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PhotoOrganocatalytic Synthesis of Lactones via a Selective C-H Activation-alkylation of Alcohols

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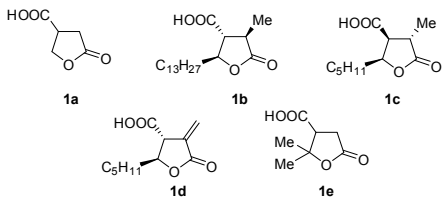
Selective C-H activation is an area of growing importance in modern Organic Chemistry. Herein, we report our efforts in combining Organocatalysis and Photocatalysis for the development of a highly efficient and selective visible-light mediated protocol for the C-H activation and addition of various alcohols to a plethora of Michael acceptors, followed by a cyclization reaction leading to the repeatedly occurring in nature motif of lactones. Utilizing phenylglyoxylic acid as the photocatalyst and common household bulbs as the light source, we describe a versatile α-alkylation/lactonization of alcohols with α,β-unsaturated esters leading to products in excellent yields. The reaction mechanism was extensively studied.

Introduction

Lactones, especially, γ-lactones, constitute a repeatedly occurring motif in natural products and molecules of biological importance that have been reported to exhibit antifungal,[1a] antibiotic,[1b] antitumor,[1c] anti-inflammatory[1d] and cytotoxic[1e] activity. Among the most common members of this family bearing a carboxylic group are paraconic acid **1a**,[2a] a non-natural compound involved in the synthesis of A-factor and in the biosynthesis of streptomycin, while its esters find important industrial applications in the perfume industry, rocellaric acid **1b**,[2b] phaseolinic acid **1c**,[2c] methylenolactocin **1d**[2d] and terebic acid **1e**[2e] (Scheme 1). Due to their importance, a plethora of synthetic methods to access lactones has been reported, with some of them utilizing as starting materials carboxylic acids,[3] terminal alkenes,[4] alkynes,[5] diols[6] or chains that contain some functional groups.[7]



1a **1b** **1c** **1d** **1e**

Scheme 1 Compounds bearing the γ-lactone moiety and a carboxylic group possessing biological properties

An alternative approach for the synthesis of substituted γ-lactones, that has been far less studied constitutes the reaction between an alcohol and an α,β-unsaturated carbonyl compound (Scheme 2). Bypassing the competing reversible oxa-Michael addition, the reaction between mainly 2-isopropanol and maleic acid or its esters has been realized employing either benzophenone-based photosensitizers with expensive mercury lamps,[8-10] or in the presence of radical initiators[11] (Scheme 2, top). An elegant variation to the above mentioned protocols was realized by Dondi and coworkers employing sunlight and a benzophenone-derived photosensitizer for the synthesis of terebic acid **1e** from

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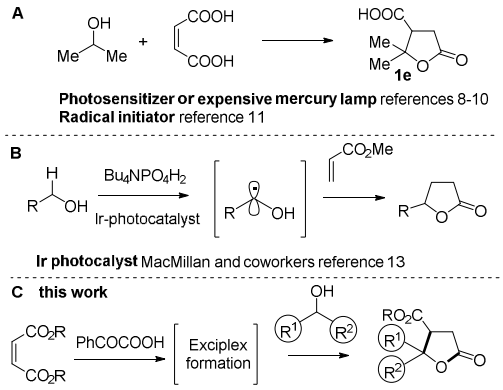
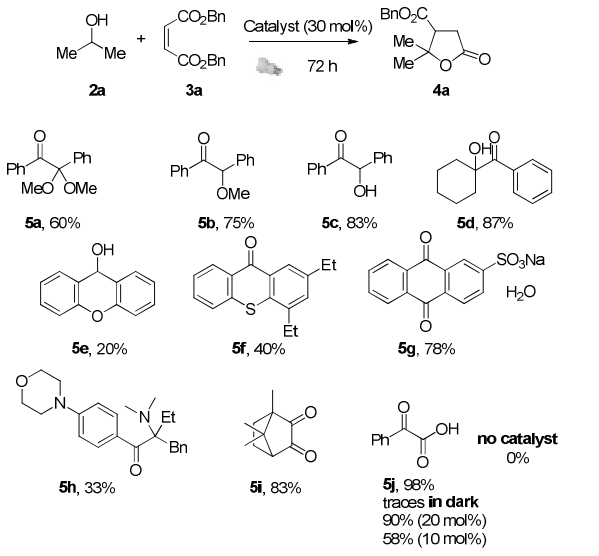


Scheme 2 Photochemical approaches for the synthesis of γ-lactones

isopropanol and maleic acid.[10] However, only a single example was reported. In all these cases, the authors postulate the generation of an α hydroxyl radical from isopropanol either from the triplet state of the excited photosensitizer or the radical initiator, which then adds via a Michael addition to the maleic acid initiating a propagation mechanism. During the last decade, Photoredox catalysis has emerged as a viable solution in longstanding problems.[12] In general, expensive transition metal catalysts are employed, which have the advantage to tune their electronic properties through ligand manipulation. Among these protocols, Macmillan and coworkers employed an iridium-based photocatalyst for the reaction between various alcohols and methyl acrylate for the synthesis of γ-lactones (Scheme 2, middle).[13] In this excellent methodology, a hydrogen bonding strategy was employed to realize a selective activation of the alcohol α-C-H bonds in the presence of a wide range of other C-H bonds, which proved to be critical for the use of numerous primary and secondary alcohols and not just isopropanol (in general, primary alcohols are difficult substrates for product formation and thus, less studied).
A far more cheaper approach and an alternative to Photoredox catalysis was the introduction of PhotoOrganocatalysis.[14,15] We have recently diverted our attention on the development of a photoorganocatalytic protocol that is easy to operate employing cheap household lamps as the source of visible light irradiation and a cheap organic and commercially available molecule as the catalyst, which enhances the concept of green chemistry.[16] In an effort to expand this photoorganocatalytic protocol, we envisaged the use of phenylglyoxylic acid as the photocatalyst for the reaction between various alcohols and diesters of maleic acid (Scheme 2, bottom). This protocol will provide a green metal-free alternative to transition-metal Photoredox catalysis, having also similarly broad substrate scope, that was absent in previous metal-free literature precedents. After extensive mechanistic studies, we concluded that phenylglyoxylic acid after visible light irradiation forms an exciplex which facilitates a selective hydrogen atom abstraction from the alcohol to produce an α hydroxyl radical that performs the Michael addition followed by lactonization.

Results and discussion

We initially investigated the reaction between isopropanol (**2a**) and dibenzyl maleate (**3a**) (Scheme 3). A variety of commercially available photoinitiators (**5a-i**) can promote the reaction in various yields. Phenylglyoxylic acid (**5j**) outperformed all other compounds tested and proved the suitable photoorganocatalyst providing the product in almost quantitative yield (Scheme 3). The progress of the reaction was monitored by NMR and the Michael addition of the α hydroxyl radical was completed after 48 h, but an additional 24 h was necessary to ensure full ring closure to lactone **4a**. Probably, the acidic carboxylic group of **5j** helps in promoting the lactonization step, since when ethyl phenylglyoxylate was employed as the catalyst, the Michael addition product was obtained as the main product. In the absence of the catalyst, the reaction did not



Scheme 3 Optimization of the photocatalytic synthesis of lactone **4a**

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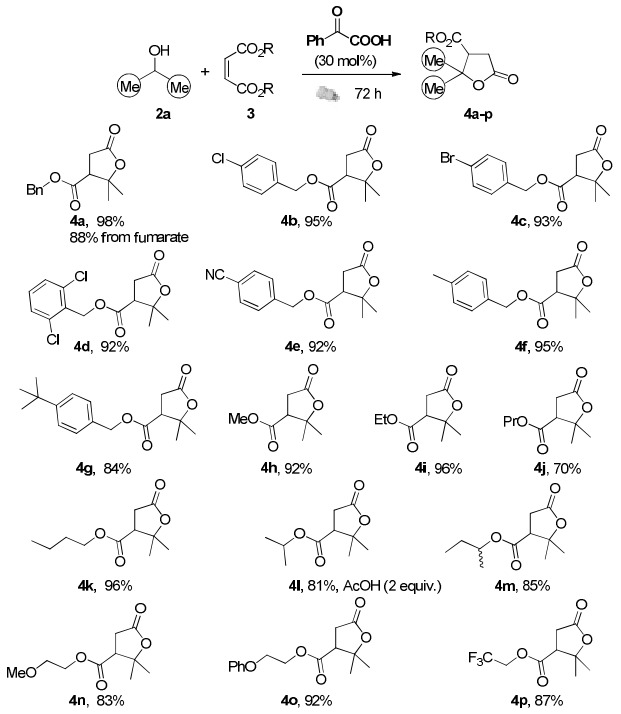
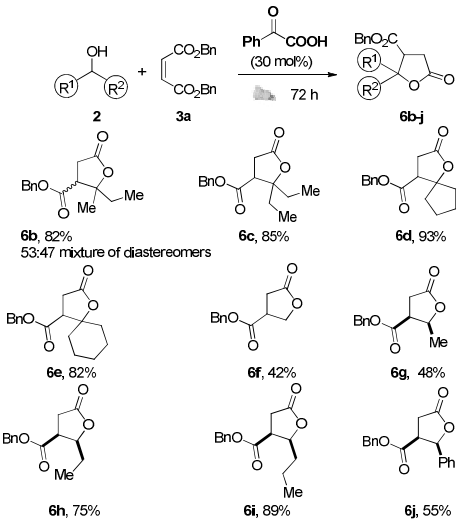
proceed. If the reaction is performed in dark, no reaction is taking place, constituting indispensable the use of both light and catalyst. Decreasing the catalyst loading led to lower yields. Since **5j**'s absorbance properties has been reported in our previous study,[16d] it was postulated that household lamps could be successfully replaced by sunlight (27 July 2016, 09:00-17:00, Athens, Greece, 37.97° N, 23.72° E), leading to similarly excellent yield.[17] This was feasible and will be discussed extensively later in the section regarding the mechanism. Thus, cheap household lamps or sunlight can be employed as the light source and a cheap, commercially available organic molecule, phenylglyoxylic acid, can be utilized to provide a green and sustainable protocol for the synthesis of lactones from readily available starting materials.

Having established the optimum reaction conditions, we turned our attention in the exploration of the substrate scope of the reaction. First, a series of diesters of maleic acid were tested for their reaction with isopropanol (Scheme 4). When dibenzyl fumarate was utilized, the same lactone **4a** was isolated in slightly lower yield than starting from dibenzyl maleate. Various substitution patterns on the benzylic moiety were well tolerated, (*para*- and *ortho*-substitution, electron withdrawing or electron donating groups) leading to excellent yields of esters of terebic acid in all cases (**4a-g**). Other alkyl esters could also be successfully employed (**4h-p**). Except from lineal alkyl esters, the use of more hindered substrates did not pose any limitation for this process, since in the cases of **4l** (additional AcOH for 24 h had to be employed after 72 h to ensure cyclization) and **4m** high yields were obtained. In the latter case, as expected, a mixture of diastereomers was isolated. One of the main disadvantages of the existing methodologies involve low-yielding reactions in the presence of other weak C-H bonds [benzylic (BDE 89.8 kcal/mol) or α-ether fragments (BDE 92.0 kcal/mol)].[13] Our photoorganocatalytic protocol provides an excellent solution to this end, since products **4a-g** and **4n-p** were obtained in high yields. This constitutes one of the few known metal-free processes that affords such results and provides complementary reactivity to the iridium catalysis.[8-11,13] A current limitation constitutes the use of amides of maleic acids that are unreactive, while the use of methyl acrylate or crotonate leads to polymerization.

In order to further expand the substrate scope of our protocol, we tested a variety of alcohols with **3a** (Scheme 5). Other secondary alcohols, both symmetric and non-symmetric afforded products **6b-e** in high yields. Moving from secondary alcohols to primary alcohols, we encountered lower yields, since the generation of the radical is slower and a primary radical is generally less stable. It has to be noted that primary alcohols have been employed successfully



Scheme 4 Substrate scope of the photocatalytic synthesis of γ-lactones



Scheme 5 Substrate scope of the photocatalytic synthesis of γ-lactones

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only when the expensive iridium catalyst was employed. Methanol could be employed leading to paraconic acid ester **6f** in moderate yield. Ethanol afforded the *cis* diastereomer **6g** also in moderate yield as a single distereomer. In these two cases, the volatility of the product could account for the lower yields observed. Moreover, propanol and butanol afforded the *cis* diastereomers of lactones in good yields. This trend that maleates affords *cis* diastereomers and fumarates leads to *trans* diastereomers is known in literature.[11] Finally, benzyl alcohol can be employed as well.

Having in hand a broad substrate scope, we turned our attention in studying the reaction mechanism. UV absorption spectra in isopropanol (using concentrations similar to those of the reaction mixture) of each individual reactant under reaction conditions showed interesting results (Figure 1). Diethyl maleate presented absorption below 300 nm, whereas phenylglyoxylic acid showed increased absorption starting in the early visible wavelength area (Figure 1, **A**). The association of an electron rich molecule with an electron accepting compound can lead to the formation of a new aggregate, called electron donor-acceptor (EDA) complex. EDA complexes are known in literature since the 1950s,[18,19] but it was only recently that Melchiorre and others have identified them as active species in photochemical reactions.[15,20] In some cases, upon addition of the two components of the EDA complex, an increase in the UV absorbance spectrum of the mixture is observed.[15] In some cases, a change in colour is also apparent. In our case, upon mixing the various reaction components (in couples), no increase in the UV absorbance was observed, excluding the possibility of an EDA complex formation. Irradiation of diethyl maleate in isopropanol did not lead to any changes (Figure 1, **B**). Similarly, irradiation of a solution of phenylglyoxylic acid in isopropanol under reaction conditions (household bulbs) did not lead to a significant increase in the absorption band (Figure 1, **C**). Noteworthy, irradiation of the reaction mixture showed a significant increase in the absorption band (310-360 nm, Figure 1, **D**). An exciplex is an excited state complex, "non-bonding" in the ground state, that cooperatively emits a photon.[12g,19] That prompted us to evaluate a possible exciplex[12g,19] mechanistic scenario between **diethyl maleate** and **phenylglyoxylic acid**. Indeed, switching to other solvents, similar increase could be observed in the UV spectrum band (however this increase in not so profound as in isopropanol). Thus, the exciplex must be initiating a hydrogen atom transfer (HAT) from isopropanol leading to a

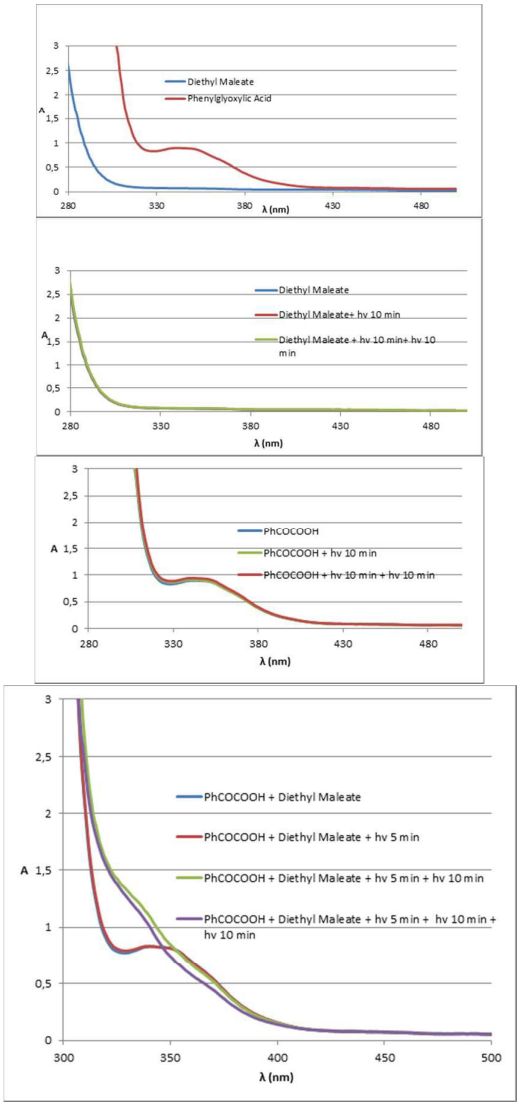

Figure 1 A. UV-Vis absorption spectra of phenylgyoxylic acid (10^{-2} M) and diethyl maleate (0.25 M), recorded in isopropanol in 1 cm path quartz cuvette. **B.** UV-Vis absorption spectra of diethyl maleate (0.25 M), recorded in isopropanol in 1 cm path quartz cuvette after consecutive irradiation. **C.** UV-Vis absorption spectra of phenylgyoxylic acid (10^{-2} M), recorded in isopropanol in 1 cm path quartz cuvette after consecutive irradiation. **D.** UV-Vis absorption spectra of the reaction mixture in 1 cm path quartz cuvette after consecutive irradiation

compound that absorbs in the 310-360 nm. This proposal is further supported by fluorescence studies.[17] No fluorescence quenching of phenylglyoxylic acid was observed with isopropanol, which states that the α hydroxyl radical is not generated by the excited phenylglyoxylic acid, as it occurs in all other literature precedents employing benzophenone derivatives as the photoinitiators, while quenching is observed

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with esters of maleic acid. The reaction was also probed by the use of ^{13}C-NMR spectroscopy (Figure 2). ^{13}C NMR spectra of diethyl maleate or phenylglyoxylic acid exhibited no differences before and after irradiation.[17] It has to be noted that in the case of phenylglyoxylic acid, an equilibrium between the keto- (189 ppm) and the gem-substituted form (hydrate or hemiacetal) (98 ppm) was evident. The mixture of phenylglyoxylic acid and diethyl maleate (in CD_3OD) presented all expected signals. After irradiation of the reaction mixture (in CD_3OD) for 20 min, additional signals (carbonyl and aromatic carbons) appeared (Figure 2). The new peak at 102 ppm can be attributed to the quaternary carbon atom of diphenyl tartaric acid (this is the compound formed after HAT from the exciplex).[17] These two facts hint that phenylglyoxylic acid, by itself, is incapable of initiating the HAT process and has to form the exciplex with diethyl maleate to do so. Benzophenone did not exhibit this phenomenon.

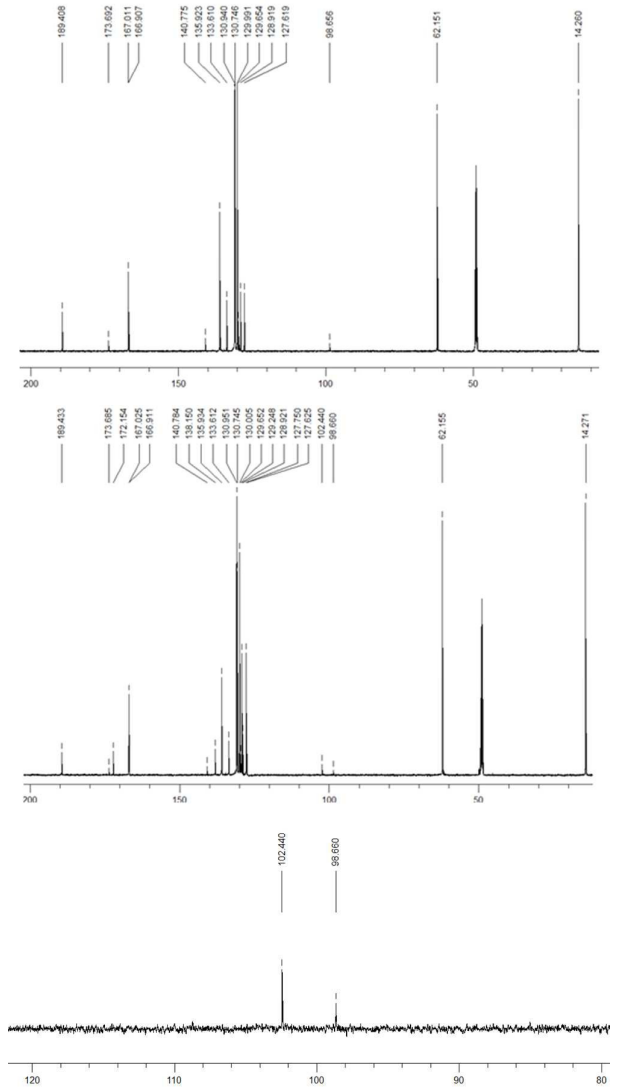

Figure 2 A. ^{13}C NMR spectrum of a mixture of phenylglyoxylic acid and diethyl maleate in CD_3OD. **B.** ^{13}C NMR spectrum of a mixture of phenylglyoxylic acid and diethyl maleate in CD_3OD after irradiation for 20 min

In a recent report, Cismesia and Yoon challenged the ability of a light-dark experiment as the sole evidence for photocatalytic closed cycle mechanism versus a chain propagation cycle.[21] Using potassium ferrioxalate as the actinometer,[21,22] the photocatalytic reaction of **2a** with **3a** using **5j** (30 mol%) as the catalyst was performed in the spectrophotometer for 8 h and the quantum yield of the reaction was calculated. This process was also repeated for various wavelengths.[17] In all cases, quantum yield values were below 1, but noteworthy the quantum yield of the reaction utilizing the actual setup proved to be 88, which verifies literature precedent that this is a radical propagation reaction.

Based on the above experiments, a proposed reaction mechanism is depicted in Scheme 6. Upon irradiation, the excited phenylglyoxylic acid forms an exciplex with dialkyl maleate via a photoinduced electron transfer (PET). This exciplex is probably a radical ion pair, as depicted in Scheme 6, resembling the exciplex formed between benzophenone and alkyl amines.[12g,23] Then, a HAT process with isopropanol affords the initial α hydroxyl radical and a radical of mandelic acid that dimerizes into diphenyl tartaric acid **I**. The increase in the absorbance in Figure 1, **D**, as well as the new peaks in ^{13}C-NMR after irradiation, can be attributed to **I**.[24] Fluorescence quenching experiments verifies the fact that excited phenylglyoxylic acid cannot initiate the HAT process by itself, since intermediate **I** is not observed (Figure 1, **C** and NMR experiments in ESI). Thus, exciplex formation between phenylglyoxylic acid and dialkyl maleate is necessary for the reaction to occur. Addition of the initial α hydroxyl radical from isopropanol to the dialkyl maleate via a Michael addition affords a new radical species, which via a radical propagation mechanism affords the Michael product that cyclizes to the final lactone.

Finally, in an attempt to further demonstrate the utility of this

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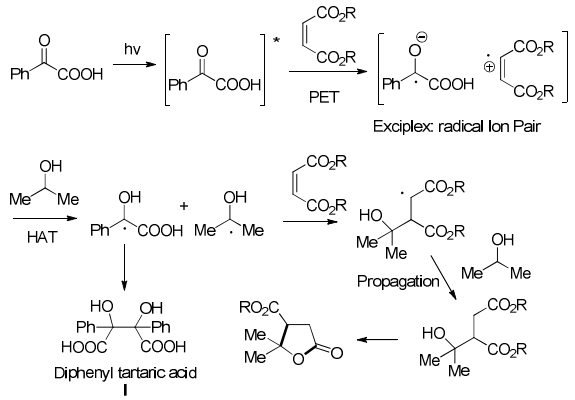
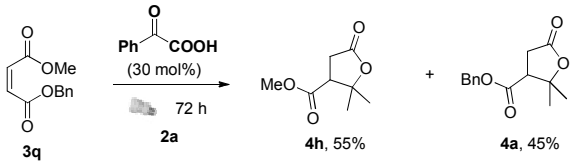


Scheme 6 Proposed reaction mechanism

process, mixed ester **3q** was employed (Scheme 7). As expected, a mixture of **4a** and **4h** was obtained. The same result was obtained under sunlight irradiation.



Scheme 7 Mixed maleate ester

Conclusions

In conclusion, a simple, cheap and efficient photoorganocatalytic protocol was developed and successfully applied to the C-H activation of primary and secondary alcohols and their reaction with diesters of maleic acid, leading to γ-lactones after cyclization. Bypassing the need for transition metal complexes, and thermal (photo)initiators, this method relies on a small organic molecule and cheap household lamps or sunlight. Extensive spectroscopic insights of the reaction suggest a new mechanism for the Michael addition, involving an exciplex. This new exciplex-based mechanism constitutes a new catalysis concept, which can open new avenues in photocatalysis and is currently studied in other reactions.

Experimental

General Procedure for the synthesis of gamma lactones

In a glass vial with a screw cap containing phenylglyoxilic acid (23 mg, 0.15 mmol, 0.3 equiv.) in the corresponding alcohol (2 mL), diester of maleic acid (0.50 mmol, 1 equiv.) was added. The vial was sealed with a screw cap and left stirring under household bulb irradiation for 3 days. The reaction progress can be monitored by GC-MS. After completion of the reaction, the product was isolated by flash silica chromatography of the crude mixture.

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17 For extensive optimization and mechanistic experiments, see Supporting Information.

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