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COMMUNICATION

Micellar Ru(II)–bipyridine photocatalysts for selective oxidation of thioethers to sulfoxides in water

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A supramolecular photocatalytic system was engineered by encapsulating a modified ruthenium(II)-bipyridine complex in stabilized polydiacetylene micelles. The colloidal nanohybrid catalyst enables selective oxidation of thioethers to sulfoxides in pure water, and can be easily recycled. The polymerized network within the micelles ensures the robustness of the assembly, while providing a confined domain that acts as a (photo)nanoreactor.

Sulfoxides play a central role in the pharmaceutical industry,[1-4] as evidenced by drugs such as omeprazole, armodafinil or sulindac. The synthesis of sulfoxides is often based on the mono-oxidation of thioethers, a tricky process due to possible over-oxidation into undesirable sulfones. Conventional methods for thioether oxidation typically involve stoichiometric and hazardous oxidants (*e.g.*, *m*CPBA, $NaIO_4$[5] or concentrated peroxides) that often require harsh reaction conditions and generate chemical waste. Accordingly, the development of environmentally-friendly and chemo-selective methods for the oxidation of sulfides is key for sustainable chemistry.

In this context, photocatalysis has emerged as a powerful alternative to stoichiometric oxidants.[6,7] A major advantage of photocatalysis is the use of ubiquitous molecular oxygen (O_2) as the terminal oxidizing source.[8] However, ground-state triplet oxygen ($^3O_2$) is poorly reactive and requires activation, which can be triggered by a photosensitizer. In fact, upon light activation, photosensitizers absorb photons and enter an excited state that can, in turn, catalytically activate oxygen.[9]

Tris(bipyridine)ruthenium(II) complexes and their derivatives are among the most prominent photosensitizers due to their suitable photophysical properties, long-lived excited states, and tunability of redox potentials.[10,11] However, the homogeneous nature of conventional Ru(II) systems in solvents often complicates catalyst removal and/or recovery, hindering their implementation in industrial or large-scale processes. A number of studies have thus sought the heterogenization of molecular photosensitizers on a solid matrix in order to overcome these limitations.[12,13] The integration of the catalyst in heterogeneous or semi-heterogeneous systems enhances local reaction control, facilitates the recovery of the catalyst and enables its recycling. Notable approaches include immobilization “on” or encapsulation “in” macromolecular structures.[14-16] Different kinds of soft materials have been used as water-dispersible photoreactors[17] and micelles, in particular, have gathered particular attention.[18-20] Over the years, researchers have used either commercial[21] or tailor-made amphiphiles[22] to create efficient micellar nanoreactors and promote a variety of reactions, including photochemical transformations.[21,23] Some of us have recently developed micellar systems for organic transformations,[24] including the photooxidation of thioethers.[25]

In continuation of our previous efforts, we report herein the development of a potent system for the selective photocatalytic oxidation of thioethers to sulfoxides under sustainable conditions, using pure water as solvent. Our strategy involves the self-assembly of diacetylene-containing amphiphiles and further polymerization to yield semi-heterogeneous stabilized micelles in which a modified ruthenium-bipyridine complex can be encapsulated (Figure 1). Micelles behave as nanoreactors, creating a favorable environment for the photo-activation of oxygen in the vicinity of thioethers.

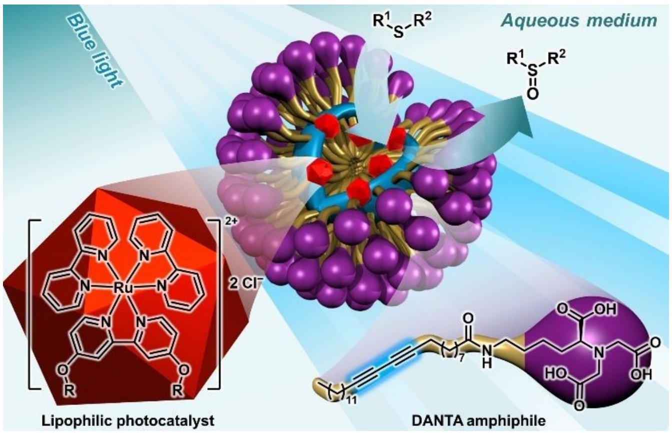

Figure 1. Overview of the stabilized micellar nanoreactor system for the selective photooxidation of sulfides into sulfoxides.

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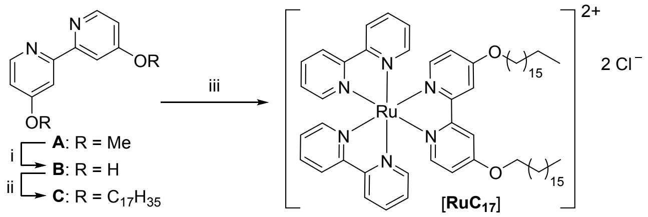
To enable the construction of the photocatalytic nanohybrid system, a lipophilic Ru(II)-bipyridine complex was first synthesized by incorporating long alkyl chains to the ligands of ruthenium. The presence of these alkyl chains makes the complex more lipophilic and suitable for encapsulation in the core of the micelles. The synthetic route towards the ruthenium complex is outlined in Scheme 1. Starting from 4,4′-dimethoxy-2,2′-bipyridine (**A**), demethylation under acidic conditions afforded the corresponding 2,2′-bipyridine-4,4′-diol (**B**) in 92% yield. Subsequent double *O*-alkylation of **B** with 1-bromoheptadecane in the presence of potassium carbonate provided the hydrophobic bipyridine **C**, bearing long alkyl chains (56% yield). Finally, coordination of ligand **C** to ruthenium was achieved by reaction with [Ru(bpy)$_2$Cl$_2$] in an ethanol/water mixture under reflux, affording the target Ru(II) complex [**RuC$_{17}$**] in 44% yield, after purification by silica gel chromatography. UV-vis spectroscopy analysis of the [**RuC$_{17}$**] complex showed the characteristic absorption maxima at 294 and 460 nm (Figure S1), and the cyclic voltammetry profile recorded in acetonitrile was similar to that of other Ru(bpy)$_3$ derivatives reported in the literature (Figure S4).

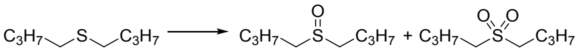


Scheme 1. Synthetic route to lipophilic complex [**RuC$_{17}$**]: (i) **A**, HBr, AcOH, reflux, 24 h; neutralization with NH$_4$OH, precipitation, 92% (ii) **B**, K$_2$CO$_3$, 1-bromoheptadecane, DMF, 80 °C, 24 h; purification by silica gel chromatography (*n*-hexane/EtOAc, 95:5), 56%. (iii) **C**, [Ru(bpy)$_2$Cl$_2$], EtOH/H$_2$O (3:1 *v*/*v*), 80 °C, overnight; purification by silica gel chromatography (CH$_2$Cl$_2$/MeOH), 44%.

With the lipophilic [**RuC$_{17}$**] photocatalyst in hand, the next step was its encapsulation within a micellar nanoreactor system to create a colloidal catalytic platform. Micelles were prepared beforehand using the methodology previously established in our group.[26] Briefly, diacetylene-containing amphiphiles (DANTA) were sonicated in an alkaline aqueous medium using an ultrasonic probe to promote micellar assembly. The mixture was then subjected to UV illumination at 254 nm to trigger photopolymerization of diyne units within the core of individual micelles through a topochemical 1,4-addition reaction. This allowed the stabilization of the micellar architectures which were then passed through a size exclusion chromatography column (Sephadex), yielding colloidal polymerized DANTA (*p*DANTA) micelles in water. The ruthenium complex was then encapsulated in polymerized micelles by simple ultrasonication, followed by filtration on a 0.22 µm membrane (see ESI for details). UV-vis spectroscopy analysis of the [**RuC$_{17}$**]@*p*DANTA colloid showed a profile comparable to that of free [**RuC$_{17}$**], confirming effective encapsulation (Figure S2). The [**RuC$_{17}$**]/micelle mass ratio was calculated to be 1 wt%.

The photocatalytic activity of the [**RuC$_{17}$**]@*p*DANTA system was then evaluated in the oxidation of thioethers, and dibutyl sulfide (**1a**) was chosen as a model compound. In addition to the encapsulation of the [**RuC$_{17}$**] photocatalyst, the central lipophilic domain of the micellar nanoreactor can also accommodate hydrophobic substrate molecules, promote their dispersion in water, and favor their transient concentration next to the photoreactive center. The best activity and selectivity were obtained with a ruthenium catalyst loading (Ru/**1a**) of 0.1 mol%, under air atmosphere, in pure water, under blue light illumination (456 nm), and at room temperature. Under these optimal conditions, full conversion was achieved after 3 h with the exclusive formation of sulfoxide **2a** (Table 1, entry 1). Of note, vigorous stirring of the reaction mixture is needed to achieve effective and reproducible oxidations. Decreasing the catalyst loading (Ru/**1a**) to 0.01 mol%, led to a lower yield in sulfoxide **2a** (13%), after 3 h (entry 2). Control experiments were performed to confirm the photocatalytic nature of the transformation. When the reaction was conducted with empty micelles, without [**RuC$_{17}$**], no conversion was detected (entry 3), eliminating the possibility of a catalytic contribution from the micellar scaffold itself. In addition, no oxidation occurred for experiments conducted in the dark (entry 4) and those conducted under oxygen-free conditions (N$_2$ atmosphere), which also led to the full inhibition of the reaction (entry 5). The latter result suggests that the photocatalytic oxidation process is aerobic in nature.

Table 1. Optimization of reaction conditions.[a]



1a **2a** **3a**

Entry	[**Ru**] (mol%)	Light	Atm.	Conv. (%)	Selectivity (**2a**/**3a**)[d]
1	0.1	465 nm	air	100	> 99:1
2	0.01	465 nm	air	13	> 99:1
3	0	465 nm	air	0	-
4	0.1	none	air	0	-
5	0.1	465 nm	N$_2$	0	-
6[b]	0.1	465 nm	air	0	-
7	0.1[c]	465 nm	air	0	-

[a] Conditions: **1** (0.1 mmol), [**RuC$_{17}$**]@*p*DANTA, H$_2$O (1 mL), 3 h, room temp.; [b] Reaction carried out w/o micelles. [c] Reaction carried out with Ru(bpy)$_3$; [d] Determined by ^{1}H-NMR.

In the above transformation, the central role played by the micellar array as nanoreactor has been demonstrated by setting up a standard photo-oxidation reaction of dibutyl sulfide in water in the presence of [**RuC$_{17}$**], but without micelles. Under these conditions, the reaction was fully heterogeneous, as opposed to semi-heterogeneous in the presence of micelles, and resulted in no detectable oxidative conversion of **1a** after 3 hours (entry 6). Moreover, when micelles were used along with standard Ru(bpy)$_3$Cl$_2$ (0.1 mol%), no transformation occurred (entry 7). This underscores the beneficial contribution of micelles as reservoirs for [**RuC$_{17}$**], oxygen, and substrate, thereby promoting semi-heterogeneous photo-oxidation.

We then committed to evaluating the applicability of the [**RuC$_{17}$**]@*p*DANTA catalytic system in the selective photocatalytic aerobic oxidation of different thioethers (Table 2). All reactions were conducted under the standard reaction conditions described above.

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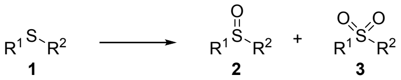
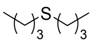
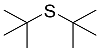
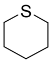
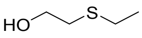
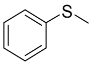
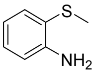
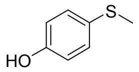
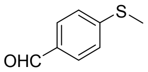
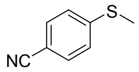
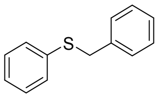
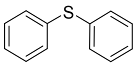
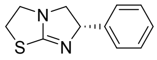
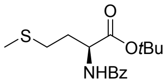
Table 2. Scope of the catalytic system.[a]



Entry	Substrate	1	Time (h)	Conv. (%)	Selectivity (**2**/**3**)[c]
1		**1a**	3	100	> 99:1
2		**1b**	3	95	90:10
3		**1c**	2	100	89:11
4		**1d**	18	33	> 99:1
5[b]		**1e**	6	100	> 99:1
6[b]		**1f**	9	100	> 99:1
7[b]		**1g**	5	100	> 99:1
8[b]		**1h**	4	90	80:20
9[b]		**1i**	8	100	55:45
10[b]		**1j**	6	50	98:2
11[b]		**1k**	12	NR	-
12[b]		**1l**	10	100	> 99:1
13		**1m**	3	100	84:16

[a] Conditions: **1** (0.1 mmol), [**RuC$_{17}$**]@*p*DANTA (0.1 mol%), H_2O (1 mL), room temperature, blue light (456 nm), air atmosphere; [b] O_2 atmosphere. [c] Determined by ^{1}H-NMR.

In comparison to dibutyl sulfide **1a**, which underwent complete selective conversion to **2a** within 3 h (entry 1), the more sterically hindered di-*tert*-butyl sulfide **1b** also reached full conversion within 3 h but exhibited slightly lower selectivity (90:10, entry 2). We then investigated cyclic thioether **1c** which was rapidly converted (2 h) to the corresponding sulfoxide **2c** with high selectivity (entry 3). The more polar aliphatic substrate **1d**, bearing a terminal hydroxyl group, exhibited lower reactivity. After 18 h, only 33% conversion was observed, although with complete selectivity towards the sulfoxide (entry 4). The reduced conversion likely reflects the less efficient interaction of the water-soluble substrate with the hydrophobic catalytic domain, underscoring the importance of substrate affinity for the core of the micellar nanoreactor. Next, a series of aryl thioethers bearing different substituents on the aromatic ring was examined. For these examples, reactions had to be conducted under oxygen atmosphere to give reproducible results. First, unsubstituted phenyl thioether **1e** was shown to afford quantitative conversion to **2e** after 6 h, with complete selectivity (entry 5). Similarly, aniline **1f** and phenol **1g** derivatives achieved full conversion within 9 h and 5 h, respectively, both with exclusive formation of the sulfoxide (entries 6 and 7). Aryl thioethers with electron-withdrawing substituents proved more problematic in terms of selectivity. In fact, aldehyde-substituted substrate **1h** reached 90% conversion after 4 h, with good yet imperfect selectivity toward the sulfoxide (80:20, entry 8) and nitrile-substituted derivative **1i** was fully converted within 8 h, albeit with mediocre selectivity (55:45, entry 9). Benzyl phenyl sulfide **1j** was only partially converted into the corresponding sulfoxide after 6 h, but with excellent selectivity (entry 10). The reduced conversion may be attributed to the very poor water dispersibility of the solid substrate, which probably hindered its access to the micellar nanoreactor. We then tested the [**RuC$_{17}$**]@*p*DANTA-mediated oxidation on diphenyl sulfane (**1k**, entry 11). However, even after 12 h under an oxygen atmosphere, no conversion was observed. This result highlights a limitation of the system, consistent with our earlier observations (entries 5-10) that mono-aromatic sulfoxides are more recalcitrant substrates than their aliphatic counterparts. Finally, two pharmaceutically relevant substrates were subjected to our photooxidation methodology. The first was levamisole (**1l**, entry 12), an anthelmintic heterocyclic drug, which was fully converted into the corresponding sulfoxide within 10 h and with full selectivity. The second was methionine derivative **1m** (entry 13), which was fully oxidized in 3 h, with good selectivity towards the sulfoxide (**2m**/**3m** 84:16).

The general activity and selectivity trends observed for this array of thioethers likely arise from a combination of substrate electronics, steric effects, and confinement within the micellar nanoreactor, which together limit uncontrolled overoxidation to sulfones.

We next sought to evaluate the recyclability of the [**RuC$_{17}$**]@*p*DANTA photocatalyst, using our model substrate **1a**. After completion of the oxidation reaction of dibutylsulfide, the sulfoxide product **2a** was extracted with diethyl ether, allowing the aqueous phase containing the nanohybrid catalyst to be directly reused, by simply adding fresh thioether **1a**, without any additional treatment. Under these conditions, the catalyst could be efficiently used over two consecutive runs with minimal loss of activity (> 95% conversion, see Figure S6). However, in subsequent runs, a decrease in performance was observed, with the conversion dropping to 80% on the third cycle and 65% on the fourth, indicating the onset of catalyst deactivation, most likely due to photodegradation. However, it should be noted that selectivity remained consistently high (100%) throughout the recycling process.

In terms of mechanistic pathways, two main ROS intermediates, namely singlet oxygen ($^1O_2$) and superoxide radical ($O_2^{\bullet-}$), could be involved in the photocatalytic oxidation of sulfides.[27-29] To investigate their implication in the [**RuC$_{17}$**]@*p*DANTA-mediated process, a series of experiments

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were conducted (Table S1). The addition of DABCO, a well-known $^1O_2$ scavenger,[30] led to a marked decrease in conversion (45%, entry 1), suggesting that singlet oxygen plays a key role in the oxidation process. On the other hand, the addition of benzoquinone, a commonly employed $O_2^{\bullet-}$ scavenger, had a milder impact on conversion (72%, entry 2), indicating that while superoxide species may be involved in this transformation, their role is less significant. Notably, conducting the reaction in D_2O instead of H_2O resulted in quantitative conversion within 2 h, compared to 3 h classically needed in H_2O (entry 3). This isotope effect is consistent with the prolonged lifetime of singlet oxygen in D_2O,[31] as quenching by collision with heavy water is reduced compared to normal water. This experiment further supports the involvement of $^1O_2$ as the main reactive species. To confirm the generation of $^1O_2$ under blue light, 1,3-diphenylisobenzofuran (DPBF) was used as a chemical probe. The latter undergoes a characteristic drop in absorbance upon reaction with $^1O_2$. Upon illumination in the presence of [**RuC$_{17}$**]@*p*DANTA, a fast attenuation of the absorbance of DPBF was observed, compared to the same experiment conducted without the photocatalyst (see Figure S5). This demonstrates the ability of the micellar [**RuC$_{17}$**] hybrid to generate singlet oxygen *in-situ* upon illumination.

In order to highlight the nanoreactor effect, we varied the volume of the micellar compartment while keeping the catalyst to thioether ratio constant. Thus, the oxidation of **1a** was carried out with 0.1 mol% of [**RuC$_{17}$**] encapsulated in variable amounts of micelles. As a reminder, with a [**RuC$_{17}$**]/*p*DANTA *w*/*w* ratio of 1:100, full conversion was reached after 3 h. Changing the photocatalyst/micelle ratio to 1:10 (*i.e.*, decreasing the quantity of micelles compared to catalyst and substrate) resulted in a drastic decrease in conversion (23%), while preserving full selectivity. Under these conditions, the amount of substrate likely surpasses the capacity of the micelles to efficiently disperse thioether **1a**, resulting in reduced conversion. In contrast, increasing the quantity of micelles ([**RuC$_{17}$**]/*p*DANTA 1:1000 *w*/*w*) had no impact in terms of conversion, kinetics, or selectivity. These observations indicate that optimal performance require balance between catalyst, substrate, and nanoreactor volume, highlighting the critical role of spatial confinement.

In conclusion, we have developed an efficient supramolecular photocatalytic system based on the encapsulation of a modified Ru(II)-bipyridine complex within *p*DANTA micelles, enabling the selective oxidation of thioethers to sulfoxides in pure water. The micellar nanoreactor efficiently concentrates apolar substrates in a confined environment that promotes high conversions while limiting overoxidation to sulfones. Importantly, the colloidal nature of the [**RuC$_{17}$**]@*p*DANTA catalyst allows straightforward product separation and catalyst reuse, demonstrating its practical potential for sustainable synthesis. Future efforts will focus on improving catalyst longevity and recyclability, as well as extending this methodology to red-light-driven photocatalysis.[32]

Author contributions

Investigation, methodology and validation: L.M. and A.P.; Writing – original draft: L.M.; Data curation, visualization, conceptualization, funding acquisition, project administration, writing – reviewing and editing: J.C.C., E.D. and E.G.; all authors revised and agreed with the present form of the paper.

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Data availability

The supporting data is provided as Supplementary information: Table S1, Figures S1–S6, and experimental details, see DOI: [URL – format https://doi.org/DOI].

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Micellar Ru(II)–bipyridine photocatalysts for selective oxidation of thioethers to sulfoxides in water

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The supporting data is provided as Supplementary information: Table S1, Figures S1–S6, and experimental details, see DOI: [URL – format https://doi.org/DOI].