nitrogen. Then, reaction was filtered to remove the base, and solvent removed under reduced pressure to give pure hypermethylated compound **4** (yield 98%).^{1}H NMR (500 MHz, D_2O) δ 4.10 (m, 2H, OH-*CH_2*-), 3.56 (t, *J* = 5.0 Hz, 2H, -CH_2-N), 3.25 (s, 9H, N(CH_3)$_3$). Anal. Calcd. For $C_5H_{14}INO$: C, 25.99; H, 6.11; N, 6.06. Found C, 25.91; H, 6.03; N, 6.01.

Synthesis of choline-aldehyde ***5***. Choline iodide **4** (459 mg, 1.98 mmol) was dissolved under nitrogen in 40 mL of acetonitrile dry. Then, 79 mg (1.98 mmol) of NaOH was added and mixture was stirred at 70°C for 3 hours. Then, a solution of aldehyde **2** (463 mg, 2.05 mmol, in 25 mL of acetonitrile dry) was added dropwise in 1 hour. Reaction was stirred under nitrogen overnight at 70°C. The reaction was monitored by TLC following the disappearance of the starting aldehyde **2**. Reaction was cooled to room temperature, solvent was removed under reduced pressure and compound **5** (yield 31%) was purified by alumina column (from CH_2Cl_2 100% to CH_2Cl_2/CH_3OH 95/5). ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.87 (s, 1H, OH), 9.91 (s, 1H, CHO), 7.45 (d, *J* = 2.0 Hz, 1H, ArH), 7.43 (d, *J* = 2.0 Hz, 1H, ArH), 4.56 (m, 2H, -CH_2-N(CH_3)$_3$), 4.00 (m, 4H, Ar-CH_2-O and O-CH_2-CH_2-), 3.44 (s, 9H, N(CH_3)$_3$), 1.42 (s, 9H, Ar-CH_3). ^{13}C NMR (125 MHz, DMSO-d_6) 109.81, 160.71, 136.95, 129.17, 128.80, 122.16, 117.74, 66.94, 55.14, 53.20, 45.71, 22.52, 14.39. ESI-MS *m*/*z* 294.2 [M]$^+$. Anal. Calcd. For $C_{17}H_{28}INO_3$: C, 48.46; H, 6.70; N, 3.32. Found C, 48.41; H, 6.62; N, 3.28.

Synthesis of aldehyde **7**. To a solution of 190 mg (0.766 mmol) of (*1R,2R*)-diphenyl-ethylendiamino-monochloride **6** [11] dissolved in 20 mL of a mixture 50/50 of methanol/ethanol was added dropwise 299 mg (0.740 mmol) of aldehyde **3**, dissolved in 10 mL of the same solvent mixture. Reaction was stirred at room temperature for 24 h. Then, solvent was removed under reduced pressure, the crude product was washed with few mL of water to remove starting reagent **6** and filtered obtaining compound **7** (yield 98%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 13.36 (s, 1H, OH), 8.74 (s, 1H, CHN), 8.55 (s br, 3H, NH_3), 7.36 (m, 2H, ArH), 7.19-7.29 (m, 10H, ArH), 5.03 (d, *J* = 10 Hz, 1H, CH methine), 4.88 (d, *J* = 10.0 Hz, 1H, CH methine), 4.35 (s, 2H, Ar-CH_2-O), 3.36 (t, *J* = 6.0 Hz, 2H, O-CH_2-CH_2-), 1.48 (m, 2H, O-CH_2-CH_2-), 1.38 (s, 9H, ArCH_3), 1.19-1.26 (m, 22H, O-CH_2-CH_2-$(CH_2)_{11}$-CH_3), 0.82 (t, *J* = 6.5 Hz, 3H, O-CH_2-CH_2-$(CH_2)_{11}$-CH_3). ^{13}C NMR (125 MHz, DMSO-d_6) 156.83, 138.65, 133.68, 129.185, 128.98, 128.54, 128.48, 128.02, 126.74, 68.29, 60.73, 57.19, 36.55, 32.55, 31.29, 29.82, 29.01, 28.70, 25.71, 25.51, 22.10, 13.96. ESI-MS *m*/*z* 599.7 [M]$^+$. Anal. Calcd. For $C_{40}H_{59}ClN_2O_2$: C, 75.62; H, 9.36; N, 4.41. Found: C, 75.54; H, 9.27; N, 4.32.

Synthesis of ***1***. To a solution of ethanol (30 mL) containing 270 mg (0.641 mmol) of **5** and 406 mg (0.641 mmol) of **7** were added slowly 190 µL of triethylamine. Mixture was stirred at room temperature overnight. Then, solvent was removed under reduced pressure and salen **1** (yield 67%) was purified by neutral alumina column (CH_2Cl_2 containing 5% of CH_3OH). ^{1}H NMR (500 MHz, $CDCl_3$) δ 13.93 (s, 1H, OH), 13.75 (s, 1H, OH), 8.38 (s, 1H, CHN), 8.34 (s, 1H, CHN), 7.14-7.24 (m, 12H, ArH), 6.97 (m, 2H, ArH), 4.75 (m, 2H, CH methine), 4.39 (s, 2H, Ar-CH_2-O), 4.31 (s, 2H, Ar-CH_2-O), 3.93 (m, 2H, -CH_2-N(CH_3)$_3$, 3.86 (m, 2H, O-CH_2-CH_2-N(CH_3)$_3$), 3.43 (t, *J* = 6.5 Hz, 2H, O-CH_2-CH_2-), 3.38 (s, 9H, N(CH_3)$_3$), 1.60 (m, 2H, O-CH_2-CH_2-), 1.42 (s, 18H, Ar-CH_3), 1.25-1.30 (m, 22H, O-CH_2-CH_2-$(CH_2)_{11}$-CH_3), 0.88 (t, *J* = 7.5 Hz, 3H, O-CH_2-CH_2-$(CH_2)_{11}$-CH_3). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.73, 166.36, 139.30, 130.00, 129.81, 129.73, 129.62, 128.38, 127.96, 127.63, 79.99, 73.60, 72.69, 70.50, 63.50, 54.92, 45.87, 31.91, 29.67, 29.29, 26.21, 22.68, 15.49, 14.11, 8.60. ESI-MS *m*/*z* 874.7 [M]$^+$. Anal. Calcd. For $C_{57}H_{84}IN_3O_4$: C, 68.31; H, 8.45; N, 4.19. Found: C, 68.22; H, 8.36; N, 4.10.

Synthesis of ***1-Mn***. In a round bottom flash containing 430 mg (0.430 mmol) of salen **1** dissolved in 15 mL of absolute ethanol was added 171 mg (0.643 mmol) of manganese (III) acetate dihydrate. Mixture was stirred at room temperature overnight. Then, solvent was removed under reduced pressure, crude product was dissolved in CH_2Cl_2 and filtered to remove the excess of manganese (III) acetate. Evaporation of solvent affords to **1-Mn** as brown precipitate (yield 98%). ESI-MS *m*/*z* 927.5 [M]$^+$. Anal. Calcd. For $C_{59}H_{72}IMnN_3O_6$: C, 64.36; H, 6.59; N, 3.82. Found: C, 64.30 H, 6.51; N, 3.75.

Enantioselective Epoxidation in Nanoreactor. In a typical run, alkene and *n*-dodecane (internal standard) were added to a stirred solution of surfactant and catalyst **1-Mn** in distilled water (1 mL) and phosphate buffer (1 mL, 0.05 M Na_2HPO_4 at pH 11.2); after the complete solubilization, NaClO was added dropwise (5 µL/10 min) to the mixture and the reaction was kept in a round-bottom flask at 25 °C in a thermostatic bath. After a certain reaction time, the aqueous solution was extracted with

1 mL of CH_2Cl_2. Combined organic extracts were dried over anhydrous $MgSO_4$, reduced to a small volume, and analyzed by GC as described above.

4. Conclusions

A new surfactant catalyst, containing a chiral Mn-salen framework, able to catalyze in water enantioselective epoxidation of non-functionalized alkenes, was here presented. Epoxidation reactions were carried out into micellar systems, containing also a commercial surfactant (CTABr), thus forming the first nanoreactor able to give enantioselectivity in water. The epoxidation reactions with 6-CN-2,2-dimethylchromene and 1,2-dihydronaphthalene exhibited excellent results, with high conversions and enantioselectivity values. Probably, a crucial role is played by the structure of the surfactant catalyst: in particular, the position of the catalytic metal center respect to the micellar aggregate leads to a different reactivity towards different alkenes. Actually, we are working on the optimization of the nanoreactor structure: in particular, the length of the aliphatic moiety of the catalyst should be crucial to improve the reactivity of aliphatic alkenes (e.g. *cis*-β-ethylstyrene).

Supplementary Materials: The following are available online at www.mdpi.com/link: NMR, gCOSY, and ESI-MS spectra.

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References

1. Welton, T. Solvents and sustainable chemistry. *Proc Math Phys Eng Sci* **2015**, *471*, 20150502, DOI: 10.1098/rspa.2015.0502.
2. Gangemi, C. M. A.; Pappalardo, A.; Trusso Sfrazzetto, G. Applications of supramolecular capsules derived from resorcin[4]arenes, calix[n]arenes and metalloligands: from biology to catalysis. *RSC Adv.*, **2015**, *5*, 51919–51933, DOI: 10.1039/C5RA09364C.
3. Kitanosono, T.; Masuda, K.; Xu, P.; Kobayashi, S. Catalytic Organic Reactions in Water toward Sustainable Society. *Chem. Rev.* **2018**, *118*, 679–746, DOI: 10.1021/acs.chemrev.7b00417.
4. (a) Cotanda, P.; Lu, A.; Patterson, J. P.; Petzetakis, N.; O'Reilly, R. K. Functionalized Organocatalytic Nanoreactors: Hydrophobic Pockets for Acylation Reactions in Water. *Macromolecules* **2012**, *45*, 2377–2384, DOI: 10.1021/ma2027462; (b) Scarso, A. Micellar Nanoreactor 2016 Encyclopedia of Inorganic and Bioinorganic Chemistry. 1–16, DOI: 10.1002/9781119951438.eibc2402; (c) Hou, S.; Xie, C.; Yu, F.; Yuan, B.; Yu, S. Selective hydrogenation of α-pinene to cis-pinane over Ru nanocatalysts in aqueous micellar nanoreactors. *RSC Adv.*, **2016**, *6*, 54806–54811, DOI: 10.1039/C6RA13099B; (d) Lee, L.-C.; Lu, J.; Weck, M.; Jones, C. W. Acid−Base Bifunctional Shell Cross-Linked Micelle Nanoreactor for One-Pot Tandem Reaction. *ACS Catal.* **2016**, *6*, 784−787, DOI:10.1021/acscatal.5b02538; (e) Vriezema, D. M.; Aragones, M. C.; Elemans, J. A. A. W.; Cornelissen, J. J. L. M.; Rowan, A. E.; Nolte, R. J. M. Self-Assembled Nanoreactors. *Chem. Rev.* **2005**, *105*, 1445−1489, DOI:10.1021/cr0300688.
5. Baleizão, C.; Garcia, H. Chiral Salen Complexes: An Overview to Recoverable and Reusable Homogeneous and Heterogeneous Catalysts. *Chem. Rev.*, **2006**, *106*, 3987–4043, DOI:10.1021/cr050973n.
6. (a) Jacobsen, E. N. in Catalytic Asymmetric Synthesis, ed. I. Ojima, VCH, Weinheim, 1993, ch. 4.2, pp. 159–202, CODEN:59PEAB; (b) Yoon, T. P.; Jacobsen, E. N. *Science*, **2003**, *299*, 1691–1693, DOI:10.1126/science.1083622; (c) Arends, I. W. E. E. Metal-Catalyzed Asymmetric Epoxidations of Terminal Olefins Using Hydrogen Peroxide as the Oxidant. *Angew. Chem., Int. Ed.*, **2006**, *45*, 6250–6252, DOI:10.1002/anie.200602044.
7. (a) McMorn, P.; Hutchings, G. J. Heterogeneous enantioselective catalysts: strategies for the immobilisation of homogeneous catalysts. *Chem. Soc. Rev.* **2004**, *33*, 108–122, DOI:10.1039/b200387m; (b) Shi, Z.-H.; Li, N.-

G.; Shi, Q.-P.; Tang, Y.-P.; Tang, H.; Shen, M.-Z.; Duan, J.-A. Immobilization of Chiral Manganese(III)-salen Complexes for Enantioselective Epoxidation of Unfunctionalised Olefins. *Curr. Org. Synth.* **2014**, *11*, 204–243, DOI:10.2174/15701794113109990058; (c) La Paglia Fragola, V.; Lupo, F.; Pappalardo, A.; Trusso Sfrazzetto, G.; Toscano, R. M.; Ballistreri, F. P.; Tomaselli, G. A.; Gulino, A. A surface-confined O]MnV(salen) oxene catalyst and high turnover values in asymmetric epoxidation of unfunctionalized olefins. *J. Mater. Chem.*, **2012**, *22*, 20561–20565, DOI:10.1039/c2jm34847k; (d) Trusso Sfrazzetto, G.; Millesi, S.; Pappalardo, A.; Toscano, R. M.; Ballistreri, F. P.; Tomaselli, G. A.; Gulino, A. Olefin epoxidation by a (salen)Mn(III) catalyst covalently grafted on glass beads. *Catal. Sci. Technol.*, **2015**, *5*, 673–679, DOI:10.1039/C4CY00831F.

8. (a) Ballistreri, F. P.; Brinchi, L.; Germani, R.; Savelli, G.; Tomaselli, G. A.; Toscano, R. M. Enantioselective epoxidations of alkenes catalyzed by (salen)Mn(III) in aqueous surfactant systems. *Tetrahedron* **2008**, *64*, 10239–10243, DOI:10.1016/j.tet.2008.08.052; (b) Ballistreri, F. P.; Gangemi, C. M. A.; Pappalardo, A.; Tomaselli, G. A.; Toscano, R. M.; Trusso Sfrazzetto, G. (Salen)Mn(III) Catalyzed Asymmetric Epoxidation Reactions by Hydrogen Peroxide in Water: A Green Protocol. *Int. J. Mol. Sci.* **2016**, *17*, 1112–11121, DOI:10.3390/ijms17071112; (c) Bérubé, C.; Barbeau, X.; Laguë, P.; Voyer, N. Revisiting the Juliá-Colonna Enantioselective Epoxidation: Supramolecular Catalysis in Water. *Chem. Commun.* **2017**, *53*, 5099–5102, DOI:10.1039/C7CC01168G; (d) Malkov, A. V.; Czemerys, L.; Malyshev, D. A. Vanadium- Catalyzed Asymmetric Epoxidation of Allylic Alcohols in Water. *J. Org. Chem.* **2009**, *74*, 3350–3355, DOI:10.1021/jo900294h; (e) Colladon, M.; Scarso, A.; Strukul, G. Towards a Greener Epoxidation Method: Use of Water-Surfactant Media and Catalyst Recycling in the Platinum-Catalyzed Asymmetric Epoxidation of Terminal Alkenes with Hydrogen Peroxide. *Adv. Synth. Catal.* **2007**, *349*, 797–801, DOI:10.1002/adsc.200600518; (f) Li, J.; Hu, F.; Xie, X.-K.; Liu, F.; Huang, Z.-Z. Synthesis of new functionalized chiral ionic liquid and its organocatalytic asymmetric epoxidation in water. *Cat. Commun.* **2009**, *11*, 276–279, DOI:10.1002/adsc.200600518.
9. (a) Prasad, S.; Achazi, K.; Bottcher, C.; Haag, R.; Sharma, S. K. Fabrication of nanostructures through self-assembly of non-ionic amphiphiles for biomedical applications. *RSC Advances* **2017**, *7*, 22121–22132, DOI:10.1039/C6RA28654B; (b) Morotti, T.; Calabrese, V.; Cavazzini, M.; Pedron, D.; Cozzuol, M.; Licciardello, A.; Tuccitto, N.; Quici, S. Zirconium phosphate/phosphonate multilayered films based on push–pull stilbazolium salt: synthesis, characterization and second harmonic generation. *Dalton Trans.*, **2008**, 2974–2982, DOI: 10.1039/b801194j; (c) Tuccitto, N.; Giamblanco, N.; Licciardello, A.; Marletta, G. Patterning of lactoferrin using functional SAMs of iron complexes. *Chem. Commun.* **2007**, 2621–2623, DOI: 10.1039/b701527e.
10. Gulino, A.; Trusso Sfrazzetto, G.; Millesi, S.; Pappalardo, A.; Tomaselli, G. A.; Ballistreri, F. P.; Toscano, R. M.; Fragalà, L. Nerve Gas Simulant Sensing by an Uranyl-Salen Monolayer Covalently Anchored on Quartz Substrates. *Chem. Eur. J.* **2017**, *23*, 1576–1583, DOI:10.1002/chem.201602292.
11. (a) Ballistreri, F. P.; Condorelli, G. G.; Fragalà, I.; Motta, A.; Pappalardo, A.; Tomaselli, G. A.; Tudisco, C.; Trusso Sfrazzetto, G. Covalent functionalization of silicon surfaces with cavitand-modified salen. *Eur. J. Inorg. Chem.* **2011**, 2124–2131, DOI:10.1002/ejic.201001239; (b) Amato, M. E.; Ballistreri, F. P.; D'Agata, S.; Pappalardo, A.; Tomaselli, G. A.; Toscano, R. M.; Trusso Sfrazzetto, G. Enantioselective Molecular Recognition of Chiral Organic Ammonium Ions and Amino Acids Using Cavitand-Salen Based Receptors. *Eur. J. Org. Chem.*, **2011**, 5674–5680, DOI:10.1002/ejoc.201100955.
12. (a) Kleij, A. W. Nonsymmetrical Salen Ligands and Their Complexes: Synthesis and Applications. *Eur. J. Inorg. Chem.* **2009**, 193–205, DOI:10.1002/ejic.200800936; (b) Pappalardo, A.; Amato, M. E.; Ballistreri, F. P.; Tomaselli, G. A.; Toscano, R. M.; Trusso Sfrazzetto, G. Pair of Diastereomeric Uranyl Salen Cavitands Displaying Opposite Enantiodiscrimination of α-Amino Acid Ammonium Salts. *J. Org. Chem.* **2012**, *77*, 7684–7687, DOI:10.1021/jo301098d; (c) D'Urso, A.; Tudisco, C.; Ballistreri, F. P.; Condorelli, G. G.; Randazzo, R.; Tomaselli, G. A.; Toscano, R. M.; Trusso Sfrazzetto, G.; Pappalardo, A. Enantioselective extraction mediated by a chiral cavitand–salen covalently assembled on a porous silicon surface. *Chem. Commun.* **2014**, *50*, 4993–4996, DOI:10.1039/C4CC00034J.
13. (a) Ballistreri, F. P. ; Pappalardo, A.; Toscano, R. M.; Tomaselli, G. A.; Trusso Sfrazzetto, G. A New Heteroditopic Chiral Uranyl–Salen Receptor for Molecular Recognition of Amino Acid Ammonium Salts. *Eur. J. Org. Chem.* **2010**, *20*, 3806–3810, DOI:10.1002/ejoc.201000566; (b) Pappalardo, A.; Ballistreri, F. P.; Li Destri, G.; Mineo, P. G.; Tomaselli, G. A.; Toscano, R. M.; Trusso Sfrazzetto, G. Supramolecular Polymer Networks Based on Calix[5]arene Tethered Poly(p-phenyleneethynylene). *Macromolecules* **2012**, *45*, 7549–

7556, DOI:10.1021/ma3015239; (c) Giuffrida, M. L.; Rizzarelli, E.; Tomaselli, G. A.; Satriano, C. ; Trusso Sfrazzetto, G. A novel fully water-soluble Cu(I) probe for fluorescence live cell imaging. *Chem. Commun*. **2014**, *50*, 9835–9838, DOI:10.1039/C4CC02147A; (d) Tuccitto, N.; Trusso Sfrazzetto, G.; Gangemi, C. M. A.; Ballistreri, F. P.; Toscano, R. M.; Tomaselli, G. A.; Pappalardo, A.; Marletta, G. Memory-Driven Order-Disorder Transition of 3D-Supramolecular Architecture Based on Calix[5]arene and Porphyrin Derivatives. *Chem. Commun.*, **2016**, *52*, 11681–11684, DOI:10.1039/C6CC06675E; (e) Puglisi, R.; Ballistreri, F. P.; Gangemi, C. M. A.; Toscano, R. M.; Tomaselli, G. A.; Pappalardo, A.; Trusso Sfrazzetto, G. Chiral Zn–salen complexes: a new class of fluorescent receptors for enantiodiscrimination of chiral amines. *New J. Chem.*, **2017**, *41*, 911–915, DOI:10.1039/C6NJ03592B.

14. Bulman Page, P. C.; Chan, Y.; Armylisas, A. H. N.; Alahmdi, M. Asymmetric epoxidation of chromenes mediated by iminium salts: Synthesis of mollugin and (3S,4R)-trans-3,4-dihydroxy-3,4- dihydromollugin. *Tetrahedron* **2016**, *72*, 8406–8416, DOI:10.1016/j.tet.2016.10.070.
15. We performed epoxidation of 6-CN-2,2-dimethylchromene without 1-Mn, with CTABr = [0.06], [alkene] = [NaClO] = 1.17 x 10-2 M, 0.05 M Na2HPO4 at pH 11.2, obtaining a conversion of 52% after 1 h, and 100% after 6 h; with 1,2-dihydronaphthalene, with the same conditions, conversion value was 38% after 1 h and 100% after 12 h while with cis-β-ethylstyrene we observed 47% of conversion after 1 h and 100 after 8 h.
16. Scheurer, A.; Mosset, P.; Spiegel, M.; Saalfrank, R. W. Reverse asymmetric catalytic epoxidation of unfunctionalized alkenes. *Tetrahedron* **1999**, *55*, 1063–1078, DOI:10.1016/S0040-4020(98)01106-5.