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ARTICLE

Substrate-Driven Iridium Photocatalysts Enable Diastereoselective Dearomative Polyoxygenation of Hydroxyquinolines

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We report a novel strategy for the direct, diastereoselective dearomative polyoxygenation of 8-hydroxyquinolines, leveraging a substrate-coordinated Ir(III) complex as a self-activating photocatalyst under visible light and atmospheric oxygen. In this system, the hydroxyquinoline substrate coordinates to the Ir pre-catalyst generating an Ir-oxyquinolate complex. This species activates the substrate and acts as a photosensitizer, promoting the generation of singlet oxygen and enabling the formation of multiple C–O bonds in a single step with excellent regio- and stereocontrol. Mechanistic investigations, including ligand exchange experiments, control reactions, and DFT studies, reveal that the reaction proceeds via selective oxygen insertion into the coordinated quinoline, followed by water-assisted hydroxylation, yielding structurally complex polyoxygenated products. This substrate-driven approach eliminates the need for external photocatalysts and demonstrates a unique strategy for the activation of heteroaromatic substrates, providing access to motifs of potential relevance in pharmaceuticals and functional materials. This work highlights how substrate–metal cooperation can be exploited to achieve transformations that are challenging or inaccessible with conventional photocatalytic systems.

Introduction

Oxidation reactions of organic compounds are key tools in the chemical industry for the production of a wide range of intermediates and products, from pharmaceuticals to fine chemicals.^{1,2} Maximizing efficiency and minimizing byproducts requires these oxidations to selectively target specific bonds or functional groups, making the process inherently challenging. Among oxidant reagents, molecular oxygen is considered ideal due to its low cost, high abundance, and minimal environmental impact, especially compared to oxidants like potassium permanganate and peracids, which generate large amounts of byproducts. In nature, selective oxyfunctionalization of organic molecules is remarkably achieved using molecular oxygen and specialized enzymes. For instance, dioxygenases are capable of directly activating O₂ and catalyzing the oxidation of aromatic substrates by the incorporation of both oxygen atoms with incredible selectivity under mild conditions (Scheme 1A).³ However, natural products, pharmaceuticals, materials and biologically active compounds are usually heterocyclic complex molecules, containing more than one different oxygen and nitrogen functionalities.⁴ Typically, the installation of the corresponding oxygen-functional groups, particularly in heterocyclic chemistry, requires multistep synthetic sequences

involving protection and deprotection strategies and the use of diverse oxidizing reagents, as precise control over the oxidation process is often challenging and commonly results in complex product mixtures (Scheme 1B).⁵ The most effective approach would be the oxidation of such heterocycles to form the desired Csp³–O bonds. Even more challenging would be to carry out the oxidation and subsequent dearomatization of these heterocycles in a single reaction step.⁶ Therefore, the development of novel, step-economical strategies for the direct dearomative oxyfunctionalization of heterocycles and aromatic starting materials would be highly desirable.

Inspired by nature, scientists have developed synthetic catalysts that mimic the function of enzymes to developed oxidation processes using O₂ as oxidant.^{7–9} These catalysts are able to achieve the direct oxidation of organic compounds, as enzymatic processes, by direct C–H hydroxylation, olefin epoxidation, Baeyer-Villiger reaction, or heteroatom oxidation. As many oxygenase enzymes contain a metallic cofactor such as Fe, Cu, and Mn, a great amount of the synthetic bioinspired catalysts developed are metallic complexes.¹⁰ The metal centre in these catalysts is key for the dioxygen activation and the formation of the reactive oxygen species as metal-oxo complexes, and radical oxygen species. Besides this strategy, the direct incorporation of oxygen to organic molecules (e.g. in sulfoxidation reactions, boronic acid oxidations or C–H oxygenations among others) can also be accomplished using photocatalysis.^{11–14} These transformations proceed via singlet oxygen activation (¹O₂) or the generation of radical oxygen species (O₂^{•−}) and form only one C–O (or S–O) bond in the molecule. In many cases, these transformations are achieved using iridium and rhodium based photocatalysts (Scheme 1C). However, the polyoxygenation of N-containing heterocycles has not been reported so far despite the relevance of the resultant compounds. In this context, hydroxyquinolines are organic

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molecules with a wide variety of applications. They are well-studied drugs for Alzheimer dementia and other diseases as well as antitumoral agents, among other biological activities.^{15–18} The C-H oxyfunctionalization of these quinoline derivatives is very challenging, as selectivity issues as well as the non-desired N-oxide formation are very likely to occur (Scheme 1B). Moreover, that transformation is of utmost importance for the pharmaceutical industry due to the necessity of preparation and identification of drug metabolites from oxidative pathways. Based on these precedents, we aim to develop the polyoxygenation of hydroxyquinolines under photocatalytic conditions using dioxygen as oxidant to promote a dearomative oxidative reaction.

Due to the excellent metal-binding ability of hydroxyquinolines, numerous oxyquinolate-metal derivatives have been reported.¹⁹ These complexes have shown great biological activities or luminescence properties for organic light emitting diodes. More recently, our research group has developed very efficient Ir(III) and Pt(II) photocatalysts using substituted 8-oxyquinolates (QO) as ligands.^{20–22} Regarding the [IrCp*Cl(QO)] complexes, we demonstrated that their photocatalytic activity can be also combined with traditional organometallic transformations thanks to their ability to undergo ligand substitution reactions.

Taking advantage of the diverse catalytic properties of [IrCp*Cl(QO)] mentioned above, we envision the development of a dearomatic photocatalytic oxyfunctionalization of

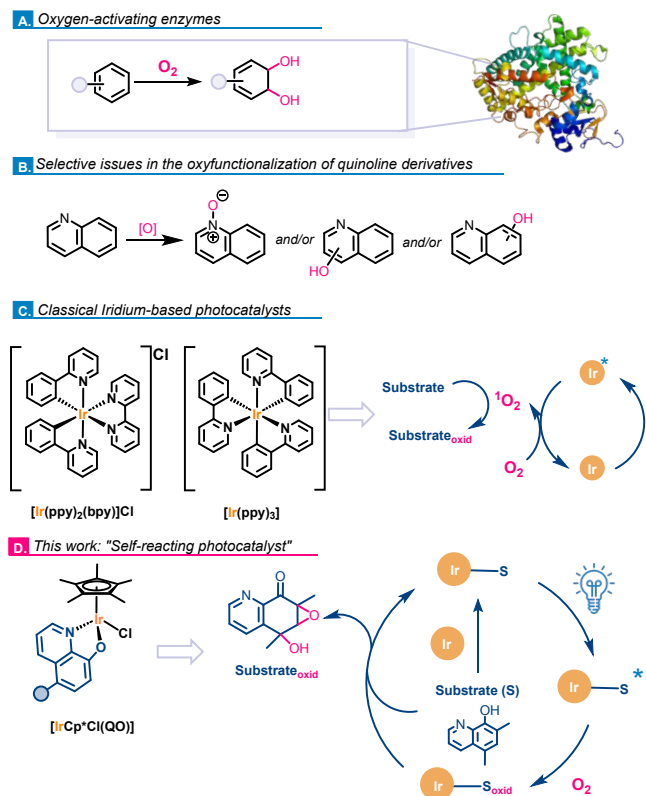
hydroxyquinolines under a non-conventional photocatalytic approach (Scheme 1D). We sought to explore the *in situ* formation of the active photocatalyst by means of the coordination of the hydroxyquinoline molecule to an Ir precursor, added to the reaction mixture in catalytic amounts. Thus, the oxyquinolate complex will act as the photocatalyst capable of activating molecular oxygen to generate singlet oxygen, eliminating the need for an additional external photocatalyst (Scheme 1D). Furthermore, coordination of the hydroxyquinoline to the iridium center activates the heterocycle toward reaction with ¹O₂. In other words, the *in situ*-formed complex will function both as the photocatalyst and as the substrate to be oxidized, operating with a catalytic amount of iridium. Upon oxidation of the hydroxyquinoline ring, the resulting, more labile oxidized ligand, can be displaced by coordination of a new hydroxyquinoline molecule. This process would enable a catalytic iridium cycle, effectively operating as a self-reacting photocatalyst system. We therefore propose that oxyfunctionalization of the quinoline derivative takes place while the substrate is coordinated to the metal center. This reactivity is anticipated to be unique to the catalytic properties of the [IrCp*Cl(QO)] family of complexes. Notably, such photocatalytic oxyfunctionalization is not feasible using [Ru(bpy)₃]²⁺, *fac*-[Ir(ppy)₃], or organic photocatalysts, as they are unable to interact directly with the hydroxyquinoline substrate (Scheme 1C).

Coordination-driven strategies in photocatalysis have emerged as a powerful means to access new reactivity, combining substrate activation with photoinduced processes. In particular, Meggers and co-workers have pioneered chiral-at-metal photocatalysis, where substrate coordination to Ir(III) or Rh(III) complexes enables light-driven transformations.²³ Complementary strategies based on non-covalent catalyst-substrate interactions have also been developed, as illustrated by the work of Yoon and co-workers, highlighting the role of preorganization in photochemical reactivity.^{24, 25} Despite these advances, the direct oxidation of the coordinated ligand itself remains largely unexplored, particularly within polyoxygenation processes. In this work, we report for the first time a new reactivity of hydroxyquinolines based on their ability to coordinate to an Ir(III) center, resulting in a complex that both activates the hydroxyquinoline substrate and acts as an oxygen photosensitizer. Additionally, the study includes mechanistic experiments and theoretical investigations to elucidate the pathway of the dearomative oxyfunctionalization reaction.

RESULTS AND DISCUSSION

Catalytic oxidation.

To evaluate our hypothesis, we tested the oxidation of 5,7-dimethyl-8-hydroxyquinoline (**1a**) in methanol using atmospheric oxygen and a 2.5 mol% of an Ir(III) complex as a proof of concept. The reaction was irradiated with a 23 W commercial fluorescent bulb white light (CFL, see supporting information for setup details) for 24 h (Scheme 2). The oxidation of **1a** proceeded smoothly in the presence of the [IrCp*Cl₂]₂ dimer, giving 28% of the polyoxygenated product **2a** (Table 1,



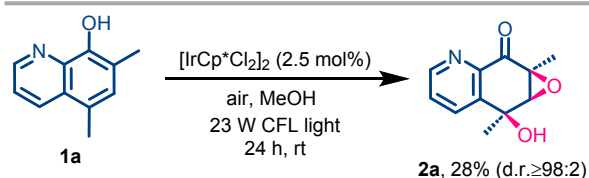
Scheme 1. Dearomative oxyfunctionalization of arenes and heteroarenes.



entry 1). It is important to highlight that this catalytic oxidation protocol enables the simultaneous oxidation of four carbon atoms within the quinoline core in a single step, leading to the formation of a tertiary alcohol and a trisubstituted epoxide with complete diastereocontrol. Based on this excellent result, we next optimized the reaction conditions for the polyoxyfunctionalization of **1a** (Table 1). First, to determine whether the observed reactivity is exclusive to $[\text{IrCp}^*\text{Cl}_2]_2$, we tested other Ir(III) species and organic photosensitizers. IrCl_3 showed no reactivity and the starting hydroxyquinoline **1a** was recovered unaltered (Table 1, entry 2). Next, we tested the well-known singlet-oxygen photosensitizers $[\text{Ir}(\text{ppy})_3]$ and Rose Bengal. Using these photocatalysts, a complete change in the outcome of the reaction was observed and dearomatized enone **3a** or **4a** were obtained as the only reaction products (Table 1, entries 3-4). This selectivity change highlights the need of a catalyst capable of both sensitizing oxygen and coordinating the hydroxyquinoline substrate for the reaction to proceed. Other light sources were also evaluated, but lower yields were obtained (see Supporting Information). Afterwards and having $[\text{IrCp}^*\text{Cl}_2]_2$ as the optimal catalyst, different solvents were evaluated (Table 1, entries 5-8). Thus, **2a** was obtained in a similar yield (26%) in the reaction conducted in

1,2-dichloroethane (1,2-DCE); however the selectivity was improved compared with that of the reaction in methanol (Table 1, entry 8). During the solvent screening, we realized that the water content in the solvents has an influence on the reaction outcome. Thus, molecular sieves were added to the reaction mixture to remove water (Table 1, entry 9). Surprisingly, the oxidation was completely inhibited, suggesting that water might be important for the reaction mechanism and that rigorously dry conditions are detrimental to the transformation. On the other hand, when 1,2-DCE containing 0.2 ppm of water was employed, **2a** was obtained in 71% yield as a single diastereomer, and in a very selective manner (Table 1, entry 10). Furthermore, these experiments seem to indicate the important role of water in the reaction mechanism as discussed below.

Having the optimal reaction conditions in hand, we next explored the applicability of the catalytic photooxidation protocol in other 8-hydroxyquinolines (Table 2). First, we found that the oxidation of the unsubstituted 8-hydroxyquinoline **1b** was unsuccessful, and only the starting material (**1b**) was recovered after 24 h (Table 2, entry 2). This dramatic change in the reactivity can only be attributed to the substitution of the quinoline ring, which seems to be crucial for the photooxidation to proceed. Intrigued by this result, we decided to deeply study the substitution effect, including type and position, in the photooxidation transformation. As the model substrate **1a** contained two methyl groups at 5- and 7-position of the quinoline ring, we explored the photooxidation of monomethylated 8-hydroxyquinolines. Thus, the polyoxidation of **1c** afforded compound **2c** in 65% yield as a single diastereoisomer (Table 2, entry 3). Next, we evaluated the effect of the methyl substituent position, testing 6-methyl-



Scheme 2. Proof of concept of the dearomative oxyfunctionalization of hydroxyquinolines.

Table 1. Optimization of the photooxidation conditions of **1a**.^a

Entry	Catalyst (x mol%)	Solvent	2a/3a/4a ratio	2a yield (%) ^b
1	$[\text{IrCp}^*\text{Cl}_2]_2$ (2.5)	MeOH	57:30:13	28
2	IrCl_3 (5)	MeOH	-	0
3	$[\text{Ir}(\text{ppy})_3]$ (5)	MeOH	0:63:37	0
4	Rose Bengal (5)	MeOH	0:0:100	0 ^c
5	$[\text{IrCp}^*\text{Cl}_2]_2$ (2.5)	MeCN	33:17:50	18
6	$[\text{IrCp}^*\text{Cl}_2]_2$ (2.5)	Toluene	84:12:4	14
7	$[\text{IrCp}^*\text{Cl}_2]_2$ (2.5)	CH_2Cl_2	57:14:29	18
8	$[\text{IrCp}^*\text{Cl}_2]_2$ (2.5)	1,2-DCE	78:14:18	26
9	$[\text{IrCp}^*\text{Cl}_2]_2$ (2.5)	1,2-DCE ^d	-	0
10	$[\text{IrCp}^*\text{Cl}_2]_2$ (2.5)	1,2-DCE ^e	92:8:0	71

^a Reaction conditions: A solution of **1a** (0.05 mmol) and the corresponding catalyst (mol%) in 2.0 mL of solvent was irradiated using a 23 W CFL of white light. ^b ¹H NMR yield calculated using 1,3,5-trimethoxybenzene as internal standard. ^c 99% ¹H NMR yield of **4a**. ^d 4 Å Molecular sieves. ^e 0.2 ppm of H₂O.

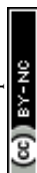


Table 2. Effect of the hydroxyquinoline substitution on the photooxidation reaction.^aView Article Online
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Entry	Compound 1	Product	Entry	Compound 1	Product
1		 2a, 71% (d.r. ≥ 98:2)	7		 2g, 51% (d.r. ≥ 98:2) ^b
2		n.r.	8		 2h, <10%
3		 2c, 65% (d.r. ≥ 98:2)	9		 2i, 48% (d.r. ≥ 98:2) ^b
4		 5d, 53%	10		 2j, 26% (d.r. ≥ 98:2)
5		 5e, 27%	11		 2k, 54% (d.r. ≥ 98:2)
6		 6f, 24% (d.r. ≥ 98:2)	12		 2l, 24% (d.r. ≥ 98:2) ^b

^a Reaction conditions: A solution of the corresponding hydroxyquinoline **1** (0.05 mmol) and the [IrCp*Cl₂]₂ catalyst (2.5 mol%) in 2.0 mL of 1,2-DCE was irradiated using a 23 W CFL of white light. ¹H NMR yield was calculated using 1,3,5-trimethoxybenzene as internal standard. N.r denotes no reaction. ^b Reaction carried out in the presence of K₂CO₃ (0.5 equiv).

and 7-methyl-8-hydroxyquinolines **1d** and **1e**, respectively (Table 2, entries 4-5). However, neither of these compounds gave the expected products **2d-e**; instead quinone derivatives **5d** and **5e** were obtained in good yields. All the above experiments indicated that the polyoxidation of hydroxyquinolines to afford products **2** can only take place for 5-methylated derivatives. To analyse if other substituents different from methyl are also tolerated, compounds **1f-1i**, bearing different substituents at position 5, were studied (Table

2, entries 6-9). 8-Hydroxyquinolines having methoxy (**1f**) and isopropoxymethyl (**1g**) groups were successfully oxidized, but two different products were obtained (Table 2, entries 6-7). Whereas the photooxygenation of isopropyl ether derivative **1g** afforded the expected compound **2g** in 51% yield, the methoxy derivative **1f** gave the epoxydiketone **6f**. The formation of the later (**6f**) could correspond to the evolution of the expected benzylic hemiketal of the oxygenated compound **2f** into a ketone moiety. By contrast, the oxidation of the chlorinated



compound **1h** seemed to be difficult to accomplish, affording a complex reaction mixture from which **2h** was identified in lower than 10% of yield (Table 2, entry 8). Furthermore, the 5-phenyl analogue **1i** led to the polyoxygenated derivatives **2i** in moderate yield as single diastereoisomers (Table 2, entry 9), demonstrating the tolerance toward different substituents at the 5-position. Bulkier 2-methylated compounds **1j-k** were also polyoxygenated to the corresponding products **2j-k** under the photocatalytic conditions (Table 2, entries 10-11). Finally, the oxidation of the 8-aminoquinoline derivative **1l** afforded the imine **2l** in 24% yield (Table 2, entry 12).

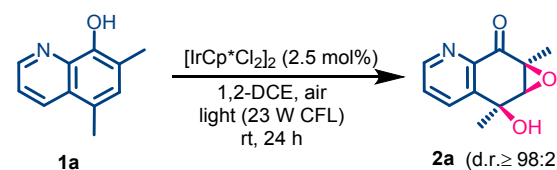
Mechanistic studies.

Intrigued by the effect of the aryl substitution on the photooxidation reaction outcome and the different selectivity obtained for the well-established photocatalysts [Ir(ppy)₃] and Rose Bengal, we decided to study the mechanism in detail, both from an experimental and a computational point of view. First, control experiments were performed (Table 3). The reaction did not proceed in the dark, under argon atmosphere or without the [IrCp*Cl₂]₂ catalyst, indicating the key role of those variables in the reaction mechanism, i.e. light, oxygen and Ir catalyst

(Table 3, entries 2-4). As previously commented in the reaction conditions optimization, the water content in the solvent affects the reaction outcome (see previously in Table 1, entry 9, 10 and Table 3, entry 5). Additionally, the photooxidation process could proceed via singlet oxygen oxidation, formed by an energy transfer process as will be detailed below. To confirm this, different experiments were conducted. First, the addition of 0.5 equivalents of DABCO, commonly used as a singlet oxygen (¹O₂) quencher,^{26, 27} to the reaction mixture led to a decrease in the reaction yield (Table 3, entry 6). However, DABCO may also participate in single-electron transfer processes. To discard the presence of reactive radicals or superoxide species, the reaction was performed in the presence of TEMPO, a well-known radical scavenger (Table 3, entry 7). The photooxidation of **1a** was not inhibited upon addition of such scavenger, confirming that radical or superoxide pathways are unlikely to be responsible for the observed reactivity. Furthermore, the reaction showed an increased yield when performed in deuterated solvent (Table 3, entries 8-9), which is consistent with the significant increase of the lifetime of ¹O₂ in such media.²⁸ Finally, to detect the presence of ¹O₂, we performed the reaction in the presence of anthracene, as a chemical trapping probe (Table 3, entry 10).²⁹ Notably, 10% of the anthracene-endoperoxide was detected in the reaction media. All these experiments indicate that singlet oxygen is the reactive oxygen species involved in the transformation.

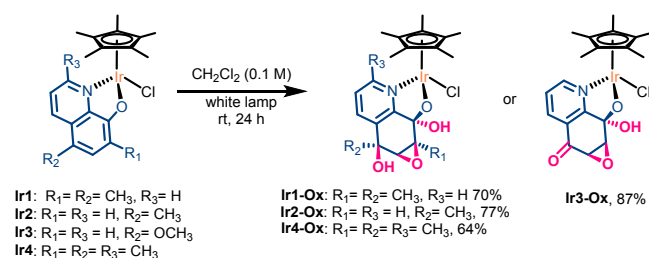
Oxyquinolate-Ir(III) complexes are active photocatalysts in different transformations.²⁰ According to this, we propose that the photocatalytic active species in the oxyfunctionalization reaction is the complex formed by the coordination of the corresponding deprotonated hydroxyquinoline to the Ir center. Based on this, we wanted to confirm whether the oxyfunctionalization of the heteroaromatic substrates takes place when the ligand is coordinated to the metal. Thus, we prepared and isolated the oxyquinolate-Ir complexes **Ir1-4** by reacting the dinuclear [IrCp*Cl₂]₂ complex with the corresponding 8-hydroxyquinoline in the presence of K₂CO₃ (See synthesis in the Supporting Information).²⁰ Next, the 8-oxyquinolate iridium complexes **Ir1-4** were submitted to the photooxidation conditions, that is, white light irradiation in the presence of air and the reaction was monitored by ¹H NMR spectroscopy (Scheme 3). After 24 h of irradiation, full conversion of **Ir1-4** into new Ir complexes was observed. The corresponding oxyfunctionalized complexes, named as **Ir1-4Ox**, were isolated in good yields (64-87%) and fully characterized. All the oxyfunctionalized Ir complexes, **Ir1-4Ox**, were unambiguously characterized by X-ray diffraction analysis. Single crystals were grown by slow diffusion of *n*-pentane into saturated dichloromethane solutions of the corresponding complexes. The structures obtained are shown in Figure 1 and the most remarkable crystallographic data is collected in Table 4 (See full data in the Supporting Information). The four polyoxyfunctionalized Ir complexes preserved the expected three-legged piano-stool geometry. The length and angle data for **Ir1-Ox**, **Ir2-Ox** and **Ir4-Ox** were compared to that of the parent **Ir1**, **Ir2**, and **Ir4** complexes.^{20, 29}

Table 3. Mechanistic experiments.^a



Entry	Deviation from reaction conditions	2a yield (%) ^b
1	-	71
2	Dark (no light)	0
3	Ar atmosphere	0
4	No catalyst	0
5	4 Å Molecular sieves	0
6	DABCO (0.5 equiv)	18
7	TEMPO (0.5 equiv)	81
8	CDCl ₃ as solvent	55
9	CHCl ₃ as solvent	39
10	Anthracene (0.5 equiv)	83 ^c

^a Reaction conditions: A solution of 5,7-dimethylhydroxyquinoline (0.05 mmol) and [IrCp*Cl₂]₂ catalyst (2.5 mol%) in 2.0 mL of dry 1,2-DCE was irradiating using a 23 W CFL of white light for 24 h. ^b ¹H NMR yield calculated using 1,3,5-trimethoxybenzene as internal standard. ^c 10% of anthracene-endoperoxide is also formed.



Scheme 3: Identification and isolation of the polyoxygenated quinolate-Ir complex.



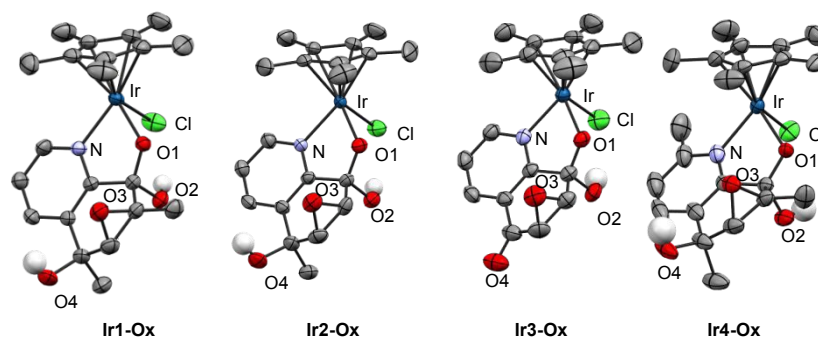


Figure 1. Structural views of complexes **Ir1-4-Ox**. Ellipsoids are shown at 50% level and hydrogen atoms are omitted for clarity except those bonded to oxygen. The complexes crystallized as a racemic mixture. Only one enantiomer is shown.

Table 4. Selected bond lengths (Å) and angles (°) for Ir(III) complexes **Ir1-4-Ox**.

Entry	Bond lengths	Ir1	Ir1-Ox	Ir2	Ir2-Ox	Ir3-Ox	Ir4	Ir4-Ox
1	Ir-N	2.090(7)	2.117(7)	2.118(12)	2.101(5)	2.108(4)	2.134(3)	2.116(3)
2	Ir-O	2.116(6)	2.074(6)	2.095(10)	2.068(3)	2.075(3)	2.073(2)	2.086(2)
3	Ir-Cl	2.396(2)	2.426(2)	2.392(4)	2.420(2)	2.418(1)	2.4046(10)	2.403(9)
4	Ir-Cp* Centroid ^a	1.772	1.771	1.774	1.765	1.776	1.778	1.776
Entry	Angles	Ir1	Ir1-Ox	Ir2	Ir2-Ox	Ir3-Ox	Ir4	Ir4-Ox
5	O-Ir-N	78.3(3)	77.45(15)	78.6(4)	77.43(4)	77.46(1)	78.73(10)	78.28(1)
6	O-Ir-Cl	87.30(19)	88.53(11)	84.5(3)	88.52(3)	87.74(10)	88.22(8)	88.29(7)
7	N-Ir-Cl	84.60(19)	84.85(13)	86.8(3)	84.84(3)	85.68(11)	84.47(7)	86.63(9)
8	Centroid Cp*-Ir-Cl ^a	128.33	126.79	126.35	127.94	128.21	128.34	128.06
9	Centroid Cp*-Ir-O ^a	127.76	127.66	129.67	126.96	124.31	122.27	125.14
10	Centroid Cp*-Ir-N ^a	133.29	134.63	133.54	133.40	134.36	137.44	133.80

^a Cp* distances and angles have been measured with respect to the ring centroid.

The Ir-N, Ir-O and Ir-Cl distances suffer slight variations, but a clear trend was not observed. For instance, the Ir-O distances were found to be slightly shorter in complexes **Ir1-Ox** and **Ir2-Ox** than those of their precursors, while the Ir-O distance in **Ir4-Ox** was slightly longer than that of **Ir4**. Ir-N distances, however, increased in **Ir1-Ox**, and decreased in **Ir2-Ox** and **Ir3-Ox**, compared to their corresponding precursors. Overall, when compared amongst them, the lengths and angles of the oxygenated complexes lied in the same range. It was surprising to find that the structure of the **Ir1-4-Ox** complexes contained three new oxygenated functional groups at the quinoline ligand, including a OH group at the 8-position. For the 5-methoxy derivative **Ir3**, its oxygenation afforded **Ir3-Ox**, bearing a ketone at the 5 position of the bicyclic ligand. This outcome aligns with the obtention of the diketone product **6f** starting from the 5-methoxy-8-hydroxyquinoline substrate **1f**, as previously commented in the scope study of the catalytic process (Table 2). It is also important to note the high stereospecificity of the protocol, as the Ir complexes formed contain up to four chiral centres (three in the case of **Ir3-Ox**) in the bicyclic ligand, observing only one diastereoisomer by ¹H NMR spectroscopy (Scheme 3). Moreover, the disposition of the new oxygenated groups is arranged as follows (Figure 1 and Scheme 3): the hydroxyl group at 5 position and the epoxide are in *cis* orientation whereas the hydroxyl located at 8 position is

trans respect to both of them. According to the stereochemistry obtained in complexes **Ir1-4Ox**, the three oxygen-functional groups seem to come from two different reagents. The previous experiments help to understand partially the mechanism and corroborate that the coordination of the hydroxyquinoline derivative (**1**) to the Ir center happens prior to its oxygenation. Considering this, a plausible mechanism was proposed (Figure 2). After formation of the quinolate-Ir(III) complex (**Ir1**), the oxygenation of the ligand with singlet oxygen takes place. This singlet oxygen is generated via interaction between the excited state of the quinolate-Ir(III) complex (**Ir1***) with atmospheric oxygen. Indeed, we observed the quenching of the excited state of the quinolate-Ir(III) complexes in the presence of oxygen (see Supporting Information). Next, the oxyquinolate ligand of the **Ir1** complex will react with ¹O₂ to form the polyoxygenated complex **Ir1-Ox**. In addition, water is proposed to play a key role in such transformation, facilitating proton transfer processes and stabilizing reactive intermediates, ultimately enabling the formation of the observed polyoxygenated complexes. Absorption and emission measurements of both type of Ir complexes (oxygenated and non-oxygenated parent complex) reveal that all parent Ir complexes exhibit stronger absorption in the visible region than the oxygenated analogues, while



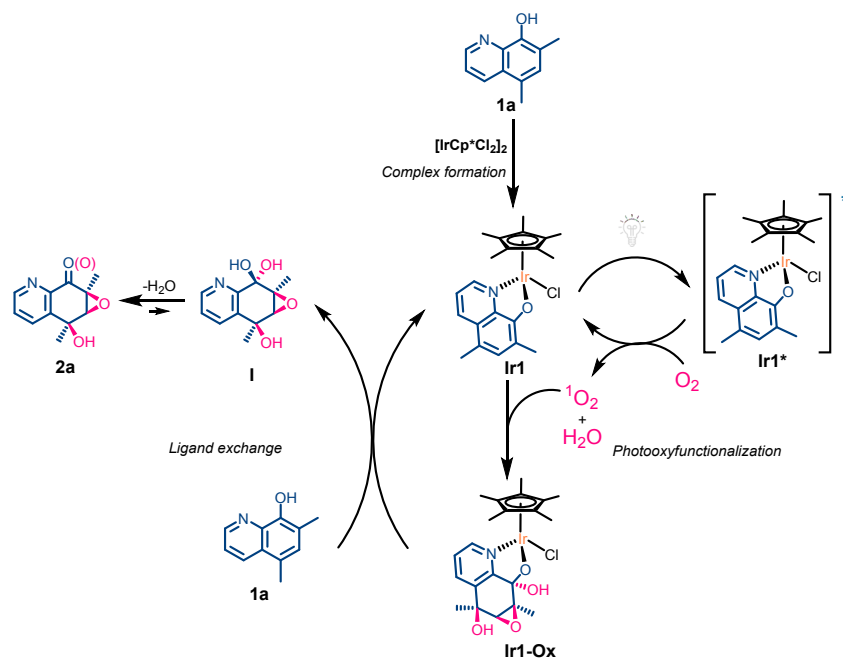


Figure 2. Simplified mechanism for the polyoxygenation of hydroxyquinolines based on experimental mechanistic studies.

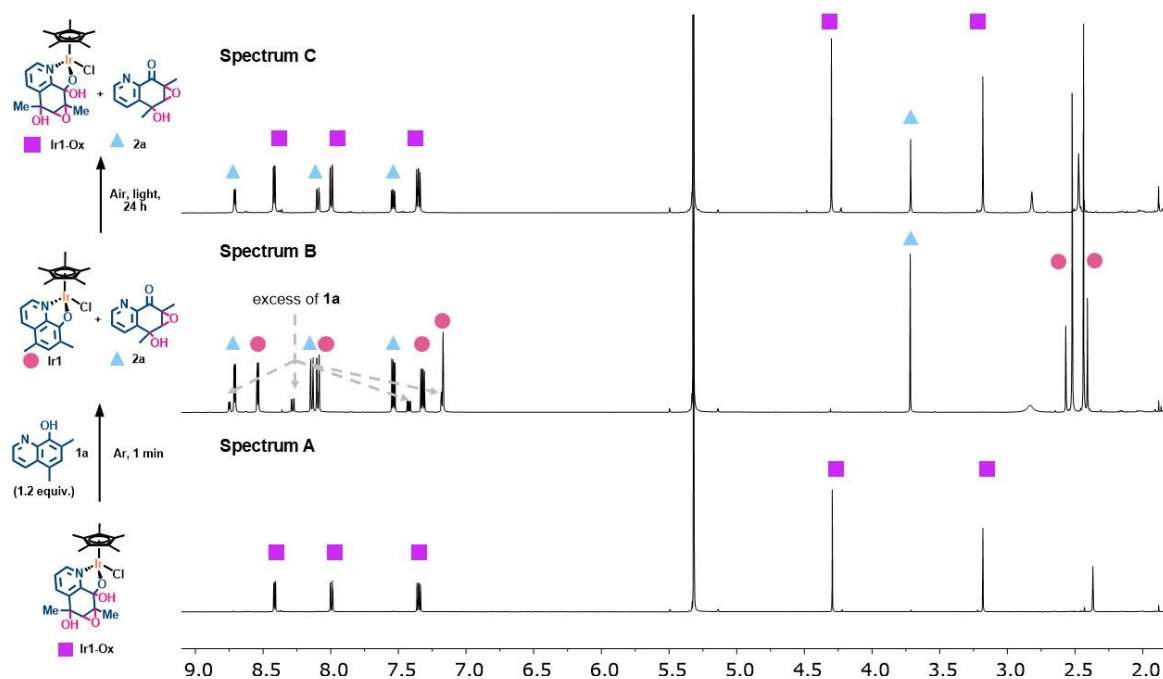


Figure 3. ¹H NMR spectra of the ligand exchange experiment.

no emission was detected for the latter complexes (see Supporting Information). These experiments are consistent with the proposed light-mediated steps.

After the oxygenation of the complex (Figure 2), a ligand exchange reaction will substitute the oxidized ligand in **Ir1-Ox** by the hydroxyquinoline derivative to recover the initial quinolate-Ir complex (**Ir1**). Lastly, the 1,2-diol in the heterocycle (**I**) will be transformed into the final ketone derivative **2a**, forming water as byproduct. To demonstrate the

ligand exchange between **1a** and the **Ir1-Ox** complex, ¹H NMR spectra were recorded to monitor the reaction (Figure 3). First, the oxygenated complex **Ir1-Ox** (Figure 3, spectrum A) was mixed with the dimethylated hydroxyquinoline **1a** at room temperature in CD₂Cl₂. In the first spectrum, acquired just after mixing both reagents (Figure 3, spectrum B), the full disappearance of the proton signals relative to complex **Ir1-Ox** was observed. In addition, the signals corresponding to **Ir1** and compound **2a** were identified, corroborating an instantaneous



ligand exchange reaction and the formation of compound **2a**. This evidence was further corroborated by DFT calculations, which afforded an equilibrium constant of 75.25 for the ligand exchange reaction (see Supporting Information for more details). Next, the reaction mixture containing **Ir1** and compound **2a** was irradiated under visible light in the presence of air (Figure 3, spectrum C). After 24 h of irradiation, complex **Ir1** was fully converted into **Ir1-Ox**, showing that the oxyfunctionalization occurs upon coordination of the hydroxyquinoline to the Ir center and the reaction of that Ir complex with singlet oxygen.

To gain deeper insight into the elemental steps and the diastereoselectivity of the reaction, we have carried out simulations with Quantum Chemistry starting from the simplified mechanism for the oxyfunctionalization of 8-hydroxyquinolines (see Figure 2 and Figure 4). The calculations were performed using density functional theory (DFT), specifically with the M06L functional.³¹ The electron density was expressed using the 6-31G(d,p) basis set for C, O, H, N, and Cl atoms.^{32, 33} The Ir atom was described with an effective core

potential (ECP) in combination with the corresponding LanL2DZ basis set.³⁴⁻³⁷ Solvent effects were considered through a Polarizable Continuum Model (PCM) of the solvation model based on density (SMD) type.³⁸ All calculations were carried out with the Gaussian16 program.³⁹

A mechanistic proposal is presented in Figure 4. In the top row of the figure, we consider the quinolinate–Ir complex with one oxygen molecule and one water molecule, both weakly bounded. The first step consists of the photoexcitation of oxygen $^3\text{O}_2$ into $^1\text{O}_2$, resulting in a minimum on the singlet potential energy surface; this structure will be taken as the energy reference and therefore has $\Delta G = 0.0 \text{ kcal}\cdot\text{mol}^{-1}$. We have studied two cycloaddition reactions of insertion of singlet oxygen into the quinolinic ring: (i) The [4+2] cycloaddition leads to an almost degenerate structure. The very low energy barrier of $\sim 3 \text{ kcal}\cdot\text{mol}^{-1}$, both in the direct and inverse reactions, leads us to conclude that an equilibrium of O_2 insertion/expulsion is established (left-top, Figure 4). (ii) The [2+2] cycloaddition

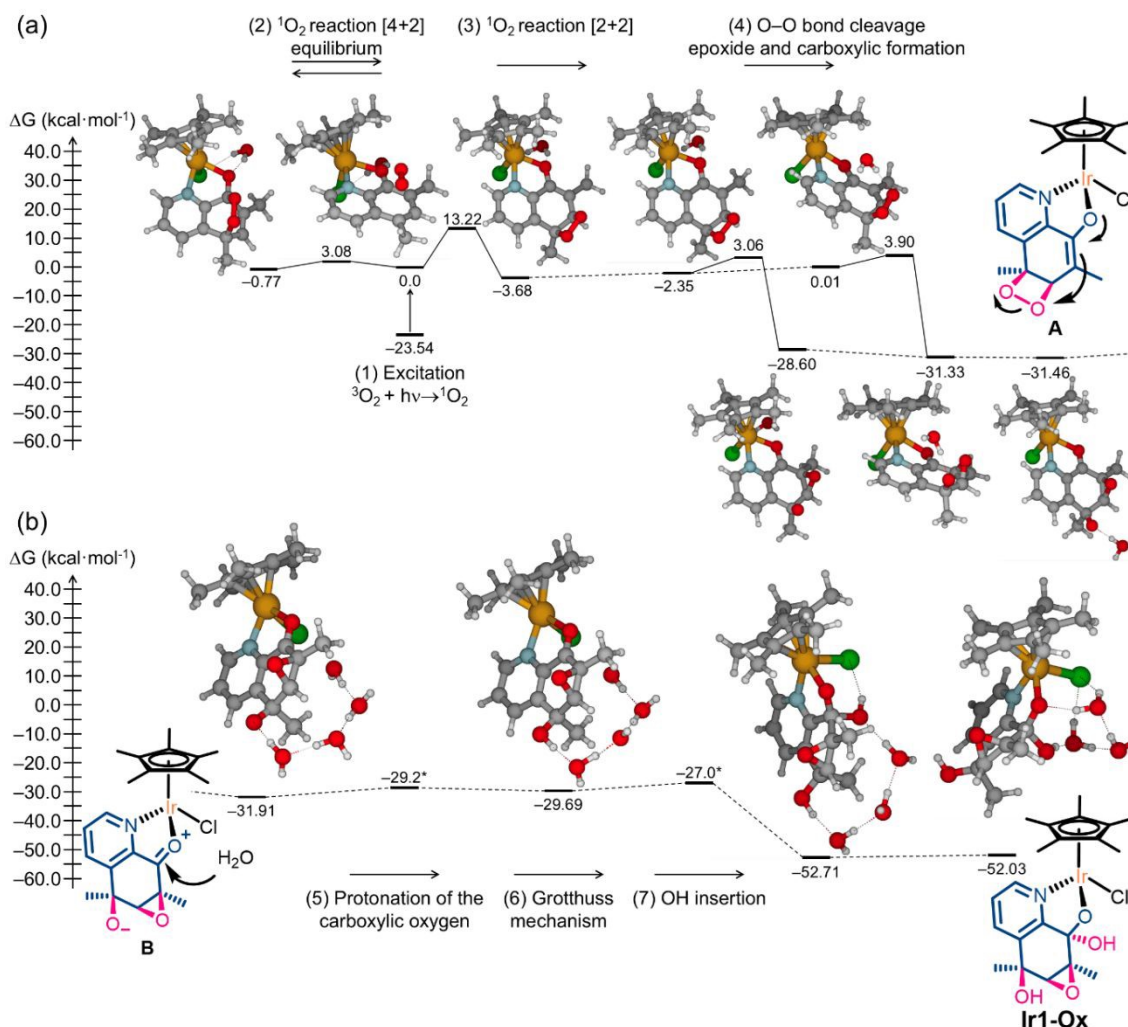


Figure 4. Potential energy surface showing minima and transition states of the proposed mechanism. (a) Upper row shows calculations including one water molecule and (b) lower row four water molecules. Relative energies ΔE are given in $\text{kcal}\cdot\text{mol}^{-1}$ and referred to the ground state complex with triplet oxygen $^3\text{O}_2$. ΔE values marked with an asterisk * have been estimated from relaxed scans simulations



produces a structure almost 4 kcal·mol⁻¹ more stable (right-top, Figure 4). The barrier of this reaction can be easily overcome because the first absorption band in the photoexcitation takes place at higher energies. This band appears approximately at 25 kcal·mol⁻¹ above the reference minimum with singlet spin multiplicity.²⁰ We rule out the equilibrium in this reaction because the new formed structure after the [2+2] addition is protected with a barrier of ~ 17 kcal·mol⁻¹. In addition, this structure evolves very rapidly through the cleavage of the O-O bond with a very low barrier of ~ 3 kcal·mol⁻¹ (structure **A** shows the associated electron density redistribution schematically). As a result, an epoxide and a carboxyl on the quinoline ring are formed (see structure **B**). We have considered two pathways for this step, one with the water molecule behind the quinoline plane and another where the water molecule is located near O₂. In both cases, the barrier is of similar height, indicating that the presence of water does not assist in breaking the O-O bond. However, water does help in stabilizing the new structure by establishing a hydrogen bond with the carboxyl group formed. Note that the new structure is at a relative energy of -30 kcal·mol⁻¹ with respect to the singlet multiplicity complex; and is even below the starting point with triplet multiplicity. That is, once the activation barrier for [2+2] addition is overcome, the complex evolves rapidly, stabilizing at an energy jump of more than 30 kcal·mol⁻¹. The role of water in the proposed mechanism is highlighted in figure 4B, where it is essential for the transformation from structure **B** to **Ir1-Ox**.

The following steps were studied assuming the presence of some water molecules around the complex. The relative energies are also referred to the complex multiplicity. Protonation of the alkoxide anion by a nearby water molecule occurs in a first step. The hydroxyl generated is stabilized by hydrogen bonds with the other water molecules. Through a Grotthuss mechanism (proton jumping), the hydroxyl group is transferred and finally inserted on the opposite face of the quinoline ring. A cooperative process with very low energy barriers ensures the effectiveness of these last steps of the mechanism. It is worth noting that the final polyoxygenated complex **Ir1-Ox** is more than 50 kcal·mol⁻¹ below the initial complex with singlet spin multiplicity, formed in an additional stabilization step. The mechanistic proposal, in which the [2+2] cycloaddition and hydroxylation occur on opposite faces of the quinoline plane, account for the formation of the experimentally observed diastereomer.

CONCLUSIONS

In this work, we have developed a novel photocatalytic strategy for the direct dearomative polyoxygenation of 8-hydroxyquinolines using molecular oxygen as the sole oxidant. This methodology enables the simultaneous installation of multiple oxygen functionalities within the heteroaromatic core in a single synthetic step, representing a significant advance over traditional multistep oxidative approaches. A key feature of this transformation is the dual role of the iridium precursor [IrCp*Cl₂]₂. Upon *in situ* coordination of the hydroxyquinoline

substrate, the resulting oxyquinolate-Ir(III) complex operates both as a photosensitizer, generating singlet oxygen, and as a substrate-activating platform. This self-reacting photocatalytic system eliminates the need for external photosensitizers. In contrast, commonly employed photocatalysts such as [Ir(ppy)₃] or Rose Bengal, although capable of sensitizing oxygen, fail to promote the same transformation due to their inability to coordinate and activate the hydroxyquinoline substrate.

The reaction proceeds with remarkable chemoselectivity and diastereoselectivity, affording a single diastereomer even in systems generating up to four stereogenic centers. Substrate scope studies reveal a strong dependence on substitution at the 5-position of the quinoline ring, highlighting the importance of electronic and steric effects in facilitating oxygen insertion and subsequent transformations.

Structural characterization of the oxygenated Ir complexes and ligand exchange experiments unequivocally demonstrate that oxyfunctionalization occurs while the substrate is coordinated to the metal center. Mechanistic investigations, supported by control experiments and DFT calculations, confirm the involvement of singlet oxygen as the reactive oxygen species. Computational studies are consistent with a [2+2] cycloaddition of ¹O₂ to the coordinated quinolate ligand, followed by O-O bond cleavage and water-assisted proton transfers that ultimately furnish the observed polyoxygenated products. Notably, trace amounts of water play a crucial role in stabilizing intermediates and enabling proton shuttling processes, whereas complete water removal inhibits the reaction.

Author contributions

A.U and L.B. carried out the optimization and scope of the reaction. S.D.T and C. F conducted the DFT calculations. A.C, S.C and J.A conceived the project and prepared the manuscript, which was edited by all other authors.

Conflicts of interest

There are no conflicts to declare.

Data availability

CCDC numbers 2466583 (**Ir4**), 2466572 (**Ir1-Ox**), 2423907 (**Ir2-Ox**), 2466582 (**Ir3-Ox**), and 2466580 (**Ir4-Ox**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

The data that support the findings of this study are available in the supplementary information (SI) of this article



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Data availability

Experimental details, general procedures, optimization of reaction conditions, characterization of products, copies of NMR spectra of all products and computational details are in the ESI.

