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Substrate-Selectivity in Catalytic Photooxygenation Processes Using a Quinine-BODIPY System

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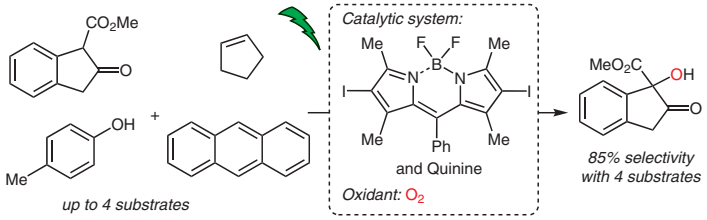

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Abstract Substrate selectivity by means of synthetic catalysts remains a challenging topic in chemistry. Here, a catalytic system combining an iodo-BODIPY photosensitizer and quinine was evaluated in the competitive photooxygenation of non-hydrogen and hydrogen-bond-donor substrates. The ability of quinine to activate hydrogen-bond-donor substrates towards photooxygenation was reported and the results were benchmarked with photooxygenation experiments in the absence of quinine.

Key words photooxygenation, singlet oxygen, substrate selectivity, BODIPY, oxidation

Vincent Coeffard studied at Université de Nantes (France) and he completed his Ph.D. studies in 2007 in the group of Professor Jean-Paul Quintard. He then moved to University College Dublin (Ireland) to work as a postdoctoral research fellow for two years in asymmetric catalysis under the guidance of Prof. Pat Guiry. He then spent ten months in Spain for a second postdoctoral experience in the group of Prof. Antonio M. Echavarren to investigate gold chemistry. In 2010, he was appointed CNRS researcher in the group of Prof. Christine Greck at Université de Versailles Saint-Quentin-en-Yvelines (France) to work on the design of organocatalysts and implementation of catalytic technologies to access enantioenriched organic architectures. In 2016, he moved to Université de Nantes where his current research interests include asymmetric organocatalysis and photochemistry.

The synthetic chemist community has been resourceful and inventive in making catalytic systems more selective and efficient to allow for the construction of densely functionalized architectures.[1] Within this context, substrate selectivity with artificial catalysts is an attractive research field in chemistry.[2,3] The challenge is even more difficult when highly reactive reagents such as singlet oxygen are involved in the functionalization of molecular scaffolds. Singlet oxygen ($^1O_2$) is a powerful oxidant which is conveniently produced by sensitization of ground state triplet oxygen under illumination of a photosensitizer.[4] Photooxygenation is a leading method for introducing oxygen atoms to organic compounds but the control of chemo-, regio-, stereo-, or substrate-selectivity remains a challenging task.[5–7]

One approach in which these demands can be achieved is through the use of two-module photosensitizers with a controlled delivery of singlet oxygen. The guiding philosophy is that one module of the photosensitizer is dedicated to the production of singlet oxygen and the second unit modulates singlet oxygen generation efficiency depending on the surrounding environment.[8] Parameters such as acidity and ion concentrations have been harnessed for controlling the production of singlet oxygen and these strategies hold great promises for photodynamic therapy.[9]

From a synthetic standpoint, our group has recently described a two-unit photosensitizer aiming at performing asymmetric hydroxylation of β-dicarbonyl compounds.[10] The photosensitizer contains an iodo-BODIPY (BODIPY: boron dipyrromethene) part enabling the production of singlet oxygen under green light illumination and a quinine unit playing a double role. The substrates are activated towards photooxygenation by quinine while in the absence of substrates at the active site of quinine, singlet oxygen is physically quenched by the quinuclidine nitrogen atom.[11] In

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light of these results, we surmised that photooxygenation in the presence or absence of quinine could be applied to substrate-selective catalysis in which the substrates involved contain different reacting functionalities. To put this strategy into practice, we envisaged two plausible scenarios (Figure 1). In a mixture of compounds with (AH) and without hydrogen-bond-donor functional groups (B), photooxygenation in the presence of a catalytic system iodo-BODIPY/quinine would selectively oxidize AH owing to the hydrogen-bond activation by the quinuclidine nitrogen atom.[12] On the contrary, substrate B would not be oxidized because of physical deactivation of singlet oxygen by quinine. The only use of iodo-BODIPY would offer a complementary route by preferentially oxidizing the substrate B deprived of hydrogen-bond-donor opportunities.

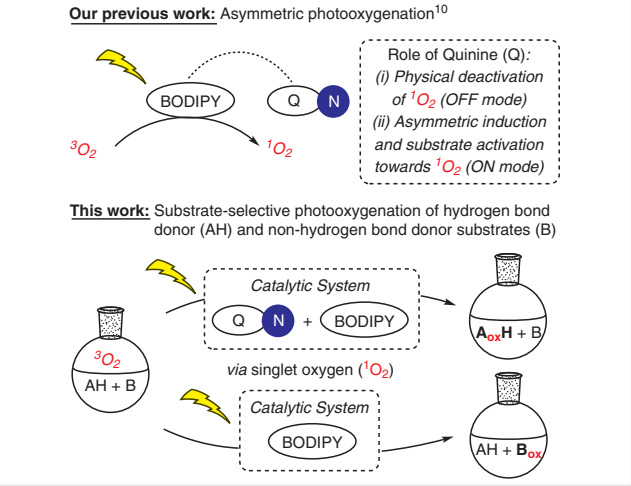


Figure 1 Concept: substrate-selective photooxygenation by using a catalytic combination of iodo-BODIPY and quinine

The initial study was focused on discovering the best quinine derivatives able to physically quench singlet oxygen. To this aim, we first investigated the photooxygenation of the non-hydrogen-bond-donor anthracene, which is a $^1O_2$ chemical trap (Figure 2). Irradiation for 45 minutes in the presence of 5 mol% of **1** led to 90% ^{1}H NMR yield of anthracene-9,10-endoperoxide **5**. Performing the same reaction in the presence of 5 mol% quinine led to a dramatic decrease in singlet oxygen insertion. Analysis of the reaction mixture showed the formation of anthracene-9,10-endoperoxide in only 33% NMR yield at the end of reaction.

As reported in the literature,[10] the quinuclidine heterocyclic framework plays a crucial role in singlet oxygen deactivation because similar results were obtained by running the photooxygenation with 5 mol% of commercially available quinuclidine. Surprisingly, the use of bifunctional photosensitizer **2**, which has been recently prepared by our group, provided the product in 74% yield after 45 minutes reaction time.[10] Linking the BODIPY **1** to the quinine heterocycle led to a higher photooxygenation activity than performing the reaction by using an equimolar amount of quinine and **1**. In light of these results, we surmised that substitution of the terminal alkene of quinine could influence the photooxygenation rate of anthracene. A mixture of **1** (5 mol%) and **3** (5 mol%) is catalytically active and the reaction is faster than when performing the photooxygenation with the catalytic system **1** (5 mol%) and quinine (5 mol%).[13] The replacement of the phenyl ring in **3** by a bulkier group (**4**) affects the catalytic activity by increasing the

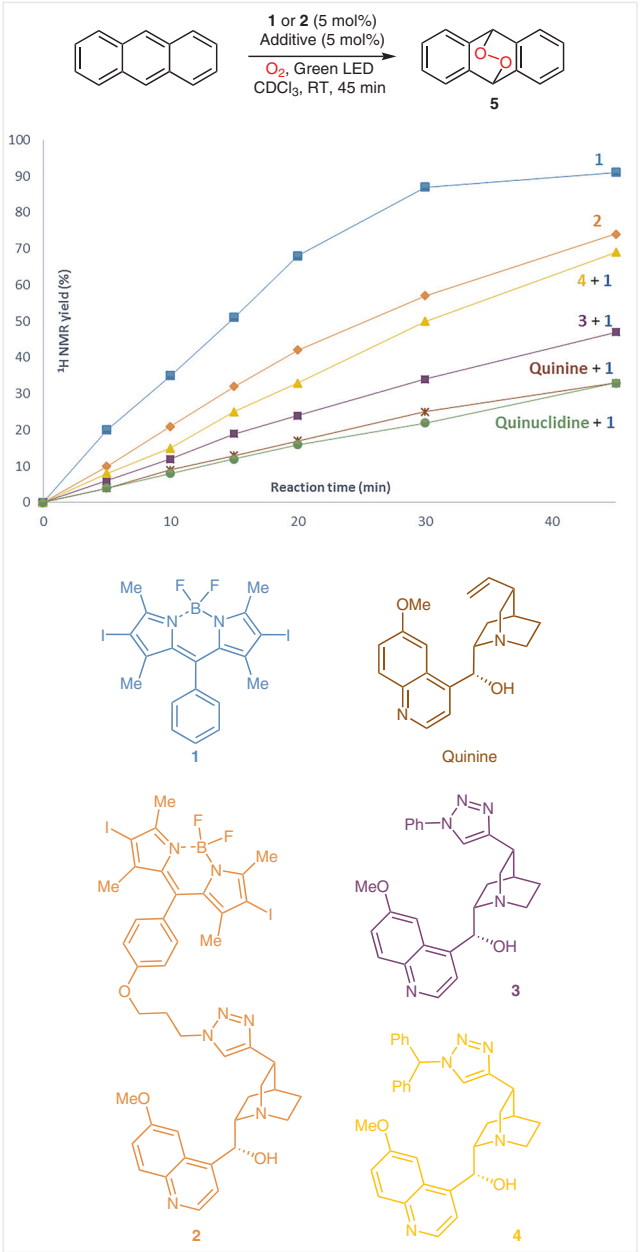
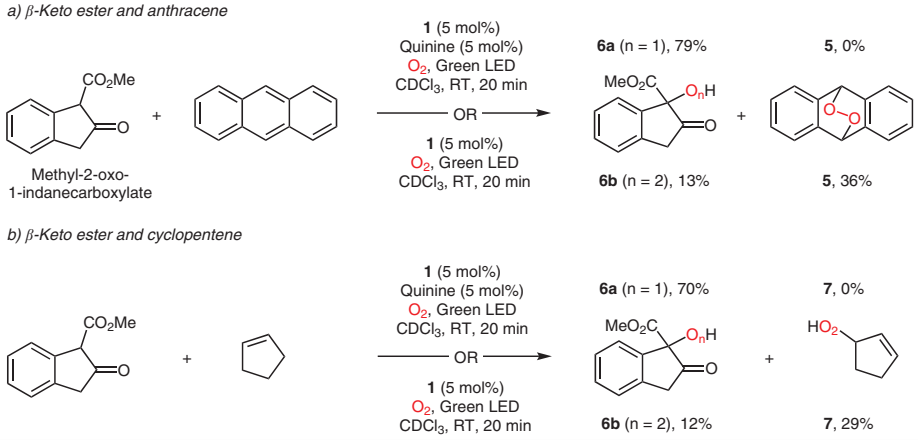


Figure 2 Conversion of anthracene versus time in the absence and in the presence of additives



Scheme 1 Competitive photooxygenation of reaction mixtures containing equimolar amounts of methyl-2-oxo-1-indanecarboxylate and non-hydrogen-bond-donor substrates. Substrate-selectivity was determined as product ratio for a better reliability. NMR yields for each product are reported by using an internal standard.

photooxygenation rate.[14] These results demonstrate the unexpected influence of the alkene functionalization on the photooxygenation activity.

On the basis of this study, quinine was chosen as the best additive to investigate substrate-selective catalysis owing to its strong ability to physically deactivate singlet oxygen when non-hydrogen-bond-donor substrates are involved. We then explored the ability of the BODIPY **1**/quinine system to selectively oxidize hydrogen-bond-donor substrates within the context of substrate-selective catalysis. In order to tackle this challenge, competitive photooxygenations of 1/1 mixtures of methyl-2-oxo-1-indanecarboxylate and non-hydrogen-bond-donor substrates were performed (Scheme 1).[15] The ability of the BODIPY **1**/quinine catalytic system to selectively oxidize hydrogen-bond-donor substrates was first investigated by pair-wise competitive experiments between methyl-2-oxo-1-indanecarboxylate, which is prone to oxidation by the BODIPY **1**/quinine combination,[10] and anthracene. Selective photooxygenation was observed and alcohol **6a** was obtained in 79% yield, whereas **5** was not detected.

The low quinine loading (5 mol%) required for preventing the photooxygenation of anthracene is well explained by comparing the values of rate constants for the chemical reaction and physical deactivation of singlet oxygen (k_T). Singlet oxygen is quenched by anthracene with k_T = 5.4 × 10^5 M^{-1} s^{-1} ($CHCl_3$), whereas the k_T value for quinine is larger by a factor of 42.5 (k_T = 2.3 × 10^7 M^{-1} s^{-1} in $CHCl_3$).[16] To investigate the potential formation of a complex between methyl-2-oxo-1-indanecarboxylate and quinine, NMR titration experiments were carried out (see Supporting Information for details). From these data, a Job plot analysis (Figure 3) was performed which supports the formation of a 1:1 complex with an association constant *K*a = 18.9 M^{-1}.

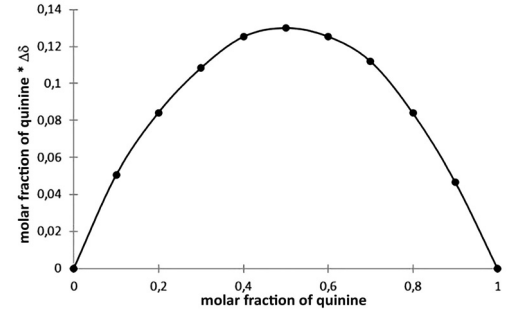
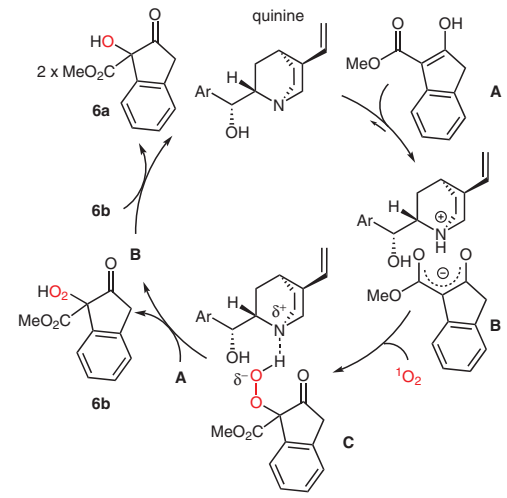
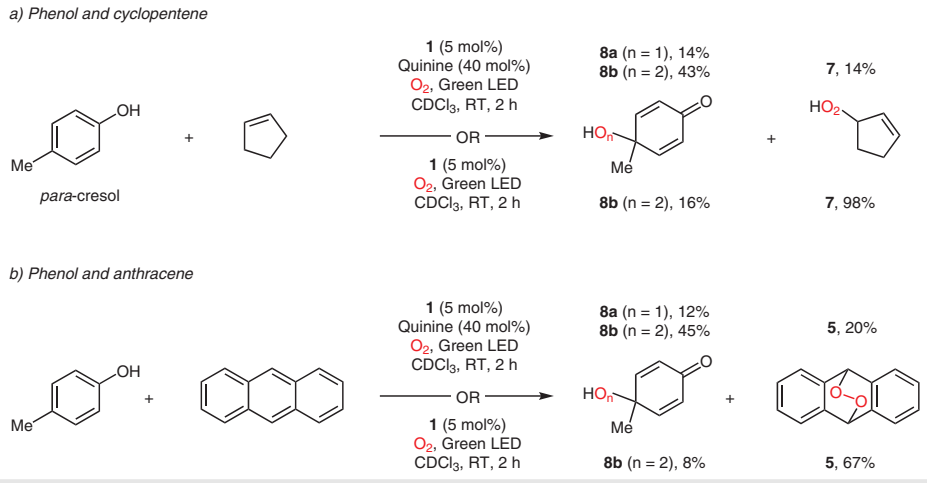


Figure 3 Job plot for the complex of quinine with methyl-2-oxo-1-indanecarboxylate



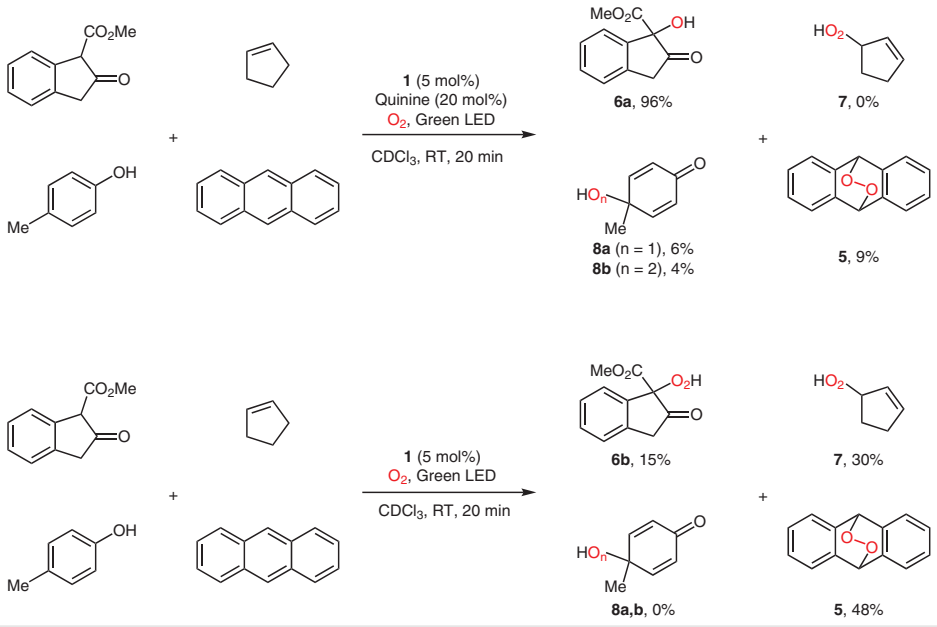
Scheme 2 Plausible mechanism for the quinine-catalyzed photooxygenation of methyl-2-oxo-1-indanecarboxylate



Scheme 3 Competitive photooxygenation of reaction mixtures containing equimolar amounts of *para*-cresol and non-hydrogen-bond-donor substrates. Substrate selectivity was determined as product ratio for a better reliability. NMR yields of each product are reported by using an internal standard.

Considering these results and literature data,[10] a plausible mechanism is shown in Scheme 2 to explain the formation of alcohol **6a**. The first step would involve the formation of the adduct **B** of quinine and methyl-2-oxo-1-indanecarboxylate for which the enol form (**A**) is the major form in $CDCl_3$. The formation of complex **B** would enhance the reactivity of the enolic system towards singlet oxygen and the intermediate **C** would be produced leading to hydroperoxide **6b**.[17] As previously reported for a similar transformation,[18] hydroperoxide **6b** could react with complex **B** to form alcohol **6a**. In light of NMR studies, a complex could also exist between **6a** and quinine (see Supporting Information).

The results obtained with a BODIPY **1**/quinine combination were compared with those of the photooxygenation promoted by BODIPY **1** (Scheme 1, a). In the absence of quinine, a mixture of hydroperoxide **6b** and anthracene-9,10-endoperoxide **5** was observed without any traces of alcohol **6a**. By using the same reaction conditions, a pair-wise competitive experiment was also performed on an equimolar mixture of methyl-2-oxo-1-indanecarboxylate and cyclopentene prone to react with singlet oxygen through an ene-



Scheme 4 Competitive photooxygenation of an equimolar pool of substrates. NMR yields are reported by using an internal standard.

reaction (Scheme 1, b).[19] In the presence of quinine, compound **6a** was selectively formed in 70% yield. Irradiation in the presence of BODIPY **1** showed that a mixture of hydroperoxides **6b** and **7** were obtained in 12 and 29% yield, respectively. In order to investigate another family of hydrogen-bond-donor substrates, competitive experiments between *para*-cresol and cyclopentene were studied (Scheme 3). A rapid screening of the quinine amount showed that the best selectivities were obtained with 40 mol% of quinine. Under these conditions, a higher substrate selectivity of **8a** and **8b** over **7** was observed. NMR titration showed the formation of a 1:1 complex with *para*-cresol and quinine with *K*a = 28.2 M^{-1} (see Supporting Information for details). By increasing the electron density of the phenyl ring, the formation of this adduct could explain the higher reactivity of *para*-cresol towards singlet oxygen.[16b] The ability of quinine to reduce peroxy quinol **8b** explains the formation of **8a**.[20] A reversal of selectivity was noticed in the absence of quinine, highlighting its importance in the reaction outcome. A similar scenario was observed by investigating the photooxygenation of a mixture of *para*-cresol and anthracene. Antracene-9,10-endoperoxide **5** was preferentially formed by using BODIPY **1** as a photosensitizer while photooxygenation of *para*-cresol was faster than that of anthracene when 5 mol% of quinine was added. In light of these results, we decided to investigate the competition between a mixture of four substrates (Scheme 4).

Photooxygenation by using a mixture of BODIPY and quinine (20 mol%) afforded selectively alcohol **6a** in 96% yield, while only trace amounts of the other products were detected. Therefore, a substrate selectivity of 85% measured as product ratio was calculated. These reaction conditions were benchmarked against photooxygenation without quinine as an additive. As expected, oxidation of hydrogen-bond-donor substrates, namely *para*-cresol and methyl-2-oxo-1-indanecarboxylate, was slower than photooxygenation of cyclopentene and anthracene. As a result, a complex reaction mixture of **6b** (15%), **7** (30%), and **5** (48%) was obtained, highlighting the crucial role of quinine in substrate selectivity.

To conclude, the results obtained in this study have clearly shown the importance of quinine as a catalytic additive in the photooxygenation outcome. Within the context of substrate-selective catalysis, pair-wise competitive photooxygenation experiments were performed by using a BODIPY photosensitizer with or without quinine. We demonstrated that a selection of hydrogen-bond-donor substrates was selectively oxidized in the presence of quinine. In contrast, singlet-oxygen-mediated oxidations of non-hydrogen-bond-donor substrates such as anthracene or cyclopentene were faster without the addition of quinine, which confirmed the singlet oxygen quenching role of quinine. Therefore, the catalytic system for a photooxidative transformation must be carefully selected by considering the nature of the substrates. Work is in progress to shed light on the importance of the alkene functionalization of quinine in photooxygenation efficiency.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0039-1690796.

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(13) **(*R*)-(6-methoxyquinolin-4-yl)((1*S*,2*S*,4*S*,5*R*)-5-(1-phenyl-1*H*-1,2,3-triazol-4-yl)quinuclidin-2-yl)methanol (3)**
Azidobenzene (417 mg, 3.5 mmol, 1 equiv) and 10,11-didehydroquinine (375 mg, 1.16 mmol, 0.33 equiv) were dissolved in a THF/H_2O 3:1 mixture (10.2:3.4 mL) in a Schlenk flask. Sodium ascorbate (95.1 mg, 0.48 mmol, 0.133 equiv) and then copper sulfate pentahydrate (30 mg, 0.12 mmol, 0.033 equiv) were added and the reaction mixture was stirred at RT for 72 h. The solution was concentrated *in vacuo*, and the resultant slurry was dissolved in CH_2Cl_2 (60 mL). The organic phase was washed with water (3 × 60 mL), dried with magnesium sulfate, and concentrated *in vacuo*. Purification by column chromatography, eluting with EtOAc/MeOH 8:2, gave the quinine derivative **3**. Yield: 178 mg (35%); mp 217–220 °C. IR (ATR): 3160, 3149, 2935, 1505, 1227, 1015, 767, 762 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.61 (d, *J* = 4.5 Hz, 1 H), 7.94 (d, *J* = 9.9 Hz, 1 H), 7.62–7.55 (m, 3 H), 7.52–7.48 (m, 1 H), 7.48–7.41 (m, 2 H), 7.40–7.34 (m, 1 H), 7.33–7.27 (m, 2 H), 5.56 (d, *J* = 4.7 Hz, 1 H), 3.89 (s, 3 H), 3.57–3.44 (m, 1 H), 3.44–3.35 (m, 1 H), 3.35–3.27 (m, 2 H), 3.13–3.05 (m, 1 H), 2.79–2.67 (m, 1 H), 2.21–2.14 (m, 1 H), 1.91–1.72 (m, 2 H), 1.71–1.58 (m, 1 H), 1.58–1.45 (m, 1 H), 0.96–0.79 (m, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 157.9, 151.6, 147.7, 147.6, 144.4, 137.2, 131.6, 129.8 (2 C), 128.7, 126.9, 121.6, 120.5 (2 C), 118.7, 118.6, 101.7, 77.4, 71.9, 59.9, 56.5, 55.9, 43.3, 33.3, 28.0, 27.6, 22.3. HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{26}H_{28}N_5O_2$: 442.2243; found: 442.2235.

(14) **(*R*)-((1*S*,2*S*,4*S*,5*R*)-5-(1-benzhydryl-1*H*-1,2,3-triazol-4-yl)quinuclidin-2-yl)(6-methoxyquinolin-4-yl)methanol (4)**
Reaction conditions described for the synthesis of **3** were applied to the preparation of **4** but diphenylmethyl azide (731 mg, 3.5 mmol, 1 equiv) was used instead of azidobenzene. Purification by column chromatography, eluting with EtOAc/MeOH 85:15, gave the quinine derivative **4**. Yield: 255 mg (41%); mp 114 °C. IR (ATR): 3143, 2926, 2874, 1506, 1238, 1028, 725, 698 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.64 (dd, *J* = 4.5, 1.9 Hz, 1 H), 7.92 (d, *J* = 9.4 Hz, 1 H), 7.51 (d, *J* = 4.8 Hz, 1 H), 7.34–7.22 (m, 7 H), 7.22–7.17 (m, 1 H), 7.01 (s, 1 H), 6.96–6.88 (m, 5 H), 5.66 (d, *J* = 3.9 Hz, 1 H), 3.81 (s, 3 H), 3.70–3.56 (m, 1 H), 3.46–3.32 (m, 2 H), 3.31–3.20 (m, 1 H), 3.08–2.98 (m, 1 H), 2.81–2.66 (m, 1 H), 2.12–2.04 (m, 1 H), 1.87–1.70 (m, 2 H), 1.68–1.53 (m, 1 H), 1.40–1.31 (m, 1 H), 0.96–0.81 (m, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 157.9, 150.1, 147.6, 146.9, 144.4, 138.2, 138.1, 131.7, 129.0 (2 C), 128.9 (2 C), 128.6, 128.5, 128.1 (2 C), 127.9 (2 C), 126.7, 121.8, 120.6, 118.6, 101.2, 71.2, 68.1, 59.6, 55.8, 43.4, 33.2, 29.8, 28.1, 27.1, 21.8. HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{33}H_{34}N_5O_2$: 532.2713; found: 532.2716.

(15) **Pair-Wise Competitive Photooxygenation Experiments; Typical Procedure**
A Schlenk flask was charged with anthracene (37.4 mg, 0.21 mmol, 1 equiv), methyl 2-oxoindane 1-carboxylate (40 mg, 0.21 mmol, 1 equiv), photosensitizer **1** (6 mg, 0.0105 mmol, 5 mol%), methyl phenyl sulfone (16.4 mg, 0.105 mmol, 0.5 equiv) as an internal standard and $CDCl_3$ (4.2 mL) to give a red solution. The reaction medium was gently bubbled through with oxygen for 5 min and then placed under an oxygen atmosphere. The homogeneous solution was irradiated with two green LEDs (1 W, 75 Lm, 535 nm typical wavelength). The distance from the light source to the irradiation Schlenk vessel was 2 cm without the use of any filters. The reaction was stirred for the appropriate reaction time and an aliquot (0.2 mL) was taken from the reaction mixture. The aliquot was diluted with $CDCl_3$ (0.4 mL) and nitrogen was bubbled through the solution to remove oxygen. The samples were then analyzed by ^1H NMR spectroscopy to determine the yield and product formation.

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