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Chiral surfactants to enhance stereoselectivity in asymmetric catalytic sulfoxidation in water

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ABSTRACT

Chiral surfactants can provide asymmetric environments in water that can enhance the stereoselectivity of chiral metal catalysts. Due to the high dynamic nature of micelles, this specific field of research has been seldom investigated. The design of the surfactant and its interaction with the catalyst is crucial to improve stereoselectivity. We report a series of chiral surfactants bearing rigid aromatic hydrophobic units based on the BINOL scaffold decorated with hydrophilic side chains. In particular, the use of anionic side chains provide better interaction with chiral Pt(II) catalysts due to ion pairing leading to improvements in the enantioselectivity of the sulfoxidation reaction of thioethers with hydrogen peroxide. This proof of concept contribution opens the way to the design of new classes of chiral designer surfactants that could be applied to move to water many classes of stereoselective reactions traditionally carried out in organic media.

1. Introduction

Stereoselective catalysis is a mature field of research that finds large applications in the pharmaceutical industry [1] since 56 % of the drugs currently in use are chiral enantiopure compounds. Most enantioselective catalysts are based on metal centers with chiral ligands or on chiral organocatalysts that provide strong interactions with the reagent through coordination or covalent bonds to discriminate the space around the substrate. Enzymes are natural catalysts *par excellence* that are characterized by extremely high stereo and enantioselectivities due to the intrinsic chirality of their peptidic structure. One peculiar aspect of enzymatic catalysis that differs largely from metal catalysis is the efficient binding of the substrate and its proper orientation within the active site in order to juxtapose specific functional groups in proximity to the real catalytic centers. The high surface interaction existing between enzymes and substrates is responsible for much of the enzymatic acceleration and selectivities. In catalysis, confinement is in fact a key requisite for selectivity and activity [2] as well as to improve stereoselectivity [3]. On this specific point, traditional chiral metal or organo-catalysis are still not optimized, in particular due to the difficult design and synthesis of large catalytic systems able to embrace and surround the substrate. The chirality of the active site of enzymes has been mimicked in recent years in the field of supramolecular catalysis thanks to the development of few self-assembled capsules and cages characterized by chiral cavities [4]. It has been demonstrated that such chiral confined environments, as the sole asymmetric units, lead to enantioenriched products [5], in some cases with very high ee% [6]. This is possible thanks to a close contact between the substrates and the cavity.

In order to cope between traditional stereoselective catalysis and sustainability, many reactions have been re-interpreted moving from the use of organic media to water with the aid of surfactants under micellar conditions, also for synthesis of active pharmaceutical ingredients [7]. In particular, stereoselective catalytic reactions in micellar media are gaining interest using micelles as the active site [8]. The most common and effective approach consists in endowing known chiral metal or organo-catalysts with covalently connected aliphatic ponytails to obtain surfactants with catalytic stereoselective head groups [9]. Alternatively, it has also been observed that in many cases [10], simply moving the same stereoselective metal catalyst from an organic medium to a micellar medium leads to enhanced stereoselectivities due to the more ordered and organized core of the micelles. However, to the best of our knowledge, only one example of stereoselective reaction exploiting purely chiral surfactants in combination with traditional catalytic

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systems is known, with moderate stereoselectivities in particular due to the high dynamic character of the micellar aggregates [11]

Herein we contribute to this specific challenging topic, reporting about the synergistic effects between chiral metal catalysts and chiral surfactants in stereoselective sulfoxidation reactions in water. We demonstrate that through a proper design of chiral surfactants it is possible to improve the enantioselectivity of traditional catalysts.

2. Results and discussion

The design of chiral surfactants was inspired by the recent works of Yoshizawa [12] and was focused on the use of rigid apolar chiral scaffolds bearing functional groups that can be easily connected to hydrophilic side chains. The large apolar portion of the surfactants favors the formation of micelles composed by a small number of units, enabling a better control of the reciprocal arrangement of the surfactant units and favoring the asymmetric environment. Because of their structure these surfactants will lead to the formation of micelles characterized by a small number of units. Chiral atropoisomeric BINOL-based compounds were selected due to three considerations: i) availability in both enantiomeric forms, ii) easy modification of the phenolic units by reaction with hydrophilic charged or neutral PEG based units, iii) easy modification on the other aromatic positions to increase their size and shape and to modulate their electronic properties.

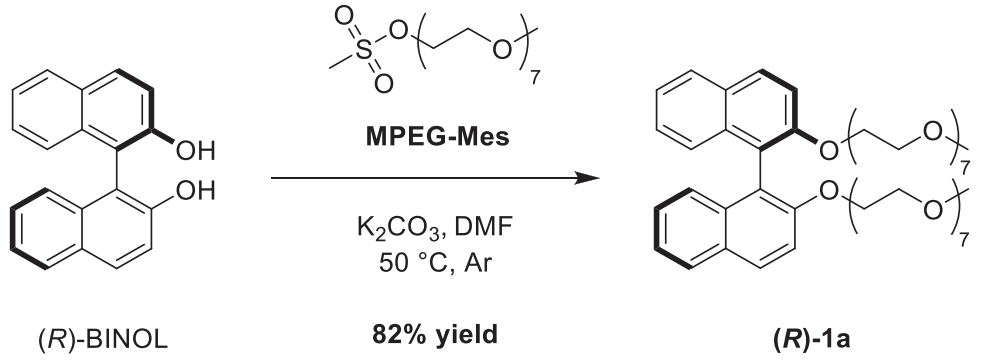
Considering the general neutral structure of most active and effective designer surfactants [13], we initially focused our attention on the synthesis of PEG substituted BINOL derivative by reaction of the enantiopure (*R*), (*S*) and racemic BINOL with methanesulfonated MPEG-350 in DMF with K_2CO_3 obtaining the corresponding compounds in nearly 75 % isolated yields (Scheme 1).

In order to obtain a series of similar surfactants bearing different electronic properties, we planned the synthesis of three more compounds bearing additional aromatic units on position 6 and 6' of the naphthyl ring bearing electron donating as well as electron withdrawing substituents. The purpose was to increase the size of the apolar core of the micelles and to impart different electron properties to promote better π-π stacking with aromatic substrates. The synthesis started from enantiopure (*S*)-BINOL in DCM that was initially brominated on position 6 and 6' by dropwise addition of a solution of bromine in DCM, while keeping the mixture at −15 °C, obtaining the dibrominated product (*S*)-6,6′-dibromo-[1,1′-binaphthalene]-2,2′-diol (*S*)-Br-BINOL with a yield of 90 %. An early attempt to obtain the enantiomers of 6,6′-dibromo-[1,1′-binaphthalene]-2,2′-diol operating the chiral resolution of the racemate using benzyl cinchonidinium chloride [14] did not work due to the high solubility of the adduct between the chiral resolving agent and the *R* enantiomer. Then, the reaction of (*S*)-Br-BINOL with phenyl, 4-methoxy-phenyl and 3,5-*bis*-trifluoromethyl-phenyl boronic acids catalyzed by $Pd(PPh_3)_4$ allowed to obtain the corresponding enantiopure functionalized BINOL derivatives **2b-d** in good yields considering the double Suzuki cross-couplings (Scheme 2). It is interesting to note that no product formation was observed employing pentafluorophenyl boronic acid. This may be due to the insufficient electron density on the aromatic boronic acid reagent that hampered the trans-metalation step of the catalytic cycle. In fact, to the best of our knowledge, there is no successful synthesis of 6,6′-*bis*(perfluoro phenyl)-[1,1′-binaphthalene]-2,2′-diol reported in the literature. The substituted BINOL derivatives **2b-d** were then reacted with mesylated MPEG-350 and, to ensure good purity of the final surfactants by removal of unreacted PEG units, it was also necessary a clever purification process involving Soxhlet extraction. The final neutral enantiopure surfactants **1b-d** were isolated in very good yields considering the double substitution reactions (Scheme 2) in up to 230 mg amounts.

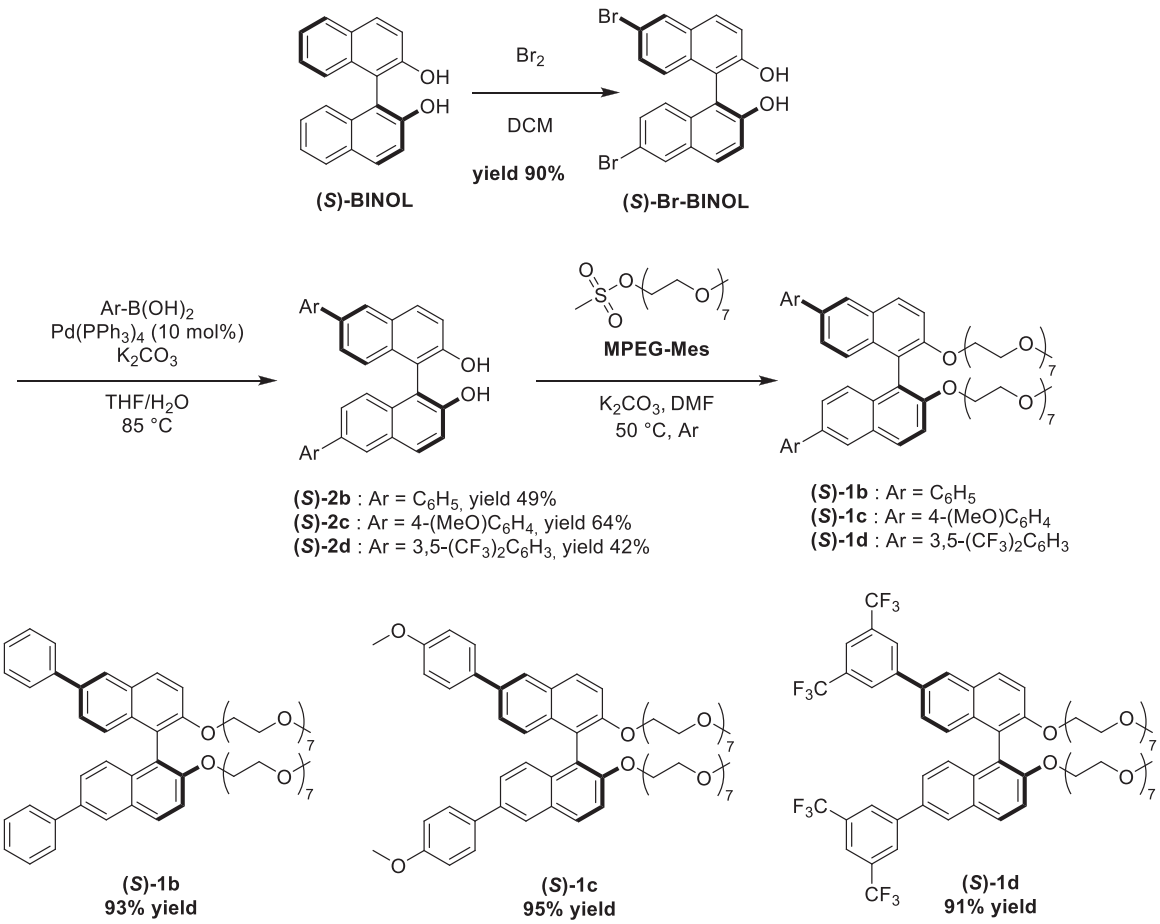
3. Aggregation in water of BINOL-based surfactants

The dissolution of the surfactants ***(rac, S, R)*-1a** in water showed immediately a foaming effect that is indicative of micelles formation. In order to determine the critical micellar concentration (CMC), we monitored the ^{1}H NMR chemical shift of the resonances of ***(R)*-1a** in D_2O at different concentrations in the range 0.1–50 mM. We observed a clear shielding effect in particular of the aromatic resonances with increasing the concentration of the surfactant in D_2O. The plot of the chemical shifts of the aromatic units of the compounds as function of the inverse of the concentration in solution [15] enabled the clear identification of the CMC of the surfactant by the intersection of the two trendlines corresponding to 1.1 mM (Fig. 1). We therefore decided to test the surfactant at concentration of 1 % w/w corresponding to 10.7 mM, which is above the CMC value. In order to confirm the presence of micelles in solution, we performed DLS analyses on 1 % w/w solution observing the presence of aggregates with an average diameter of 4.5 ±0.1 nm (see supporting information). Comparable size of the aggregates were determined also by pseudo 2D DOSY experiment, with an average diameter of 5.2 nm (see supporting information).

We repeated the determination of the CMC also for the racemic compound obtained with the same reaction from racemic BINOL corresponding to 1.7 mM, which is a slightly higher value compared to the enantiopure compound (Fig. 1). This small difference is also an intriguing indication that the aggregates that form in water above the CMC are somehow different for the enantiopure surfactant with respect to the racemic one. In fact, in the case of the racemic surfactant, a mixture of units of different stereochemistry are present, which can give rise to diastereoisomeric micelles depending on the stereochemistry of the single surfactant units, while for the enantiopure surfactant also the micelles are strictly enantiopure. Therefore, the two kinds of micelles have to be considered diastereoisomeric, and probably they are also composed by a different number of units or at least arranged in different ways.



Scheme 1. Synthesis of enantiopure BINOL-based surfactant ***(R)*-1a.** With the same reaction products ***(S)*-1a** and ***(rac)*-1a** were obtained in 78 and 72 % yields, respectively.



Scheme 2. General synthesis of the diverse enantiopure functionalized BINOL-based surfactants.

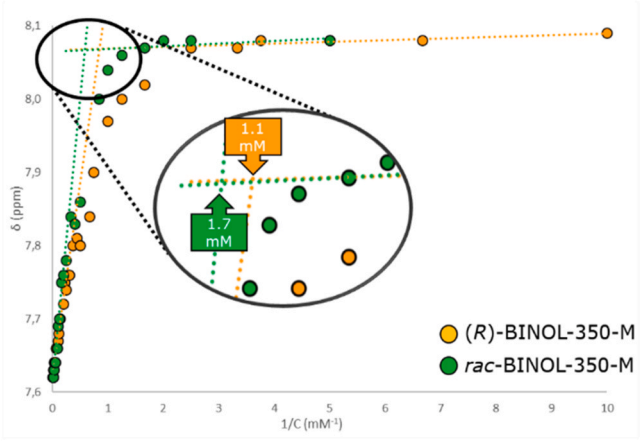


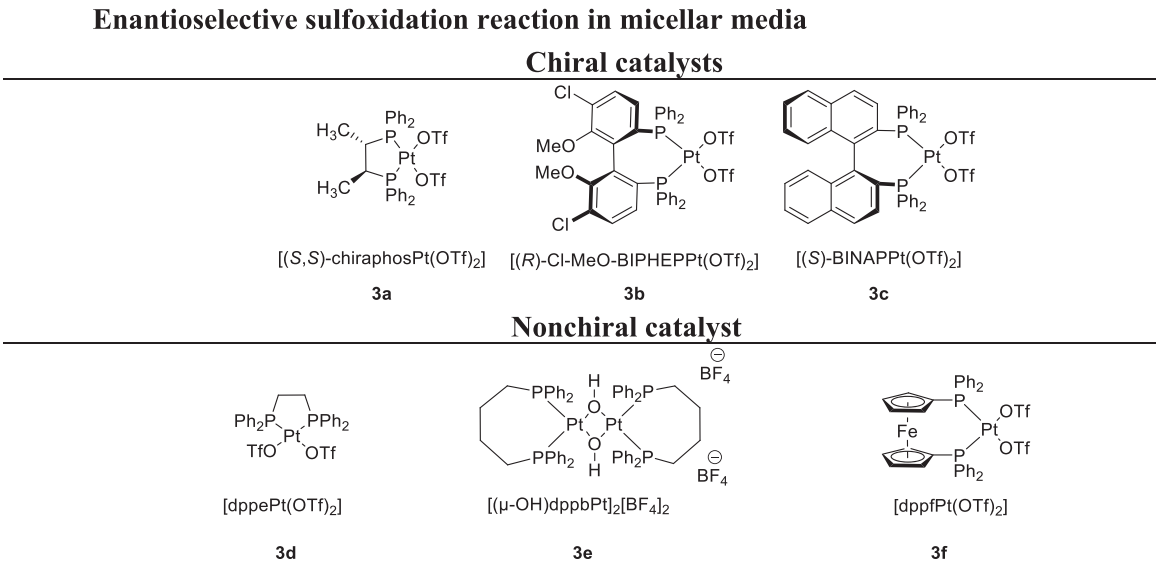
Fig. 1. Comparison between CMC determination graphs of **(*R*)-1a** and **(*rac*)-1a**.

4. Enantioselective sulfoxidation reaction in micellar media

To explore the effect of chiral surfactants in asymmetric catalysis, we selected a reaction and a class of chiral catalysts characterized by low enantioselectivities, to better discriminate the contribution provided by the chiral micelles (Scheme 3). The oxidation of thioethers with hydrogen peroxide mediated by a series of chiral Pt(II) catalysts was then investigated using thioanisole as substrate (Table 1).

As a reference the reaction was first carried out in organic solvent using three catalyst bearing different chiral ligands like (*S,S*)-chiraphos **3a**, (*R*)-Cl-MeO-BIPHEP **3b** and (*S*)-BINAP **3c** observing low enantioselectivities with up to 21 % ee (Table 1, entry 1). Then we repeated the reactions in water with the aid of 1 % w/w of the neutral surfactant **(*S*)-1a**. Under identical experimental conditions the reactions with the same three catalysts led to small but constant improvement of the enantioselectivity (Table 1, entry 4). Moreover, it is curious to note that performing the reaction with catalyst **3a**, but moving from the organic medium to water employing surfactant **(*S*)-1a** led also to the reverse of the favored enantiomer. The same three catalysts were then tested in water with **(*R*)-1a** as enantiomer of the previous surfactant observing in all cases a decrease of enantioselectivity (Table 1, entry 5). The match and mismatch effects observed with **(*S*)-1a** and **(*R*)-1a** surfactants are due to the diastereoisomeric interactions of the chiral catalysts with the two enantiopure micellar media. In a further experiment the three catalysts were tested with the racemic surfactant **(*rac*)-1a** observing even lower or in some cases no enantioselectivities, which is expected due to the formation in solution of many diastereoisomeric micelles comprising a wide range of combinations of (*S*) and (*R*) surfactants (Table 1, entry 6).

Then we tested the best performing catalysts **3a** and **3b** with the series of surfactants **(*S*)-1b-d** all with the common *S* configuration of the BINOL unit but bearing extended aromatic apolar moieties (Table 1, entries 7–9). This turned out to be detrimental for the stereoselectivity of the reaction observing with catalyst **3a** ee values in the range +6 and −5 %, in both cases lower than with the smaller surfactant **(*S*)-1a**. The same trend was observed with catalyst **3b** leading to ee in the range 19–22 % with the three surfactants **(*S*)-1b-d**, in all cases lower compared to the reaction with **(*S*)-1a**. Both series of tests with the elongated surfactants confirmed their limited ability to positively affect the stereoselectivity of the reaction. An attempt was also made testing a



Scheme 3. Structure of the Pt(II) catalysts tested in the asymmetric sulfoxidation reaction under micellar conditions with chiral surfactants.

recent designer surfactant that was proposed by our research group based on the employment of sitosterol as the apolar chiral portion of the surfactant, covalently connected to the PEG unit, [16] but no asymmetric induction was observed. It is therefore likely that the interaction between the chiral catalysts and the surfactants so far investigated is too weak and dynamic to favor better levels of stereoselectivity.

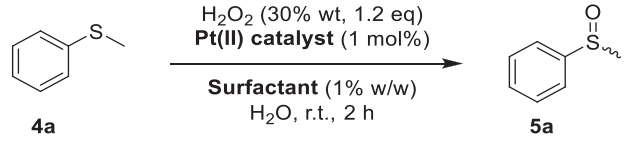
We then changed perspective and decided to modify the hydrophilic portion of the chiral surfactants introducing an anionic sulfonate moiety that could better interact by ion pairing with the positively charged catalysts. Accordingly, we synthesized the BINOL based anionic surfactant **(*S*)-1e** by reaction of (*S*)-BINOL with 1,4-butane sultone under basic conditions obtaining the product in 91 % yield (Scheme 4). The new surfactant showed good micellization properties with a CMC of 16.2 mM (see Supporting Information). Also in this case DLS analyses showed the presence of aggregates with an average diameter of 0.9 ±0.1 nm, while by pseudo 2D DOSY experiment the aggregates showed an average diameter of 1.7 nm (see supporting information). It is worth noting that the difference observed between the two analytical techniques is a common phenomenon, in particular for charged surfactants, as a consequence of the electrostatic effects imparted by the small sodium counter-cations on the micellar aggregates that leads to enhanced diffusion coefficients determined by DLS [17].

The three catalysts **3a-c** were then tested at 1 % w/w of **(*S*)-1e** in water, above the CMC, observing in all cases improved enantioselectivities with respect to the **(*S*)-1a** (Table 1, entry 10). In particular catalyst **3c** was used in the presence of the anionic surfactant **(*S*)-1e** leading to ee up to 41 %. To underline the positive effect provided by the enantiopure surfactant **(*S*)-1e**, we repeated the same catalytic test using sodium dodecyl sulfate as achiral anionic surfactant leading to only 10 % ee (Table 1, **e**ntry 3), demonstrating the positive asymmetric induction provided by the chiral surfactant. A control experiment with the chiral surfactant **(*S*)-1e** but in the absence of the catalyst led to only 3 % of the sulfoxide **5a** as racemic compound, thus ruling out the direct oxidation of the thioanisole by hydrogen peroxide. It is therefore likely that the anionic surfactant acts as a counter-anion with respect to the *bis*-cationic chiral catalysts creating a more asymmetric environment in proximity of the accessible coordination site of the metal, where hydrogen peroxide activation takes place.[10] This resembles examples of couteranion enantioselective metal catalysis, a specific catalytic approach where the chiral anion in close proximity of an achiral cationic metal center provide the asymmetric induction [18–21]. We also investigated the possible asymmetric induction provided by surfactant **(*S*)-1e** in the reaction mediated by achiral Pt(II) catalysts bearing dppe **3d**, dppb **3e** or dppf **3 f** ligands (Scheme 3). In all cases the corresponding sulfoxides were obtained in racemic form (see Supporting Information).

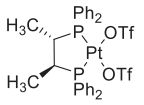
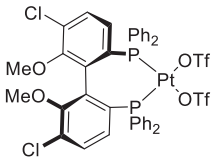
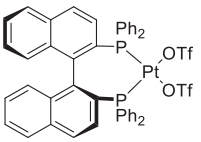
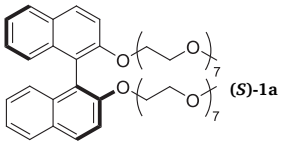
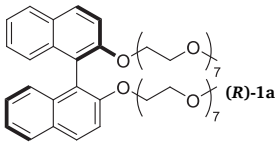
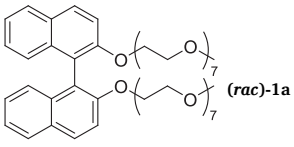
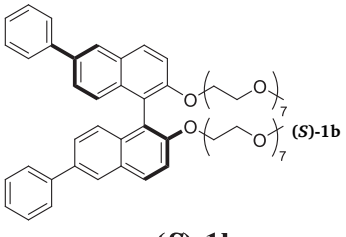
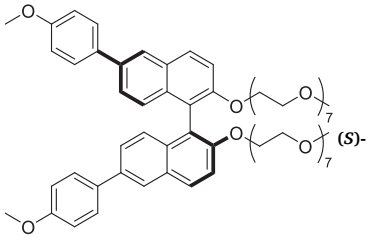
We continued the catalytic screenings with catalyst **3b** to optimize both sulfoxide yield and enantioselectivity, varying the reaction time and the relative amounts of hydrogen peroxide, catalyst and chiral surfactant **(*S*)-1e** (Table 2). As expected, while the increase of oxidant led to enhanced yields albeit with slight decrease of enantioselectivity (Table 2, entry 2–4), using higher amounts of chiral surfactant led to a detrimental effect on the sulfoxide yields (Table 2, entry 5 and 6). This is likely to be due to a sort of dilution effect when more micelles are present, and catalyst and substrates are less confined [10]. The doubling of the catalyst loading (Table 2, entry 7) did not enhance sulfoxide formation probably due to low solubility of the catalyst already when 1 mol %.

Overall, the subsequent tests were carried out using the same amounts of catalyst and surfactant and with five equivalents of hydrogen peroxide. We then extended the catalytic system to a wide range of substrates characterized by different sizes, shapes, and electronic properties (Table 3). For the series of aryl methyl sulfides with different substituents in the *para* position we observed similar product yields in water with **(*S*)-1e** compared to $CDCl_3$, which is an interesting result considering that some substrates are solid. Considering the electronic effects imparted by the substituents in the aryl units, it is clear that the reaction in $CDCl_3$ shows a volcano profile of the enantioselectivity of the reaction, with lower enantiomeric excesses for highly electron rich and electron poor substrates, while better stereoselectivities were observed with substituents with intermediate electronic properties. In particular, it is interesting to note that substrates showing lower enantioselectivity are also those characterized by more polar and hydrophilic groups in para position. This could be somehow related to a lower interaction of such substrates with the hydrophobic portion of the chiral surfactant driven by the hydrophobic effect. The profile is clearly described in the plot reported in Fig. 2A reporting the ee of the reactions as a function of the σ_{para} Hammett, with better ee for substrates with σ_{para} in the range −0.2 – 0.2. This stereoselectivity profile suggests that the recognition of the prochiral thioether occurs not only based on purely electronic properties like for instance when π-π interactions between aromatic substrates and catalyst takes place, but a combination of effects, including possible interactions with water. It is also interesting to note that for most investigated substrates, in particular for those with

Table 1
Enantioselective thioanisole **4a** oxidation with hydrogen peroxide mediated by chiral Pt(II) catalysts under different micellar conditions with chiral and achiral surfactants.

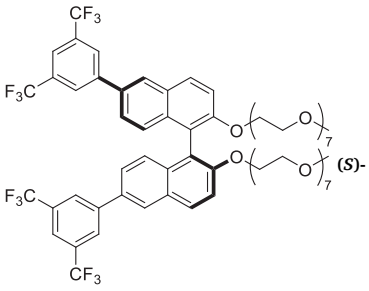
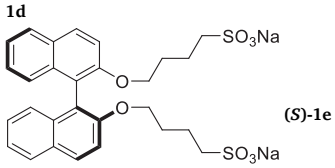


4a **5a**

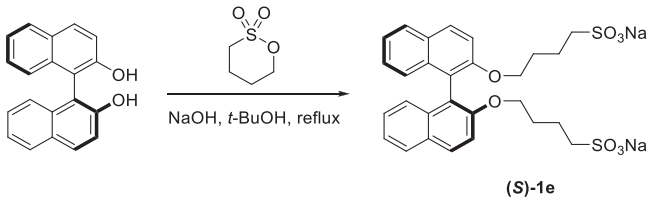
	Medium/surfactant	Sulfoxide 5a Yield (%)[a], ee (%)[b] with catalyst 3a	Sulfoxide 5a Yield (%)[a], ee (%)[b] with catalyst 3b	Sulfoxide 5a Yield (%)[a], ee (%)[b] with catalyst 3c
		 **3a**	 **3b**	 **3c**
1	$CDCl_3$	65, 5	47, 21	55, 8 (*S*)
2	Water with no surfactant[b]	-	7, 20	-
3	Sodium dodecyl sulfate (SDS) 1 % w/w	-	27, 10	-
4	 **(*S*)-1a** **(*S*)-1a**	48, 11 (*S*)	40, 31	36, 15 (*S*)
5	 **(*R*)-1a** **(*R*)-1a**	32, 2 (*S*)	21, 23	15, 1 (*S*)
6	 **(*rac*)-1a** **(*rac*)-1a**	14, 2 (*S*)	47, 11	13, 1 (*S*)
7	 **(*S*)-1b** **(*S*)-1b**	22, 6	6, 22	-
8	 **(*S*)-** **(*S*)-1c** **1c**	65, 5 (*S*)	6, 19	-

(*continued on next page*)

Table 1 (*continued*)

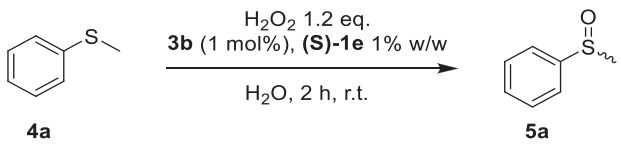
9	 **(*S*)-1d**	37, 2 (*S*)	6, 22	-
10	 **(*S*)-1e**	63, 16 (*S*)	13, 41	10, 30 (*S*)

a) Determined by ^{1}H NMR on organic extract; b) Determined by chiral HPLC. Major enantiomer *R* unless differently reported close to the ee value.



Scheme 4. Synthesis of the anionic chiral surfactant **(*S*)-1e** bearing sulfonated hydrophilic headgroups and BINOL based hydrophobic portion.

Table 2
Enantioselective thioanisole **4a** oxidation with hydrogen peroxide mediated by Pt(II) catalyst **3b** in water with surfactant **(*S*)-1e** under different experimental conditions.



4a **5a**

#	Deviation of experimental conditions from scheme	Sulfoxide 5a Yield (%)[a]	Sulfoxide 5a ee (%)[b]
1	As in scheme	13	41
2	Reaction time 4 h	18	33
3	H_2O_2 2.5 eq.	29	34
4	H_2O_2 5.0 eq.	47	34
5	Surfactant loading **(*S*)-1e** 5 % w/w	7	1
6	Catalyst **3b** 2 mol%	15	34

a) Determined by ^{1}H NMR on organic extract; b) Determined by chiral HPLC, major enantiomer *R*.

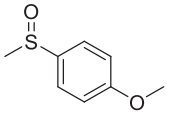
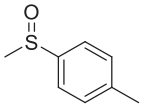
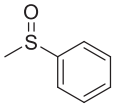
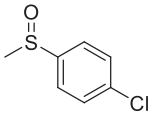
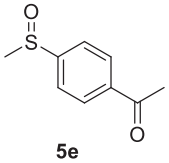
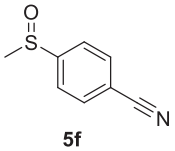
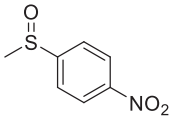
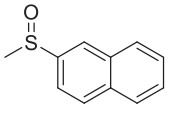
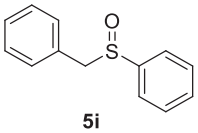
intermediate electronic effects, the use of the enantiopure surfactant **(*S*)-1e** led to an enhancement of the enantioselectivity of the reactions with respect to the use of chloroform as organic solvent (Fig. 2A). The value of the enantiomeric ratio (er) rather than the ee is directly correlated to the ratio between the two kinetic constants for the two enantiomers. The effect of the chiral surfactant can be underlined observing the plot of Fig. 2B reporting the difference between the natural logarithm of the er for the reaction with the **(*S*)-1e** and the reaction in chloroform as function of the σ_{para} Hammett. The values are proportional to the gap in the $\Delta\Delta G^{\neq}$ for the two enantiomeric pathways provided by the chiral surfactant **(*S*)-1e** with respect to the organic solvent. Apart from substrate **4b**, most of the others show a decreasing trend with σ_{para} suggesting a predominant but not exclusive electronic effect on the asymmetric induction provided by the chiral surfactant.

As further substrates, we investigated naphthyl methyl sulfide **4 h** and benzyl phenyl sulfide **4i**. The first one did not show improvements of enantioselectivity in water **(*S*)-1e**, while the second led to an increase of the ee from 29 % in $CDCl_3$ to 41 % in water with the chiral surfactant. This demonstrates that, as frequently observed in stereoselective catalysis, it is rather difficult to predict the level of stereoselectivity by comparing the size and shape of the substrates. Many other complex phenomena, like combination of steric and supramolecular attractive and repulsive interactions could largely change the level of stereoselectivity.

Since the combination of a chiral catalyst with a chiral surfactant provides two diastereoisomeric catalytic systems as function of the combination of the configurations of both species, we synthesized the other enantiomer of the surfactant **(*R*)-1e** following the above reported procedures and we tested catalyst **3b** with the new surfactant using all the thioether substrates (Table 3). Comparing the results with **(*R*)-1e** and **(*S*)-1e** it is clear that for most substrates the enantioselectivity was worse with the former surfactant. The plot reported in Fig. 2C shows an almost linear trend of the difference between the Ln of the er for the reactions with **(*S*)-1e** and **(*R*)-1e** as function of the σ_{para} Hammett, evidencing the matching combination between the (*S*) surfactant with the (*R*) configuration of the catalyst **3b**. For the most electron rich substrate **4b** the data do not fit the trend, thus again suggesting that electronic effects provide only a partial description of the complex network of interactions existing between the substrate, the catalyst and the chiral surfactant. Mastering these interactions is fundamental to improving the stereoselectivity of the reactions.

We also performed a control experiment testing catalyst **3b** with the racemic surfactant **(±)-1e** for substrate **4a** observing the formation of the corresponding sulfoxide with 30 % yield and 39 % ee, which is a value in between what observed with enantiopure **(*S*)-1e** (41 % ee, Table 3) and **(*R*)-1e** (36 % ee, Table 3). With racemic surfactant the micelles are composed of many possible combinations of *R* and *S* molecules, ranging from enantiopure *S* micelles to enantiopure *R* micelles, with many intermediate combinations in between. Each of these micellar environments could express potentially a different ee in combination with catalyst **3b**. The fact that the experimental ee with the racemic **(±)-1e** is an intermediate value between what observed with enantiopure **(*S*)-1e** and **(*R*)-1e** suggests that probably the catalyst interacts strongly on the surface of the micelle with one molecule of

Table 3
Substrate scope for the enantioselective sulfoxidation with hydrogen peroxide mediated by Pt(II) catalyst **3b** in $CDCl_3$ compared to water with **(*S*)-1e** and **(*R*)-1e** leading to the sulfoxides **5b-i**.

Sulfoxide product	Yield $CDCl_3$ (%)[a]	ee $CDCl_3$ (%)[b]	Yield H_2O/(*S*)-1e (%)[a]	ee H_2O/(*S*)-1e (%)[b]	Yield H_2O/(*R*)-1e (%)[a]	ee H_2O/(*R*)-1e (%)[b]
 **5b**	89	18	82	21	81	21
 **5c**	78	23	74	46	78	33
 **5a**	47	21	13	41	79	36
 **5d**	52	36	47	53	46	50
 **5e**	16[c]	4[c]	28[c]	6[c]	37[c]	6[c]
 **5f**	19	10	6	5 (*S*)	70[c]	0[c]
 **5g**	28[c]	6[c]	17[c]	0[c]	18[c]	3[c]
 **5h**	96[c]	29[c]	93[c]	23[c]	94[c]	22[c]
 **5i**	26	29	11	41	95[c]	23[c]

a) Determined by ^1H NMR on organic extract; b) Determined by chiral HPLC, major enantiomer R unless differently reported close to the ee value; c) Reaction time 24 h.

surfactant at a time, either **(*S*)-1e** leading to higher ee, or **(*R*)-1e** with lower ee. This supports the general picture where the *bis*-cationic chiral catalysts makes ion-pairing with one molecule of *bis*-anionic chiral surfactant. It is in this chiral environment that H_2O_2 is activated by the Pt(II) center[10] and where also the thioether has to sneak in to reach the activated oxidant, to be eventually transformed into enantioenriched sulfoxide. We also attempted to investigate the positioning of catalyst **3b** in the micellar system formed by **(*S*)-1e** running NOESY experiments, but no clear cross peaks between the aromatic resonances of the catalyst and those of the surfactant were unequivocally determined.

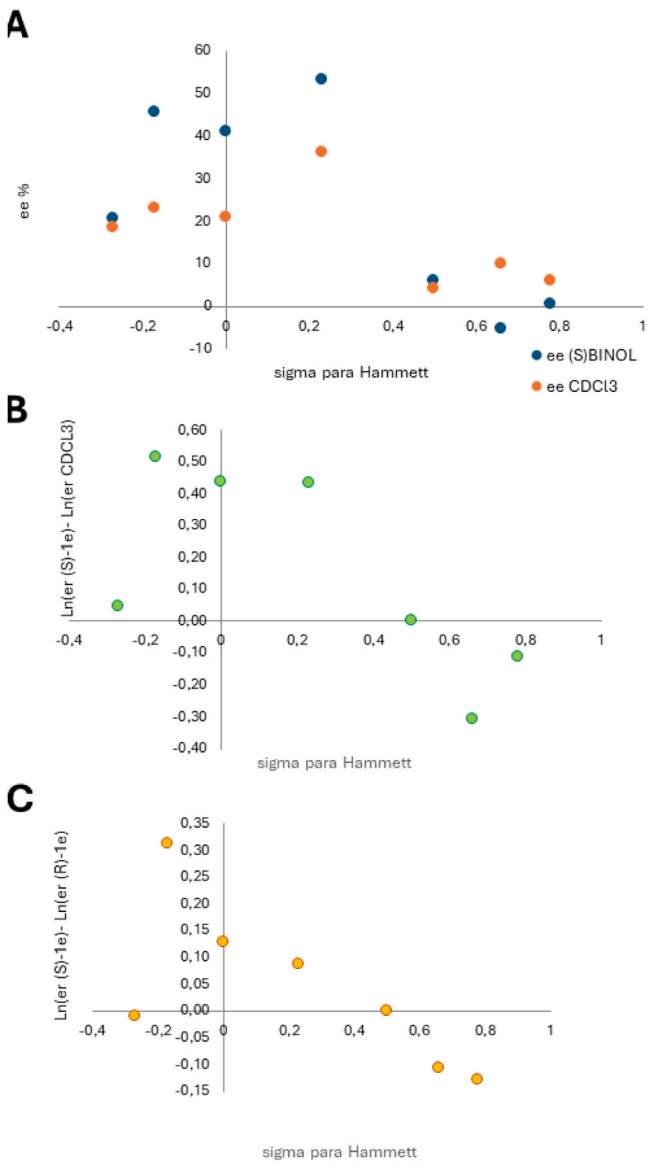


Fig. 2. A) Plot of the ee of the sulfoxidation reactions with catalyst **3b** in water with **(*S*)-1e** and in $CDCl_3$ as function of σ_{para} Hammett; **B)** Plot of the difference of the ln(er **(*S*)-1e**)-ln(er ($CDCl_3$)) for the reaction mediated by **3b** using the **(*S*)-1e** or chloroform-d as function of σ_{para} Hammett, respectively. **C)** Plot of the difference of the ln(er **(*S*)-1e**)-ln(er **(*R*)-1e**) for the reaction mediated by **3b** using the **(*S*)-1e** or **(*R*)-1e** surfactant as function of σ_{para} Hammett, respectively.

5. Conclusions

In conclusion, we demonstrated that the stereoselectivity of a chiral transition metal catalyst can be improved with respect to the reaction in organic solvent when operating in water in combination with a proper chiral surfactant. The design of the surfactant is the key issue to be optimized. To promote a close contact, a suitable approach consists in using a surfactant bearing anionic hydrophilic units in order to establish ion-pairing with cationic catalysts, while the chiral hydrophobic portion of the amphiphile should be preferably rigid, aromatic, and symmetric. Using BINOL-based hydrophobic units we prepared several chiral surfactants, among which the most promising resulted a *bis*-anionic derivative that, in combination with chiral Pt(II) *bis*-cationic catalysts, led to enhanced stereoselectivities in the asymmetric sulfoxidation of thioethers with hydrogen peroxide with a wide range of substrates. It is likely that even though the enantiomeric excesses were not high, the synergistic effect of the use of chiral micelles was confirmed with different catalysts, chiral surfactants and its absolute configuration and substrates. Certainly, a deep optimization of the overall catalytic system is mandatory in order to achieve very high enantioselectivities, for instance using chiral scaffolds that provide more rigid units pointing in the same direction of the anionic side chains. The seminal results presented in this work represent a proof of concept and will certainly spur our group and others in further investigating this topic, aiming at mimicking the high stereoselectivities imparted by the active site of enzymes characterized by large chiral cavities. Chiral micelles can become suitable asymmetric environments that in proximity of chiral catalysts lead to more asymmetric environments in which prochiral substrates have to sneak in, thus leading to enhanced asymmetric inductions.

CRediT authorship contribution statement

Alessandro Scarso: Writing – review & editing, Writing – original draft, Validation, Supervision, Project administration, Funding acquisition, Data curation, Conceptualization. **Davide Frigatti:** Writing – review & editing, Supervision, Investigation, Formal analysis, Data curation. **Tommaso Lorenzetto:** Writing – review & editing, Supervision, Investigation, Formal analysis, Data curation. **Fabrizio Fabris:** Writing – review & editing, Supervision, Conceptualization. **Paolo Sgarbossa:** Writing – review & editing, Supervision, Investigation, Formal analysis, Conceptualization. **Enrico Liviero:** Formal analysis. **Camilla Stefani:** Formal analysis.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.cattod.2024.114924.

References

[1] a) J. Ceramella, D. Iacopetta, A. Franchini, M. De Luca, C. Saturnino, I. Andreu, M. S. Sinicropi, A. Catalano, Appl. Sci. 12 (2022) 10909, https://doi.org/10.3390/app122110909;
b) M.M. Coelho, C. Fernandes, F. Remião, M.E. Tiritan, Molecules 26 (2021) 3113, https://doi.org/10.3390/molecules26113113.
[2] a) B. Mitschke, M. Turberg, B. List, Chem 6 (2020) 2515–2532, https://doi.org/10.1016/j.chempr.2020.09.007;
b) Y. Yu, J.-M. Yang, J. Rebek Jr., Chem 6 (2020) 1265–1274, https://doi.org/10.1016/j.chempr.2020.04.014.
[3] a) T.M. Bräuer, Q. Zhang, K. Tiefenbacher, Angew. Chem. Int. Ed. 55 (2016) 7698–7701, https://doi.org/10.1002/anie.201602382;
b) T.M. Bräuer, Q. Zhang, K. Tiefenbacher, J. Am. Chem. Soc. 139 (2017) 17500–17507, https://doi.org/10.1021/jacs.7b08976.
[4] F. Begato, G. Licini, C. Zonta, Angew. Chem. Int. Ed. 62 (2023) e202311153, https://doi.org/10.1002/anie.202311153.
[5] a) C. Tan, D. Chu, X. Tang, Y. Liu, W. Xuan, Y. Cui, Chem. Eur. J. 25 (2019) 662–672, https://doi.org/10.1002/chem.201802817;

b) M. Morimoto, S.M. Bierschenk, K.T. Xia, R.G. Bergman, K.N. Raymond, F. D. Toste, Nat. Catal. 3 (2020) 969–984, https://doi.org/10.1038/s41929-020-00528-3.
[6] a) S.M. Bierschenk, J.Y. Pan, N.S. Settineri, U. Warzok, R.G. Bergman, K. N. Raymond, F.D. Toste, J. Am. Chem. Soc. 144 (2022) 11425–11433, https://doi.org/10.1021/jacs.2c04182;
b) Z. Lu, T.K. Ronson, A.W. Heard, S. Feldmann, N. Van-thuyne, A. Martinez, J. R. Nitschke, Nat. Chem. 15 (2023) 405–412, https://doi.org/10.1038/s41557-022-01103-y.
[7] a) T.N. Ansari, G. Xu, A. Preston, P. Gao, Org. Process Res. Dev. 28 (2024) 816–830, https://doi.org/10.1021/acs.oprd.3c00453;
b) N. Compagno, R. Profeta, A. Scarso, Curr. Opin. Green. Sust. Chem. 39 (2023) 100729, https://doi.org/10.1016/j.cogsc.2022.100729.
[8] T. Lorenzetto, D. Frigatti, F. Fabris, A. Scarso, Adv. Synth. Catal. 364 (2022) 1776–1797, https://doi.org/10.1002/adsc.202200225.
[9] T. Lorenzetto, F. Fabris, A. Scarso, Curr. Opin. Coll. Interf. Sci. 64 (2023) 101689, https://doi.org/10.1016/j.cocis.2023.101681.
[10] A. Scarso, G. Strukul, Adv. Synth. Catal. 347 (2005) 1227–1234, https://doi.org/10.1002/adsc.200505030.
[11] B.A. Shairgojray, A.A. Dar, B.A. Bhat, Catal. Commun. 83 (2016) 58–61, https://doi.org/10.1016/j.catcom.2016.05.010.
[12] a) M. Yoshizawa, L. Catti, Acc. Chem. Res. 52 (2019) 2392–2404, https://doi.org/10.1021/acs.accounts.9b00301;
b) L. Catti, H. Narita, Y. Tanaka, H. Sakai, T. Hasobe, N.V. Tkachenko, M. Yoshizawa, J. Am. Chem. Soc. 143 (2021) 9361–9367, https://doi.org/10.1021/jacs.0c13172;
c) Y. Satoh, L. Catti, M. Akita, M. Yoshizawa, J. Am. Chem. Soc. 141 (2019) 12268–12273, https://doi.org/10.1021/jacs.9b03419;
d) H. Narita, L. Catti, M. Yoshizawa, Angew. Chem. Int. Ed. 60 (2021) 12791–12795, https://doi.org/10.1002/anie.202102547;
e) L. Catti, R. Sumida, M. Yoshizawa, Coord. Chem. Rev. 460 (2022) 214460, https://doi.org/10.1016/j.ccr.2022.214460.
[13] T. Lorenzetto, G. Berton, F. Fabris, A. Scarso, Catal. Sci. Technol. 10 (2020) 4492–4502, https://doi.org/10.1039/D0CY01062F.
[14] Y. Wang, J. Sung, K. Ding, Tetrahedron 56 (2000) 4447–4451, https://doi.org/10.1016/S0040-4020(00)00368-9.
[15] J. Zhao, B.M. Fung, Langmuir 9 (1993) 1228–1231, https://doi.org/10.1021/la00029a013.
[16] T. Lorenzetto, D. Frigatti, F. Fabris, A. Scarso, J. Organomet. Chem. 964 (2022) 122316, https://doi.org/10.1016/j.jorganchem.2022.122316.
[17] E. Sutherland, S.M. Mercer, M. Everist, D.G. Leaist, J. Chem. Eng. Data 54 (2009) 272–278, https://doi.org/10.1021/je800284g.
[18] D.B. Llewellyn, D. Adamson, B.A. Arndtsen, Org. Lett. 2 (2000) 4165–4168, https://doi.org/10.1021/ol000303y.
[19] S. Mayer, B. List, Angew. Chem. Int. Ed. 45 (2006) 4193–4195, https://doi.org/10.1002/anie.200600512.
[20] R.J. Phipps, G.L. Hamilton, F.D. Toste, Nat. Chem. 4 (2012) 603–614, https://doi.org/10.1038/nchem.1405.
[21] M. Mahlau, B. List, Angew. Chem. Int. Ed. 52 (2013) 518–533, https://doi.org/10.1002/anie.201205343.