RESEARCH ARTICLE

Low-Impact Synthesis of γ-Lactones Through Photoinduced Baeyer-Villiger Oxidation of Cyclic Ketones

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Abstract: A photocatalyzed oxidation of functionalized cyclobutanones to access γ-lactones has been performed in acetonitrile at room temperature, using anthraquinone derivatives as catalysts in the presence of TFA. The best reaction results were obtained by using 3 mol % of 9,10-anthraquinone as a catalyst under 370 nm irradiation in an O_2 environment. The scope and the limitations of this reaction have been investigated using both 2- and 3-substituted cyclobutanones, as well as enantiopure ketones, to obtain full preservation of their stereochemical identity after the oxidation. The process furnishes in most cases the desired compounds with high purity after catalyst removal by simple filtration, and reducing the production of solvents waste.

Introduction

Five-membered cyclic esters, better known as γ-lactones, are recurring motifs contained in a wide range of biomolecules.[1] It is possible to identify γ-lactones in the aroma components of Whiskey and Cognac (whiskey and Cognac lactone),[2] in plants extract, (eg., rubrynolide and paeonylactone-A),[3] in microorganisms, as in the case of mupircocin H (mupH),[4] and in marine fungi (harzialactone A).[5] Furthermore, a certain number of γ-lactones endowed with pheromonal activity have been isolated from insects, including muricatacin and Japolnilure.[6] On the other hand, several synthetic derivatives have been developed over the years for the treatment of various pathologies such as the diuretic spironolactone (Aldactone™),[7] aldosterone antagonists for the treatment of primary or secondary hyperaldosteronism, and arterial hypertension, or mycophenolat-mofetil (Cellcept™), a drug employed to prevent rejection in kidney, heart, or liver transplants.[8]

In addition to their pharmaceutical, agrochemical, and food applications, γ-lactones represent fundamental synthetic intermediates for both the fine chemical and polymer industries.[9] Due to the presence of this scaffold in complex molecules with so different applications, several synthetic protocols to achieve diversified γ–lactones have been intensively studied over the years. The most traditional strategies are certainly the intramolecular esterification processes, lactonization of unsaturated carboxylic acids[10] or by S_Ni of epoxyacids[11] and γ-halogen-acids.[12] Conversely, metallo-[13] organo-[14] and photocatalyzed synthetic strategies[15] have allowed access to functionalized γ-lactones through the intermolecular reaction between α,β-unsaturated esters, and alcohols (Figure 1).

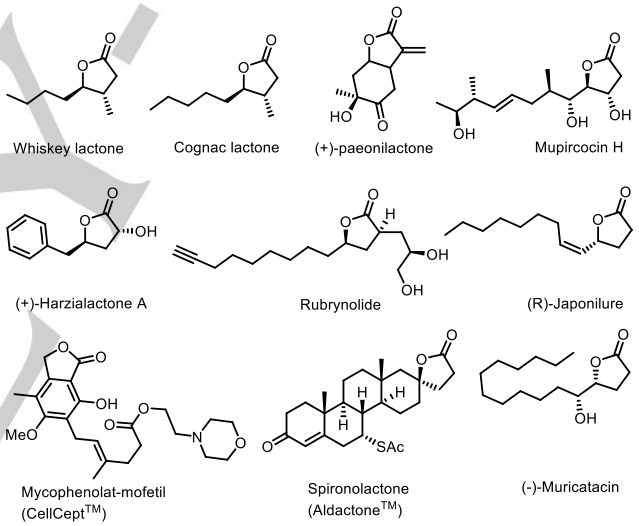


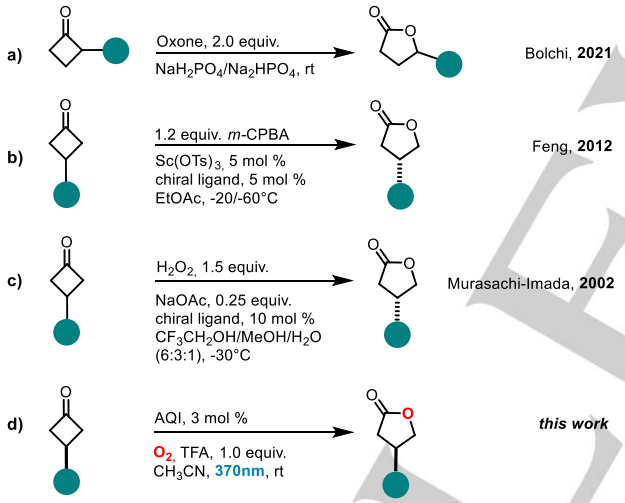
Figure 1. Selected bioactive γ-lactone derivatives .

Despite the abundance of synthetic approaches concerning the preparation of five membered ring lactones, the oxidation of cyclic ketones through the Baeyer-Villiger (BV) reaction still represents an efficient and widely applied process.[16] In particular, the oxidation of cyclobutanone derivatives (CB) has been proposed for the regio-, stereo-, and enantioselective synthesis of γ-lactone building blocks. To cite some examples, stoichiometric amounts of Oxone™ have been used to perform the oxidation of 2-substituted CBs in aqueous NaH_2PO_4/Na_2HPO_4 buffer solution accessing to 5-aryldihydrofuran-2(3*H*)-one compounds[17] (Scheme 1, a). The use of *meta*-chloro perbenzoic acid (*m*-CPBA) in combination with $Sc(OTf)_3$ and chiral ligands was reported by Feng[18] in 2012 to desymmetrize 3-substituted cyclobutanones in excellent *e.r.* and yields (Scheme 1, b). Moreover, the use of 2,2'-diperoxyphenic acid and copper (II)-chiral bisoxazoline (BOX) ligand complexes have also been reported,[19] accessing 4-aryldihydrofuran-2(3*H*)-ones in moderate *e.r.* and good chemical yields. Nevertheless, H_2O_2 has been efficiently used in the

enantioselective BV oxidation of four-membered ring ketones as reported by Murasachi and Imada[20] in 2002 (Scheme 1, c) and by Miller in 2018.[21] Again, regio- and stereoselective enzymatic strategies have been proposed to perform valuable oxidations of cyclic ketones.[22]

The photooxygenation of organic compounds constitutes a straightforward strategy for synthetic applications and industrial processes, with a low environmental impact as an important advantage.[23] In this context, various authors have reported the use of anthraquinone (AQ) derivatives as valid photocatalysts to be used in oxidation reactions of alcohols to ketones[24] and organic sulfides to sulfoxides/sulfones.[25] Since these catalytic strategies are extremely relevant from a socio-economic and environmental point of view, inspired by recent works reported by Wolf,[26] Konig,[27] and Hollmann[28] concerning the use of organic catalysts for photooxidation purposes, we undertook a study on the oxidation of strained carbocyclic ketones, to access the corresponding lactones using O_2.

Herein we report the light-driven oxidation of functionalized cyclobutanones to γ-lactones mediated by catalytic amounts of anthraquinones and molecular oxygen at atmospheric pressure, as a source of reactive oxygen species, as summarized in Scheme 1d. To date, there are no examples of photoinduced Baeyer-Villiger oxidation of ketones based on the use of O_2 as oxidizing reagent.

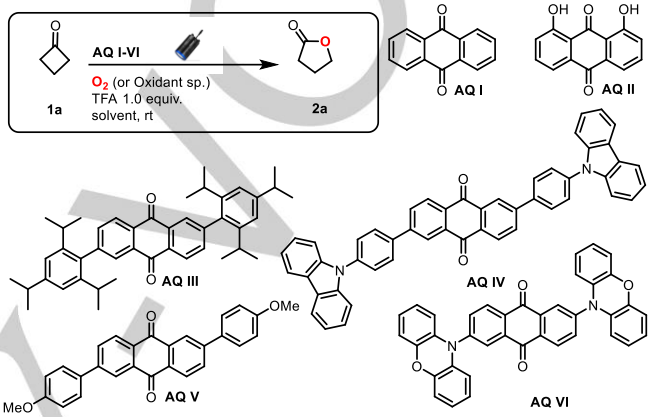


Scheme 1. Representative oxidation strategies for the synthesis of γ-lactones from functionalized cyclobutanones.

Results and Discussion

Our investigation began with the selection of a panel of AQs (AQ**I**-**VI**) intended for use as photocatalysts in oxygen-mediated oxidation reactions, targeting the conversion of **1a** into the corresponding lactone **2a**. The reactions were conducted in dry DMF (1.5 M) under an oxygen atmosphere (balloon) and subjected to irradiation with UV-visible light (Table 1). Employing 3.5 mol% AQ**I** (390 nm), lactone **2a** was quantified in 27% conversion (entry 1) by ^{1}H qNMR after 16 hours of reaction. However, a comparable experiment conducted with the same catalyst and the addition of TFA (1.0 equiv.) resulted in a 64% conversion (entry 2). Moreover, extending the exposure of the reaction mixture to light for 24-48 hours failed to yield any increase in conversion. Whilst, none of the anthraquinones AQ**II**, **IV**-**VI** performed well under the reported reaction conditions (entries 4 and 7-9) except for AQ**III**, which led to a conversion of about 50% after 24 h reaction (entry 4). Better conversion to **2a** (84%) was observed when DMF was replaced by ACN (entry 3). With the aim of further implementing this conversion, other solvents (MeOH, MeOH/H_2O (1:1), EtOH, DCM, hexane, DMA, EtOAc) were screened (SI, table S1). However, none of these solvents outperformed ACN.

Table 1. Photoinduced oxidation of cyclobutanone. Catalyst ad reaction conditions screening.



Entry[a]	AQ	Ox species	Solvent	Light/λ	Time/h	**2a** conv.%[b]
1	**I**	O_2	DMF	390 nm	16	27
2	**I**	O_2	DMF	390 nm	16	64
3	**I**	O_2	ACN	390 nm	24	84
4	**II**	O_2	DMF	425 nm	24	10
5	**III**	O_2	DMF	365 nm	24	50
6	**IV**	O_2	ACN	390 nm	24	12
7	**V**	O_2	ACN	370 nm	24	13
8	**VI**	O_2	ACN	375 nm	24	5
9	**VI**	O_2	ACN	400 nm	24	7
10	**I**	O_2	ACN	370 nm	12	>98
11	**I**	O_2 [c]	ACN	370 nm	24	78
12	**I**	air	ACN	370 nm	24	3

[a] Reactions were performed in a 10 mL Pyrex vial equipped with a stirring bar and sealed with a crimp cap. **1a** (3.12 mmol), AQ**I**-**VI** (3.5 mol%), TFA (3.12 mmol), acetonitrile (2 mL). Oxygen was introduced into the reaction environment by connecting a gas ballon to the vial; [b] Conversions were determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard; [c] Oxygen was bubbled with a needle in the reaction environment throughout the experiment.

At this point, the TFA loading was evaluated. Experiments conducted in the presence of the acid between 1.0 and 2.0

equivalents did not substantially modify the course of the reaction, accessing the respective lactone products **2a** in high yields. However, in experiments in which the TFA loading was higher (3.0-4.0 equiv.), the reactions performed less well in terms of chemical conversion and purity of the reaction products (Table S2). Subsequently, a relevant investigation on catalyst loading was conducted. Catalyst concentrations lower than 3% allow satisfactory yields of the respective lactones **2a**. Moreover, lowering AQ**I** loading led to a notable increase in reaction times. Increasing the catalyst loading by >4% gave low conversions and solubility problems. For this reason, we decided to continue our studies using an optimal concentration of AQ**I** equal to 3.0% (entry 10). for variations in the initial reaction conditions and their optimization see Table S3.

Taking into account the absorption spectra of AQ**I** in ACN (Figure 2, a) showing two principal absorption bands between 290 and 370 nm, not perturbated by the addition of **1a** and TFA (Figure 2, b), we performed further experiments by irradiating the reaction solutions of **1a**/AQ **I**/TFA at λ = 370 nm.

After 16h reaction, we could appreciate by ^{1}H qNMR analysis full conversion of **1a** into **2a** after 12 h reaction (entry 10). On the other hand, substituting molecular oxygen with air did not lead to obtaining the desired product in satisfactory yields (entry 12).

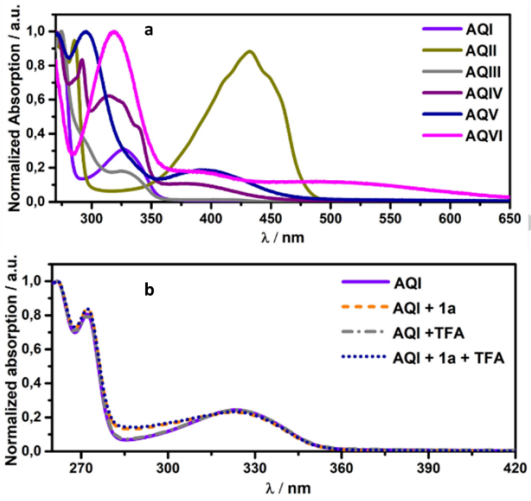
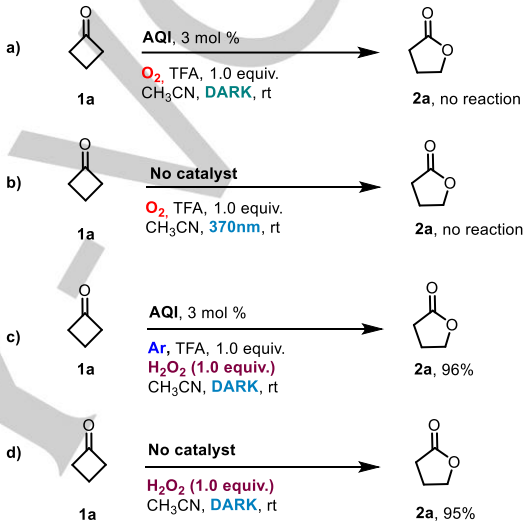


Figure 2. [a] Absorption spectra of AQ**I-VI** (conc. 1x10^{-5} M in ACN); [b] absorption spectra of AQ**I** in the presence of **1a** and TFA in ACN.

Finally, to be sure that the studied process was driven by light, control experiments were carried out. At first, the oxidation of **1a** was performed in the dark (AQ**I**/TFA/O_2). After 24 h, compound **2a** was not detected in the reaction mixture, and the starting material was recovered unchanged (Scheme 2, a). Light dependence was also assessed through experiments conducted with repeated light-dark cycles, at three-hour intervals. From these tests emerged that during irradiation the reaction proceeds rapidly and stops when the light is turned off. When the lamp is turned back on, the reaction resumes at the same rate until completion (Figure S1). Nevertheless, reactions carried out without AQ**I** were unsuccessful (Scheme 2, b), confirming that this transformation occurs through the photoexcitation of the anthraquinone species and the production of oxygen reactive species, able to trigger the light-driven BV reaction. Finally, the addition of hydrogen peroxide in reactions protected from light (with and/or without AQ**I**) were carried out, causing the oxidation of the four-membered ring to afford **2a** in 94-96% (Scheme 2, c and d).

With the premise of better understanding this oxidative process, the electrochemical behavior of anthraquinones **I-VI** were investigated through cyclic voltammetry (CV) techniques in a three-electrode undivided cell in anhydrous ACN. Under the operational conditions, AQ**I** showed two reversible redox peaks (Figure S3), at $E^{red}_{1/2}$ = -1.40 and -1.86 V, according to literature[29] (in Figures S2-S5 the cyclic voltammograms of the other AQs are reported). While AQ**II** and AQ**IV** both show two reversible or quasi-reversible peaks, in the cases of AQ**III** and AQ**V** the shape of the curves could suggest the existence of an electrochemical-chemical mechanism, whereas the low solubility of AQ**VI** seems to hamper the CV measurement (Table S4).



Scheme 2. Role of AQ **I** and background reactions investigations.

Furthermore, since the presence of TFA plays an important role in the photocatalytic properties of AQ**I**, also CV measurements upon successive additions of this acid were performed, to highlight any modification in the electrochemical response.[30] As can be observed in Figures 3a and 3b, the addition of TFA strongly modifies the electrochemical features of AQ**I**.

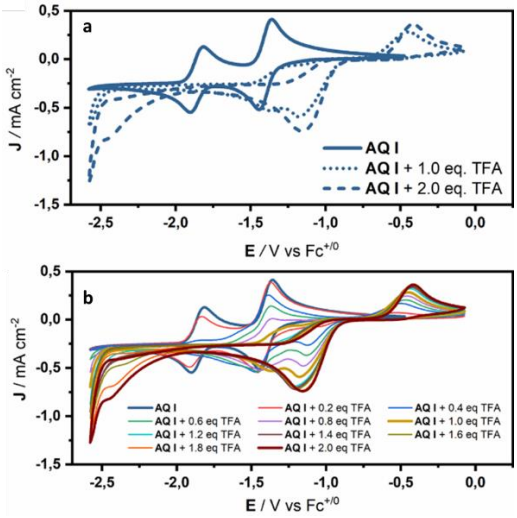


Figure 3. Cyclic voltammetry of AQ**I** upon sequential addition of TFA in ACN.

Indeed, upon the successive addition of TFA, the two redox couples progressively disappeared, whereas a cathodic and an anodic peak appeared at -1.19 and -0.43 V, respectively. This feature suggests, in conjunction with the intensity of the reduction peak, a single 2-electron reduction process in the presence of TFA, rather than the two 1-electron processes observed under dry and anhydrous conditions. Furthermore, the addition of TFA led to the formation of a cathodic current with an onset at around -2.5 V. To have a global picture of our reaction environment, CV measurements in ACN were also conducted for TFA and cyclobutanone **1a** in such a way that we could relate the redox potentials of all the species involved in the synthetic process (Figure S6). From this study, it was determined that AQ**I** represents the most easily reducible species ($E^{red1}_{1/2}$ = -1.40V), followed by TFA (E_{rid} = -2.20V, -2.68V). While cyclobutanone **1a** shows the lowest values among the three reaction partners (E_{rid} = -3.10V).

Photophysical measurements aimed at obtaining useful information for understanding the reaction mechanism are summarized in Figure 4 and in the SI. In detail, AQ**I** photoexcitation at 360 nm shows an emission band centered at 545 nm which is selectively quenched by the addition of increasing amounts of TFA (Figure 4, c and d). Whereas, quenching experiments conducted by adding cyclobutanone **1a** (Figure 4, a) did not induced any significant changes in the emission properties of anthraquinone **I**. Meanwhile, oxygen bubbling caused a slight decrease in the emission intensity[24c] (Figure 4, b).

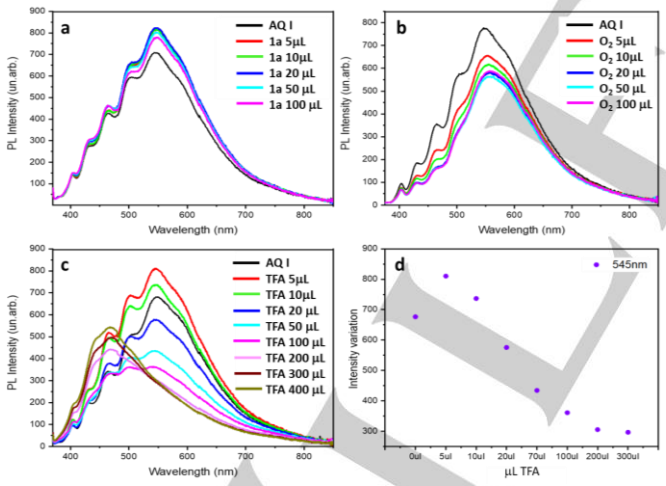
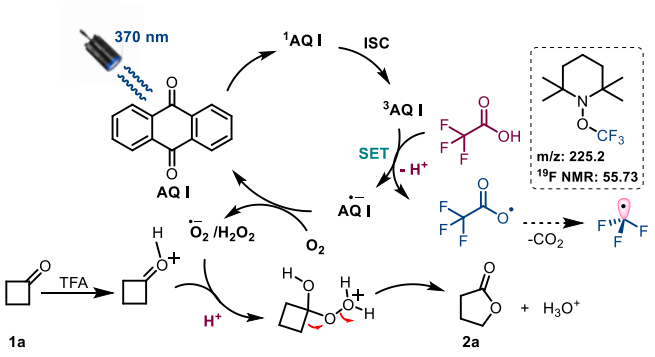


Figure 4. Quenching experiments of the AQ**I** (2.0 mM in ACN) emission band centered at 545 nm and by excitation at 360 nm by the addition of: a) of **1a**; b) O_2; c) TFA; d) Emission intensity variation of AQ**I** by adding progressive amounts of TFA.

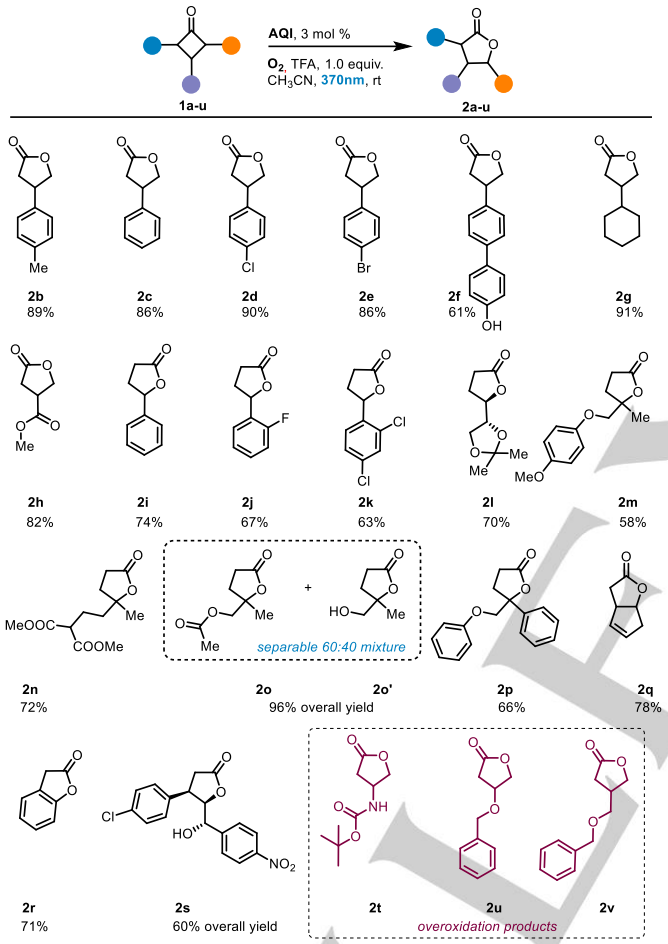
This led us to think that TFA could effectively act as a sacrificial reducing agent for AQ**I** during the photoinduced BV oxidation of CBs by producing superoxide radicals. In this regard, taking into consideration the fact that the formal abstraction of a hydrogen atom from TFA would lead to the formation of trifluoroacyl radicals and that upon loss of CO_2, this species would generate the trifluoromethyl radical, we attempted to capture it by adding one equivalent amount of TEMPO to the reaction mixtures. TEMPO-CF_3 formation was observed by ^{19}F NMR analysis (20%) showing the characteristic singlet peak at 55.73 ppm (Figure S12) and by mass spectrometry (*m/z* 225.2), supporting the hypothesis of a possible radical mechanism for this transformation[31] (Figure S13). This finding was supported by determining the excited state reduction potential of AQ**I** in acetonitrile ($E^{*red}_{1/2}$ = +3.29), which was then juxtaposed with the documented value of $E^{ox}_{1/2}$ (+2.70 V) for TFA.[31c] These calculations suggest that AQ**I** in its excited state exhibits potential for oxidizing trifluoroacetic acid, thus facilitating the initiation of a SET process (SI). Once identified TFA as the sacrificial reducing agent in the photooxidation of CBs, we pointed out our attention to the determination of the reactive oxygen species. At first, *in situ* Raman analyses were performed to detect H_2O_2 in the reaction media (Figure S11). However, we were not able to highlight the formation of H_2O_2 in the reaction environment over time. On the contrary, by sampling known volumes of a cyclobutanone **1a** to **2a** photooxidation reaction, carried out under the operating conditions reported above, and by adding to this a 0.4 mM solution of 2,7-dichlorofluorescein (2,7-DCF), we were able to observe a progressive increase in fluorescence (Figures S9 and 10), proportional to the conversion of **1a** to **2a** which was separately monitored by ^1H NMR. According to the present results and the previous literature reports,[32,33] a plausible mechanism for the BV photo-oxidation of cyclic ketones **1** catalyzed by AQ**I** is proposed in Scheme 3. Photoexcitation of AQ**I** under irradiation at 370 nm generates ^{1}AQ**I** which is prone to intersystem crossing process (ISC) leading to ^{3}AQ**I**. This species can undergo single electron transfer (SET) in the presence of TFA, yielding AQ**I** $^{\bullet-}$. Then, electron transfer from AQ**I** $^{\bullet-}$ to O_2 would finally lead to the formation of the reactive superoxide radical $O_2^{\bullet-}$ (mostly indicated as an H_2O_2 precursor in acidic media).[34] The nucleophilic attack by the superoxide radical or hydrogen peroxide[35] towards the cyclobutanone carbonyl group causes the formation of an α-peroxy cyclobutyl intermediate, which is susceptible to ring expansion. This process would be thermodynamically favored as the formation of the lactone derivatives is followed by a notable decrease in the strain energy (SE) of the cyclic systems (SE, cyclobutanone: 26.4 Kcal/mol; SE, γ-lactone: 7.69 Kcal/mol), according to the general scheme used to describe oxidative processes in BV conditions.[36,37,38]



Scheme 3. Proposed mechanism for the photo-oxidation of cyclobutanones **1** to γ-lactones **2** under 370 nm irradiation.

With this work model in hand, we explored the scope and the limitations of this transformation (Scheme 4) by submitting a

series of cyclobutanones to O_2-mediated photocatalyzed BV oxidation under the best operational conditions described above. Symmetric 3-substituted cyclobutanones **1b-h** were easily converted in good to excellent yields to the corresponding γ-lactones **2b-h**. Photooxidation of 2-substituted cyclobutanones **1i-l** proceeded well, affording the desired cyclic esters in good to excellent conversion and satisfactory yields. However, ^{1}H NMR analysis of the crude compounds highlighted the presence of 5-10% of the γ-keto esters **B** (Scheme 5), probably formed by benzylic hydrogen abstraction (HAT) and the further reaction of the formed radical species with the reactive oxygen.[39] On the other hand, lactones **2m**, **2n**, and **2p** were isolated in good yields after a one hour reaction.



Scheme 4. Synthesis of γ-lactones through photoinduced Baeyer-Villiger oxidation of cyclic ketones **2b-v**.

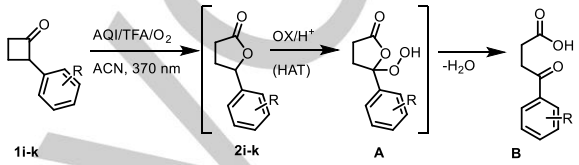
Oxidation of (1-methyl-2-oxocyclobutyl)methyl acetate **1o**, led to the isolation in high yields (86%) of the corresponding (2-methyl-5-oxotetrahydrofuran-2-yl)methyl acetate **2o** in 47% yield accompanied by a 39% of the separable alcohol derivative **2o'**, most likely due to acid hydrolysis promoted by the TFA once the water concentration increases in the reaction environment.

The bicyclic compounds **1q** and **1r** were oxidized in a chemo- and regioselective manner, leading to the isolation of the fused γ-lactones **2q** and **2r** in 78% and 71% respectively. This result is noteworthy, as BV-like oxidative procedures previously reported in the literature have often led to the formation of lactone regioisomeric mixtures. However, in this case, it is possible to obtain only the thermodynamically most favored product.[40]

Oxidation of the enantiopure ketone (*R,S*)-**1l** accessed to the known lactone (*R,R*)-**2l** in 70% yield, with full preservation of its stereochemical identity.

Analogously, the enantiomerically enriched cyclobutanone **1s** provided the desired lactone **2s** in good yields.[41] Nevertheless, it should be noted that the photooxidation of cyclic ketones **1t-v** was not accomplished, and under our operational conditions we were not able to isolate the desired compounds **2t-v**.

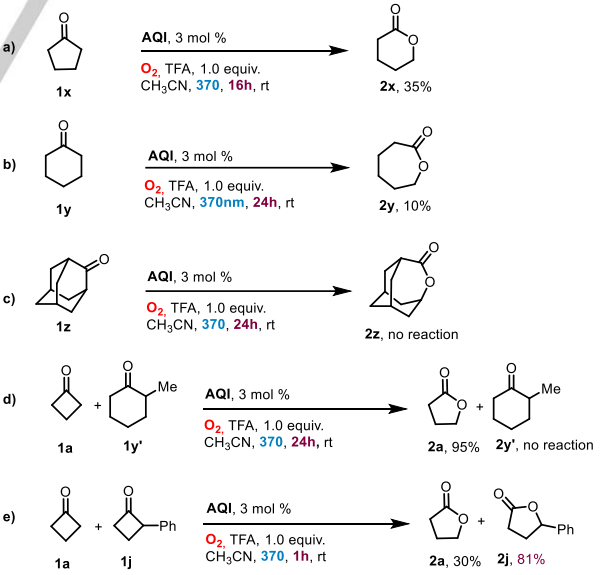
This failure can be justified by calling into question collateral processes of H-abstraction[39] for the benzyl derivatives and, SET pathways for the amine derivative.[42] However, we did not conduct further studies that could lead to the resolution of this issue.



Scheme 5. Proposed mechanism for the phenyl lactones overoxidation and the formation of γ-keto acids **B**.

At this point, we attempt the BV photooxidation of a panel of other cyclic ketones. However, as reported in Scheme 6 (a, b), we recorded moderate (**2x**, 35%, a) to poor yields (**2y**, <10%, b). Finally, attempts to perform the photo-oxidation of adamantanone were unsuccessful (scheme 6, c).

Although it is known that BV reactions can lead to obtaining these compounds through thermal processes, mainly conducted with peroxides, we believe that the lack of reactivity of five- and six-membered cyclic ketones under the developed reaction conditions can be partially related to consistent differences in their strain release energies.[36,37]



Scheme 6. Attempted synthesis of δ- and ε-lactones through photoinduced Baeyer-Villiger oxidation of cyclic ketones **2x-z** and related competition experiments.

This aspect was also investigated with competition experiments in which a 1:1 mixture of CB **1a** and 2-methyl cyclohexanone **1y'** was subjected to a photooxidation reaction, leading to the

exclusive obtaining of lactone **2a** (Scheme 6, d). Instead, subjecting a 1:1 mixture of CBs **1a** and **1j** to photooxidation leads to the formation of both lactones **2a** and **2j**, in which the lactone deriving from the more reactive cyclobutanone was the majority product (Scheme 6, e). These results are also justified by previous studies in which it is reported that the oxidation reactions of cyclobutanone with H_2O_2 are up to 800 times faster than those of cyclohexanone.[36,37] Conversely, this feature reveals that this photo-oxygenation process can be used as a mild and selective way to access γ-lactones.

Experimentally it has been observed that the solubility of AQ**I** in acetonitrile is influenced by the concentration of the various species in solution and in particular by the amounts of water.[38] As the photo-oxidation reaction of cyclobutanones progresses, the H_2O concentration increases causing the lowering in the solubility of the photocatalyst, causing its precipitation from the reaction environment. This observation allowed us to develop a two-step purification procedure based on AQ**I** removal by filtration, and further solvent evaporation. By using this protocol, all the lactones **2** resulted sufficiently pure to allow us full characterization and quantification.

Given the easy recovery of AQ**I** (>90% without further optimization) and its stability under the developed reaction conditions, we evaluated its potential reuse. For this purpose, the recovered anthraquinone catalyst was redissolved in acetonitrile and used to catalyze new cyclobutanone **1b** photo-oxidations. From this study it emerged that AQ**I** can efficiently promote the formation of lactones **2b** over five cycles, keeping the conversions almost constant or in any case higher than 90% (Figure 5). It should also be noted that no decomposition of the photocatalyst was ever observed, which makes us think that this photocatalyst can be reused for a greater number of transformations.

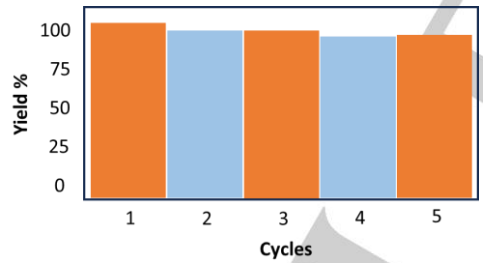


Figure 5. Cycle recovery performance of catalyst **AQI**

Conclusion

In summary, a novel chemo- and regioselective protocol for the efficient photooxidation of four-membered ketones has been developed, enabling access to a variety of valuable γ-lactones in good to excellent yields. This mild and wasteless synthetic strategy is based on the use of molecular oxygen through photoactivation by 9,10-anthraquinone and in the presence of TFA as a sacrificial reagent. The reaction itself can be considered as a formal Baeyer-Villiger which can be used as a valid alternative with low environmental impact to classic oxidation methodologies based on the use of organic peroxides. The photocatalyst is used with low loading and is easily recovered from the reaction environment by simple filtration and reused several times. To rationalize the mechanism of the proposed synthetic process, spectroscopic and electrochemical studies were carried out, allowing to identification of the salient phases that underlie the production of the oxidizing species and opening new scenarios for other applications in photocatalysis.

Experimental Section

General Procedure for the photo-oxidation of cyclic ketones using AQI as photocatalyst: To a solution of cyclobutanone **1** (0.2 mmol) and AQ**I** (3 mol %) in acetonitrile (3.0 mL) was added TFA (0.2 mmol, 1.0 equiv.). The reaction mixture was stirred at room temperature under irradiation at λ = 370 nm using a Kessil lamp PR II gen. When completed, the reaction mixture was filtered and the filtrate was washed with cold acetonitrile. The resulting organic solution was concentrated under reduced pressure and the residue (if needed) was purified by flash column chromatography to yield the corresponding γ-lactones **2**. Additional references cited withing the supporting information 43-59.

Acknowledgements

We acknowledge MIUR for the financial support (PRIN-PNRR 2023). FSC 2020-Piano Stralcio (Fondo per lo Sviluppo e la Coesione–DOT1304455) is gratefully acknowledged for financing Maria Chiara Cabua's PhD grant. The authors acknowledge the University Research Services Centre (CeSAR)-UniCA for technical support with particular reference to the mass-spectrometry analysis, and NMR service.

Keywords: Anthraquinones • Photo-oxidation • Cyclobutanone • γ-Lactone • Photocatalysis

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Entry for the Table of Contents

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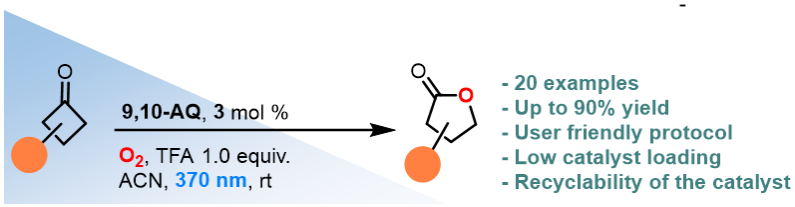

A photocatalyzed oxidation of functionalized cyclobutanones to access γ-lactones has been performed in acetonitrile at room temperature, using 9,10-anthraquinone as catalysts in the presence of TFA. The process furnish good to excellent yields of the desired compounds in 4-16h reaction and after simple filtration of the recyclable catalyst.

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