PQS-Enabled Visible-Light Iridium Photoredox Catalysis in Water at Room Temperature

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COMMUNICATION

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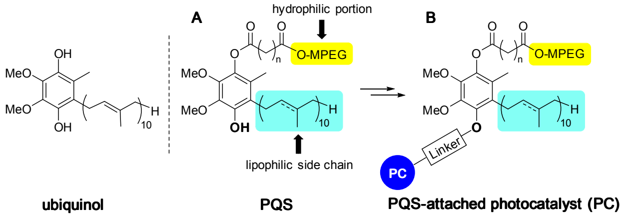
An amphoteric PQS-attached photocatalyst has been prepared that undergoes self-aggregation in water into nanomicelles. This covalently bound species enables Ir-based photoredox catalysis to be conducted in the absence of additives or co-solvents. Representative reactions are described using this new catalytic system, which require no additional investment of external energy in the form of heating or cooling. The entire aqueous reaction mixture readily undergoes *in-flask* recycling and thus, represents a sustainable precious metal technology.

One goal for the future of organic chemistry is to be able to mimic nature's processes that produce chemicals by exploiting water as the reaction medium, and visible light as the sole energy source; both are safe, inexpensive, abundant, and clean. To harvest this energy for the promotion of organic transformations, visible-light photoredox catalysis is being broadly developed.[1] Over the last decade this area has witnessed extensive growth and development as a powerful tool in organic synthesis[2] following introduction of organo-SOMO catalysis.[3] Moreover, water has also been utilized as a solvent for visible light-mediated reactions. Early on, Willner and co-workers developed a unique two-phase photocatalytic system for the reduction of 1,2-dibromostilbene using a water / ethyl acetate mixture, together with an alkylviologen for shuttling electrons between the two phases.[4] Later, a biphasic mixture of water / toluene was employed for photoredox-catalyzed C–P bond formation.[5] Water has also been used as co-solvent for photocatalytic strategies involving homogeneous reactions.[6] Among these, water serves as a substrate in some cases,[6c, 7] and it was reported by Rueping's group that small amounts of water could even promote photocatalytic cycloadditions of *N*-substituted hydroxylamines with alkenes.[8] Nonetheless, organic solvents are typically required in these reactions to assist with substrate solubilization. Indeed, few examples have been reported involving photocatalysis conducted solely in water.[9]

There are additional major issues associated with photocatalysts containing precious metals, such as polypyridyl complexes of ruthenium and iridium, which include both their future availability and cost. Iridium-based catalysts, in particular, and in organic solvents under homogeneous conditions, present special challenges for their recycling. We envisioned that not only could photoredox catalysis be merged with micellar catalysis to enable reactions to be run in water, but that this approach would also allow for recycling of the entire aqueous medium, including the iridium-containing photocatalyst.

The PQS platform is based on ubiquinol, the reduced form of the dietary supplement CoQ_{10} (Scheme 1, A) and has been developed previously by our group.[10] It contains a hydrophilic (MPEG) component, a lipophilic (50 carbon) side chain, and a remaining –OH group available to which a catalyst can be covalently attached and that will reside within the hydrophobic inner core where catalysis takes place. This amphiphilic species PQS has been converted into recyclable catalysts containing, as examples, Ru carbene complexes for olefin metathesis reactions in water at room temperature,[10,11] an *L*-proline-containing analog for asymmetric organo-catalysis,[11] and a nonracemic BINAP ligand-containing catalyst for Rh-catalyzed asymmetric conjugate additions.[13] Inspired by these successes, we endeavored to attach a classic photocatalyst *fac*-Ir(ppy)$_3$, which itself is insoluble in water, to PQS (Scheme 1, B). The resulting surfactant bearing a covalently bound iridium complex serves



Scheme 1 PQS and PQS-attached photocatalyst.

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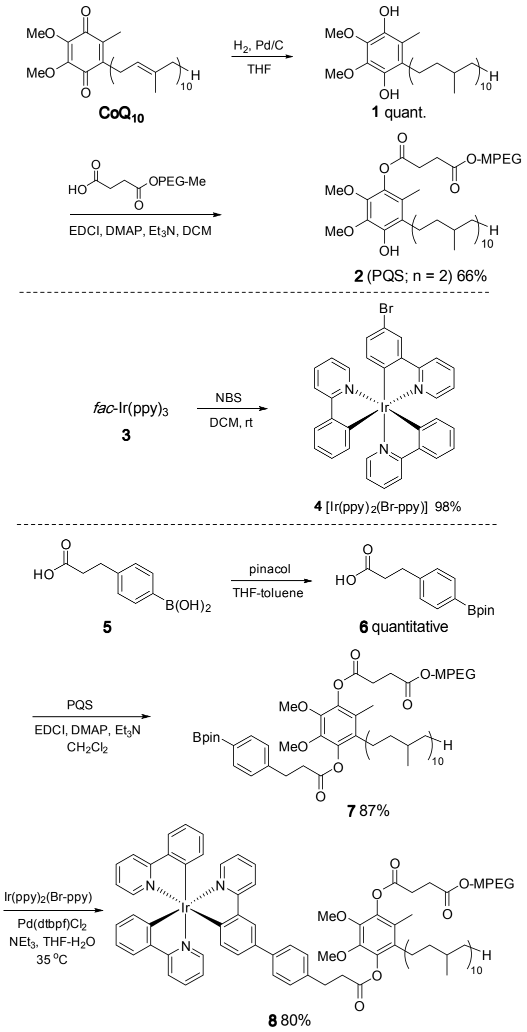
not only as the source of a photoredox catalyst, but also in the form of its derived nanomicelles, as the reaction medium. Upon completion of a photo-induced process, the aqueous micellar medium containing the Ir catalyst could be readily extracted "in-flask" with a minimum amount of an organic solvent for product isolation, leaving behind the reaction medium poised for reuse.

Ubiquinol could be employed as the building block for the preparation of PQS, as described in previous reports.[10-13] However, in this case, CoQ_{10} serves best as the starting material for the synthesis of catalyst **8**. It is shelf-stable, readily available in quantity, and is smoothly converted (e.g., *in vivo*) to its hydroquinone form, ubiquinol.[14] Hydrogenation of $CoQ_{10,}$ however, affords not only the corresponding hydroquinone quantitatively, but simultaneously reduces the ten double bonds in the side chain to arrive at product **1** (Scheme 2). Monoesterification of **1** with PEGylated succinic acid (where MPEG = MPEG-2000) afforded fully side-chain reduced PQS derivative **2**.



Scheme 2 Preparation of PQS-attached photocatalyst **8**.

Photocatalyst **3** upon treatment with NBS yielded derivative **4**,[15] along with generation of a small amount of by-product $Ir(ppy)(Br\text{-}ppy)_2$ detected by MALDI analysis (see Supporting Information). The reaction between boronic acid **5** and pinacol led to building block acid **6**,[16] which was esterified to give the unsymmetrical triester **7**. Lastly, Suzuki-Miyaura coupling between **7** and $Ir(ppy)_2(Br\text{-}ppy)$ catalyzed by $Pd(dtbpf)Cl_2$ in aqueous THF gave the PQS-attached iridium complex **8** in 80% yield.

The electrochemical behaviour was measured by cyclic voltammetry using ferrocene as the internal standard, and the oxidation peak of catalyst **8** was observed at + 0.75 V vs. SCE (see Supporting Information). Dissolution of this catalyst **8** in pure water results in the formation of self-aggregated nanoparticles, as a mix of sphere of *ca.* 30-60 nm in diameter as determined by cryo-TEM analysis (Figure 1).

With micelle-forming catalyst **8** in hand, we sought to explore photoreactions in water. Based on literature reports, sulfonyl chlorides were found to undergo single-electron reduction by the excited state of $Ir(ppy)_3$ to generate sulfonyl radicals.[17] Since we had previously demonstrated the reactivity of sulfonyl radicals in micelles,[18] the reaction between alkene **9a** and sulfonyl chloride **10a** in water was chosen for initial study. A first attempt at difunctionalization of α-methylstyrene (**9a**) in an aqueous medium containing 2 mol % catalyst **8** gave the β-hydroxysulfone **11a** in good yield (Table 1, entry 1). The

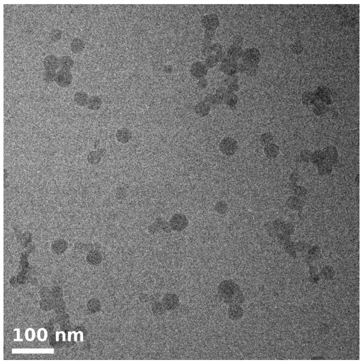
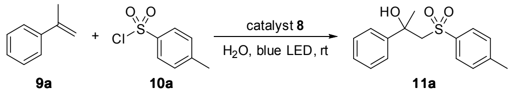


Fig. 1 Cryo-TEM analysis of photocatalyst **8**.

Table 1 Optimization studies[a]

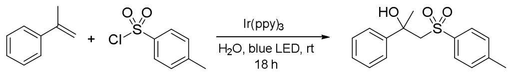


Entry	Amount of catalyst **8**	[M] mol/L	Yield (%)[b]
1	2 mol %	0.5	88
2	1 mol %	0.5	90
3	0.5 mol %	0.5	36
4	0	0.5	NR
5	1 mol %	0.25	79
6[c]	1 mol %	0.5	NR

[a] Unless otherwise mentioned, experiments were carried out with **9a** (0.25 mmol), **10a** (0.375 mmol) and catalyst **8** in deoxygenated water with the irradiation of a blue LED lamp (5 W) under argon for 18 h at rt. [b] Isolated yields of **11**. [c] The experiment was performed without light irradiation.

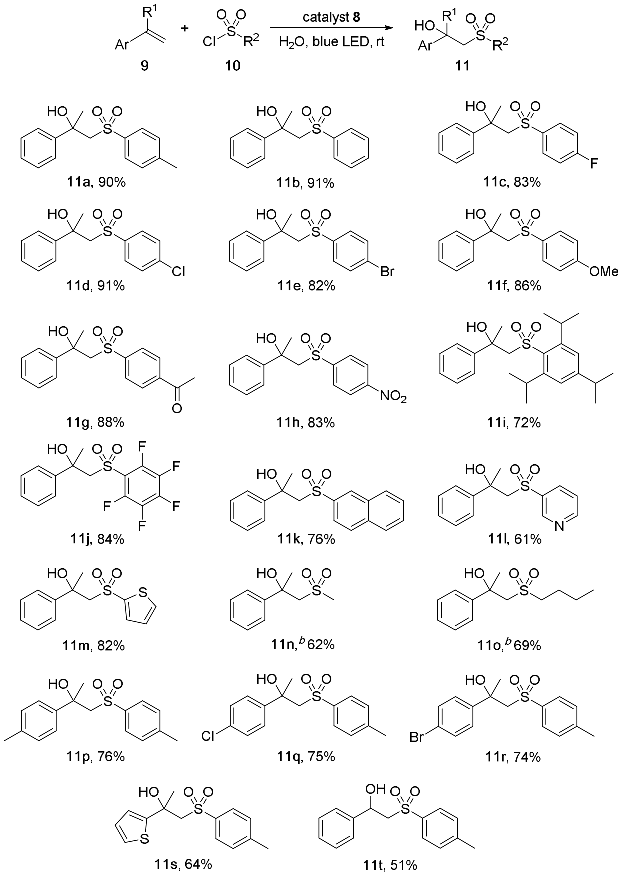
influence of the amount of catalyst **8** was then examined, leading to the most effective level being 1 mol % (entry 2). The yield dropped to only 36% upon further reduction to 0.5 mol % catalyst (entry 3). No reaction was detected without catalyst (entry 4). Adjusting the reaction concentration to 0.25 mol/L also resulted in a lower yield (entry 5). A control experiment documents that light is essential for this chemistry to occur (entry 6). An "on water" experiment to establish the extent of background reaction with catalyst **3** gave the product **11a** in poor yield, with most of the mass balance attributed to the starting material (Scheme 3).

Having identified optimal reaction conditions for this photoredox catalysis in water, substrate scope was next investigated. As revealed in Table 2, a variety of benzenesulfonyl chlorides carrying electron-donating, -neutral, and -withdrawing substituents at the *para* position reacted with **9a** smoothly to give the desired products in good yields. The substituents, including alkyl, halo, alkoxy, acetyl, and nitro, were all tolerated. It is important to note that carbon-halogen bonds remained intact throughout this photochemical process (**11c-e**, **j**), providing potentially valuable handles for further elaboration *via* transition-metal catalysis. The reaction of α-methylstyrene and substrate **10i** gave product **11i** in modest yield notwithstanding the considerable steric bulk in the starting sulfonyl chloride. Heteroaryl sulfonyl chlorides could also provide targeted products successfully (**11l**, **m**). Modest yields were obtained by the reaction of alkylsulfonyl chlorides, even when three equivalents of sulfonyl chlorides were used (**11n**, **o**). Other variations in the styrene or styrene-like partners were also tested and led to the expected products (**11p-s**). The effect of the methyl residue in **9** (R^1 = Me) was apparent by comparison between yields for products **11a** *vs.* **11t**.



Scheme 3 The corresponding "on water" reaction catalyzed by Ir$(ppy)_3$.

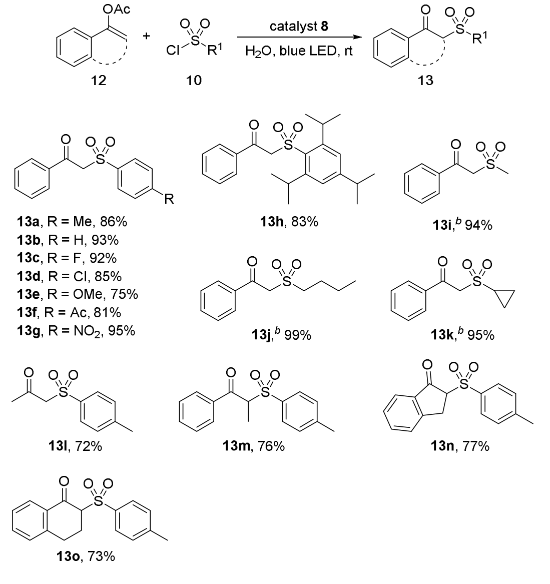
Table 2 Difunctionalization of alkenes catalyzed by the PQS-attached photocatalyst[a]



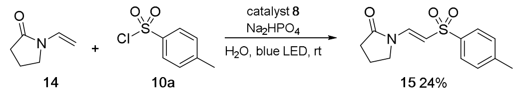
[a] Unless otherwise mentioned, experiments were carried out with **9** (0.25 mmol), **10** (0.375 mmol) and catalyst **8** in deoxygenated water (0.5 mL) with irradiation using a blue LED lamp (5 W) under argon for 18 h at rt. [b] 3 equiv of alkylsulfonyl chloride were used.

Efforts to extend the scope of these reactions in nanomicelles led to the successful preparation of β-ketosulfone derivatives from visible light-mediated reactions between sulfonyl chlorides and enol acetates (Table 3).[17b,18] The same optimized photocatalysis conditions could be directly for these radical processes. Several sulfonyl chlorides were tested, whereupon their exposure to enol acetates in the presence of catalyst **8** yielded the corresponding β-ketosulfone. Use of alkylsulfonyl chlorides, by contrast, now afforded excellent yields (**13i-k**). Isopropenyl acetate also serves as substrate leading to product **13l**, while branched enol acetates gave equally satisfactory yields of sulfonylation products (**13m-o**).

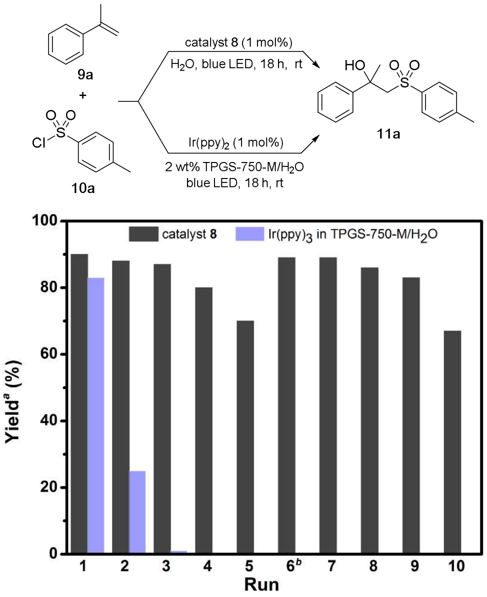
Table 3 Sulfonylation of enol acetates catalyzed by the PQS photocatalyst **8**[a]



[a] Unless otherwise mentioned, experiments were carried out with **12** (0.25 mmol), **10** (0.375 mmol) and catalyst **8** in deoxygenated water (0.5 mL) with irradiation by a blue LED lamp (5 W) under argon for 12 h at rt. [b] 3 equiv of alkylsulfonyl chloride were used.

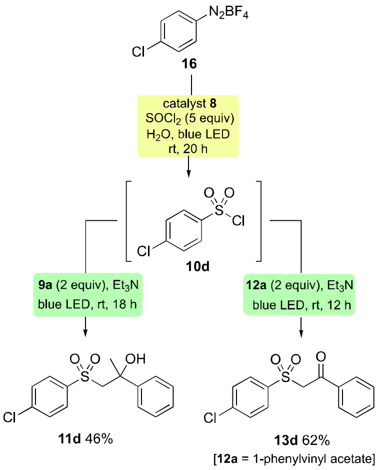


Scheme 4 Sulfonylation of enamide **14** catalyzed by PQS photocatalyst **8**.

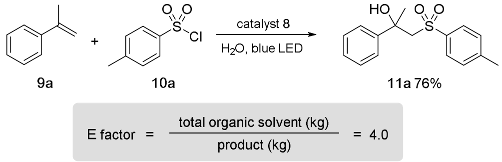


^{a} Isolated yields. ^{b} 0.5 mol % catalyst was added before the reaction.

Fig. 2 Comparison between in-flask recycling of catalyst $Ir(ppy)_3$ in TPGS-750-M/H_2O *vs.* catalyst **8**.



Scheme 5 Two step, 1-pot reactions enabled by catalyst **8** in water at rt.



$$\text{E factor} = \frac{\text{total organic solvent (kg)}}{\text{product (kg)}} = 4.0$$

Scheme 6 E Factor determination.

We next turned our attention to sulfonylation of an enamide using catalyst **8** in water. However, the coupling of sulfonyl chloride **10a** and enamide **14** only gave the desired product **15** in low yield (Scheme 4).

Recycling of PQS-attached photocatalyst **8** could be achieved by *in-flask* extraction with methyl *t*-butyl ether (MTBE) once a reaction had reached completion (see Supporting Information). The aqueous medium containing catalyst **8** could then be recycled for four runs with the products isolated in yields from 70 to 88%, before an additional amount (0.5 mol %) of catalyst **8** was added (Figure 2). The resulting aqueous mixture could then be recycled for another five runs. Overall, the total investment of iridium catalyst **8** for these ten reactions was 1.5 mol % (i.e., 1500 ppm / reaction). Although, as mentioned above, the on-water reaction (i.e., in the absence of any surfactant) did not give a good result, difunctionalization of alkene **9a** by catalyst **3** in aqueous TPGS-750-M led initially to β-hydroxysulfone **11a** in good yield. Nonetheless, in an attempt to recycle the aqueous medium, extraction under otherwise identical conditions led to loss of most of the iridium complex into the organic phase. As expected, therefore, the yield dropped to 25% in the second run, and only a trace of product could be detected beyond that, highlighting the importance of the covalent linkage between the photocatalyst and PQS.

A method for aromatic chlorosulfonylation to produce arylsulfonyl chloride *via* photoredox catalysis has been developed recently by von Wangelin's group.[19] Based on this report, a two-step, 1-pot sequence applying PQS-attached catalyst **8** could be demonstrated (Scheme 5). Thus, aryl diazonium salt **16** reacted with SO_2 and HCl generated *in situ* to give arylsulfonyl chloride **10d**, which was subjected to photo-coupling with alkene **9a** or an enol acetate to generate **11d** and **13d**, respectively.

Calculation of the E Factor associated with this photocatalysis in water, based on usage of organic solvent for the model system, is shown in Scheme 6. The value was 4.0, based on MTBE used for product extraction, which is considerably below that expected from the corresponding reaction run in a typical organic solvent.[20,21]

Conclusions

In summary, photoredox catalysis conducted in water at room temperature has been enabled by a newly designed photocatalyst-containing surfactant, which self-aggregates to provide nanoreactors in which the chemistry occurs. Sulfonylation of a selected group of both alkenes and enol acetates gives the desired products in moderate-to-excellent yields upon exposure to an Ir-containing PQS-attached photocatalyst, in the absence of any organic solvents or additives, and under mild conditions. In this chemistry, water serves as a "green" reaction medium, and visible light is harnessed as a safe and renewable source of chemical potential. Moreover, this represents a sustainable system where both the aqueous medium and a precious metal catalyst could be recycled several times without removal from the reaction vessel, resulting in a net usage of iridium at the ppm level.

Conflicts of interest

There are no conflicts of interest to declare.

Acknowledgements

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