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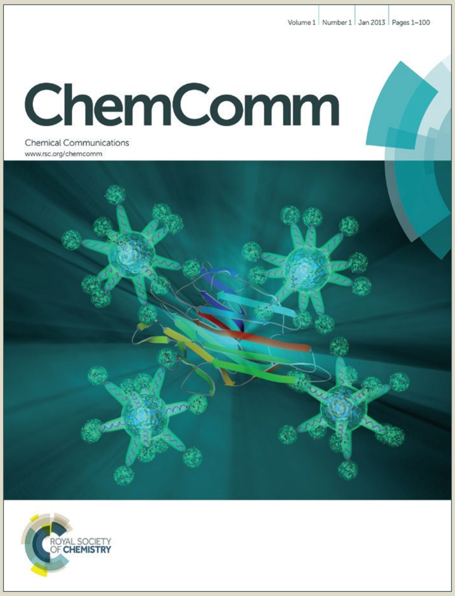

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Pt(II) Coordination Complexes as Visible Light Photocatalysts for the Oxidation of Sulfides in Batch and Flow[†‡]

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A new catalytic system for the photooxidation of sulfides based on Pt(II) complexes is presented. The catalyst is able to oxidize a large number of sulfides containing aryl, alkyl, allyl, benzyl, as well as more complex structures such as heterocycles and methionine aminoacid, with complete chemoselectivity. In addition, the first sulfur oxidation in continuous flow has been developed.

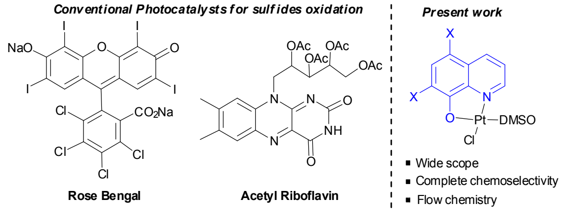

Figure 1. Visible light photocatalysts for the photooxidation of sulfides.

During recent years, visible light photoredox catalysis has been established as a powerful tool for the synthesis of molecules by selective activation of bonds under mild conditions.[1] The catalysts involved in most of the processes are Ru(II) and Ir(III) complexes[2] or photoorganocatalysts such as eosyn Y or flavin.[3] By contrast, few studies have focused on the development of photocatalysts based on other metal complexes such as Fe, Cu, Au,[4] even though complexes such as the platinum organometallic complexes[5a-b] have been widely studied as photosensitizers in solar cells and as electrophosphorescence sensors.[5c-d] A more recent trend in this field is the implementation of photochemical processes in flow reactors that have solved the limitations associated with the scale-up of photochemical reactions for industrial purposes.[6] Most of the continuous flow reactions have been developed using mainly ruthenium and iridium complexes.

During the past few years, our group has synthetized different coordination complexes based on platinum(II) and and hydroxyquinoline ligands which have proved to be excellent candidates as antitumoral complexes (Figure 1).[7] The yellow-orange colour of these compounds and the photophysical properties of hydroxyquinoline-platinum(II) complexes describe in the literature,[5e-f] led us to postulate whether these platinum complexes could be used as visible light photocatalysts for different transformations.

To test this hypothesis, the oxidation of sulfides as the model reaction was proposed.[8] Chemoselective oxidation of sulfides to sulfoxides has been extensively studied due to the importance of sulfoxides in organic synthesis, medicinal chemistry and natural products.[9] Traditionally, this oxidation has been achieved under metal catalysis using peroxides or peracids as the oxidants. However, the over-oxidation to sulfones, and the safety issues associated with handling peroxides (*m*-CPBA, peracetic acid) are the main drawbacks associated with its use in industrial processes. Interestingly, the metal photo-oxidation of sulfides using atmospheric O_2 proved to be a safer alternative. The different catalytic systems reported for this plausible metal-photooxidation have a narrow scope and large number of by-products.[10] Two organic photocatalysts, i.e. tetra-*O*-acetylriboflavine and Rose Bengal have been reported.[11] These two organocatalysts presented some limitations due to the restricted use of benzyl or *tert*-butyl sulfides (due to their more difficult oxidation), and the formation of aldehydes as byproducts in some cases, and over-oxidation to sulfones. Furthermore, both catalysts are unstable, making their use in industrial processes difficult. In addition, despite the importance of these structures in industrial chemistry continuous flow sulfur oxidation has not yet been reported. For these reasons, a more robust and soluble catalyst which capable of oxidising a large variety of sulfides in both, batch and flow reactors would be highly desirable. In this communication, the oxidation of sulfides

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† Dedicated to Prof. Jose Luis García Ruano on the occasion of his retirement.

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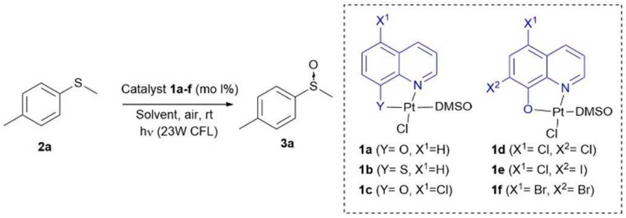
using a platinum(II) coordination complex as the photocatalyst, and the development of both batch and flow processes are presented.

As mentioned above, we have previously reported the synthesis of platinum(II) complexes containing 8-hydroxyquinolines derivatives as ligands (see Table 1).[7] These complexes display metal-to-ligand charge-transfer (MLCT) bands in the visible spectrum region, in which the maximum absorption strongly depends on the substituents of the hydroxyquinoline ligand (see ESI). As a result, modifications to the structure or the coordinating atoms of the quinoline ligand would allow easy tuning of the excited state properties of the complexes. For this reason, this family of platinum(II) complexes are good candidates as visible light photocatalysts.

To evaluate this catalytic system, we began by performing the oxidation of methyl-*p*-tolylsulfide (**2a**) with 5 mol% of the corresponding complex **1a-f** under visible light (23W commercial fluorescent bulb) for 24 h (Table 1). We found that the Pt complexes **1c**, **1d** and **1f** allowed the complete oxidation of sulfide **2a** after 24 h (entries 3, 4 and 6), but only a low conversion was achieved using photocatatalyst **1a** (entry 1). As expected and due to the lack of absorption of complexes **1b** and **1e** in the visible light region (see ESI), these catalysts did not produce any conversion (entries 2 and 5). In order to evaluate the most active catalyst, the oxidation was performed using 2.0 mol% of the catalysts **1c**, **1d** and **1f** (entries 7, 8 and 9), which revealed that the most active catalyst was complex **1c**. The catalytic activity of **1c** was compared with that of the most commonly used commercial metallic photocatalysts (entries 7, 10-11). Under the same reaction conditions $Ru(bpy)_3Cl_2$ and $Ir(ppy)_3$ resulted in lower conversions (68-85%) when compared with the platinum complex **1c**. In the next stage we screened different solvents decreasing the catalyst loading of **1c** up to 1.0 mol% (entries 12-17). The use of toluene led to a sluggish oxidation (entry 14) while moderate conversions were achieved in CH_2Cl_2 (entry 13). The most polar solvents such as DMF, EtOH or MeOH gave good conversions (entries 12, 15-16). In a mixture of $EtOH:H_2O$, which is considered to be a 'green' solvent, the oxidation of sulfide **2a** took place within 24 h (entry 17) or reduced up to 10 h by irradiating with blue-LED under 2 mol% of catalyst (entry 19).

Once the optimal conditions had been determined, the oxidation of sulfides of a different nature using the platinum photocatalyst **1c** could be studied (Table 2). In addition, the reaction was scaled up to 3.0 mmol without any erosion in the yield (entry 2). Sulfides containing electron-donating or electron-withdrawing groups at the aryl moiety (**2b-d**) were also oxidized, but for the electron-deficient aryl groups, longer reaction times were needed to obtain high conversions (entries 3-5). The oxidation of sulfides containing other alkyl groups, instead of methyl group, was also possible (entries 6-8). Therefore, cyclopropyl, allyl or benzyl sulfides were also oxidized with good yields (66-88%), without detection of benzaldehyde, sulfone or unidentified byproducts as was found with other catalytic systems.[11] Dialkyl sulfides, including the sterically hindered *tert*-butilmethylsulfide, were oxidized to sulfoxides **3h-i** in high yields and within short times (entries 9-10). It is noteworthy that in all the oxidations studied, the reaction was completely chemoselective and neither sulfone,

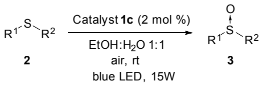
Table 1. Catalyst screening and optimization of reaction conditions.[a]



Entry	Catalyst (mol%)	Solvent	Time (h)	Conversion (%)[b]
1	**1a** (5)	DMF	24	34
2	**1b** (5)	DMF	24	<5
3	**1c** (5)	DMF	24	100
4	**1d** (5)	DMF	24	100
5	**1e** (5)	DMF	24	<5
6	**1f** (5)	DMF	24	100
7	**1c** (2)	DMF	24	100
8	**1d** (2)	DMF	24	44
9	**1f** (2)	DMF	24	40
10	$Ru(bpy)_3Cl_2$ (2)	DMF	24	68
11	$Ir(ppy)_3$ (2)	DMF	24	85
12	**1c** (1)	DMF	24	65
13	**1c** (1)	CH_2Cl_2	24	51
14	**1c** (1)	Toluene	24	10
15	**1c** (1)	MeOH	24	96
16	**1c** (1)	EtOH	24	61
17	**1c** (1)	$EtOH:H_2O$	24	100
18	**1c** (1)[c]	$EtOH:H_2O$	21	100
19	**1c** (2)[c]	$EtOH:H_2O$	10	100

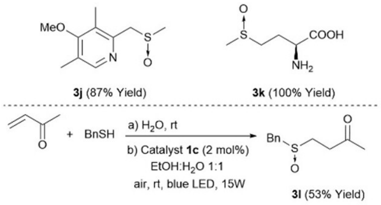
[a] Reactions were carried out with **2a** (0.3 mmol) and 1-5 mol % of the indicated catalyst in 2 mL of the indicated solvent under visible light irradiation. [b] Determined by ^1H NMR analysis of the crude mixture. [c] Blue LED irradiation.

Table 2. Photo-oxidation of different sulfides (**2**) under blue-LED irradiation and **1c**.[a]



Entry	R^1	R^2	Time (h)	Sulfoxide	Yield[b] (%)[c]
1	p-Me-C_6H_4	Me	10	**3a**	98 (100)
2	p-Me-C_6H_4	Me	25	**3a**	97[d](100)
3	p-MeO-C_6H_4	Me	27	**3b**	91 (100)
4	p-CN-C_6H_4	Me	48	**3c**	62 (70)
5	o-Br-C_6H_4	Me	48	**3d**	83 (98)
6	Ph	Cyclopropyl	48	**3e**	88 (100)
7	Ph	Benzyl	48	**3f**	83 (100)
8	Ph	Allyl	48	**3g**	62 (100)
9	Bu	Bu	13	**3h**	85 (100)
10	*t*-Bu	Me	13	**3i**	79 (100)

[a] All reactions were carried out using **2** (0.3 mmol) and 2 mol% of catalyst **1c** in 2 mL of a mixture 1:1 $EtOH:H_2O$ under blue-LED irradiation. [b] Yield after purification by flash chromatography. [c] Between brackets, conversion yield determined by ^1H NMR analysis of the crude mixture. [d] Reaction carried out using 3 mmol of **2**.



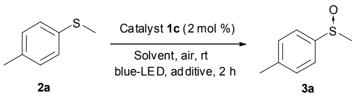
Scheme 1. Photooxidation of building blocks with relevant biological applications.

nor any other byproduct, was detected by ^{1}H NMR.

It is also important to demonstrate the applicability of the platinum catalyst by testing the oxidation of more functionalized sulfides such us **2j**, which contain a benzylic and oxidizable nitrogen, and an unprotected methionine aminoacid **2k**. The selection of these substrates was also motivated by the importance of the corresponding sulfoxides (**3j** and **3k**) as important compounds in medicinal chemistry and natural products[12] (top, Scheme 1). In both cases, the sulfoxides **3j** and **3k** were easily obtained producing yields of 87% and 100%, respectively, without any traces of byproducts. In addition, the synthesis of ketosulfoxide **3l**, which have been used as useful intermediates in synthesis,[9] was synthesized in one-pot (bottom, Scheme 1). First, the thio-Michael reaction took place, which was irradiated by blue LED and promoted the oxidation to the sulfoxide **3l**.

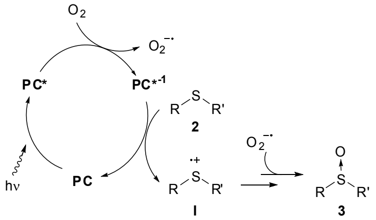
In order to gain further insight into the mechanism, additional experiments were we carried out (Table 3). The reaction did not take place in the absence of light (i.e. in the dark), without the catalyst or under an argon atmosphere, which indicates the key roles of the catalyst, O_2, and light in the oxidation process (see ESI). Two main mechanisms for the visible light photocatalytic oxidation of sulfides have been proposed in the literature.[10-11] The first deals with singlet oxygen oxidation, which is formed via an energy transfer process, and the second involves radical intermediates via electron-transfer. The discrimination between these two mechanism pathways is not easy but some indirect tests can indicate the predominant one. It is well known that oxidations via $^1O_2$ can be accelerated using deuterared solvents.[11b] However, we did not observed any change in the oxidation rate using MeOH or deuterated MeOH (compare entries 1 and 2, and ESI for the complete kinetic experiment). The addition of DABCO, as scavenger of $^1O_2$, neither induced any significant change in the oxidation rate (entry 3). Furthermore, the oxidation of methyl-*p*-nitrophenylsulfide was not possible, which suggests a radical type mechanism. Benzoquinone and 1,4-dimethoxybenzene are known to be scavengers of the superoxide radical and sulfide radical cations, respectively.[11a] Thus, the oxidation in the presence of 0.5 equiv. of benzoquinone was almost totally inhibited (entry 4), whereas the use of de 1,4-dimethoxybenzene, as the sulfur radical cation scavenger, led to a decrease in the conversion (entry 5). All the evidence described above together with the non-oxidation of methyl-*p*-nitrophenylsulfide and an 11% conversion in the oxidation of diphenylsulfide point to the outline proposed in Scheme 2 as a plausible mechanism. The photocatalyst (PC) is excited to PC* by the visible light. Then, the PC* may be oxidized generating the oxygen radical anion. Next, the PC is recovered by one-electron oxidation of sulfide **2**, generating a radical cation **I**. Finally, the sulfide radical cation **I** could react with the oxygen radical anion or the water to produce the final sulfoxides. To know the source of the oxygen in the sulfoxide, we have carried out the oxidation of **2a** in a 1:1 mixture of dry EtOH/$H_2{}^{18}O$ as solvent. The mass analysis of the resulting sulfoxide (**3a**) showed a 155.05 m/z peak as the only product and no trace of the labelled sulfoxide was detected. This evidence suggests the superoxide anion as the oxygen source.

Table 3. Mechanistic experiments in the presence of enhancers or scavengers.

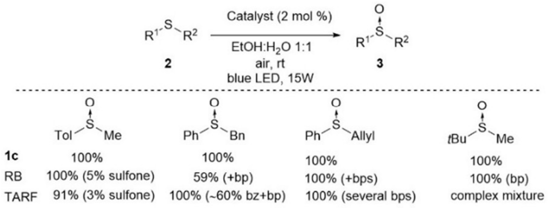


Entry	Solvent	Additive (mol%)	Conversion (%)[a]
1	MeOH	-	40
2	MeOH-D_4	-	40
3	MeOH	DABCO (0.5)	39
4	MeOH	Benzoquinone (0.5)	3
5	MeOH	1,4-dimethoxybenzene (0.5)	26

[a] Conversion determined by ^{1}H NMR analysis of the crude mixture.



Scheme 2. Mechanistic proposal for the photo-oxidation (PC= photocatalysts).



Scheme 3. Comparative study of catalyst **1c** with Rose Bengal (RB) and tetra-O-acetylriboflavine (TARF) (bp=byproducts, bz= benzaldehyde). (see ESI for spectra).

We have carried out a comparison with the previous catalytic systems (acetylriboflavin, and rose Bengal) under the same reaction conditions. These results have been included in scheme 3 (for NMR of the crude reactions see ESI). As it can be observed, the most selective and reactive catalyst is **1c**. With other catalysts lower conversion or the presence of different byproducts (over-oxidation, aldehydes, and unidentified products) were detected by NMR. With this study, it is clearly demonstrated that the present method is the most chemo-selective and reliable one.

The scale-up of the photo-chemical processes can easily be adapted to flow chemistry. Our flow system consisted of a HPLC pump and an O_2 gas cylinder both connected through a T-mixer to the coil reactor, which was made from FEP capillary tube with a reactor volume of 4.1 mL (see Figure 2 and ESI for more details). To irradiate the system, a blue LED device (15 W) was assembled around the coil reactor. After extensive screening and optimization of the conditions, it was found that the use of O_2 was necessary in order to have an appropriate residence time (from hours to minutes), with 1.0 mol% of platinum catalyst **1c**, in a 9:1 mixture of EtOH/H_2O. Using this flow system, the full conversion for the oxidation of methyl-*p*-tolylsulfide (**2a**) was achieved in only 11 min residence time (entry 1, Table 3). The flow-oxidation of the other representative sulfides (**2**) was also carried out. For each substrate, small variations in the flow rate of the solvent and O_2 were carried out to obtain the best conversions (see Table 3). The *o*-bromophenyl derivative **2d** was more difficult to oxidize than the methyl-*p*-tolylsufide **2a**, and under optimum conditions a 50% conversion was obtained after 82 min residence time (entry 2). Alkyl-aryl sulfides **2e-g** were oxidized with a good conversion to the corresponding sulfoxides **3e-g** (entries 3-6) in a residence time of 37 - 40 min. Furthermore, the dialkylsulfoxides (**2h**), the bulkier *t*-butyl derivative **2i** and the heterocycle **2j** were easier to oxidize with a 100% conversion within 10 - 23 min (entries 6-8).

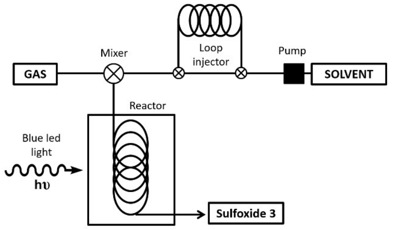
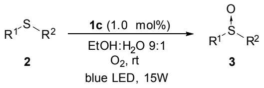


Figure 2. Description of the flow system used for the photooxidation of sulfides.

Table 3. Photooxidation of different sulfides using flow chemistry.[a]



Entry	Sulfoxide **3**	Solvent flow rate (mL/min)	O_2 flow rate (mL/min)	Residence time (min)	Conv (%)[b]
1	**3a**	0.04	0.33	11	100
2	**3d**	0.01	0.04	82	50
3	**3e**	0.01	0.09	39.5	78
4	**3f**	0.01	0.09	40	94
5	**3g**	0.01	0.1	37	76
6	**3h**	0.04	0.35	10.5	99
7	**3i**	0.02	0.34	11.5	100
8	**3j**	0.01	0.17	23	100

[a] The continuous flow experiments were carried out using a mixture of EtOH:H_2O (9:1), catalyst **1c** (1.0 mol%) and 3.2 equiv of dioxane. [b] Conversion determined by HPLC or GC analysis of the crude mixture.

In conclusion, a new photocatalyst for the oxidation of sulfides based on Pt(II) coordination complexes is presented. The catalyst is able to oxidize sulfides containing different aryl or alkyl groups, heterocycles, or unprotected methionine with excellent yields, and without over-oxidation to sulfone or the formation of other by products.

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